Esophageal and Esophagogastric Junction Cancers, Version 2.2023

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ABSTRACT

Cancers originating in the esophagus or esophagogastric junction constitute a major global health problem. Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma, which differ in their etiology, pathology, tumor location, therapeutics, and prognosis. In contrast to esophageal adenocarcinoma, which usually affects the lower esophagus, esophageal SCC is more likely to localize at or higher than the tracheal bifurcation. Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic disease. The implementation of biomarker testing, especially analysis of HER2 status, microsatellite instability status, and the expression of programmed death-ligand 1, has had a significant impact on clinical practice and patient care. Targeted therapies including trastuzumab, nivolumab, ipilimumab, and pembrolizumab have produced encouraging results in clinical trials for the treatment of patients with locally advanced or metastatic disease. Palliative management, which may include systemic therapy, chemoradiation, and/or best supportive care, is recommended for all patients with unresectable or metastatic cancer. Multidisciplinary team management is essential for all patients with locally advanced esophageal or esophagogastric junction cancers. This selection from the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers focuses on the management of recurrent or metastatic disease.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

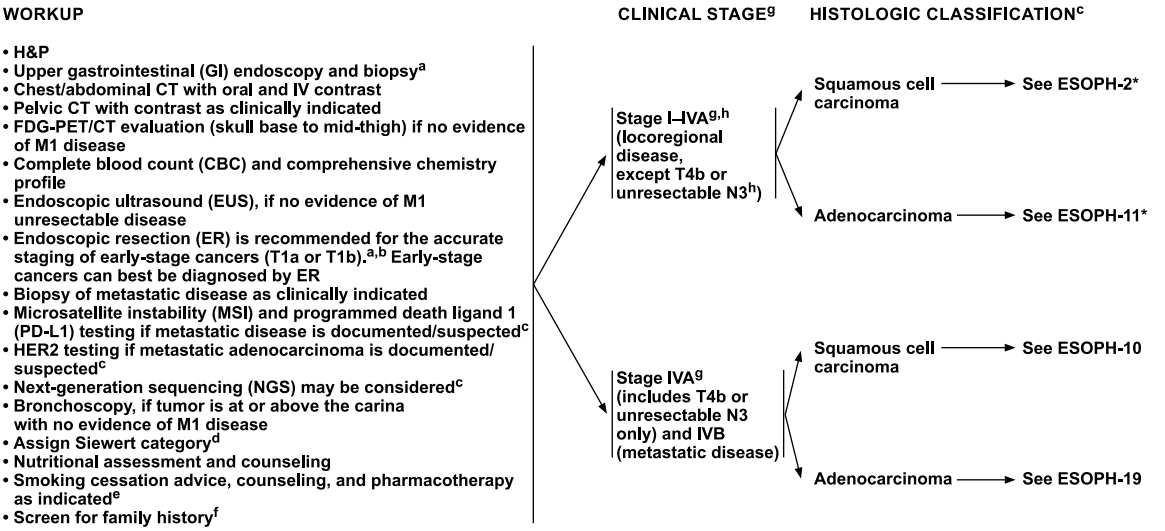
The complete NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Esophageal and Esophagogastric Junction Cancers Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Esophageal and Esophagogastric Junction Cancers Panel members can be found on page 422. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A*).
[b] ER may also be therapeutic for early-stage cancers.
[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C*).
[e] See NCCN Guidelines for Smoking Cessation†.
[f] See Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers (ESOPH-D*). Also see NCCN Guidelines for Colorectal Cancer Screening†, Genetic/Familial High-Risk Assessment: Colorectal†, and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic†.
[g] See Staging (ST-1*) for tumor classification.
[h] Celiac nodal involvement in cancers of the esophagogastric junction (EGJ)/distal esophagus should be considered for combined modality therapy.

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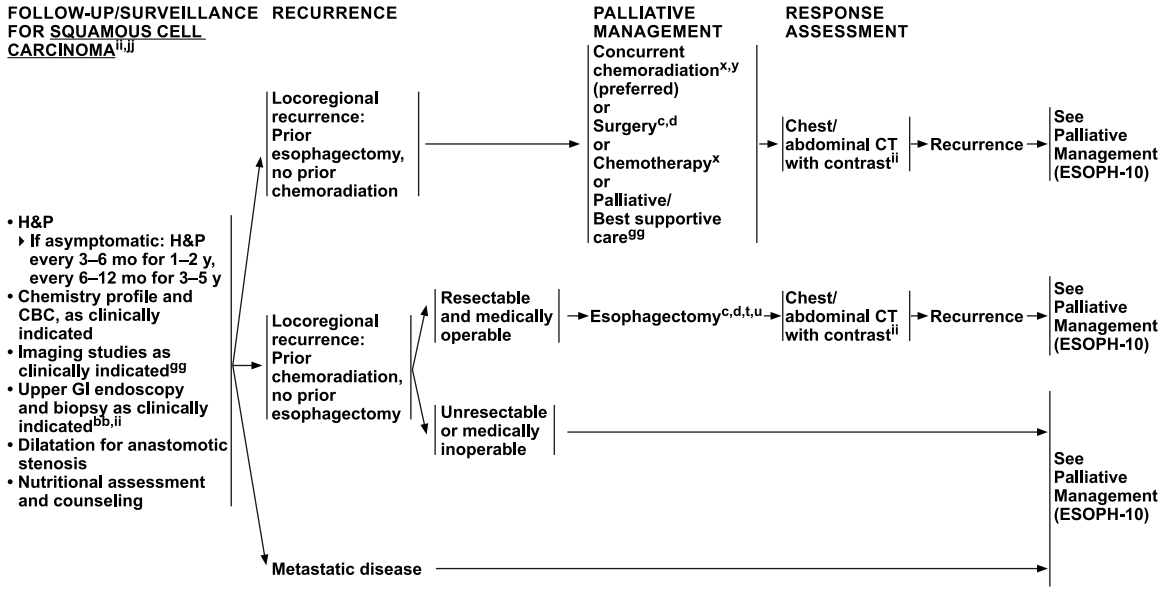
Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus or esophagogastric junction (EGJ) constitute a major global health problem.[1] Globally, there were an estimated 604,000 new cases and more than 544,000 deaths in 2020, making esophageal cancer the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related deaths in the world.[2,3] The global incidence of esophageal and EGJ cancers shows wide geographic variations, with a 60-fold difference between high- and low-incidence regions.[4] The highest-incidence area, often referred to as the "esophageal cancer belt," spans from northern Iran through Central Asia and into Northern China.[1,5] Other high-incidence areas include Southern and Eastern Africa and Northern France.[6] In contrast, esophageal cancer is one of the least frequently diagnosed cancers in North America. It is the twentieth most frequently diagnosed cancer and the eleventh leading cause of cancer-related deaths in the United States.[7] In 2023, an estimated 21,560 people are expected to be diagnosed and 16,120 people are expected to die of this disease.[8] Although still relatively rare, incidence rates have been increasing in the United States over the past several years and the 5-year survival rate remains low.[8]

Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma, which differ in their etiology, pathology, tumor location, therapeutics, and prognosis.[9] In contrast to adenocarcinoma, SCC is more likely to localize at or higher than the tracheal bifurcation, has a proclivity for earlier lymphatic spread, and is associated with a poorer prognosis.[9,10] SCC is the most common histology in Eastern Europe and Asia, and adenocarcinoma is most common in North America and Western Europe. Tobacco and alcohol consumption are major risk factors for SCC, whereas tobacco use is a moderate risk factor for adenocarcinoma.[11–13] The risk for SCC decreases substantially after smoking cessation, whereas the risk for adenocarcinoma remains unchanged even several years after smoking cessation.[14,15] SCC has become less common in North America and Western Europe in recent decades due to reduced tobacco and alcohol use, and now accounts for less than 30% of all esophageal cancers in the United States and Western Europe.[1]

In contrast, the incidence of esophageal adenocarcinoma has increased in North America and Western Europe, likely reflecting rising rates of obesity.[1] High body mass index has been established as the strongest risk factor for adenocarcinoma of the esophagus.[12,16,17] Obesity contributes to the development of gastroesophageal reflux disease (GERD), a major underlying cause of esophageal adenocarcinoma.[18–20] GERD is associated with



[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C*).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G*).
*Available online, in these guidelines, at NCCN.org.

[bb] See Post-Treatment Surveillance–Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5*).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H*).
[ii] See Principles of Surveillance (ESOPH-I*).
[jj] See Principles of Survivorship (ESOPH-J*).

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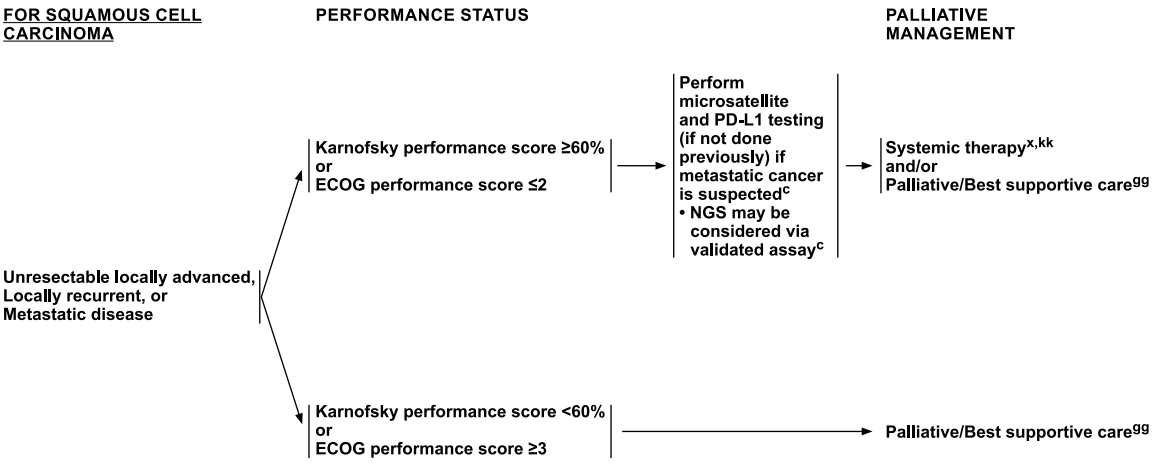
the development of Barrett esophagus, a precancerous condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[21] Patients with Barrett esophagus have a 30- to 60-times greater risk of developing adenocarcinoma of the esophagus than the general population.[19] Older age, male gender assigned at birth, long-standing GERD, hiatal hernia size, and the length of Barrett esophagus are strongly associated with higher grades of dysplasia and increased risk of esophageal adenocarcinoma development.[22–24]

This selection from the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers focuses on the management of recurrent or metastatic disease (to view the complete and most recent version of these Guidelines, visit NCCN.org).

Staging

The TNM staging system used by the AJCC is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. Staging recommendations for esophageal and EGJ cancers presented in the Eighth Edition of the AJCC Cancer Staging Manual include clinical staging (cTNM; newly diagnosed, not-yet-treated patients), pathologic staging (pTNM; patients undergoing resection without prior treatment), and post neoadjuvant pathologic staging (ypTNM; patients receiving preoperative therapy).[10] The Eighth Edition also introduced modifications regarding tumors located at the EGJ. Using this system, tumors with an epicenter located >2 cm into the proximal stomach are now staged as gastric carcinomas, even if the EGJ is involved. Tumors involving the EGJ with an epicenter ≤2 cm into the proximal stomach will still be staged as esophageal carcinomas.

The Eighth Edition of the AJCC Cancer Staging Manual provides additional resources for esophageal and EGJ cancers not available in the Seventh Edition, including the incorporation of newly constructed cTNM and ypTNM stage groupings, to fulfill unmet needs in staging patients under different circumstances. The stage groupings presented in the Eighth Edition are based on updated data with a significantly increased sample size and number of risk adjustment variables. The current stage groupings were determined using a risk-adjusted random survival forest analysis of collated data generated by the Worldwide Esophageal Cancer Collaboration for 22,654 patients spanning 6 continents who were treated with esophagectomy alone or esophagectomy with preoperative and/or postoperative therapy.[10] Use of these data reflects the current preference for treating locally advanced esophageal cancers with preoperative therapy and represents a major advancement over the seventh edition, which was entirely



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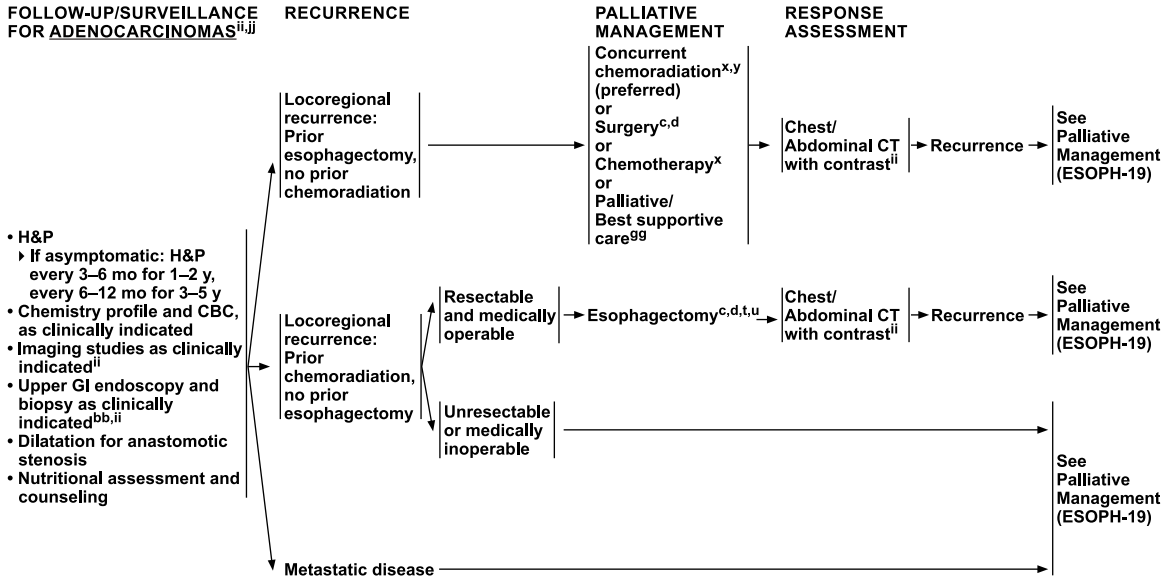
based on data from patients treated with esophagectomy alone. The availability of these data led to the ability to explicitly define cTNM and ypTNM cohorts and stages. The larger dataset also allowed for better separation of SCC and adenocarcinoma staging.[10] However, limitations of this data set still remain, including missing patient variables, heterogeneity of clinical staging among different centers, and poor representation of untreatable or inoperable patients, such as those with T4b and M1 cancers. Additionally, the exact modalities used to arrive at the initial clinical stages were not available for analysis. Nevertheless, the Eighth Edition of the AJCC Cancer Staging Manual represents the best worldwide clinical esophageal cancer staging data currently available. Survival analysis of this dataset revealed that survival decreased with increasing anatomic tumor size and depth (pT), presence of regional lymph node metastases (pN), presence of distant metastases (pM), increasing histologic grade (G1–4), and advancing age.[25,26] Survival increased with a more distal location of cancer within the esophagus. In addition, survival was significantly affected by histopathologic type, with SCC having worse survival than adenocarcinoma.[26] Analysis of this larger dataset also illuminated significant differences in outcome when comparing the same stage groups between patients receiving preoperative therapy versus those treated with surgery alone, emphasizing the importance of having separate pTNM and ypTNM stage groupings to stage patients more accurately within each treatment algorithm.

In esophageal cancer, patient survival is best correlated with the final pathologic stage, regardless of whether the patient has received preoperative therapy.[10] Although surgical pathology yields the most accurate staging, advances in endoscopic techniques and imaging modalities such as endoscopic ultrasound (EUS), CT, and 18-fluorodeoxyglucose (FDG)-PET/CT have greatly improved the accuracy of clinical staging.[27] In general, initial staging of locoregional disease is usually best done with a combination of CT and EUS, while staging of possible distant metastatic disease is best assessed with FDG-PET/CT.[28] Locoregional staging with preoperative EUS provides the most accuracy for cT staging and is the only method capable of delineating the layers of the esophageal wall.[29] In a meta-analysis of 49 studies, EUS provided good sensitivity and specificity for accurately cT staging advanced-stage disease.[30] However, EUS has shown poor accuracy for distinguishing between early-stage tumors limited to the mucosa (cT1a) from those extending into the submucosa (cT1b).[30–33] Therefore, endoscopic resection, which is essential for the accurate staging of early-stage cancers, should be performed for early-stage tumors (cT1a and cT1b ≤2 cm) as it provides more accurate information on the depth of tumor invasion than EUS.[34,35] Ultimately, a cancer that is completely



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[ii] See Principles of Surveillance (ESOPH-I*).
[jj] See Principles of Survivorship (ESOPH-J*).

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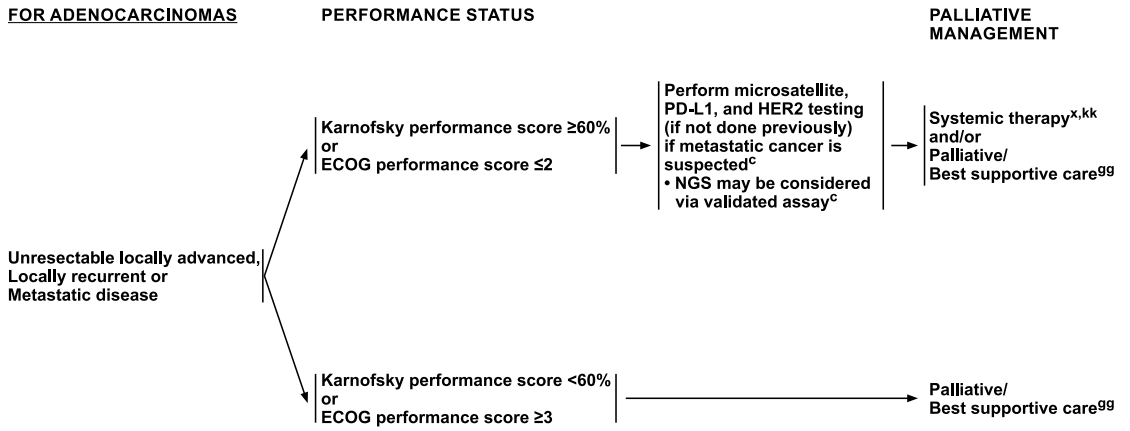
removed by endoscopic resection should be assigned pathologic staging.[10]

CT of the chest and abdomen with oral and intravenous contrast or FDG-PET/CT from skull base to mid-thigh can be used to determine the location of the primary tumor and its proximity to other structures. Although FDG-PET/CT has higher sensitivity for detecting esophageal cancer than CT alone, it has a limited role in cT staging other than for determining invasion of the mediastinum.[36] The diagnostic benefit of FDG-PET/CT is particularly limited in early-stage (cT1) tumors because of the low prevalence of distant metastases and the high rate of false-positive FDG-PET/CT findings.[37,38] FDG-PET/CT also has limited ability to differentiate between cT1, cT2, and cT3 tumors.[10,28] Although the intensity of FDG uptake and cT category are positively related, this association is weak.[37,39,40] Therefore, chest/abdominal CT scan should be performed with oral and intravenous contrast in all patients as part of the initial workup (as well as pelvic CT scan with contrast if clinically indicated), and FDG-PET/CT should be reserved for patients with no evidence of M1 disease.

Although CT and FDG-PET/CT may be used to describe the locoregional lymph nodes (cN), these techniques are suboptimal for detecting locoregional nodal metastasis because of their low sensitivity.[29,39,41–44] CT has a pooled sensitivity of 30%–60% for detecting enlarged nodes >1 cm.[27] FDG-PET/CT also has a low pooled sensitivity (~51%) in locoregional nodal assessment because these nodes are often obscured by the metabolic activity in the primary tumor.[45] In contrast, EUS has high sensitivity (~85%) for assessing the degree of nodal involvement.[30] Furthermore, the addition of fine-needle aspiration (FNA) to EUS (EUS-FNA) has shown greater sensitivity and accuracy than either EUS alone or CT scan in the evaluation of cN staging, especially in assessing locoregional and celiac lymph nodes.[30,46–48] In a study that compared the performance characteristics of EUS and EUS-FNA for preoperative cN staging in 74 patients with esophageal cancer, EUS-FNA was more sensitive (93% vs 63%; $P=.01$) and accurate (93% vs 70%; $P=.02$) when compared with EUS alone.[47] In another study that compared the performance characteristics of CT, EUS, and EUS-FNA for preoperative cN staging in 125 patients with esophageal cancer, EUS-FNA was more sensitive than CT (83% vs 29%; $P<.001$) and more accurate than CT (87% vs 51%; $P<.001$) or EUS alone (87% vs 74%; $P=.012$).[48] Additionally, a retrospective review of 148 patients with esophageal cancer who underwent nodal staging with EUS-FNA and FDG-PET found that the addition of FDG-PET did not alter nodal staging in any patient with complete EUS-FNA,



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suggesting a limited role for FDG-PET alone in detecting locoregional metastatic nodes.[49]

Although contrast-enhanced CT is the most widely used modality for detecting distant metastases in esophageal cancer, FDG-PET/CT is more sensitive than CT alone for staging cM disease.[10,28,39,41,50] The addition of FDG-PET improves the detection of distant metastases that may remain occult on CT scan of the chest and abdomen, thereby allowing proper patient selection for surgical resection.[10,28] In a prospective multicenter trial of 129 patients with esophageal cancer without definite distant metastases, PET identified metastatic sites in 41% of cases and altered management in 38% of cases.[51] However, potential pitfalls of FDG-PET/CT include the poor detection of hepatic metastases when the CT component is performed without intravenous contrast and the high rate of false-positive FDG-PET findings.[37,38,43,44]

In North America, where screening programs for early detection of esophageal and EGJ cancers are not in use or practical because of low incidence, diagnosis is often made late in the disease course. At diagnosis, nearly 50% of patients have cancer that extends beyond the locoregional confines of the primary tumor. Fewer than 60% of patients with locoregional cancers can undergo a curative resection. Approximately 70%–80% of resected specimens harbor metastases in the regional lymph nodes. Thus, patients in North America often have advanced-stage disease at the time of initial diagnosis, which is reflected by the low survival rates seen with esophageal and EGJ cancers in this region.

Pathologic Review and Biomarker Testing

Pathologic review and biomarker testing play important roles in the diagnosis, classification, and molecular characterization of esophageal and EGJ cancers. Classification based on histologic subtype and molecular features helps to improve early diagnosis and has implications for therapy. An accumulation of genetic aberrations occurs during esophageal carcinogenesis, including overexpression of growth factors and/or receptors, alterations in DNA damage response, and loss of genomic stability. Characterization of these pathways has enabled the application of molecular pathology to aid in the management of esophageal and EGJ cancers.

Principles of Pathologic Review

A specific diagnosis of esophageal SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise specified are staged using the TNM staging system for SCC.[10] In addition to the histologic type, the pathology report (regardless of the specimen

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Table 1 Pathologic Review

Specimen Type	Analysis/Interpretation/Reporting[a]
Biopsy	Include in pathology report: • Invasion, if present; high-grade dysplasia in Barrett esophagus is reported for staging purposes as intraepithelial neoplasia (dysplasia) (Tis)[b,c,d] • Histologic type[e] • Grade[f] • Presence or absence of Barrett esophagus
Endoscopic resection	Include in pathology report: • Invasion, if present[b,d] • Histologic type[e] • Grade[f] • Depth of tumor invasion • Vascular/lymphatic invasion • Status of mucosal and deep margins
Esophagogastrectomy, without prior chemoradiation	For pathology report, include all elements as for EMR plus: • Location of tumor midpoint in relationship to EGJ[g] • Whether tumor crosses EGJ • Lymph node status and number of lymph nodes recovered
Esophagogastrectomy, with prior chemoradiation	• Tumor site should be thoroughly sampled, with submission of entire EGJ or ulcer/tumor bed for specimens s/p neoadjuvant therapy without grossly obvious residual tumor • For pathology report, include all elements as for resection without prior chemoradiation plus assessment of treatment effect

[a] Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at http://www.cap.org) for reporting pathologic findings is recommended.
[b] For purposes of data reporting, Barrett esophagus with HGD in an esophageal resection specimen is reported as "intraepithelial neoplasia (dysplasia) (Tis)."[1]
[c] Biopsies showing Barrett esophagus with suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.[2]
[d] Invasion of a thickened and duplicated muscularis mucosae should not be misinterpreted as invasion of the muscularis propria in Barrett esophagus.[3]
[e] A specific diagnosis of squamous cell carcinoma or adenocarcinoma should be established when possible for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the tumor node metastasis (TNM) system for squamous cell carcinoma.1
[f] Pathologic grade is needed for stage grouping in the AJCC TNM 8th edition.[1]
[g] Midpoint of tumors arising in the proximal 2 cm of the stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[1]

type) should include specifics about tumor invasion and pathologic grade, which are required for staging (see ESOPH-B 1 of 6, above). The pathology report of a biopsy or endoscopic mucosal resection specimen should also document the presence or absence of Barrett esophagus. Biopsies showing Barrett esophagus with suspected dysplasia should be reviewed by a second expert GI pathologist for confirmation.[52] Barrett esophagus with HGD is reported as intraepithelial neoplasia (dysplasia) (Tis) for staging purposes.[10]

Assessment of Treatment Response

Response of the primary tumor to previous chemotherapy and/or radiation therapy (RT) should be reported. The prognostic significance of pathologic complete response after induction therapy in patients with esophageal cancer has been demonstrated in several studies.[53–59] Residual primary tumor in the resection specimen following preoperative therapy is associated with shorter overall survival (OS) for both SCC and adenocarcinoma of the esophagus.[54,56,60,61] In a retrospective study of 235 patients, posttreatment pathologic stage was the best predictor of survival outcome for patients with locoregional carcinoma of the esophagus or EGJ who underwent preoperative chemoradiation followed by esophagectomy.[60]

Although scoring systems for tumor response in esophageal cancer have not been uniformly adopted, the panel recommends using the modified Ryan scheme in the College of American Pathologists (CAP) Cancer Protocol for Esophageal Carcinoma because it generally provides good reproducibility among pathologists (see ESOPH-B 2 of 6, page 400).[62,63] The following scheme is suggested: 0 (complete response; no viable cancer cells, including lymph nodes); 1 (near complete response; single cells or rare small groups of cancer cells); 2 (partial response; residual cancer cells with evident tumor regression, but more than single cells or rare small groups of cancer cells); and 3 (poor or no response; extensive residual cancer with no evident tumor regression). Because of the impact of residual nodal metastases on survival, it is recommended that lymph nodes be included in the regression score.[64] Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

Principles of Biomarker Testing

Presently, immunohistochemistry (IHC) and/or molecular testing for HER2/*ERBB2* status, microsatellite instability (MSI) or mismatch repair (MMR) status, programmed death ligand 1 (PD-L1) expression, tumor mutational burden-high (TMB-H) status, neurotrophic tropomyosin-related kinase

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Treatment Response

Response of the primary tumor to previous chemotherapy and/or radiation therapy should be reported. Residual primary tumor in the resection specimen following neoadjuvant therapy is associated with shorter overall survival for both adenocarcinoma[4-6] and SCC of the esophagus.[7]

Although scoring systems for tumor response in esophageal cancer have not been uniformly adopted, in general, three-category systems provide good reproducibility among pathologists.[6,8,9] The modified Ryan scheme in the CAP Cancer Protocol for Esophageal Carcinoma (available at http://www.cap.org)[8,9] should be used. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor. Although the system described by Wu was originally limited to assessment of the primary tumor, it is recommended that lymph nodes be included in the regression score[10] because of the impact of residual nodal metastases on survival.

Table 2[h]

Tumor Regression Score[9]	CAP Cancer Protocol Description
0 (Complete response)	No viable cancer cells, including lymph nodes
1 (Near complete response)	Single cells or rare small groups of cancer cells
2 (Partial response)	Residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells
3 (Poor or no response)	Extensive residual cancer with no evident tumor regression

[h] Reproduced and adapted with permission from Shi C, Berlin J, Branton PA, et al. Protocol for the examination of specimens from patients with carcinoma of the esophagus. In: Cancer Protocol Templates. Northfield, IL: College of American Pathologists; 2017 (available at http://www.cap.org).

(NTRK) gene fusions, rearranged during transfection (*RET)* gene fusions and *BRAF* V600E mutations are used in the clinical management of advanced esophageal and EGJ cancers. When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated next-generation sequencing (NGS) assay performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved environment may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, *NTRK* gene fusions, *RET* gene fusions, and *BRAF* V600E mutations. The use of IHC, in situ hybridization (ISH), or targeted polymerase chain reaction (PCR) should be considered first, followed by NGS testing as appropriate. The biomarker panel is expected to enlarge as more subgroups are identified.

Assessment of HER2 Overexpression

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of esophageal and EGJ cancers.[65] However, unlike in breast cancer, the prognostic significance of HER2 status in esophageal and EGJ cancer is unclear. Some studies have reported that HER2 positivity is correlated with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[66,67] HER2 positivity also seems to be associated with poorer survival in patients with SCC of the esophagus.[68] Although further studies are needed to assess the prognostic significance of HER2 status in esophageal cancer, the addition of HER2 monoclonal antibodies to chemotherapy regimens is a promising treatment option for patients with HER2 overexpression–positive disease.

The reported rates of HER2 positivity in esophageal and EGJ cancers vary widely (2%–45%)[66] and are more frequently seen in adenocarcinoma of the esophagus (15%–30%) than in SCC (5%–13%).[68–71] Additionally, HER2 positivity has been reported to be higher in patients with EGJ adenocarcinomas than in patients with gastric adenocarcinomas.[72–74] The HER-EAGLE study, which examined the HER2 positivity rate in a large multinational population of nearly 5,000 patients with gastric or EGJ adenocarcinoma, reported that 14.2% of samples were HER2 overexpression positive.[75] HER2 positivity was significantly higher in EGJ tumors versus stomach tumors and in intestinal subtypes versus diffuse subtypes. In the ToGA trial, HER2-positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[76] Therefore, classification of gastroesophageal cancers based on histologic subtype and primary tumor location may have implications for therapy.

HER2 testing is recommended for esophageal or EGJ adenocarcinoma patients at the time of diagnosis if metastatic

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Overexpression or Amplification of HER2 in Esophageal and EGJ Cancers

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or EGJ for whom trastuzumab[i] therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) methods is recommended.[11] NGS offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and MSI status. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic esophageal/EGJ adenocarcinoma.

Table 3 Immunohistochemical Criteria for Scoring HER2 Expression in Esophageal and EGJ Cancers[j,k]

	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cluster of five or more cancer cells with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

[i] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[j] The NCCN Guidelines Panel recommends that HER2 IHC be ordered/performed first, followed by ISH methods in cases showing 2+ (equivocal) expression by IHC. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. Cases with HER2:CEP17 ratio ≥2 or an average HER2 copy number ≥6.0 signals/cell are considered positive by ISH/FISH.

[k] Reprinted and adapted from Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35:446-464 with permission from the American Society of Clinical Oncology.

adenocarcinoma is documented or suspected. In concordance with HER2 testing guidelines from CAP, the American Society for Clinical Pathology, and ASCO,[77] the NCCN Guidelines recommend using IHC and, if needed, ISH techniques to assess HER2 status in esophageal and EGJ cancers. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression of metastatic adenocarcinoma.

IHC evaluates the membranous immunostaining of tumor cells, including the intensity and extent of staining and the percentage of immunoreactive tumor cells, with scores ranging from 0 (negative) to 3+ (positive). In 2008, Hofmann et al[78] refined this 4-tiered scoring system to assess HER2 status in gastric cancer by using a cut-off of ≥10% immunoreactive tumor cells in resection specimens.[74] It should be noted that when scoring a biopsy specimen, a cluster with 5% immunoreactive tumor cells is sufficient for scoring. In a subsequent validation study (n=447, prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[79] This modified HER2 scoring system is therefore recommended by the panel (see ESOPH-B 3 of 6, this page). A score of 0 (membranous reactivity in <10% of cancer cells) or 1+ (faint membranous reactivity in ≥10% of cancer cells) is considered to be HER2-negative. A score of 2+ (weak to moderate membranous reactivity in ≥10% of cancer cells) is considered equivocal and should be additionally examined by fluorescence in situ hybridization (FISH) or other ISH methods. FISH/ISH results are expressed as the ratio between the number of copies of the *ERBB2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (*ERBB2*:CEP17). Alternatively, FISH/ISH results may be given as the average *ERBB2* copy number per cell. Cases that have an IHC score of 3+ (strong membranous reactivity in ≥10% of cancer cells) or an IHC score of 2+ and are FISH/ISH positive (*ERBB2*:CEP17 ratio ≥2 or average *ERBB2* copy number ≥6 signals/cell) are considered HER2 positive. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing.

MSI or MMR Testing

Testing for MSI by PCR/NGS or MMR by IHC should be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with programmed cell death protein 1 (PD-1) inhibitors.[80] MSI status is assessed by PCR or NGS to measure gene expression levels of microsatellite markers (ie, *BAT25*, *BAT26*, *MONO27*, *NR21*, *NR24*).[81]

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing[l]

- Testing for MSI by polymerase chain reaction (PCR)/NGS or MMR by IHC should be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with programmed cell death protein 1 (PD-1) inhibitors.[12] The testing is performed on formalin-fixed paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[13] Testing should be performed only in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment in the appropriate clinical context.

  - MMR Interpretation
    - ◊ No loss of nuclear expression of MMR proteins: No evidence of dMMR (low probability of MSI-H)
    - ◊ Loss of nuclear expression of one or more MMR proteins: dMMR
  - MSI Interpretation
    - ◊ MSI-stable (MSS)
    - ◊ MSI-low (MSI-L)
      - – 1%–29% of the markers exhibit instability
      - – 1 of the 5 National Cancer Institute (NCI) or mononucleotide markers exhibits instability
    - ◊ MSI-H
      - – ≥30% of the markers exhibit instability
      - – 2 or more of the 5 NCI or mononucleotide markers exhibit instability

PD-L1 Testing

- PD-L1 testing may be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with PD-1 inhibitors. A companion diagnostic test for use on FFPE tissue should be used in identifying patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.
- Assessment of PD-L1 Protein Expression in Esophageal and EGJ Cancers
  - This is a qualitative immunohistochemical assay using anti–PD-L1 antibodies for the detection of PD-L1 protein in FFPE tissues from esophageal or EGJ cancers. A minimum of 100 tumor cells must be present in the PD-L1–stained slide for the specimen to be considered adequate for PD-L1 evaluation. A specimen is considered to have PD-L1 expression if the combined positive score (CPS) ≥1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

[l] PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by dMMR function.

MMR deficiency is evaluated by IHC to assess nuclear expression of proteins involved in DNA MMR (ie, MLH1, MSH2, MSH6, PMS2).[82] PCR/NGS for MSI and IHC for MMR proteins measure different biologic effects caused by deficient MMR function. Testing is performed on formalin-fixed, paraffin-embedded tissue, and results are interpreted in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines (see ESOPH-B 4 of 6, this page).[83] Testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors may be referred to a genetics counselor for further assessment in the appropriate clinical context.

PD-L1 Testing

PD-L1 testing may be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with PD-1 inhibitors. A companion diagnostic test should be used to identify patients for treatment with PD-1 inhibitors. The companion diagnostic test is a qualitative IHC assay using anti-PD-L1 antibodies for the detection of PD-L1 protein levels in formalin-fixed, paraffin-embedded tumor tissue. A minimum of 100 tumor cells must be present in the PD-L1-stained slide for the specimen to be adequately evaluated. Combined positive score (CPS) is determined by the number of PD-L1–stained cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells evaluated, multiplied by 100. A specimen is considered to have PD-L1 expression if the CPS is ≥1. PD-L1 testing should be performed only in CLIA-approved laboratories. Determination of the PD-L1 tumor proportion score is also considered an option.

Liquid Biopsy

The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA in the blood, hence a form of liquid biopsy.[67,84] Liquid biopsy is being used in patients who are unable to undergo a clinical biopsy for disease surveillance and/or management (see ESOPH-B 5 of 6, page 403). The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. In a study that analyzed the genomic alterations of 55 patients with advanced gastroesophageal adenocarcinomas using NGS performed on plasma-derived circulating tumor DNA, 69% of patients had one or more characterized alterations theoretically targetable by an FDA-approved agent (on- or off-label).[67] Therefore, for patients who have advanced or metastatic esophageal/EGJ cancers and who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

- **At present, several targeted therapeutic agents, trastuzumab,[i] pembrolizumab/nivolumab,[m] and entrectinib/larotrectinib, selpercatinib, and dabrafenib/trametinib, have been approved by the FDA for use in esophageal and EGJ cancers. Trastuzumab is based on testing for HER2 overexpression. Pembrolizumab/nivolumab are based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. The FDA granted approval for the use of select TRK inhibitors for *NTRK* gene fusion-positive solid tumors, and selpercatinib for *RET* gene fusion-positive tumors. Dabrafenib/trametinib has been approved for tumors with *BRAF* V600E mutations. When limited tissue is available for testing, or the patient is unable to undergo a traditional biopsy, sequential testing of single biomarkers or use of limited molecular diagnostic panels may quickly exhaust the sample. In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI status, MMR deficiency, TMB, *NTRK* gene fusions, *RET* gene fusions, and *BRAF* V600E mutations. The use of IHC/ISH/targeted PCR should be considered first followed by NGS testing as appropriate.**

Liquid Biopsy[14,15]

- **The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.**

[i] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[m] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.

†To view the most recent version of these guidelines, visit NCCN.org.

NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.

Treatment Guidelines

The management of patients with esophageal and EGJ cancers requires the expertise of several disciplines, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, case managers, nurses, palliative care specialists, and other supporting disciplines are also desirable. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of patients with localized esophagogastric cancers (see ESOPH-E, page 404). The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the patient.

Workup

Patients with newly diagnosed disease should undergo a complete history and physical examination, CBC, comprehensive chemistry profile, and upper GI endoscopy with biopsy of the primary tumor (see ESOPH-1, page 394). Histologic evaluation is required for correct diagnosis of SCC or adenocarcinoma; the extent of tumor involvement into the EGJ and cardia should be clearly documented, where applicable. CT scan (with oral and intravenous contrast) of the chest and abdomen should also be performed. Pelvic CT with contrast should be obtained when clinically indicated. EUS and FDG-PET/CT evaluation from skull base to midthigh are recommended if metastatic disease is not evident. Endoscopic resection is recommended for the accurate staging of early-stage cancers (T1a or T1b). Endoscopic resection may also be therapeutic for early-stage disease. Biopsy of metastatic disease should be performed as clinically indicated and may be used for biomarker testing. Assessment of Siewert tumor type should also be included as part of the initial workup in all patients with EGJ adenocarcinoma.[85,86] If the tumor is located at or above the carina and there is no evidence of metastatic disease, bronchoscopy (including biopsy of any abnormalities and cytology of the washings) should be performed in nonmetastatic setting. For patients in whom the upper GI tract cannot be visualized, a double contrast barium study of the upper GI tract is an alternative option. Nutritional assessment and counseling as well as smoking cessation advice, counseling, and pharmacotherapy (as indicated) are recommended for all patients.

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

Category 1 evidence supports the notion that the combined modality therapy is effective for patients with localized esophagogastric cancer.[1,2,3] The NCCN Panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients.

The combined modality therapy for patients with localized esophagogastric cancer may be optimally delivered when the following elements are in place:

- **The involved institution and individuals from relevant disciplines are committed to jointly reviewing the detailed data on patients on a regular basis. Frequent meetings (either once a week or once every two weeks) are encouraged.**
- **Optimally at each meeting, all relevant disciplines should be encouraged to participate and these may include: surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines are also desirable.**
- **All long-term therapeutic strategies are best developed after adequate staging procedures are completed, but ideally prior to any therapy that is rendered.**
- **Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions.**
- **A brief documentation of the consensus recommendation(s) by the multidisciplinary team for an individual patient may prove useful.**
- **The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient.**
- **Re-presentation of select patient outcomes after therapy is rendered may be an effective educational method for the entire multidisciplinary team.**
- **A periodic formal review of relevant literature during the course of the multidisciplinary meeting is highly encouraged.**

[1] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
[2] Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-1627.
[3] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730.

ESOPH-E

MSI and PD-L1 testing are recommended at the time of diagnosis if metastatic disease is documented or suspected and HER2 testing is recommended if metastatic adenocarcinoma is documented or suspected. NGS may be considered via a validated assay. The guidelines also recommend screening for family history of esophageal or EGJ cancers. Referral to a cancer genetics professional is recommended for those with a family history or a known high-risk syndrome associated with esophageal and EGJ cancers.

Initial workup enables patients to be classified into 2 clinical stage groups:

- Locoregional cancer: stage I–IVA (except T4b or unresectable N3)
- Metastatic cancer: stage IVA (T4b or unresectable N3 only) and IVB

Management of Recurrent or Metastatic Disease

When locoregional recurrence develops after prior chemoradiation therapy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option (see ESOPH-9 and ESOPH-18, pages 395 and 397, respectively). Concurrent chemoradiation (preferred for those who had not previously received chemoradiation), surgery, chemotherapy, biologic agents, and palliative management/best supportive care are recommended options for patients who develop a locoregional recurrence after prior esophagectomy. Those who are medically unable to tolerate major surgery and those who develop an unresectable or metastatic recurrence should receive palliative management. If not done previously, MSI or MMR, PD-L1, and HER2 (only for adenocarcinoma) testing should be performed in patients with documented or suspected metastatic disease. NGS may be considered via a validated assay.

Palliative management and best supportive care are always indicated for patients with unresectable locally advanced, recurrent, or metastatic disease. The decision to offer palliative/best supportive care alone or with systemic therapy depends on the patient's performance status (see ESOPH-10 and ESOPH-19, pages 396 and 398, respectively). The ECOG Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[87–89] Patients with higher ECOG PS scores are considered to have worse performance status while lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score $<60\%$ or an ECOG PS score ≥ 3 should be offered palliative/best supportive care only. Systemic therapy can be offered in

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA
First-Line Therapy • Oxaliplatin is preferred over cisplatin due to lower toxicity.
Preferred Regimens • HER2 overexpression positive[f] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[d,g,17] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[d,g,17] • HER2 overexpression negative[f] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[d,g,19] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20] ▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26]
Other Recommended Regimens • Fluorouracil[b,h] and irinotecan[i,27] • Paclitaxel with or without carboplatin or cisplatin [i,28-32] • Docetaxel with or without cisplatin [i,33-36] • Fluoropyrimidine [i,25,37,38] (fluorouracil[b] or capecitabine) • Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,i,39,40]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.
[f] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[i] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

†To view the most recent version of these guidelines, visit NCCN.org.

addition to palliative/best supportive care for patients with better performance status (KPS score ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared with palliative/best supportive care alone has been demonstrated in small cohorts of patients with esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma trials.[90,91] In a phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n=33), EGJ (n=59), or stomach (n=76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine-based combination chemotherapy.[91] After a median follow-up of 12 months, the median OS was 5.2 months for patients in the docetaxel and best supportive care group compared with 3.6 months for those in the best supportive care alone group (P=.01). In another randomized phase III study, the addition of second-line chemotherapy with irinotecan significantly prolonged OS compared with best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n=40).[90] Median survival was 4 months in the irinotecan and best supportive care group compared with 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual.

A Cochrane database systematic review of 5 randomized controlled trials involving 750 patients with advanced esophageal or EGJ cancer demonstrated a benefit in OS for patients receiving chemotherapy and/or targeted therapy and best supportive care compared with those receiving best supportive care alone.[92] The only individual agent found by more than one study to improve both OS and progression-free survival (PFS) was ramucirumab. Although the addition of palliative chemotherapy or targeted therapy increased the frequency of grade ≥3 adverse events, treatment-related deaths did not increase. Importantly, patient-reported quality of life often improved with the addition of systemic therapy to best supportive care. Therefore, the addition of systemic therapy to best supportive care can improve the quality of life and may prolong survival in patients with advanced esophageal or EGJ cancers.

Systemic Therapy for Locally Advanced or Metastatic Disease

First-Line Therapy

Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic esophageal or EGJ cancers.[90–92] First-line systemic therapy regimens with 2 cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of 3 cytotoxic

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA
First-Line Therapy • Oxaliplatin is preferred over cisplatin due to lower toxicity.
Preferred Regimens ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab[d,g,41] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and nivolumab[d,g,41] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26] ‣ Nivolumab and ipilimumab[d,g,41]
Other Recommended Regimens • Fluorouracil[b,h] and irinotecan[27] • Paclitaxel with or without carboplatin or cisplatin[28-32] • Docetaxel with or without cisplatin[33-36] • Fluoropyrimidine[25,37,38] (fluorouracil[b] or capecitabine) • Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,39,40]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.

†To view the most recent version of these guidelines, visit NCCN.org.

drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.[93] Oxaliplatin is preferred over cisplatin due to lower toxicity.

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).[74] An FDA-approved biologic medical product that is similar to trastuzumab (a biosimilar) is an appropriate substitute. Pembrolizumab can also be added to this regimen for treatment of advanced HER2 overexpression–positive adenocarcinoma (see ESOPH-F 4 of 20) provided no contraindications exist.[94] Preferred regimens for HER2 overexpression–negative disease include nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin for adenocarcinoma tumors with PD-L1 expression levels by CPS of greater than or equal to 5 (category 1) or CPS of less than 5 (category 2B), and pembrolizumab combined with fluoropyrimidine (fluorouracil or capecitabine) and either cisplatin (category 1) or oxaliplatin for adenocarcinoma or SCC tumors with PD-L1 expression levels by CPS of greater than or equal to 10 or CPS of less than 10 (category 2B).[95,96] Preferred regimens for SCC tumors also includes nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and either cisplatin or oxaliplatin and nivolumab combined with ipilimumab (see ESOPH-F 5 of 20, this page).[97] See "Targeted Therapies" (page 409) for more information on nivolumab, pembrolizumab, and ipilimumab.

The preferred regimens for HER2 negative disease also includes a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin[98–100] or cisplatin (see ESOPH-F 4 of 20 and 5 of 20, page 405 and this page, respectively).[98,101–103] A phase III trial conducted by the German Study Group compared treatment with fluorouracil and cisplatin to FOLFOX in patients (n=220) with previously untreated advanced adenocarcinoma of the stomach or EGJ.[98] Results showed that FOLFOX was associated with significantly less toxicity and showed a trend toward improved median PFS (5.8 vs 3.9 months; P=.77) compared with fluorouracil and cisplatin (FLP). However, there was no significant difference in median OS (10.7 vs 8.8 months, respectively) between the 2 groups. FOLFOX resulted in significantly superior response rates (41.3% vs 16.7%; P=.12), time to treatment failure (5.4 vs 2.3 months; P<.001), and PFS (6.0 vs 3.1 months; P=.029), and improved OS (13.9 vs 7.2 months) compared with FLP in patients over 65 years (n=94). Therefore, FOLFOX offers reduced toxicity and similar efficacy compared with fluorouracil plus cisplatin and may also be associated with improved efficacy in older adult patients.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

ADENOCARCINOMA
Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42] • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive[43] • Docetaxel (category 1)[35,36] • Paclitaxel (category 1)[31,32,44] • Irinotecan (category 1)[44-47] • Fluorouracil[b,h] and irinotecan[45,48,49] • Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[50]
Other Recommended Regimens • Ramucirumab (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[51] • Irinotecan and cisplatin[22,52] • Fluorouracil and irinotecan + ramucirumab[b,h,53] • Irinotecan and ramucirumab[54] • Docetaxel and irinotecan (category 2B)[55]
Useful in Certain Circumstances • Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[56,57] • Pembrolizumab[d,g] for MSI-H or dMMR tumors[58-60] • Pembrolizumab[d,g] for TMB high (≥10 mutations/megabase) tumors[61] • Dostarlimab-gxly for MSI-H or dMMR tumors[d,g,j,62] • Dabrafenib and trametinib for *BRAF* V600E mutated tumors[63] • Selpercatinib for *RET* gene fusion-positive tumors[64]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[j] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.

†To view the most recent version of these guidelines, visit NCCN.org.

Recommendations for the use of regimens combining a platinum agent with capecitabine as first-line therapy have been extrapolated from trials involving patients with advanced gastric cancer.[100,103–105] Results of a meta-analysis suggest that OS was superior in patients with advanced gastroesophageal cancer treated with capecitabine-based combinations compared with patients treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.[106] Therefore, capecitabine and oxaliplatin is also a preferred regimen for first-line treatment of patients with advanced esophageal or EGJ cancers. The GO2 phase III trial demonstrated that a low-dose capecitabine and oxaliplatin regimen (60% of the standard dose) was noninferior in terms of PFS and resulted in significantly lower toxicities and better overall treatment utility in older and/or frail patients with advanced gastroesophageal cancers (n=514).[107] Therefore, this low-dose regimen is recommended as an alternative to standard-dose capecitabine and oxaliplatin for older and/or frail patients with advanced or metastatic disease. See "Principles of Systemic Therapy – Regimens and Dosing Schedules" in the algorithm (page 405) for recommended modifications to this regimen.

First-line treatment with irinotecan-based regimens has been explored extensively in clinical trials involving patients with advanced or metastatic gastroesophageal cancers.[108–114] The results of a randomized phase III study comparing fluorouracil and irinotecan (FOLFIRI) to cisplatin and fluorouracil (CF) in patients with advanced gastric or EGJ adenocarcinoma (n=337) showed that FOLFIRI was noninferior to CF in terms of PFS, but not in terms of OS or time to progression.[109] FOLFIRI was also associated with a more favorable safety profile. A more recent phase III trial (French Intergroup Study) compared FOLFIRI with ECF (CF and epirubicin) as first-line treatment in patients (n=416) with advanced or metastatic gastric or EGJ adenocarcinoma.[114] After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECF (5.1 vs 4.2 months; P=.008).[114] However, there were no significant differences in median PFS (5.3 vs 5.8 months; P=.96), median OS (9.5 vs 9.7 months; P=.95), or response rate (39.2% vs 37.8%). Importantly, FOLFIRI was less toxic and better tolerated than ECF. Therefore, FOLFIRI may be recommended as a first-line therapy option for patients with advanced or metastatic esophageal or EGJ adenocarcinoma.

Docetaxel, cisplatin, and fluorouracil (DCF) has also demonstrated activity in patients with locally advanced or metastatic gastroesophageal cancer.[115,116] An international phase III study (V325) that randomized 445

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

SQUAMOUS CELL CARCINOMA
Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Nivolumab (category 1)[d,g,65] • Pembrolizumab[d,g] for tumors with PD-L1 expression levels by CPS of ≥10 (category 1)[66] • Docetaxel (category 1)[35,36] • Paclitaxel (category 1)[31,32,44] • Irinotecan (category 1)[44-47] • Fluorouracil[b,h] and irinotecan[45,48,49]
Other Recommended Regimens • Irinotecan and cisplatin[22,52] • Docetaxel and irinotecan (category 2B)[55]
Useful in Certain Circumstances • Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[56,57] • Pembrolizumab[d,g] for MSI-H or dMMR tumors[58-60] • Pembrolizumab[d,g] for TMB high (≥10 mutations/megabase) tumors[61] • Dostarlimab-gxly[d,g,j] for MSI-H or dMMR tumors[62] • Dabrafenib and trametinib for *BRAF* V600E mutated tumors[63] • Selpercatinib for *RET* gene fusion-positive tumors[64]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[j] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.

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patients with untreated advanced gastric or EGJ cancer to receive either DCF or CF found that the addition of docetaxel to CF significantly improved time to progression, OS, and overall response rate (ORR).[116] However, DCF was associated with increased toxicities including myelosuppression and infectious complications.[116] Various modifications of the DCF regimen have demonstrated improved safety compared with the DCF regimen evaluated in the V325 study.[117–120] Therefore, due to concerns regarding toxicity, dose-modified DCF or other DCF modifications should be used as alternative options to the standard DCF regimen for first-line therapy. Additional regimens for first-line therapy include paclitaxel with either carboplatin or cisplatin,[121–123] docetaxel with cisplatin,[115,124] or single-agent fluoropyrimidine (fluorouracil or capecitabine),[102,125,126] docetaxel,[91,127] or paclitaxel.[128,129]

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy depends on prior therapy and performance status. Ramucirumab (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) in combination with paclitaxel (preferred) or as a single agent are recommended for second-line or subsequent therapy (see ESOPH-F 6 of 20, page 407).[130,131] Fam-trastuzumab deruxtecan-nxki is a second-line treatment option for patients with HER2 overexpression–positive adenocarcinoma who have received prior trastuzumab-based therapy.[132] Nivolumab is preferred for second-line or subsequent therapy for esophageal SCC (category 1; see ESOPH-F 7 of 20, this page).[133] Pembrolizumab is preferred for second-line therapy for esophageal SCC with PD-L1 expression levels by CPS of ≥10 (category 1).[134] See "Targeted Therapies" (page 409) for more information on ramucirumab, nivolumab, pembrolizumab, and fam-trastuzumab deruxtecan-nxki.

Single-agent docetaxel,[91,127] paclitaxel,[128,129,135] and irinotecan[90,135–137] are also category 1 preferred options for second-line or subsequent therapy (see ESOPH-F 6 of 20 and 7 of 20, page 407 and this page, respectively). In a randomized phase III trial (COUGAR-02), single-agent docetaxel was shown to significantly increase 12-month OS compared with active symptom control alone (5.2 vs 3.6 months, respectively; hazard ratio [HR], 0.67; P=.01).[91] A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the 2 groups (9.5 months in the paclitaxel group vs 8.4 months in the irinotecan group; HR, 1.13; P=.38).[135]

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.[136,138,139] A phase II trial

investigating the efficacy and toxicity of FOLFIRI in patients (n=40) with refractory or relapsed esophageal or gastric cancer reported an ORR of 29% and median OS of 6.4 months. Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in patients with advanced gastric cancer (n=59) treated with FOLFIRI in the second-line setting.[136] Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.[140] In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%).

The trifluridine and tipiracil regimen was approved by the FDA in 2019 for previously treated recurrent or metastatic gastric and EGJ adenocarcinoma[141] based on results of the global phase III TAGS trial, in which 507 patients with heavily pretreated metastatic gastric or EGJ adenocarcinoma were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n=337) or placebo plus best supportive care (n=170).[142] This study reported an improvement in median OS by 2.1 months with the trifluridine and tipiracil regimen compared with placebo (HR, 0.69; 95% CI, 0.56–0.85; *P*=.0003). PFS was also significantly longer in the trifluridine and tipiracil group (2.0 vs 1.7 months; HR, 0.57; 95% CI, 0.47–0.70; *P*<.0001). The most frequently reported grade 3–4 toxicities were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%). Patients aged 65 years or over had a higher incidence of moderate renal impairment compared with the overall study population (31% vs 17%).[143] Improvements in median OS and PFS and a similar safety profile were observed in a subgroup analysis of patients with metastatic EGJ adenocarcinoma (n=145).[144] Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic EGJ adenocarcinoma in the third-line or subsequent setting. However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume EGJ adenocarcinoma who have minimal or no symptoms and the ability to swallow pills.

Other recommended regimens for second-line or subsequent therapy include irinotecan and cisplatin,[99,108] ramucirumab combined with irinotecan[145] or FOLFIRI (for adenocarcinoma only),[146] and irinotecan and docetaxel (category 2B).[111] Options that are useful in certain circumstances include pembrolizumab[80,82,147] or dostarlimab-gxly[148] for MSI-H/dMMR tumors, pembrolizumab for TMB-H (≥10 mutations/megabase) tumors,[149] entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors,[150,151] dabrafenib and trametinib for *BRAF* V600E mutated tumors,[152] and selpercatinib for *RET* gene fusion positive tumors.[153] See next section ("Targeted Therapies") for more information on these agents.

Targeted Therapies

At present, several targeted therapeutic agents, trastuzumab, pembrolizumab, nivolumab, entrectinib/larotrectinib, selpercatinib, and dabrafenib/trametinib, have been approved by the FDA for use in advanced esophageal and EGJ cancers. Treatment with trastuzumab is based on testing for HER2 overexpression.[141] Treatment with pembrolizumab or nivolumab is based on testing for MSI by PCR/NGS or MMR by IHC, PD-L1 expression by IHC, or high TMB by NGS.[80,82,95,147,149,154,155] The FDA has granted approval for the use of select TRK inhibitors for *NTRK* gene fusion-positive solid tumors,[156,157] selpercatinib for *RET* gene fusion-positive tumors,[153] and dabrafenib/trametinib for tumors with *BRAF* V600E mutations.[152] When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, *NTRK* gene fusions, *RET* gene fusions, and *BRAF* V600E mutations. The use of IHC/ISH/targeted PCR should be considered first, followed by NGS testing as appropriate.

Trastuzumab

The ToGA trial was the first randomized prospective phase III trial that evaluated the efficacy and safety of trastuzumab in HER2 overexpression–positive advanced gastric and EGJ adenocarcinoma.[74] In this trial, 594 patients with HER2 overexpression positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.[74] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up times were19 months and 17 months, respectively, in the 2 groups. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy in patients with HER2 overexpression–positive disease (13.8 vs 11 months, respectively; *P*=.046). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment of patients with HER2 overexpression–positive advanced gastroesophageal adenocarcinoma. In a posthoc subgroup analysis, the addition of trastuzumab to chemotherapy further improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n=446; 16 vs 11.8 months; HR, 0.65) compared with those with tumors that were IHC 0 or 1+ and FISH positive (n=131; 10 vs 8.7 months; HR, 1.07).

The phase II HERXO trial assessed the combination of trastuzumab with capecitabine and oxaliplatin in the first-line treatment of patients with HER2 overexpression–positive advanced gastric or EGJ adenocarcinoma (n=45).[158] At a median follow-up of 13.7 months, PFS and OS were 7.1 and 13.8 months, respectively, and 8.9%, 37.8%, and 31.1% of patients achieved a complete response, partial response, and stable disease. The most frequently reported grade 3 or higher adverse events were diarrhea (26.6%), fatigue (15.5%), nausea (20%), and vomiting (13.3%). In a retrospective study of 34 patients with HER2 overexpression–positive metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2 overexpression positive tumors.[159] The ORR with this regimen was 41%, and median PFS and OS were 9.0 months and 17.3 months, respectively. The most frequent grade 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combinations of trastuzumab with capecitabine and oxaliplatin or with modified FOLFOX are effective regimens with acceptable safety profiles in patients with HER2 overexpression–positive gastroesophageal cancers. Therefore, trastuzumab should be added to first-line chemotherapy in combination with a fluoropyrimidine and a platinum agent (oxaliplatin is preferred over cisplatin due to lower toxicity) in patients with advanced HER2 overexpression–positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab may be combined with other chemotherapy agents for first-line therapy but should not be continued in second-line therapy.[160]

Nivolumab

Nivolumab is a monoclonal PD-1 antibody that was approved by the FDA in May 2021 for the treatment of patients with completely resected esophageal or EGJ tumors with residual pathologic disease who had received preoperative chemoradiation.[161] This approval was based on results from the phase III Checkmate-577 trial, which evaluated the safety and efficacy of nivolumab (n=532) versus placebo (n=262) in this setting.[162] After a median follow-up of 24.4 months, median disease-free survival was significantly longer in the nivolumab group compared with the placebo group (22.4 vs 11 months; HR, 0.69; $P<.001$). The disease-free survival benefit with nivolumab was observed regardless of PD-L1 expression levels. Grade 3–4 adverse events occurred in 13% of patients in the nivolumab group and 6% in the placebo group. The most common adverse events in the nivolumab group were fatigue, rash, musculoskeletal pain, and pruritus. Postoperative nivolumab is a new effective treatment option for patients at high risk for recurrence due to the presence of residual pathologic disease following preoperative chemoradiation and R0 resection.

Nivolumab was also approved by the FDA in April 2021, in combination with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with advanced or metastatic esophageal or EGJ adenocarcinoma.[163] This approval was based on results from the phase III Checkmate-649 trial, which randomized 1,581 patients with previously untreated, HER2-negative, unresectable gastric, EGJ, or esophageal adenocarcinoma to receive chemotherapy alone or nivolumab plus chemotherapy (capecitabine and oxaliplatin or modified FOLFOX).[95] The addition of nivolumab to chemotherapy resulted in significant improvements in OS (14.4 vs 11.1 months; HR, 0.71; $P<.0001$) and PFS (7.7 vs 6 months; HR, 0.68; $P<.0001$) compared with chemotherapy alone in patients with a PD-L1 CPS of ≥5 (n=955). Additional results also showed some improvement in OS and PFS in patients with a PD-L1 CPS of ≥1 (n=1,296; OS, 14 vs 11.3 months; HR, 0.77; PFS, 7.5 vs 6.9; HR, 0.74) and in all randomly assigned patients (OS, 13.8 vs 11.6; HR, 0.8; PFS, 7.7 vs 6.9; HR, 0.77). Among all patients, 59% of those in the nivolumab plus chemotherapy group and 44% of those in the chemotherapy alone group experienced grade 3–4 treatment-related adverse events. The most common any-grade treatment-related adverse events were nausea, diarrhea, and peripheral neuropathy across both groups. Sixteen treatment-related deaths occurred in the nivolumab plus chemotherapy group compared with 4 in the chemotherapy alone group. Therefore, nivolumab plus fluoropyrimidine- and oxaliplatin-based chemotherapy is a preferred first-line treatment option for patients with HER2-negative esophageal or EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥5 (category 1) or <5 (category 2B).

In May 2022, nivolumab was approved in combination with fluoropyrimidine- and platinum-based chemotherapy and in combination with ipilimumab for the first-line treatment of patients with advanced or metastatic esophageal SCC based on results of the phase III CheckMate-648 trial.[97] In this trial, 970 patients with previously untreated unresectable advanced, recurrent, or metastatic esophageal SCC were randomized to receive nivolumab plus chemotherapy, nivolumab plus the monoclonal antibody ipilimumab, or chemotherapy alone. Ipilimumab is an immune checkpoint inhibitor that targets CTLA-4. After a minimum 13-month follow-up, median OS was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone among patients with tumor cell PD-L1 expression of ≥1% (15 vs 9 months; HR = 0.54; $P<.001$) as well as in the overall population (13 vs 11 months; HR = 0.74; $P=.002$). OS was also significantly longer in the nivolumab plus ipilimumab group than in the chemotherapy alone group in patients with tumor cell PD-L1 expression of ≥1% (14 vs 9 months; HR= 0.64; $P=.001$)

and in the overall population (13 vs 11 months; HR = 0.78; P=.01). The incidence of grade 3 or 4 treatment-related adverse events was 47% with nivolumab plus chemotherapy, 32% with nivolumab plus ipilimumab, and 36% with chemotherapy alone. Based on these data, nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin or cisplatin as well as nivolumab plus ipilimumab are recommended as preferred regimens for treatment of esophageal SCC. Patients with tumor cell PD-L1 expression of ≥1%, which was 91% of patients, benefited from both regimens. Therefore, the NCCN panel recommends these 2 regimens irrespective of CPS score.

Nivolumab was FDA-approved in June 2020 for the treatment of patients with unresectable advanced, recurrent, or metastatic esophageal SCC after prior fluoropyrimidine- and platinum-based chemotherapy.[164] This approval was based on results from the international phase III ATTRACTION-3 trial, which compared nivolumab to chemotherapy in patients with advanced esophageal SCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen.[133] Patients (n=419) were randomized 1:1 to receive nivolumab or investigator's choice of chemotherapy (either docetaxel or paclitaxel). Median OS was significantly improved in patients receiving nivolumab compared with those receiving chemotherapy (10.9 vs 8.4 months; P=.019). Importantly, the OS benefit was observed regardless of tumor PD-L1 expression levels. The ORR was 19.3% in the nivolumab arm versus 21.5% in the chemotherapy arm, with a median response duration of 6.9 and 3.9 months, respectively. Grade 3–4 treatment-related adverse events occurred in 18% of patients in the nivolumab group, the most common being anemia, and in 63% of patients in the chemotherapy group, the most common being decreased neutrophil count. Since nivolumab was associated with a significant improvement in OS and a favorable safety profile compared with chemotherapy, it is a category 1 recommendation in this setting and represents a new and effective second-line treatment option for patients with previously treated advanced esophageal SCC.

Pembrolizumab

First-line treatment with the PD-1 antibody pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy was approved by the FDA in March 2021 for patients with locally advanced or metastatic esophageal or EGJ tumors.[165] This approval was based on data from the phase III KEYNOTE-590 trial, which randomized 749 patients with previously untreated, locally advanced, or metastatic esophageal SCC, esophageal adenocarcinoma, or EGJ adenocarcinoma to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy.[96] At a median follow-up of 22.6 months, statistically significant improvements in OS and PFS were observed in patients randomized to pembrolizumab plus chemotherapy. Median OS was 13.9 months for the pembrolizumab arm versus 8.8 months for the chemotherapy arm in patients with SCC and PD-L1 CPS ≥10 (HR, 0.57; P<.0001), 12.6 versus 9.8 months in patients with SCC (HR, 0.72; P=.0006), 13.5 versus 9.4 months in patients with PD-L1 expression ≥10 (HR, 0.62; P<.0001), and 12.4 versus 9.8 months in all patients (HR, 0.73; P<.0001). Pembrolizumab plus chemotherapy was also superior to placebo plus chemotherapy for PFS in patients with SCC (6.3 vs 5.8 months; HR, 0.65; P<.0001), PD-L1 CPS ≥10 (7.5 vs 5.5 months; HR, 0.51; P<.0001), and in all patients (6.3 vs 5.8 months; HR, 0.65; P<.0001). The most common adverse events in patients who received pembrolizumab were nausea, constipation, diarrhea, vomiting, stomatitis, fatigue, decreased appetite, and weight loss. Grade 3 or higher treatment-related adverse events occurred in 72% of patients receiving pembrolizumab and 68% of those receiving placebo. Based on these results, pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy may be used for the first-line treatment of patients with SCC or adenocarcinoma with PD-L1 expression levels by CPS of ≥10 (category 1 in combination with cisplatin) or <10 (category 2B).

Pembrolizumab can also be added to first-line fluoropyrimidine, platinum, and trastuzumab based on the results of an interim analysis of the first 264 patients enrolled in the phase III KEYNOTE-811 trial, which compared pembrolizumab to placebo in combination with trastuzumab and the investigator's choice of chemotherapy with fluorouracil and cisplatin or capecitabine and oxaliplatin in patients with previously untreated advanced HER2-positive gastric or EGJ adenocarcinoma.[94] Results showed an improved ORR (74% vs 52%; P=.00006) and median duration of response (10.6 vs 9.5 months) with the addition of pembrolizumab compared with placebo. Complete responses were also more frequent in the pembrolizumab group compared with placebo (11% vs 3%). Similar incidence of adverse events was observed in the pembrolizumab and placebo groups (57% of participants in both groups), the most common being diarrhea, nausea, and anemia. Therefore, pembrolizumab combined with trastuzumab and fluoropyrimidine and platinum-based chemotherapy is a preferred option for treatment of patients with advanced HER2 overexpression–positive adenocarcinoma.

In 2019, the FDA approved pembrolizumab for the second-line treatment of esophageal SCC with PD-L1 expression levels by CPS of ≥10 based on the results of the KEYNOTE-180 and KEYNOTE-181 trials.[166] In the phase II single-arm KEYNOTE-180 trial, which evaluated pembrolizumab monotherapy in 121 patients with progressive disease after ≥2 prior lines of therapy, the ORR was 9.9% among all patients.[167] The ORR was 14.3% among patients with esophageal SCC (n=63), 5.2% among patients with

adenocarcinoma (n=58), 13.8% among patients with PD-L1–positive tumors (n=58), and 6.3% among patients with PD-L1–negative tumors (n=63). Overall, 12.4% of patients had grade 3–5 treatment-related adverse events and 5 patients discontinued treatment because of toxicity. Long-term results demonstrated a durable clinical benefit for pembrolizumab in this treatment population.[168] These results demonstrated the efficacy and tolerability of pembrolizumab in heavily pretreated esophageal SCC with high PD-L1 expression. The phase III KEYNOTE-181 trial evaluated pembrolizumab versus investigator's choice of chemotherapy (docetaxel, paclitaxel, or irinotecan) as second-line therapy in 628 patients with advanced SCC or adenocarcinoma of the esophagus or EGJ.[134] Patients (401 with SCC and 222 with PD-L1 CPS ≥10) were randomized to pembrolizumab or chemotherapy and randomization was stratified by histology (SCC vs adenocarcinoma) and region (Asia vs rest of world). Pembrolizumab significantly improved median OS (9.3 vs 6.7 months; *P*=.007) and 12-month OS rates (43% vs 20%) compared with chemotherapy in patients with esophageal SCC tumors with PD-L1 CPS ≥10. Fewer patients had grade 3–5 treatment-related adverse events with pembrolizumab compared with chemotherapy (18% vs 41%). Based on these data, pembrolizumab is a category 1, preferred second-line therapy option for patients with advanced esophageal SCC with PD-L1 expression levels by CPS of ≥10.

Pembrolizumab was FDA approved in 2017 for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed aftr prior treatment and who have no satisfactory alternative treatment options.[169] This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across 5 multicenter single-arm clinical trials.[80,82,147] The ORR was 39.6% and responses lasted ≥6 months for 78% of those who had a response to pembrolizumab. There were 11 complete responses and 48 partial responses, and the ORR was similar irrespective of cancer type. Therefore, pembrolizumab is a second-line or subsequent therapy option for patients with MSI-H/dMMR gastroesophageal tumors.

In June 2020, the FDA approved pembrolizumab for the treatment of patients with metastatic TMB-H solid tumors, as determined by an FDA-approved test, that progressed after prior treatment and who have no satisfactory alternative treatment options.[170] This approval was based on a retrospective analysis of 102 patients enrolled in the KEYNOTE-158 trial who had tumors identified as TMB-H.[149] The ORR for these patients was 29%, with a 4% complete response rate. The median duration of response was not reached, with 50% of patients having response durations for ≥24 months. Based on these data, pembrolizumab may be used for the second-line or subsequent treatment of patients with TMB-H gastroesophageal tumors. However, it should be noted that no patients with gastroesophageal cancer were included in the KEYNOTE-158 trial.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in 2 phase III clinical trials.[130,131] An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[130] In this study, 355 patients were randomized to receive ramucirumab (n=238) or placebo (n=117). Median OS was 5.2 months in patients treated with ramucirumab compared with 3.8 months for those in the placebo group (*P*=.047). Ramucirumab was associated with higher rates of hypertension than placebo (16% vs 8%), whereas rates of other adverse events were similar.

The international phase III RAINBOW trial evaluated paclitaxel with or without ramucirumab in patients (n=665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.[131] Patients randomized to receive ramucirumab plus paclitaxel (n=330) had significantly longer median OS (9.63 months) compared with patients receiving paclitaxel alone (n=335; 7.36 months; *P*<.0001). The median PFS was 4.4 months and 2.86 months, respectively, and the ORR was 28% for ramucirumab plus paclitaxel compared with 6% for paclitaxel alone (*P*=.0001). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel. An exposure-response analysis revealed that ramucirumab was a significant predictor of OS and PFS in both studies.[171] Based on these results, ramucirumab (as a single agent or in combination with paclitaxel) was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy. The guidelines recommend ramucirumab as a single agent (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) or in combination with paclitaxel (preferred) as treatment options for second-line or subsequent therapy in patients with advanced or metastatic esophageal or EGJ adenocarcinoma.[130,131]

Ramucirumab combined with FOLFIRI can be an option for second-line or subsequent therapy for patients with advanced esophageal or EGJ adenocarcinoma. In a multi-institutional retrospective analysis of 29 patients with advanced gastric or EGJ adenocarcinoma who received FOLFIRI plus ramucirumab in the second-line setting, the ORR was 23% with a disease control rate of 79%.[146] Median PFS was 6 months and median OS was

13.4 months. Six- and 12-month OS were 90% and 41%, respectively. No new safety signals were observed with the combination treatment, making FOLFIRI plus ramucirumab a safe, nonneurotoxic alternative to ramucirumab plus paclitaxel. Ramucirumab combined with irinotecan is also an option for second-line or subsequent therapy for patients with advanced adenocarcinoma.[145]

Due to the results of the international phase III RAINFALL trial, in which treatment with ramucirumab did not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma, the addition of ramucirumab to first-line chemotherapy is not recommended at this time.[172]

Fam-trastuzumab Deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of trastuzumab and a cytotoxic topoisomerase I inhibitor connected by a cleavable tetrapeptide-based linker. The efficacy and safety of fam-trastuzumab deruxtecan-nxki in advanced or metastatic gastric or EGJ adenocarcinoma was evaluated in the phase II DESTINY-Gastric01 trial, which included 188 patients with progressive disease after at least 2 prior lines of therapy, including trastuzumab.[132] Patients were randomized 2:1 to receive either fam-trastuzumab deruxtecan-nxki or physician's choice of chemotherapy (paclitaxel or irinotecan). The confirmed objective response rate for patients on fam-trastuzumab deruxtecan-nxki was 40.5% compared with 11% for those on chemotherapy. OS (12.5 vs 8.4 months; P=.0097), median PFS (5.6 vs 3.5 months), and duration of response (11.3 vs 3.9 months) were also higher in the fam-trastuzumab deruxtecan-nxki group compared with the chemotherapy group. Fam-trastuzumab deruxtecan-nxki resulted in more toxicities than systemic chemotherapy in this trial. The most common adverse events (grade 3 or higher) were a decreased neutrophil count (51% of the fam-trastuzumab deruxtecan-nxki group and 24% of the chemotherapy group), anemia (38% and 23%, respectively), and decreased white blood cell count (21% and 11%). Fam-trastuzumab deruxtecan-nxki–related interstitial lung disease or pneumonitis occurred in 12 patients, resulting in one drug-related death (due to pneumonia). No drug-related deaths occurred in the physician's choice group. The FDA has approved fam-trastuzumab deruxtecan-nxki to treat patients with HER2 overexpression–positive tumors in second-line or subsequent therapy. Therefore, fam-trastuzumab deruxtecan-nxki may be used as a second-line or subsequent treatment option for patients with HER2 overexpression–positive adenocarcinoma after failure of prior trastuzumab-based regimen. However, careful patient selection and close monitoring of patients for excessive toxicity is recommended.

Entrectinib and Larotrectinib

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode TRK fusion proteins (TRKA, TRKB, TRKC), which have increased kinase function and are implicated in the oncogenesis of many solid tumors including head and neck, thyroid, soft tissue, lung, and colon.[151,173] Although believed to be extremely rare in gastroesophageal cancers, one case report provides evidence that *NTRK* gene fusions occur in gastric adenocarcinoma and may be associated with an aggressive phenotype.[174–176] No such case report for *NTRK* gene fusions in esophageal or EGJ cancers has yet been published.

In 2018, the FDA granted accelerated approval to the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged ≥12 years) with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, that are either metastatic or for which surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[157] This FDA approval was based on data from 3 multicenter single-arm clinical trials. Patients with prospectively identified *NTRK* gene fusion-positive cancers were enrolled into 1 of 3 protocols: a phase I trial involving adults (LOXO-TRK-14001), a phase I–II trial involving children (SCOUT), or a phase II trial involving adolescents and adults (NAVIGATE).[151] A total of 55 patients with unresectable or metastatic solid tumors harboring an *NTRK* gene fusion who experienced disease progression after systemic therapy were enrolled across the 3 protocols and treated with larotrectinib. The most common cancer types represented were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR across the 3 trials was 75%, with a complete response rate of 22%. At a median follow-up of 9.4 months, 86% of the patients with a response were either continuing treatment with larotrectinib or had undergone curative-intent surgery. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Response duration was ≥6 months for 73%, ≥9 months for 63%, and ≥12 months for 39% of patients. At the time of data analysis, the median duration of response and PFS had not been reached. Adverse events were predominantly grade 1, the most common being increased aspartate aminotransferase levels, vomiting, constipation, and dizziness. The SCOUT (ClinicalTrials.gov identifier: NCT02637687) and NAVIGATE (ClinicalTrials.gov identifier: NCT02576431) trials are still actively recruiting patients with *NTRK* gene fusion-positive tumors.

In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with metastatic non-small cell lung cancer whose tumors are *ROS1*-positive.[156] The approval of entrectinib for the treatment of *NTRK* gene

fusion-positive tumors was based on data from 3 multicenter, single-arm, phase I and phase II clinical trials. A total of 54 patients aged ≥18 years with metastatic or locally advanced *NTRK* gene fusion-positive solid tumors were enrolled into 1 of the 3 protocols (ALKA-372-001, STARTRK-1, or STARTRK-2).[150] The most common cancer types represented were sarcoma, non-small cell lung cancer, mammary analog secretory carcinoma, breast, thyroid, and colorectal. The ORR across the 3 trials was 57%, with a complete response rate of 7%. Response duration was ≥6 months for 68% of patients and ≥12 months for 45% of patients. The median duration of response was 10 months. The most common grade 3–4 treatment-related adverse events were increased weight and anemia, and the most common serious treatment-related adverse events were nervous system disorders. STARTRK-2 (ClinicalTrials.gov identifier: NCT02568267) is still actively recruiting patients with *NTRK* gene fusion-positive tumors. Based on these data, entrectinib and larotrectinib are recommended as second-line or subsequent treatment options for patients with *NTRK* gene fusion-positive gastroesophageal tumors.

Dostarlimab-gxly

Dostarlimab-gxly, an anti-PD-1 antibody, was approved by the FDA in August 2021 for the treatment of patients with dMMR recurrent or advanced solid tumors that have progressed on or after prior treatment, who have no satisfactory alternative treatment options, and who had not previously received a PD-1 or PD-L1 inhibitor.[177] This approval was based on data from the nonrandomized phase 1 multicohort GARNET trial, which evaluated the safety and antitumor activity of dostarlimab-gxly in 209 patients with dMMR solid tumors who had not received prior PD-1, PDL-1, or CTLA4 inhibitors.[148,178] The majority of patients had endometrial or GI cancers. The ORR was 42%, with a 9% complete response rate and 33% partial response rate, and the median duration of response was 35 months. The most common treatment-related adverse events were fatigue, anemia, diarrhea, and nausea. Immune-mediated adverse events also occurred, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities. Based on these data, dostarlimab-gxly may be used for second-line or subsequent therapy for patients with MSI-H/dMMR gastroesophageal tumors.

Dabrafenib and Trametinib

In June 2022, the FDA granted tumor agnostic approval for the combination of dabrafenib, a B-Raf inhibitor, and trametinib, a MEK inhibitor, for treatment of patients with unresectable or metastatic solid tumors with *BRAF* V600E mutations who have progressed following prior treatment and have no satisfactory alternative treatment options.[179] This approval was based in part on data from the phase II BRF117019 and NCI-MATCH trials, which enrolled a combined 131 adult patients with various *BRAF* V600E mutated tumors types.[152,179] In subprotocol H (EAY131-H) of the NCI-MATCH platform trial, patients with *BRAF* V600E mutated solid tumors (except for melanoma, thyroid cancer, or colorectal cancer) received combined dabrafenib and trametinib continuously until disease progression or intolerable toxicity. The ORR was 38% ($P<.0001$) and PFS was 11.4 months.[152] The median OS in this cohort was 29 months. For the 131 patients across both trials, the ORR was 41%. The most common treatment-related adverse events included pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, and vomiting. Based on these data, dabrafenib and trametinib may be used for second-line or subsequent therapy for patients with *BRAF* V600E mutated gastroesophageal tumors.

Selpercatinib

In September 2022, the FDA granted tumor agnostic approval for selpercatinib, a tyrosine kinase inhibitor, for treatment of patients with locally advanced or metastatic solid tumors with *RET* gene fusions who have experienced progression after prior treatment and have no satisfactory alternative treatment options.[180] This approval was based on an interim analysis of data from the ongoing phase I/II LIBRETTO-001 trial, which evaluated 41 patients with *RET* fusion-positive tumors (other than non-small cell lung cancer and thyroid cancer) who received selpercatinib until disease progression or unacceptable toxicity.[153] The ORR was 44% with a duration of response of 25 months. The most common treatment-related adverse events included edema, diarrhea, fatigue, dry mouth, hypertension, and abdominal pain. The most common grade 3 or higher treatment-related adverse events were hypertension, increased alanine aminotransferase and increased aspartate aminotransferase. Based on these data, selpercatinib may be used for second-line or subsequent therapy for patients with *RET* gene fusion-positive gastroesophageal tumors.

Palliative/Best Supportive Care

The goals of palliative/best supportive care are to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of the stage of the disease or the need for other therapies. In patients with advanced or metastatic esophageal or EGJ cancer, palliative/best supportive care provides symptom relief and improvement in overall quality of life, and may result in prolongation of life. This is especially true when a multimodality interdisciplinary approach is pursued. Therefore, a multimodality interdisciplinary approach to palliative/best supportive care of patients with esophageal and EGJ cancers is encouraged.

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Dysphagia most often arises due to obstruction, but it can also be associated with tumor-related dysmotility. Assessing the extent of disease and severity of swallowing impairment, preferably through a standardized scoring scale,[181] is essential to initiate appropriate interventions for long-term palliation of dysphagia in patients with esophageal cancer. Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Individualized management of esophageal cancer-related dysphagia is strongly encouraged. Patients with dysphagia who are not candidates for curative surgery should be considered for palliation of their symptoms. Palliative management of dysphagia can be achieved through multiple modalities, although placement of permanent or temporary self-expanding metal stents (SEMS) is the most common and can achieve long-term results.[182] However, the guidelines emphasize that stent placement is generally not advised in patients who are surgical candidates due to concerns that stent-related adverse events may preclude future curative surgery.

A clinical trial involving 45 patients with esophageal carcinoma found that temporary placement of SEMS with concurrent radiation therapy significantly reduced the total number of patients with one or more complications (P=.042) and increased resultant PFS and OS rates (P=.005 and P=.001, respectively) compared with permanent stent placement.[183] Additionally, membrane-covered stents have been shown to have significantly better palliation than conventional bare metal stents because of the decreased rate of tumor ingrowth, which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[182] However, the optimal extent of the covering to prevent recurrent obstruction is unknown. In a recent trial of 98 patients with malignant dysphagia randomized to receive either a fully covered or partially covered SEMS, there was no significant difference in recurrent obstruction between the 2 stent types (19% for fully covered SEMS vs 22% for partially covered SEMS; P=.65).[184] The times to recurrent obstruction and the rates of adverse events were also similar. Another recent trial investigating stent migration found no significant differences in either migration distance or migration frequency between the 2 stent types.[185] However, there was a trend toward better dysphagia relief with the fully covered stents as measured by the Watson and Ogilvie dysphagia scores (P=.081 and P=.067, respectively). These results suggest that fully covered SEMS may not lower the recurrent obstruction or stent migration rates compared with partially covered SEMS, but may be more effective in the palliation of dysphagia.

The optimal stent diameter needed to effectively palliate dysphagia in patients with esophageal cancer is also unknown. Although some data suggest lower migration and recurrent obstruction rates with larger-diameter covered expandable metal stents, these may be associated with a higher risk of stent-related complications.[186] In a prospective trial, 100 patients with unresectable esophageal cancer were randomized to receive a SEMS with either an 18- or 23-mm shaft diameter—but with identical design—and followed until death.[187] Dysphagia was resolved after stent placement in 95% of patients in both groups. The incidence of adverse events was similar in both groups, but there was a trend toward longer survival in the small-diameter group (median survival, 5.9 vs 3 months; P=.10). After 6 months, the cumulative incidence of recurrent dysphagia was 38% versus 47% in the small-diameter versus large-diameter group, respectively (P=.23). These data suggest that small- and large-diameter esophageal SEMS provide similar palliation of dysphagia, with a trend toward increased survival with the use of small-diameter stents.

A phase III randomized controlled trial compared the efficacy of chemoradiation versus radiation therapy alone for the palliation of malignant dysphagia in 220 patients with esophageal cancer.[188] Palliative chemoradiation showed a slight, but statistically insignificant, increase in the percentage of patients experiencing dysphagia relief compared with radiation therapy alone (45% vs 35%; P=.13), with minimal improvements in PFS (4.1 vs 3.4 months; P=.58) and OS (6.9 vs 6.7 months; P=.88). However, patients receiving chemoradiation experienced significantly higher rates of grade 3–4 toxicities than patients receiving radiation therapy alone (36% vs 16%; P=.0017). Therefore, a short course of radiation therapy alone may be used for palliation of dysphagia symptoms in patients with esophageal cancer.

Obstruction

For patients with severe esophageal obstruction (those able to swallow liquids only), treatment options include endoscopy- or fluoroscopy-guided placement of fully or partially covered SEMS, as described previously, and endoscopic lumen enhancement (wire-guided dilation or balloon dilation). Caution should be exercised when dilating malignant strictures, as this may be associated with an increased risk of perforation.[189] For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, generally performed via simultaneous retrograde (via a gastrostomy tract) and antegrade endoscopy. Surgical or radiologic placement of a jejunostomy or gastrostomy tube may be necessary to provide adequate hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful. Other options for palliation of esophageal obstruction

include external beam radiation therapy, chemotherapy, or surgery (in select patients). Brachytherapy may be considered instead of external beam radiation therapy, if a lumen can be restored that allows for the use of appropriate applicators to decrease excessive radiation therapy dose to mucosal surfaces. Single-dose brachytherapy was associated with fewer complications and better long-term relief of obstruction compared with the use of metal stents.[190] However, brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy. Photodynamic therapy can effectively treat esophageal obstruction, but is less commonly performed due to associated photosensitivity and costs.

Pain

Patients experiencing cancer-related pain should be assessed and treated according to the NCCN Guidelines for Adult Cancer Pain (available at NCCN.org). Severe, uncontrolled pain following stent placement should be treated with immediate endoscopic removal of the stent.

Bleeding

Acute bleeding from esophageal cancer may represent a preterminal event secondary to tumor-related aortoesophageal fistulization. Bleeding that occurs primarily from the tumor surface may be controlled with endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation. However, limited data suggest that while endoscopic therapies may initially be effective, endoscopic intervention may lead to precipitous exsanguination and is associated with a high rate of recurrent bleeding.[191] Chronic blood loss from esophageal cancer can be managed with external beam radiation therapy.

Nausea and Vomiting

Patients experiencing nausea and vomiting should be treated according to the NCCN Guidelines for Antiemesis (available at NCCN.org). Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if luminal enhancement is indicated.

Summary

Cancers of the esophagus and EGJ are common in many parts of the world, and incidence rates have been rising in the United States. Tobacco and alcohol use are major risk factors for developing SCC of the esophagus. Obesity, GERD, and Barrett esophagus are the major risk factors for developing adenocarcinoma of the esophagus or EGJ. In addition, some hereditary cancer predisposition syndromes are associated with an increased risk of developing esophageal and EGJ cancers. The NCCN panel strongly recommends multidisciplinary team management as essential for all patients with esophageal or EGJ cancers. Best supportive care is an integral part of treatment, especially in patients with unresectable locally advanced, recurrent, or metastatic disease. Targeted therapies, including trastuzumab, nivolumab, ipilimumab, pembrolizumab, ramucirumab, dostarlimab-gxly, entrectinib/larotrectinib, selpercatinib and dabrafenib/trametinib, have produced encouraging results in patients with advanced or metastatic cancers. The panel encourages patients with esophageal and EGJ cancers to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances in the management of these diseases.

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Individual Disclosures for the NCCN Esophageal and Esophagogastric Junction Cancers Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Jaffer A. Ajani, MD	Amgen Inc.; Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; Delta Fly Pharma; Gilead Sciences, Inc.; LaNova; Leap; Merck & Co., Inc.; miracogne; NIT; Novartis Pharmaceuticals Corporation; Prolinx; Roche Laboratories, Inc.; Taiho Pharmaceuticals Co., Ltd.; Trascenta; Zymeworks	Amgen Inc.; ARCUS; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; BeiGene; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Daiichi- Sankyo Co.; DAVA/OM; Geneos; Gilead Sciences, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Servier; STEBA; Turning Point; zymeworks	Chimeric	Medical oncology
David J. Bentrem, MD, MS	None	None	None	Surgery/Surgical oncology
David Cooke, MD	None	None	None	Surgery/Surgical oncology
Carlos Corvera, MD	None	None	None	Radiotherapy/Radiation oncology
Thomas A. D'Amico, MD	None	None	None	Surgery/Surgical oncology
Prajnan Das, MD, MS, MPH	None	None	None	Radiotherapy/Radiation oncology
Peter C. Enzinger, MD	None	ALX Oncology; Arcus Bioscience; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Blueprint Medicines; Bristol-Myers Squibb Company; Chimeric Therapeutics; Coherus; Daiichi- Sankyo Co.; Ideaya; Istari; Legend; Loxo; MSD; Novartis Pharmaceuticals Corporation; Ono; Servier; Turning Point Therapeutics; Xencor; Zymeworks	None	Medical oncology
Thomas Enzler, MD, PhD	None	None	None	Medical oncology; Hematology/Hematology oncology
Farhood Farjah, MD	National Cancer Institute; National Heart, Lung, and Blood Institute	Expert Witness for the United States of America in a case involving the care of a patient with lung cancer	None	Surgery/Surgical oncology
Hans Gerdes, MD	None	None	None	Gastroenterology; Internal medicine
Michael Gibson, MD, PhD	AbbVie, Inc.; Papivax; Soligenix	Coheres; Daiichi- Sankyo Co.; Flagship Biosciences; Merck & Co., Inc.; National Cancer Institute; Teckro; UpToDate	Bristol-Myers Squibb Company	Medical oncology; Hematology/Hematology oncology
Patrick Grierson, MD, PhD	Aclaris Therapeutics	None	None	Medical oncology
Wayne L. Hofstetter, MD	None	None	None	Surgery/Surgical oncology
David H. Ilson, MD, PhD[a]	None	Amgen Inc.; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Daiichi- Sankyo Co.; Eli Lilly and Company; Merck & Co., Inc.; Roche Laboratories, Inc.; Taiho Pharmaceuticals Co., Ltd.	MacroGenics; Merck & Co., Inc.	Medical oncology; Internal medicine
Shadia Jalal, MD	TESARO, Inc.	None	None	Medical oncology
Rajesh N. Keswani, MD	None	Boston Scientific Corporation; Neptune Medical	None	Gastroenterology; Internal medicine
Sunnie Kim, MD	None	Daiichi- Sankyo Co.; Merck & Co., Inc.	None	Medical oncology
Lawrence R. Kleinberg, MD	Bristol-Myers Squibb Company; Incyte Corporation; Novartis Pharmaceuticals Corporation; Novocure	None	None	Radiotherapy/Radiation oncology
Samuel Klempner, MD[a]	Leap Therapeutics	Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; Daiichi- Sankyo Co.; Exact Sciences; Merck & Co., Inc.; Mersana; Novartis Pharmaceuticals Corporation; sanofi-aventis U.S.; Servier	None	Medical oncology
Jill Lacy, MD	None	Aptitude Health; ASCO; Deciphera Pharmaceuticals, Inc.; Equinox; FirstWorld; Genentech, Inc.; Guidepoint; Ipsen; Novartis Pharmaceuticals Corporation; Techspert	None	Medical oncology
Frank Licciardi	None	None	None	Patient advocacy
Quan P. Ly, MD	None	None	None	Surgery/Surgical oncology
Kristina A. Matkowskyj, MD, PhD	None	Astellas Pharma US, Inc.; Elephas Bio; Merck & Co., Inc.	None	Pathology
Michael McNamara, MD	None	None	None	Medical oncology
Aaron Miller, MD, PhD	None	None	None	Medical oncology
Sarbajit Mukherjee, MD, MS[a]	Ipsen	None	None	Medical oncology
Mary F. Mulcahy, MD	None	None	None	Hematology/Hematology oncology; Medical oncology
Darryl Outlaw, MD	None	None	None	Medical oncology
Kyle A. Perry, MD	None	None	None	Surgery/Surgical oncology
Jose Pimiento, MD	None	ADVOCARE, wellness company	None	Surgery/Surgical oncology
George A. Poultsides, MD, MS	None	None	None	Surgery/Surgical oncology
Scott Reznik, MD[a]	None	None	None	Surgery/Surgical oncology
Robert E. Roses, MD	None	None	None	Surgery/Surgical oncology
Vivian E. Strong, MD[a]	None	None	None	Surgery/Surgical oncology
Stacey Su, MD	None	None	None	Surgery/Surgical oncology
Hanlin L. Wang, MD, PhD	PathAI	Astellas Pharma US, Inc.	None	Pathology
Georgia Wiesner, MD	None	None	None	Genetics
Christopher G. Willett, MD	None	None	None	Radiotherapy/Radiation oncology
Danny Yakoub, MD, PhD	None	None	None	Surgery/Surgical oncology
Harry Yoon, MD	BeiGene; Boston Biomedical; Bristol-Myers Squibb Company; CARsgen; Elevar; Macrogenics; Merck & Co., Inc.	Amgen Inc.; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; AstraZeneca/Daiichi Sankyo; BeiGene; Bristol-Myers Squibb Company; MacroGenics; Novartis Pharmaceuticals Corporation; Novartis-Tisle; OncXerna; Zymeworks	None	Medical oncology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:

David H. Ilson, MD, PhD: Amgen Inc., Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Bayer HealthCare, Bristol-Myers Squibb Company, Daiichi- Sankyo Co., MacroGenics, Merck & Co., Inc., Roche Laboratories, Inc., and Taiho Pharmaceuticals Co., Ltd.
Samuel Klempner, MD: Nuvalent, and Turning Point Therapeutics
Sarbajit Mukherjee, MD, MS: Esophageal Cancer Action Network
Scott Reznik, MD: Onconano
Vivian E. Strong, MD: Merck & Co., Inc.