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Esophageal and Esophagogastric Junction Cancers

Clinical Practice Guidelines in Oncology

Jaffer A. Ajani, MD; James S. Barthel, MD; David J. Bentrem, MD; Thomas A. D'Amico, MD; Prajnan Das, MD, MS, MPH; Crystal S. Denlinger, MD; Charles S. Fuchs, MD, MPH; Hans Gerdes, MD; Robert E. Glasgow, MD; James A. Hayman, MD, MBA; Wayne L. Hofstetter, MD; David H. Ilson, MD, PhD; Rajesh N. Keswani, MD; Lawrence R. Kleinberg, MD; W. Michael Korn, MD; A. Craig Lockhart, MD, MHS; Mary F. Mulcahy, MD; Mark B. Orringer, MD; Raymond U. Osarogiagbon, MD; James A. Posey, MD; Aaron R. Sasson, MD; Walter J. Scott, MD; Stephen Shibata, MD; Vivian E. M. Strong, MD; Thomas K. Varghese, Jr., MD; Graham Warren, MD, PhD; Mary Kay Washington, MD, PhD; Christopher Willett, MD; and Cameron D. Wright, MD

Overview

Upper gastrointestinal tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach constitute a major health problem around the world. An estimated 37,640 new cases of and 25,070 deaths from upper gastrointestinal cancers occurred in the United States in 2010.[1] A dramatic shift in the location of upper gastrointestinal tumors has occurred in the United States.[2,3] Changes in his-

NCCN Clinical Practice Guidelines in Oncology for Esophageal and Esophagogastric Junction Cancers

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, esophageal carcinoma, chemotherapy, chemoradiation, combined modality therapy, surgery, resection, multidisciplinary care, biologic therapy, organ preservation *(JNCCN* 2011;9:830–887)

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Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

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

Please Note

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Disclosures for the NCCN Guidelines Panel for Esophageal and Esophagogastric Junction Cancers

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers panel members can be found on page 887. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

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tology and location of upper gastrointestinal tumors have also been observed in some parts of Europe.[4] In Western Hemisphere countries, the most common site of esophageal cancer is in the lower third of the esophagus, where it often involves the EGJ.

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide.[5] An estimated 16,640 new cases of and 14,500 deaths from esophageal cancer occurred in United States in 2010.[1] It is endemic in many parts of the world, particularly in developing nations. The incidence of esophageal cancer represents one of the widest variations, with a 60-fold difference between high- and low-incidence regions.[6] High prevalence areas include Asia, southern and eastern Africa, and Northern France.[7]

Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma.[8] Esophageal adenocarcinoma may be associated with a better long-term prognosis after resection than SCC.[9] However, more concrete data are desirable for such an assertion. SCC is most common in the endemic regions of the world and adenocarcinoma is most common in nonendemic areas, such as North America and many Western European countries. Both SCC and adenocarcinoma are more common in men. SCCs have become increasingly less common, accounting for fewer than 30% of all esophageal malignancies in the United States and Western Europe. Adenocarcinoma is diagnosed predominantly in white men in whom the incidence has risen

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NCCN Esophageal and Esophagogastric Junction Cancers Panel Members

*[a]Jaffer A. Ajani, MD/Chair†¤
The University of Texas MD Anderson Cancer Center
[d,f]James S. Barthel, MD¤Þ
H. Lee Moffitt Cancer Center & Research Institute
David J. Bentrem, MD¶
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
[b]Thomas A. D'Amico, MD¶
Duke Cancer Institute
[c]Prajnan Das, MD, MS, MPH§
The University of Texas MD Anderson Cancer Center
[a]Crystal S. Denlinger, MD†
Fox Chase Cancer Center
Charles S. Fuchs, MD, MPH†
Dana-Farber/Brigham and Women's Cancer Center
[d,f]Hans Gerdes, MD¤Þ
Memorial Sloan-Kettering Cancer Center
[b]Robert E. Glasgow, MD¶
Huntsman Cancer Institute at the University of Utah
[c,f]James A. Hayman, MD, MBA§
University of Michigan Comprehensive Cancer Center
[b]Wayne L. Hofstetter, MD¶
The University of Texas MD Anderson Cancer Center
[a]David H. Ilson, MD, PhD†Þ
Memorial Sloan-Kettering Cancer Center
[d,f]Rajesh N. Keswani, MD¤
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
[c]Lawrence R. Kleinberg, MD§
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
W. Michael Korn, MD¤†
UCSF Helen Diller Family Comprehensive Cancer Center
[a]A. Craig Lockhart, MD, MHS†
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
[a,f]Mary F. Mulcahy, MD‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
[b]Mark B. Orringer, MD¶
University of Michigan Comprehensive Cancer Center
[a]Raymond U. Osarogiagbon, MD†Þ‡
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute
James A. Posey, MD†
University of Alabama at Birmingham Comprehensive Cancer Center
Aaron R. Sasson, MD¶
UNMC Eppley Cancer Center at The Nebraska Medical Center
[b]Walter J. Scott, MD¶
Fox Chase Cancer Center
Stephen Shibata, MD†
City of Hope Comprehensive Cancer Center
Vivian E. M. Strong, MD¶
Memorial Sloan-Kettering Cancer Center
[b]Thomas K. Varghese, Jr., MD¶
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
Graham Warren, MD, PhD§
Roswell Park Cancer Institute
[e]Mary Kay Washington, MD, PhD≠
Vanderbilt-Ingram Cancer Center
[c]Christopher Willett, MD§
Duke Cancer Institute
[b]Cameron D. Wright, MD¶
Massachusetts General Hospital Cancer Center

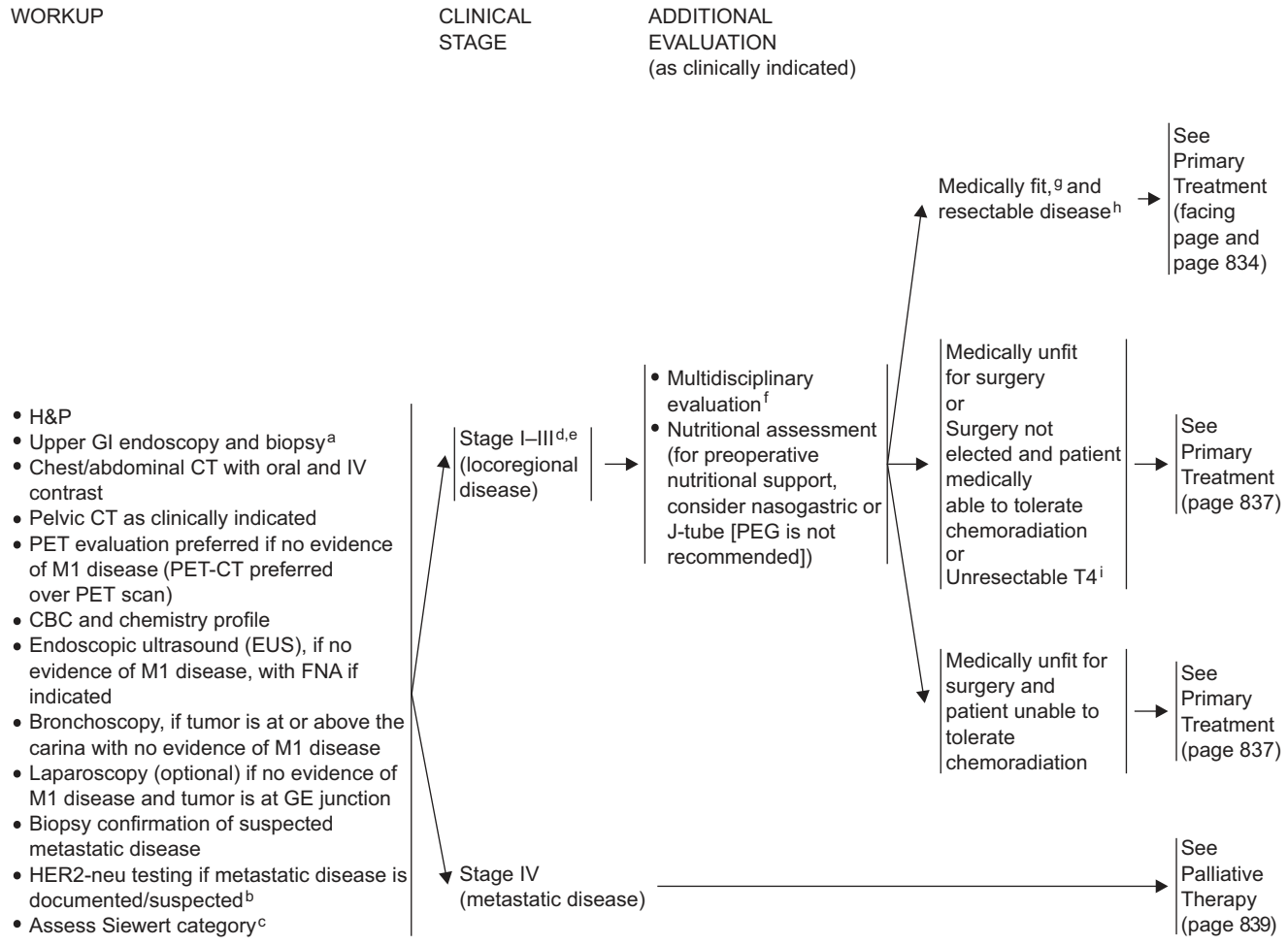
NCCN Staff: Nicole McMillian, MS, and Hema Sundar, PhD

KEY:

*Writing Committee Member

Subcommittees: [a]Principles of Systemic Therapy; [b]Principles of Surgery; [c]Principles of Radiation Therapy; [d]Principles of Endoscopic Staging and Therapy; [e]Principles of Pathologic Review and HER2-neu Testing; [f]Principles of Best Supportive Care. (Please note: underlining denotes the lead of the subcommittee)

Specialties: †Medical Oncology; ¤Gastroenterology; ÞInternal Medicine; ¶Surgery/Surgical Oncology; §Radiotherapy/Radiation Oncology; ‡Hematology/Hematology Oncology; ≠Pathology



[a] See Principles of Endoscopic Staging and Therapy (pages 840 and 841).
[b] See Principles of Pathologic Review and HER2-neu Testing (pages 842-845).
[c] Siewert JR. Carcinoma of the cardia: carcinoma of the gastroesophageal junction classification, pathology, and extent of resection. Dis Esophagus 1996;9:173-182; and Siewert RJ, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg 2000;232:353-361.
[d] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
[e] Resectable T4: involvement of pericardium, pleura, or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases(N+).
[f] See Principles of Multidisciplinary Team Approach (page 846).
[g] Medically able to tolerate major abdominal and/or thoracic surgery.
[h] See Principles of Surgery (pages 847 and 848).
[i] Unresectable T4: T4 tumors with Involvement of the heart, great vessels, trachea, or adjacent organs, including liver, pancreas, lung, and spleen, are unresectable.

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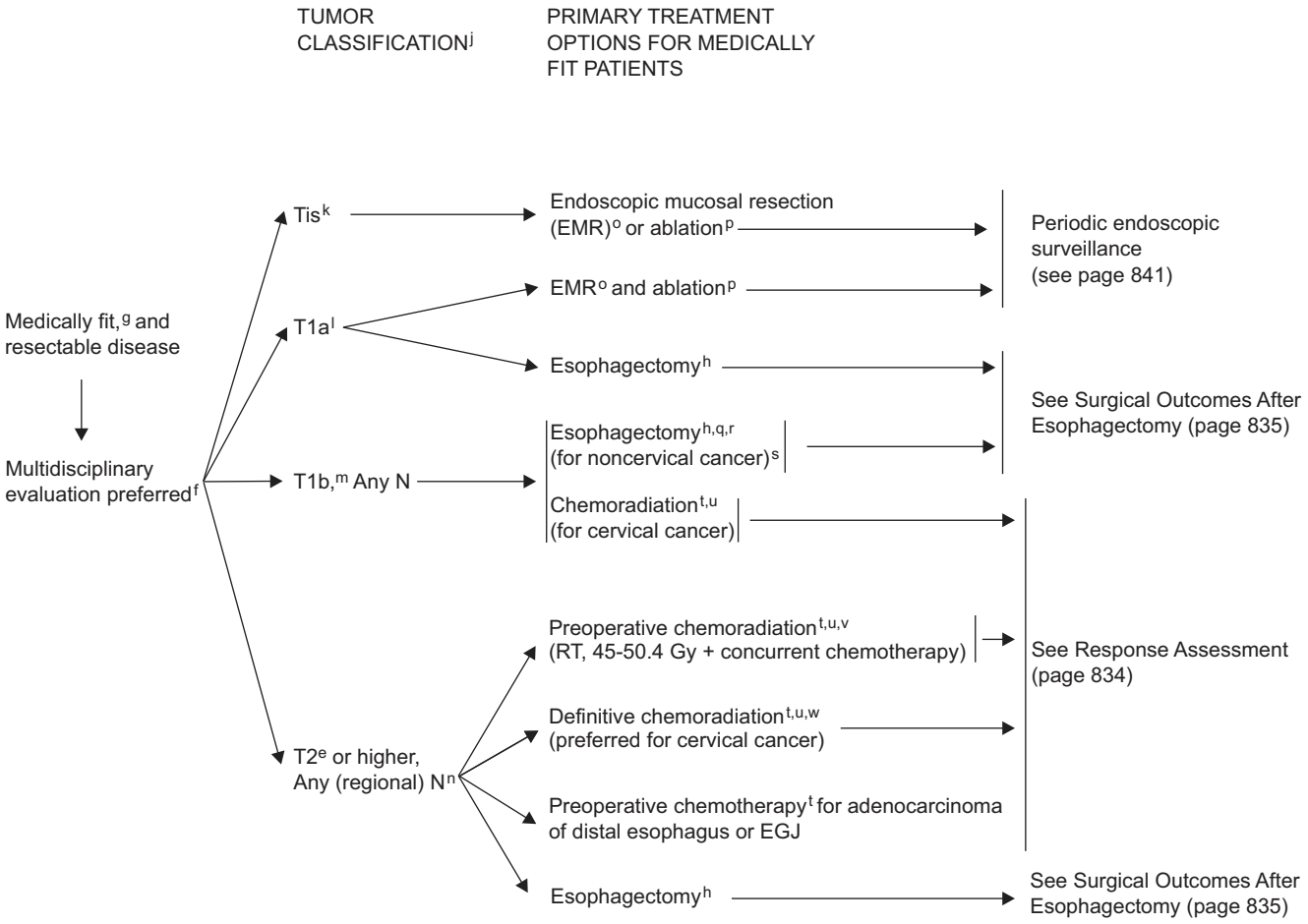
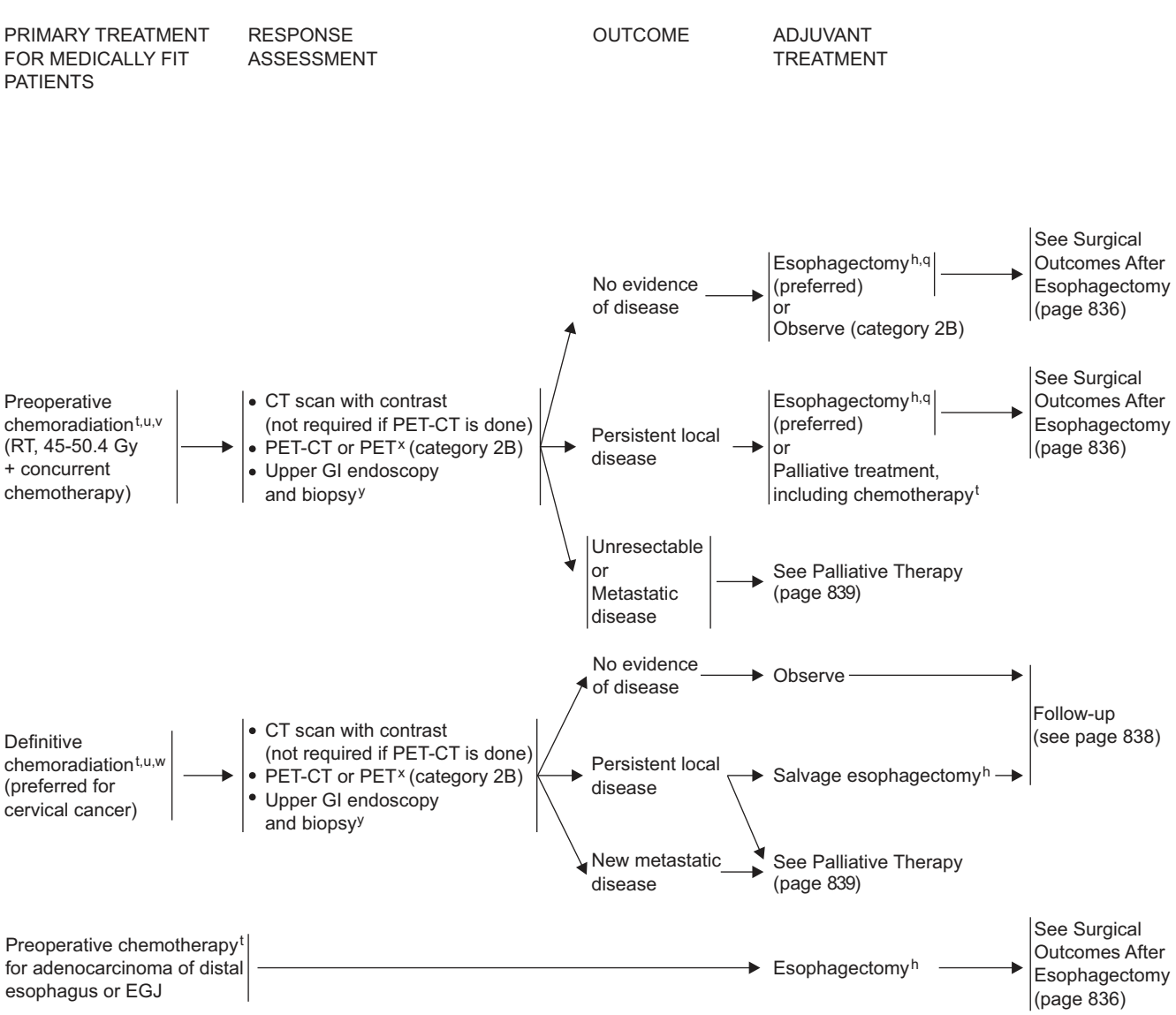


[e]Resectable T4: involvement of pericardium, pleura, or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases (N+).
[f]See Principles of Multidisciplinary Team Approach (page 846).
[g]Medically able to tolerate major abdominal and/or thoracic surgery.
[h]See Principles of Surgery (pages 847 and 848).
[j]See Staging Table, available online, in these guidelines, at www.NCCN.org (ST-1).
[k]Tis: Defined as high-grade dysplasia or carcinoma in situ.
[l]T1a: Defined as tumors involving the mucosa but not invading the submucosa.
[m]T1b: Tumors invading the submucosa.
[n]Preclinical staging cannot establish the number of positive nodes.
[o]May be applied to Tis or T1a, defined as tumor involving the mucosa, but not invading the submucosa.
[p]Ablation may not be needed for squamous cell lesions that are completely excised. See Principles of Endoscopic Staging and Therapy (pages 840 and 841).
[q]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[r]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[s]Surgery is preferred for noncervical cancer, but if the patient declines surgery, see Primary Treatment for Medically Unfit Patients pathway (page 837).
[t]See Principles of Systemic Therapy (pages 849-854).
[u]See Principles of Radiation Therapy (page 855).
[v]Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (Gaast AV, van Hagen P, Hulshof M, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study [abstract]. J Clin Oncol 2010;28(Suppl 1):Abstract 4004.)
[w]Surgery is preferred for adenocarcinomas. Chemoradiation can be considered for squamous cell carcinoma.



[h] See Principles of Surgery (pages 847 and 848).
[q] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[t] See Principles of Systemic Therapy (pages 849-854).
[u] See Principles of Radiation Therapy (page 855).
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[w] Surgery is preferred for adenocarcinomas. Chemoradiation can be considered for squamous cell carcinoma.
[x] Assessment ≥ 5-6 weeks after completion of preoperative therapy.
[y] See Principles of Endoscopic Staging and Therapy: Posttreatment Surveillance (page 841).

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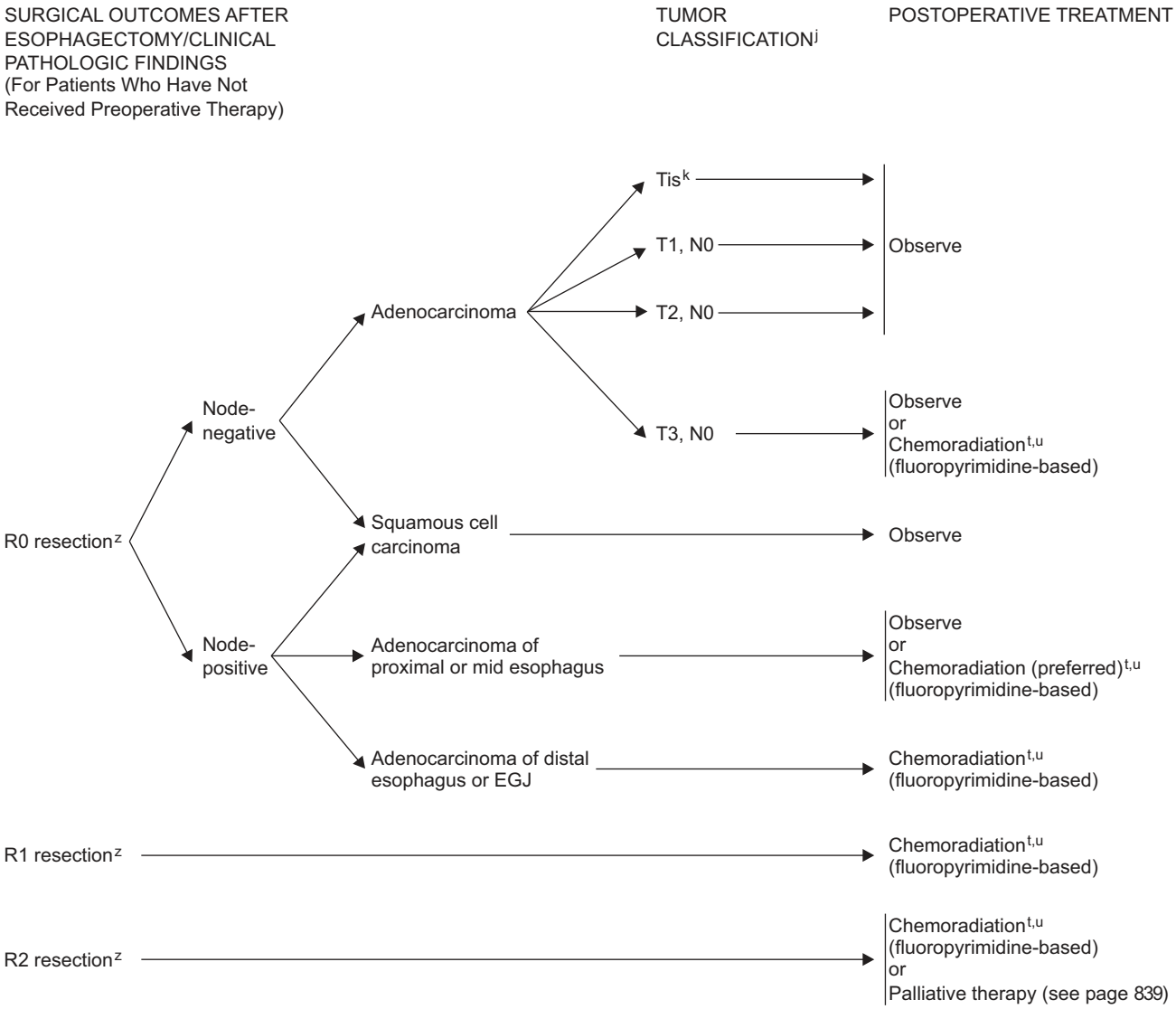
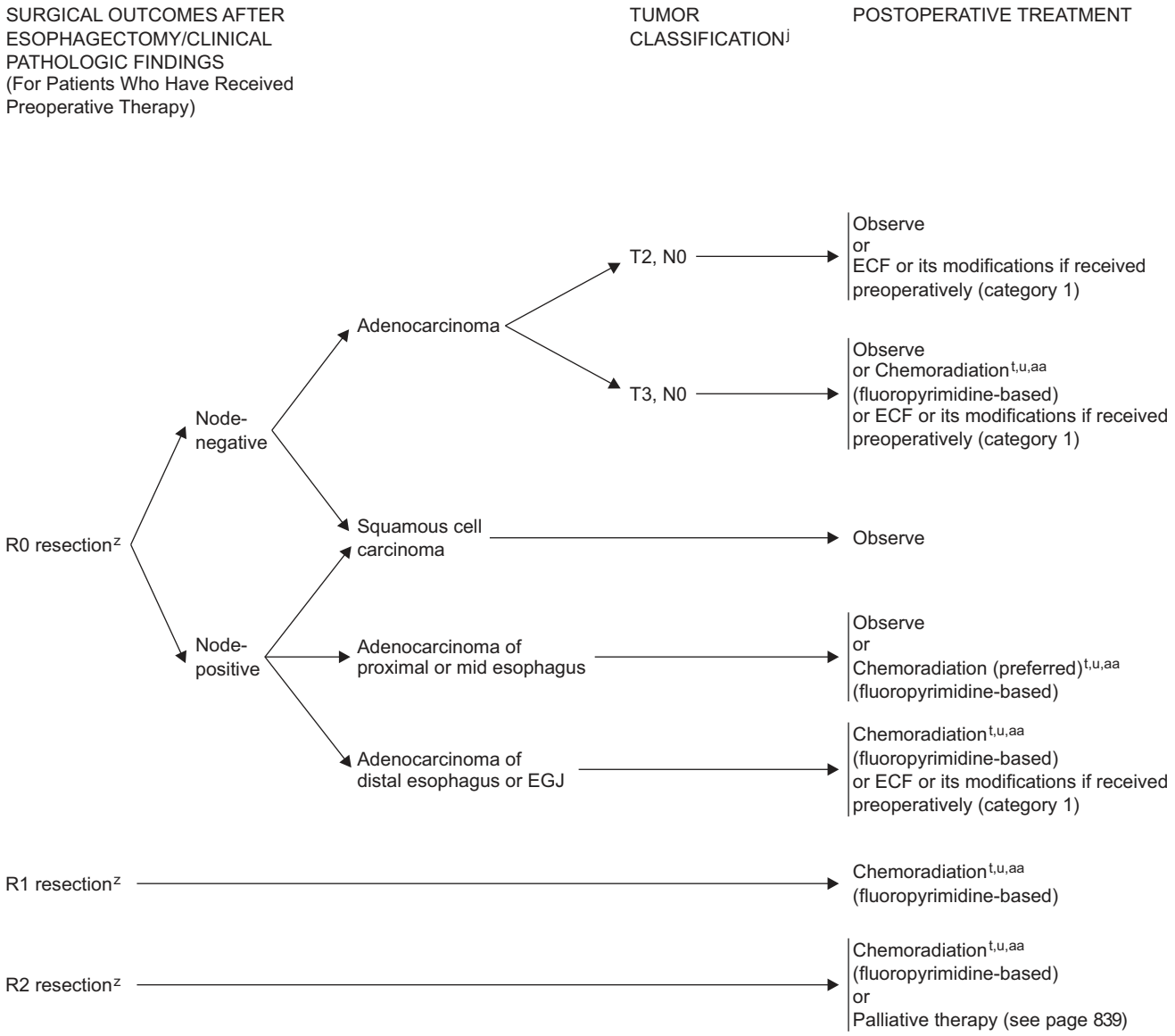
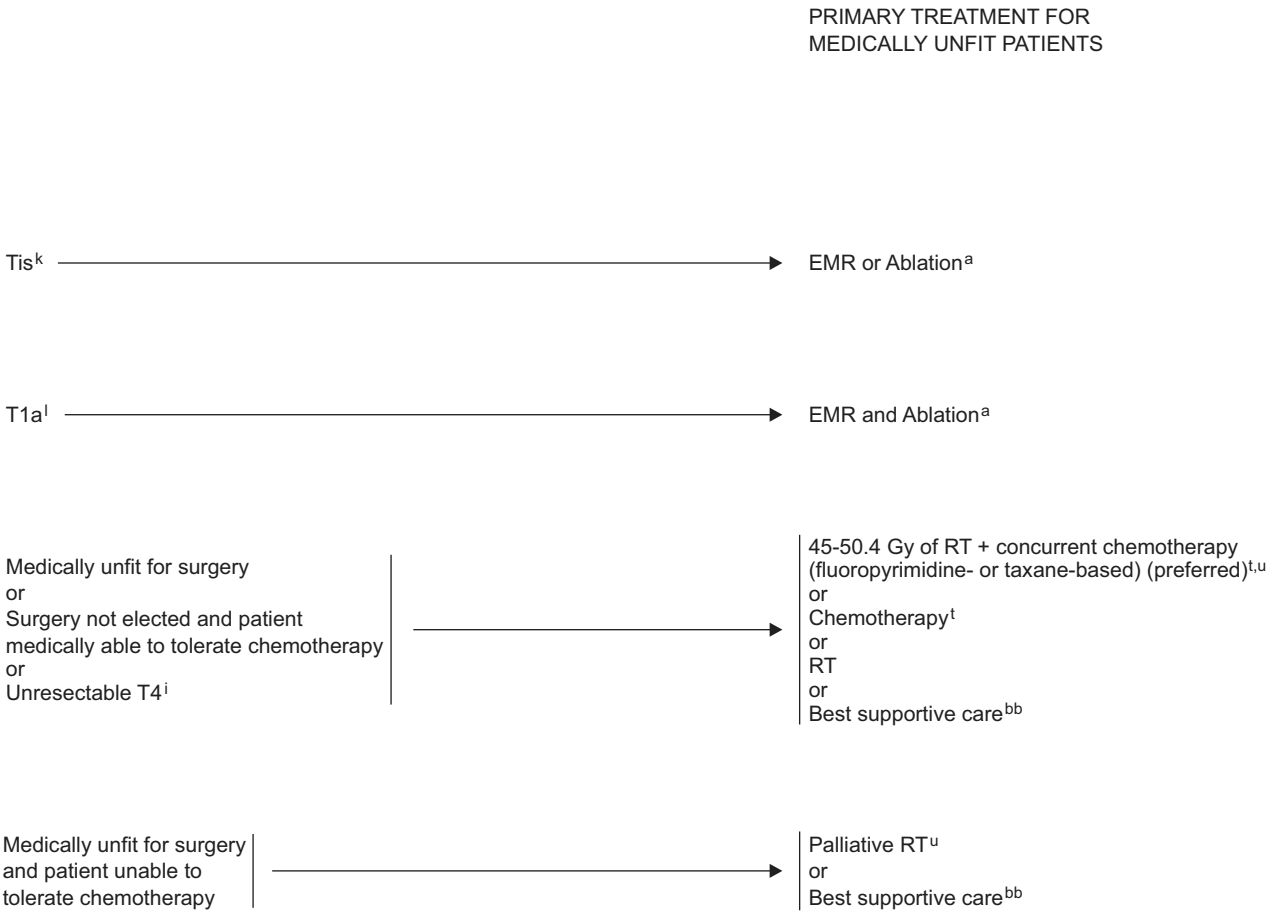


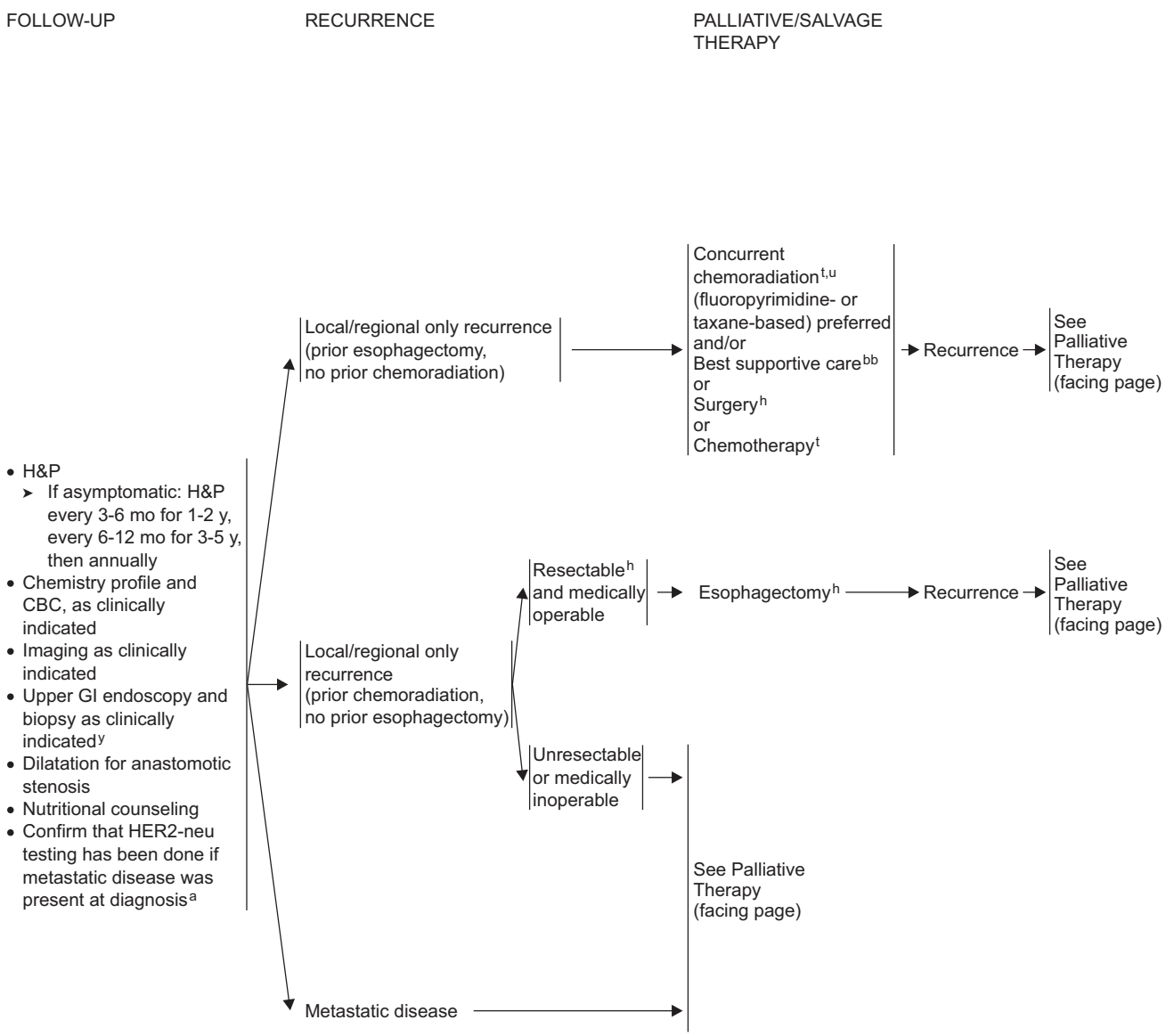
[j]See Staging Table, available online, in these guidelines, at www.NCCN.org (ST-1).
[k]Tis: Defined as high-grade dysplasia or carcinoma in situ.
[t]See Principles of Systemic Therapy (pages 849-854).
[u]See Principles of Radiation Therapy (page 855).
[z]R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1B.



[j]See Staging Table, available online, in these guidelines, at www.NCCN.org (ST-1).
[t]See Principles of Systemic Therapy (pages 849-854).
[u]See Principles of Radiation Therapy (page 855).
[z]R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1B.
[aa]Postoperative chemoradiation only if not received preoperatively.



[a] See Principles of Endoscopic Staging and Therapy (pages 840 and 841).
[k] Tis: Defined as high-grade dysplasia or carcinoma in situ.
[i] Unresectable T4: T4 tumors with involvement of the heart, great vessels, trachea, or adjacent organs, including liver, pancreas, lung, and spleen, are unresectable.
[l] T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[t] See Principles of Systemic Therapy (pages 849-854).
[u] See Principles of Radiation Therapy (page 855).
[bb] See Principles of Best Supportive Care (pages 856 and 857).



[a] See Principles of Pathologic Review and HER2-neu Testing (pages 842-845).
[h] See Principles of Surgery (pages 847 and 848).
[t] See Principles of Systemic Therapy (pages 849-854).
[u] See Principles of Radiation Therapy (page 855).
[y] See Principles of Endoscopic Staging and Therapy: Posttreatment surveillance (page 841).
[bb] See Principles of Best Supportive Care (pages 856 and 857).

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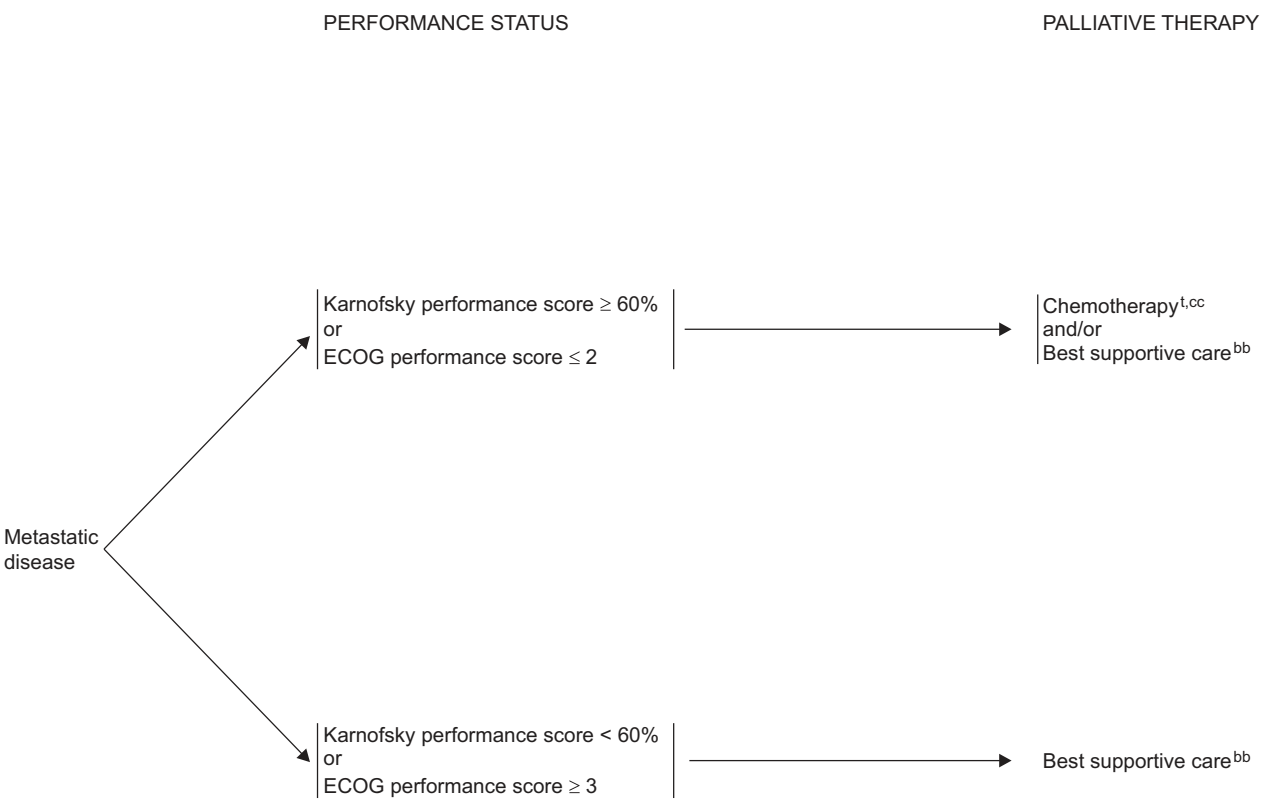

[t]See Principles of Systemic Therapy (pages 849-854).
[bb]See Principles of Best Supportive Care (pages 856 and 857).
[cc]Further treatment after 2 sequential regimens should be dependent on performance status and availability of clinical trials.

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Endoscopy has become an important tool in the diagnosis, staging, treatment, and surveillance of patients with esophageal cancer. Although some endoscopy procedures can be performed without anesthesia, most are performed with the aid of conscious sedation administered by the endoscopist or assisting nurse, or deeper anesthesia (monitored anesthesia care) provided by the endoscopist, a nurse, a nurse anesthetist, or an anesthesiologist. Some patients who are at risk of aspiration during endoscopy may require general anesthesia.

DIAGNOSIS

- Diagnostic and surveillance endoscopies are performed with the goal of determining the presence and location of esophageal cancer and to biopsy any suspicious lesions. Thus, an adequate endoscopic examination addresses both of these components.
- The location of the tumor relative to the teeth and the esophagogastric junction (EGJ), length of the tumor, extent of circumferential involvement, and degree of obstruction should be carefully recorded to assist with treatment planning. If present, the location, length, and circumferential extent of Barrett's esophagus should be characterized in accordance with the Prague criteria,[1] and mucosal nodules should be carefully documented.
- High-resolution endoscopic imaging and narrow-band imaging are presently available and may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[2]
- Multiple biopsies (6-8) using standard-size endoscopy forceps should be performed to provide sufficient material for histologic interpretation. Larger forceps are recommended during surveillance endoscopy of Barrett's esophagus for the detection of dysplasia.[3] Endoscopic mucosal resection (EMR) of focal nodules can be performed in the setting of early-stage disease to provide accurate T staging, including degree of differentiation and vascular and or lymphatic invasion, with the potential of being therapeutic.[4]
- Cytologic brushings or washings are rarely adequate in the initial diagnosis but can be useful in confirming persistent disease after treatment.

STAGING

- Endoscopic ultrasound (EUS) performed before any treatment is important in the initial clinical staging of neoplastic disease. Careful attention to ultrasound images provides evidence of depth of tumor invasion (T stage), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N stage), and occasionally signs of distant spread, such as lesions in surrounding organs (M stage).[5]
- Hypoechoic (dark) expansion of the esophageal wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal esophageal wall corresponding with greater depths of tumor penetration, correlating with higher T stages. A dark expansion of layers 1-3 corresponds with infiltration of the superficial and deep mucosa plus the submucosal (T1 disease). A dark expansion of layers 1-4, correlates with penetration into the muscularis propria (T2 disease), and expansion beyond the smooth outer border of the muscularis propria, correlates with invasion of the adventitia (T3 disease). Loss of a bright tissue plane between the area of tumor and surrounding structures, such as the trachea, aorta, liver, correlates with infiltration of tumor into surrounding organs (T4 disease).
- Mediastinal and perigastric lymph nodes are readily seen with EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well-circumscribed, rounded structures in these areas correlates with the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but is also confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[6] FNA should be performed on suspicious lymph nodes if it can be done without traversing an area of primary tumor or major blood vessels, and if it will affect treatment decisions. The preprocedure review of CT and PET scans, when available, is recommended before esophagogastroduodenoscopy/EUS to enable familiarity with the nodal distribution for possible FNA.
- Obstructing tumors may increase the risk of perforation while performing staging EUS examinations. The use of wire-guided EUS probes, or mini-probes, may permit EUS staging with a lower risk. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate but there is increased risk of perforation after dilation.

[1] Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 2006;131;1392-1399.
[2] Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Endoscopy 2010;42:351-359.
[3] Komanduri S, Swanson G, Keefer L, Jakate S. Use of a new jumbo forceps improves tissue acquisition of Barrett's esophagus surveillance biopsies. Gastrointest Endosc 2009;70:1072-1078, e1071.
[4] Thomas T, Singh R, Ragunath K. Trimodal imaging-assisted endoscopic mucosal resection of early Barrett's neoplasia. Surg Endosc 2009;23:1609-1613.
[5] Barbour AP, Rizk NP, Gerdes H, et al. Endoscopic ultrasound predicts outcomes for patients with adenocarcinoma of the gastroesophageal junction. J Am Coll Surg 2007;205:593-601.
[6] Keswani RN, Early DS, Edmundowicz SA, et al. Routine positron emission tomography does not alter nodal staging in patients undergoing EUS-guided FNA for esophageal cancer. Gastrointest Endosc 2009;69:1210-1217.

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY (cont.)

TREATMENT:

- The goal of EMR and/or ablation is the complete removal of all Barrett's metaplasia and eradication of early malignancy.
- Early-stage disease, Tis, also known as high-grade dysplasia, must be fully characterized, including evaluating presence of nodularity and lateral spread, and ruling out multifocal disease. This is important to permit decisions on endoscopic treatment with ablative methods such as radiofrequency ablation (RFA), cryoablation, photodynamic therapy (PDT), or EMR.[7-10] All focal nodules should be resected rather than ablated.
- T1a disease, carcinoma limited to the lamina propria or muscularis mucosae, in the absence of evidence of lymph node metastases, lymphovascular invasion, or poor differentiation grade can be treated with full EMR. EUS staging before proceeding with mucosal resection in the setting of carcinoma is recommended. Ablative therapy of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed after mucosal resection.
- Esophageal dilation can be performed with the use of dilating balloons or bougies to temporarily relieve obstruction from tumors, or treatment-related strictures. Caution should be exercised to avoid overdilation, to minimize the risk of perforation.
- Long-term palliation of dysphagia can be achieved with endoscopic tumor ablation using Nd:YAG Laser, PDT and cryotherapy, or endoscopic- and radiographic-assisted insertion of expandable metal or plastic stents.[11,12]
- Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic- or radiographic-assisted placement of feeding gastrostomy or jejunostomy. Placement of a gastrostomy in the preoperative setting may compromise the gastric vasculature, thereby interfering with the creation of the gastric conduit in the reconstruction during esophagectomy, and should be avoided.

POSTTREATMENT SURVEILLANCE:

- Assessment with endoscopy with biopsy and brushings should be performed ≥ 5-6 weeks after completion of preoperative therapy.
- EUS examinations performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the present stage of disease.[13] Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.[14]
- Endoscopic surveillance after definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS performed in conjunction with endoscopy examinations has a high sensitivity for recurrent disease.[15] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.
- Endoscopic surveillance after ablative therapy or EMR of early esophageal malignancy should continue after completion of treatment. Biopsies should be taken of the neosquamous mucosa even in the absence of mucosal abnormalities because dysplasia may occasionally be present beneath the squamous mucosa.
- Endoscopic surveillance should also include a search for the presence of Barrett's esophagus and 4-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent high-grade and low-grade dysplasia using RFA or cryoablation should be considered. Ablation of nondysplastic Barrett's esophagus is not recommended.
- For follow-up, patients with Tis or T1a who undergo EMR should have endoscopic surveillance every 3 months for 1 year, then annually.

[7]Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-2288.
[8]Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010;71:680-685.
[9]Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007;66:460-468.
[10]Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57:1200-1206.
[11]Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gastrointest Endosc 1995;42:507-512.
[12]Vakil N, Morris AI, Marcon N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. Am J Gastroenterol 2001;96:1791-1796.
[13]Ribeiro A, Franceschi D, Parra J, et al. Endoscopic ultrasound restaging after neoadjuvant chemotherapy in esophageal cancer. Am J Gastroenterol 2006;101:1216-1221.
[14]Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg 2009;249:764-767.
[15]Lightdale CJ, Botet JF, Kelsen DP, et al. Diagnosis of recurrent upper gastrointestinal cancer at the surgical anastomosis by endoscopic ultrasound. Gastrointest Endosc 1989;35:407-412.

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

TABLE 1 Pathologic Review

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

Continued on facing page
See references on page 845

[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's esophagus with high-grade dysplasia in an esophageal resection specimen is reported as "carcinoma in situ (Tis)." The term "carcinoma in situ" is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states.[1]
[c] Biopsies showing Barrett's 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's 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 TNM system for squamous cell carcinoma.[1]
[f] Pathologic grade is needed for stage grouping in the AJCC TNM 7th edition.[1]
[g] Tumors arising in the proximal stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[1]

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING (cont.)

Assessment of Treatment Response

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

Although grading systems for tumor response in esophageal cancer have not been uniformly adopted, in general, 3-category systems provide good reproducibility among pathologists.[6,8,9] The following system developed specifically for the esophagus, by Wu et al.,[6] is reported to provide good interobserver agreement, but other systems, such as the one suggested by the CAP Cancer Protocol for Esophageal Carcinoma (available at http://www.cap.org),[9] may also be used. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

TABLE 2

Tumor Regression Grade[9]	Wu et al.[6] Description	Ryan et al.[8] Description
0 (Complete response)	No residual cancer cells	No cancer cells
1 (Moderate response)	1%-50% residual cancer; rare individual cancer cells or minute clusters of cancer cells	Single cells or small groups of cancer cells
2 (Minimal response)	> 50% residual cancer cells, often grossly identifiable at primary site	Residual cancer cells outgrown by fibrosis
3 (Poor response)		Minimum or no treatment effect; extensive residual cancer

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See references on page 845

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING (cont.)

Assessment of Overexpression of HER2-neu in Esophageal Carcinoma

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) is recommended to confirm tumors with 2+ expression by IHC. The following criteria used in the ToGA trial[10] are recommended:

TABLE 3 Immunohistochemical Criteria for Scoring HER2-neu Expression in Gastric and Esophagogastric Junction Cancers*

	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2-neu 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	Cancer cell cluster 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	Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal (FISH is recommended)†
3+	Strong complete, basolateral or lateral membranous reactivity in ⊠ 10% of cancer cells	Cluster of ≥ 5 cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

*Reprinted and adapted from Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–697, with permission from Elsevier.

†The NCCN Guidelines Panel recommends that cases showing 2+ (equivocal) overexpression of HER2-neu on IHC should be additionally examined by FISH or other in situ hybridization methods.

See references on facing page

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING--REFERENCES

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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 caring for 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 2 weeks) are encouraged.
- Optimally at each meeting, all relevant disciplines should be encouraged to participate, which may include surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines is also desirable.
- All long-term therapeutic strategies are best developed after adequate staging procedures are completed but ideally before any therapy 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.

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PRINCIPLES OF SURGERY

- Before surgery, clinical staging to assess resectability should be performed with CT scan of the chest and abdomen, whole-body PET (integrated PET-CT is preferred), and endoscopic ultrasound.

- Before surgery, all patients should be assessed by an esophageal surgeon for physiologic ability to undergo esophageal resection.[1] Esophageal resection should be considered for all physiologically fit patients with resectable esophageal cancer (> 5 cm from cricopharyngeus).

- Cervical or cervicothoracic esophageal carcinomas < 5 cm from the cricopharyngeus should be treated with definitive chemoradiation.

- Resectable esophageal or esophagogastric junction cancer:
  - T1a tumors, defined as tumors involving the mucosa but not invading the submucosa, may be considered for EMR + ablation or esophagectomy in experienced centers.[2-6]
  - Tumors in the submucosa (T1b) or deeper may be treated with esophagectomy.
  - T1-T3 tumors are resectable even with regional nodal metastases (N+), although bulky, multistation lymphatic involvement is a relative contraindication to surgery, to be considered in conjunction with age and performance status.
  - T4 tumors with involvement of pericardium, pleura, or diaphragm are resectable.

- Unresectable esophageal cancer:
  - T4 tumors with involvement of the heart, great vessels, trachea, or adjacent organs, including liver, pancreas, lung, and spleen, are unresectable.
  - Most patients with multistation, bulky lymphadenopathy should be considered unresectable, although lymph node involvement should be considered in conjunction with other factors, including age, performance status, and response to therapy.
  - Patients with EGJ and supraclavicular lymph node involvement should be considered unresectable.
  - Patients with distant (including nonregional lymph nodes) metastases (stage IV) are unresectable.

- The type of esophageal resection is dictated by the location of the tumor, the available choices for conduit, surgeon experience, and surgeon and patient preference.

- In patients who are unable to swallow well enough to maintain nutrition during induction therapy, esophageal dilatation or a feeding jejunostomy tube are preferred to a gastrostomy (which may compromise the integrity of gastric conduit for reconstruction).

- Acceptable operative approaches for resectable esophageal or esophagogastric junction cancer:
  - Ivor Lewis esophagogastrectomy (laparotomy + right thoracotomy)
  - McKeown esophagogastrectomy (right thoracotomy + laparotomy + cervical anastomosis)
  - Minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy + limited right thoracotomy)[7,8]
  - Minimally invasive McKeown esophagogastrectomy (right thoracoscopy + limited laparotomy/laparoscopy + cervical anastomosis)
  - Transhiatal esophagogastrectomy (laparotomy + cervical anastomosis)
  - Robotic minimally invasive esophagogastrectomy
  - Left transthoracic or thoracoabdominal approaches with anastomosis in chest or neck

- Acceptable conduits:
  - Gastric (preferred)
  - Colon
  - Jejunum

- Acceptable lymph node dissections:[9]
  - Standard
  - Extended (en bloc)

- In patients undergoing esophagectomy without induction chemoradiation, at least 15 lymph nodes should be removed to achieve adequate nodal staging. The optimum number of nodes after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.[10]

- Patients who develop localized, resectable esophageal cancer after definitive chemoradiation can be considered for salvage esophagectomy if they do not have distant recurrence.[11]

- Patients with potentially resectable esophageal cancer should undergo multidisciplinary review. Esophageal resection, EMR, and other ablative techniques should be performed in high-volume esophageal centers by experienced surgeons and endoscopists.[12,13]

See references on page 848

PRINCIPLES OF SURGERY--REFERENCES

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PRINCIPLES OF SYSTEMIC THERAPY

- Chemotherapy regimens recommended for advanced esophageal/esophagogastric adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status, medical comorbidities, toxicity profile, and HER2-neu expression (for adenocarcinoma only)
- The use of 3-drug regimens for advanced disease should be reserved for patients who are medically fit, with a good performance status (ECOG performance status of 0 or 1), and with access to frequent toxicity assessment.
- Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting amore favorable toxicity profile without a compromise of efficacy
- Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Infusional 5-FU and capecitabine may be used interchangeably (except as indicated). Infusion is the preferred route compared with bolus 5-FU.[1]
- Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile
- For localized esophageal/esophagogastric adenocarcinoma, preoperative chemoradiation is the preferred approach.
- On completion of chemotherapy, patients should be assessed for response and monitored for any long-term complications.
- Please refer to the Principles of Radiation Therapy for the radiation therapy administration details (page 855).

Continued on page 850
See references on pages 852-854

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

PRINCIPLES OF SYSTEMIC THERAPY* (cont.)

Preoperative Chemoradiation
- Paclitaxel and carboplatin (category 1)[2,3]
- Cisplatin and fluoropyrimidine (5-FU or capecitabine) (category 1)[4-6]
- Oxaliplatin and fluoropyrimidine (5-FU† or capecitabine)[8-9]
- Paclitaxel and cisplatin[10]
- Carboplatin and 5-FU (category 2B)[11]
- Irinotecan and cisplatin (category 2B)[12]
- Docetaxel or paclitaxel and fluoropyrimidine (5-FU or capecitabine) (category 2B)[13-16]
- Oxaliplatin, docetaxel, and capecitabine (category 2B)[16]

Perioperative Chemotherapy
(3 cycles preoperative and 3 cycles postoperative)
(Only for adenocarcinoma of the distal esophagus or esophagogastric junction):
- ECF (epirubicin, cisplatin, and 5-FU) (category 1)[17]
- ECF modifications (category 1)[18]
  - Epirubicin, oxaliplatin, and 5-FU
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

Sequential Chemotherapy and Chemoradiation
- Irinotecan and cisplatin[19-21]
- Paclitaxel and cisplatin[19]
- Docetaxel and cisplatin[22]
- 5-fluorouracil and cisplatin; 5-fluorouracil and paclitaxel[13]

Definitive Chemoradiation
- Cisplatin and fluoropyrimidine (5-FU or capecitabine) (category 1)[5,23]
- Oxaliplatin and fluoropyrimidine (5-FU† or capecitabine)[7-9,24]
- Paclitaxel or docetaxel and cisplatin[10,25,26]
- Paclitaxel and carboplatin (category 2B)[3]
- Irinotecan and cisplatin (category 2B)[12]
- Docetaxel or paclitaxel and fluoropyrimidine (5-FU or capecitabine) (category 2B)[14-16]
- Oxaliplatin, docetaxel, and capecitabine (category 2B)[16]

Postoperative Chemoradiation (only for adenocarcinoma)
- 5-FU (bolus) and leucovorin (category 1)[27]
- LV5FU2 before and after infusion 5-FU or capecitabine with radiation (preferred)[28-30]

Cont. on facing page
See references on pages 852-854

*For dosing schedules, visit www.NCCN.org.

†Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, see the discussion.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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PRINCIPLES OF SYSTEMIC THERAPY* (cont.)

Definitive Chemotherapy for Metastatic or Locally Advanced Cancer (where chemoradiation is not indicated)

First-Line Therapy

Two-drug regimens or single agent preferred. Three-drug regimens should be reserved for medically fit patients with good performance status (PS) and access to frequent toxicity evaluation.

- Trastuzumab with chemotherapy for HER2-neu overexpressing adenocarcinoma (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents; not recommended for use with anthracyclines)[31] (see Principles of Pathologic Review and HER2-neu Testing [pages 842-845])
- DCF (docetaxel, cisplatin, and 5-FU†) (category 1)[32]
- DCF modifications (preferred over DCF) (category 2A; category 2B for docetaxel, carboplatin, and 5-FU)[33-38]
  - Docetaxel, oxaliplatin, and 5-FU†
  - Docetaxel, carboplatin, and 5-FU
- ECF (category 1)[39,40]
- ECF modifications (category 1)[40]
  - Epirubicin, oxaliplatin, and 5-FU
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine
- Fluoropyrimidine (5-FU† or capecitabine) and cisplatin (category 1)[31,41-44]
- Fluoropyrimidine (5-FU† or capecitabine) and oxaliplatin[42,45]
- Fluoropyrimidine (5-FU†) and irinotecan[43,46-48]
- Paclitaxel with cisplatin or carboplatin[49-51]
- Docetaxel with cisplatin[37,52,53]
- Docetaxel and irinotecan (category 2B)[54]
- Fluoropyrimidine (5-FU or capecitabine)[43,55,56]
- Docetaxel or paclitaxel[57-59]

Second-Line Therapy

Dependent on prior therapy and PS:

- Trastuzumab with chemotherapy for HER2-neu overexpressing adenocarcinoma if not used in first-line therapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents; not recommended for use with anthracyclines)[31] (see Principles of Pathologic Review and HER2-neu Testing [pages 842-845])
- Irinotecan and cisplatin[45,60]
- Irinotecan and fluoropyrimidine (5-FU† or capecitabine) (category 2B)[61,62]
- Irinotecan and docetaxel (category 2B)[54]
- Irinotecan and mitomycin (category 2B)[63,64]
- Docetaxel or paclitaxel (category 2B)[57-59]
- Irinotecan (category 2B)[65-67]

Alternative Regimens to be Considered (May be Combined With Other Regimens When Appropriate) (category 2B):

- Gemcitabine, 5-FU, and leucovorin[68]
- Pegylated liposomal doxorubicin, cisplatin, and 5-FU[69]
- Mitomycin and irinotecan[70]
- Mitomycin, cisplatin, and 5-FU[39]
- Mitomycin and 5-FU[71,†]
- Etoposide[72,73]
- Erlotinib[74,75]
- Cetuximab[76]

See references on pages 852-854

*For dosing schedules, visit www.NCCN.org.

†Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, see the discussion.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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PRINCIPLES OF RADIATION THERAPY

General Radiation Information

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, medical oncologists, radiologists, gastroenterologists, and pathologists.
- CT scans, barium swallow, endoscopic ultrasound (EUS), endoscopy reports, and PET or PET/CT scans, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders before simulation.

Simulation and Treatment Planning

- Use of CT simulation and 3D treatment planning is strongly encouraged.
- When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily setup.
- The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified on the planning scan and other examinations listed in the General Radiation Information section above. The clinical target volume (CTV) should include the areas at risk for microscopic disease. The relative risk of nodal metastases at a specific nodal location is dependent on the site of origin of the primary tumor. The planning target volume (PTV) should include the tumor plus a nominal 5-cm cephalad and caudal margin, and a 1.5- to 2-cm radial margin.[1,2] The uncertainties arising from respiratory motion should also be taken into consideration.
- Lung dose guidelines: Normal lung (> 2 cm outside the target volume) should not receive more than 40 Gy. To reduce the incidence of postoperative pulmonary complications (and symptomatic pneumonitis), a guideline is to limit the proportion of total lung receiving 20 Gy or more to 20% and 10 Gy or more to 40%, although it is recognized that these guidelines may be exceeded as needed to achieve other important planning goals, and as further information becomes available.
- Intensity-modulated radiation therapy (IMRT) may be appropriate in selected cases to reduce dose to normal structures, such as heart and lungs. In designing IMRT plans, for structures such as the lungs, attention should be given to the lung volume receiving low to moderate doses, and the volume receiving high doses.

Blocking

- Custom blocking is necessary to reduce unnecessary dose to normal structures, including liver (60% of liver < 30 Gy), kidneys (at least 2/3 of one kidney < 20 Gy), spinal cord (< 45 Gy), heart (1/3 of heart < 50 Gy, effort should be made to keep the left ventricle doses to a minimum), and lungs.*

Dose

- 45-50.4 Gy (1.8-2 Gy/d)[3]

Supportive Therapy

- Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks.
- During irradiation, patients are seen for status check at least once a week with notation of vital signs, weight, and blood counts.
- Antiemetics should be given on a prophylactic basis when appropriate. Antacid and antidiarrheal medications may be prescribed when needed.
- If estimated caloric intake is < 1500 kcal/d, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomies or nasogastric feeding tubes may be placed to ensure adequate caloric intake.
- Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery.

*Lung Dose Volume Histogram (DVH) parameters as predictors of pulmonary complications in patients with esophageal cancer treated with concurrent chemoradiotherapy should be strongly considered, although consensus on optimal criteria has not yet emerged. Every effort should be made to keep the lung volume and doses to a minimum. Treating physicians should be aware that the DVH reduction algorithm is hardly the only risk factor for pulmonary complications. DVH parameters as predictors of pulmonary complications in patients with esophageal cancer are an area of active development among the NCCN Member Institutions and others.

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PRINCIPLES OF BEST SUPPORTIVE CARE[1-6]

The goal of best supportive care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. For esophageal cancer, interventions undertaken to relieve major symptoms may result in significant prolongation of life. This appears to be particularly true when a multimodality interdisciplinary approach is pursued, and therefore, a multimodality interdisciplinary approach to palliative care of the esophageal cancer patient is encouraged.

Dysphagia

- Assess the extent of disease, the functional degree of swallowing impairment and confirm the cause of dysphagia
- Functional degrees of swallowing impairment
  - Unable to swallow saliva
  - Able to swallow liquids only
  - Able to swallow semisolid food (consistency of baby food)
  - Able to swallow solid food cut into pieces < 18 mm in diameter and thoroughly chewed
  - Able to eat solid food without special attention to bite size or chewing (dysphagia symptoms may be intermittent)
- Dysphagia arising from esophageal cancer most often is from obstruction, but occasionally may be primarily from tumor related dysmotility.

Obstruction:

- Complete esophageal obstruction
  - Endoscopic lumen restoration
  - Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
    - Surgical or radiologic placement of jejunal or gastrostomy tube
  - External beam radiation therapy
    - Brachytherapy may be considered in place of external beam radiation if lumen can be restored using appropriate applicators during the delivery of brachytherapy to decrease excessive dose deposition on mucosal surfaces. Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.
  - Chemotherapy
  - Surgery
    - May occasionally be useful in carefully selected patients
- Severe esophageal obstruction (able to swallow liquids only)
  - Endoscopic lumen enhancement
    - Wire-guided dilation or balloon dilation
    - Endoscopy or fluoroscopy-guided placement of covered expandable metal stents
      - Although data suggest a lower migration and reobstruction rate with the larger-diameter covered expandable metal stents, they may be associated with a higher risk of other complications
    - Other measures as stated above
- Moderate esophageal obstruction (able to swallow semisolid food)
  - Endoscopic lumen enhancement as necessary
    - Measures stated above may be considered

Pain

- If patient is experiencing tumor-related pain, then the pain should be assessed and treated in accordance with the PAIN-1 section of NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
  - Severe uncontrolled pain after esophageal stent placement should be treated emergently with endoscopic removal of the stent once uncontrollable nature of pain is established.

Bleeding

- Acute bleeding from esophageal cancer may represent a preterminal event secondary to tumor-related aortoesophageal fistualization. Endoscopic assessment and intervention may lead to precipitous exsanguination, and therefore, should be undertaken cautiously.
  - If bleeding seems to be primarily from tumor surface, then endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation may be useful for control of bleeding.
- Chronic blood loss from esophageal cancer
  - External beam radiation therapy

Nausea/Vomiting

- Patients experiencing nausea and vomiting should be treated in accordance with the NCCN Clinical Practice Guidelines in Oncology for Antiemesis (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
- Nausea and vomiting may be associated with luminal obstruction, and therefore endoscopic or fluoroscopic evaluation should be performed to determine if luminal enhancement is indicated.

See references on facing page

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more steeply. However, adenocarcinoma is gradually increasing in men of all ethnic backgrounds and also in women.[2]

Tobacco and alcohol abuse are major risk factors for SCC, whereas the use of tobacco is a moderate established risk factor for adenocarcinoma.[10–12] Risk of SCC decreases substantially after smoking cessation; unlike in SCC, the risk for adenocarcinoma remains unchanged even after several years of smoking cessation.[13,14] Obesity and high body mass index (BMI) have been established as strong risk factors for esophageal adenocarcinoma.[11,15,16] Individuals in the highest quartile for BMI had a 7.6-fold increased risk of developing esophageal adenocarcinoma compared with those in the lowest quartile, whereas SCC was not associated with BMI.[17,18]

Gastroesophageal reflux disease (GERD) and Barrett's esophagus are the other 2 major risk factors for adenocarcinoma of the esophagus.[19–22] GERD is associated with high BMI and is also a risk factor for Barrett's esophagus, a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[23] Patients with Barrett's esophagus have 30 to 60 times greater risk of developing esophageal adenocarcinoma than the general population.[21] Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with higher grades of dysplasia.[24,25] These preliminary results warrant further prospective evaluation as predictors of risk for the development of high-grade dysplasia (HGD) and esophageal adenocarcinoma in patients with Barrett's esophagus.

Patients with SCC of the esophagus and esophageal adenocarcinoma are also at increased risk of developing second primary cancers, such as head and neck and lung cancers.[26]

Staging

The tumor (T), node (N), and metastasis (M) classification developed by the American Joint Committee on Cancer (AJCC) in 2002 was based on pathologic review of the surgical specimen in patients who had surgery as primary therapy. The revised 2010 AJCC staging classification (available online, in these guidelines, at www.NCCN.org [ST-1]) is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) in 4627 patients who were treated with esophagectomy alone without induction or postoperative therapy.[27] In the data reported by WECC, survival decreased with increasing depth of tumor invasion (pT), presence of regional lymph node metastases (pN), and presence of distant metastases (pM).[28] In addition, survival was somewhat worse for pT1b (submucosal) tumors than for pT1a (intramucosal) tumors. Survival was worse for SCC than adenocarcinomas. The revised staging system includes separate stage groupings for SCC and adenocarcinoma. The revised staging system is for the esophageal and EGJ cancers, including cancer within the first 5 cm of the stomach that extends into the EGJ or distal thoracic esophagus. However, this new classification may not work well for baseline clinical staging or in patients who have had preoperative therapy. This new classification has several other shortcomings, including inclusion of the proximal 5 cm of stomach, lack of guidance for regional resectable and unresectable cancer, and emphasis on the number of nodes rather than their anatomic locations and significance.

Patient outcomes may correlate with the initial clinical stage of the cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage. Although surgical pathology yields the most accurate staging, preclinical staging has improved since the advent of better imaging techniques.[29] In North America and many western European countries, where screening programs for early detection of esophageal cancer 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. Fewer than 60% of patients with locoregional cancer can undergo a curative resection, and 70% to 80% of resected specimens harbor metastases in the regional lymph nodes. Thus, clinicians are often dealing with an advanced-stage incurable cancer in newly diagnosed patients.

Esophagogastric Junction

Siewert[30] classified the adenocarcinoma of the esophagogastric (AEG) junction into 3 types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass. If the epicenter of the tumor or more than 66% of the tumor mass

is located more than 1 cm above the anatomic EGJ, then the tumor is classified as an adenocarcinoma of the distal esophagus, type I (AEG type I). If the epicenter of the tumor or tumor mass is located within 1 cm proximal and 2 cm distal to the anatomic EGJ, it is classified as AEG type II. If the epicenter of the tumor or more than 66% of the tumor mass is located more than 2 cm below the anatomic EGJ, the tumor is classified as AEG type III.[30]

In 2000, the classification was changed slightly.[31] AEG type I includes tumors with a center that is 5 cm proximal or distal to the anatomic cardia and these tumors arise from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett's esophagus) and may infiltrate the EGJ from above. AEG type II tumors or true carcinoma of the cardia arise immediately at the EGJ. AEG type III tumors or subcardiac gastric carcinoma infiltrate the EGJ from below.

In the revised AJCC staging system, tumors whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extends into the EGJ or esophagus, are classified as adenocarcinoma of the esophagus for the purposes of staging.[27] All other cancers with a midpoint in the stomach lying more than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into the EGJ or esophagus are staged using the gastric cancer staging system. This approach remains a subject of disagreement and debate.

Various techniques used to determine this include barium esophagography, esophagoscopy, and CT. An individualized therapeutic approach may be preferred for specific patients and tumor locations, based on thorough pretreatment staging. Therapeutic decisions may be refined according to the location of the individual tumor and specific requirements for local control.

Principles of Pathology

Biopsy

A specific diagnosis of SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the TNM system for SCC.[27] In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade (required for stage grouping), and include the presence or absence of Barrett's esophagus. In the case of endoscopic mucosal resection (EMR) or esophageal resection specimens, the depth of tumor invasion and the status of mucosal and deep margins should also be recorded. In an esophageal resection specimen, Barrett's esophagus with HGD is reported as carcinoma in situ (Tis).[27] Biopsies showing Barrett's esophagus with a suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.[32] The pathology report of the biopsy of the surgical specimen should also document the location of the tumor in relationship to the EGJ, lymph node status, and the number of lymph nodes recovered. For esophagectomy with prior chemoradiation, the tumor site should be thoroughly sampled, including the entire EGJ or ulcer bed after neoadjuvant therapy without grossly obvious residual tumor.

Assessment of Treatment Response

The prognostic significance of complete pathologic response and histologic tumor regression after neoadjuvant therapy in patients with adenocarcinoma and SCC of the esophagus has been shown in several studies.[33–38] Posttherapy pathologic stage was the best predictor of survival for patients with locoregional carcinoma of the esophagus or EGJ who underwent preoperative chemoradiation followed by esophagectomy.[39]

Several tumor regression grading (TRG) systems have been developed to assess the pathologic response to preoperative neoadjuvant therapy. Mandard et al.[40] proposed a 5-tiered grading system based on the percentage of residual cancer cells and the extent of fibrosis. Tumor regression (TRG 1–3 vs. TRG 4–5) remained a significant predictor of disease-free survival after preoperative chemoradiation and surgery. Chirieac et al.[39] used a 4-tiered classification system based on the extent of residual cancer (0%, 1%–10%, 11%–50%, and > 50% [gross residual carcinoma]). Overall survival was significantly better for patients with no residual carcinoma (133 months) than it was for patients with more than 50% residual carcinoma (10.5 months). However, overall survival was not significantly different between patients with 1% to 10% and those with 11% to 50% residual carcinoma. Based on these results, Wu et al.[41] developed a 3-tiered classification system: P0 (0% residual carcinoma), P1 (1%–50% residual carcinoma), and P2 (> 50% residual carcinoma). Although grading sys-

tems for tumor response in esophageal cancer have not been uniformly adopted, the 3-tiered system generally has been reported to have excellent interobserver agreement among pathologists on grading the extent of residual carcinoma in patients with esophageal and EGJ cancers (see page 843).

Assessment of HER2-neu overexpression

Human epidermal growth factor receptor 2 gene (HER2, also known as *HER2*-neu) is a member of the human epidermal growth factor receptor (EGFR) family and is implicated in the development of various solid tumour types. *HER2*-neu amplification and overexpression are more frequent in esophageal adenocarcinomas (15%–30%) than SCC of the esophagus (5%–13%).[42–44] *HER2*-neu overexpression in gastroesophageal cancers varies widely (2%–45%).[45] *HER2*-neu positivity has been reported to be higher in EGJ cancers than in gastric cancers.[46,47] In the Trastuzumab for Gastric Cancer (ToGA) trial, which evaluated the addition of trastuzumab to chemotherapy in HER2-neu–positive advanced gastric cancer, HER2-neu positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[48] The prognostic significance of *HER2-neu* expression in patients with esophageal cancer is not clear. *HER2-neu* overexpression has been shown to correlate with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[45] *HER2-neu* overexpression seems to be associated with poorer survival, especially in patients with SCC of the esophagus.[42]

For patients with unresectable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or EGJ, assessment for tumor HER2-neu overexpression should be performed using immunohistochemistry and/or fluorescence in situ hybridization (FISH), following the 4-tier *HER2-neu* scoring system used in the ToGA trial (see page 844).[49,50] In cases showing weak to moderate complete, basolateral, or lateral membranous reactivity in more than 10% of cancer cells (immunohistochemistry score = 2), the *HER2*-neu overexpression is considered equivocal and should be confirmed with immunohistochemistry and FISH. Specimens with strong complete, basolateral, or lateral membranous reactivity in 10% or more of cancer cells (immunohistochemistry score = 3) in resection specimens, or in a cluster of 5 or more tumor cells in biopsy specimens, are considered positive for *HER2-neu* overexpression.

Surgery

Surgery is a major component of treatment for resectable disease. One of the major developments in the surgical therapy of esophageal cancer has been the marked reduction in surgical morbidity and mortality as a result of improvements in staging techniques, patient selection, support systems, and surgical experience. Recent randomized trials have showed that preoperative chemoradiation (CALGB 9781) and perioperative chemotherapy (MAGIC trial, predominantly a gastric cancer trial, including a small group of patients with lower esophageal and EGJ cancers) significantly improved survival in patients with resectable esophageal and gastroesophageal cancer.[51,52] With the incidence of esophageal cancer, particularly adenocarcinoma of the distal esophagus increasing dramatically, the hope is that surveillance programs will continue to detect earlier-stage disease, thus increasing the number of patients who can benefit from resection.

Currently, staging studies such as endoscopic ultrasound (EUS) and integrated PET/CT scans are used to select patients for surgery, exclude metastatic disease, and identify and quantify lymph node involvement. For patients with locally advanced disease, lymph node involvement has been shown to be a strong independent predictor of poor survival with surgery alone. These patients are therefore considered for induction therapy followed by surgery. In the future, molecular biologic techniques may result in improved prognostic stratification, patient selection for surgical therapy, and overall survival.[53–55]

Surgical Approaches

Several strategies and approaches are acceptable for esophagogastrectomy in patients with resectable esophageal or EGJ cancers.[56] The type of esophageal resection is dictated by the size, stage, and location of the primary tumor, and the surgeon's experience and the patient's preference. The optimal location of the anastomosis has been debated. Potential advantages of a cervical anastomosis include more extensive resection of the esophagus, possibility of avoiding thoracotomy, less-severe symptoms of reflux, and less-severe complications related to anastomotic leak. Advantages of a thoracic anastomosis may include lower incidence of anastomotic leak, lower stricture rate, and lower rate of left recurrent nerve injury. In a prospective randomized trial, cervical and thoracic

anastomoses after esophageal resection were equally safe when performed in a standardized way.[57] Gastric conduit is preferred for esophageal reconstruction and is preferred by most esophageal surgeons.[58] Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[59]

Ivor Lewis esophagogastrectomy (right thoracotomy and laparotomy) and the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis) are the 2 standard options to achieve transthoracic esophagogastrectomy. Ivor Lewis esophagogastrectomy, the most frequently used procedure for transthoracic esophagogastrectomy, uses laparotomy and right thoracotomy, with upper thoracic esophagogastric anastomosis (at or above the azygos vein).[60] The stomach is mobilized for use as the conduit, with dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries. This approach may be used for lesions at any thoracic location, but proximal esophageal margin will be inadequate for tumors in the middle esophagus.

Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[61] The stomach is mobilized for use as the conduit as in the Ivor Lewis esophagogastrectomy. This procedure is completed through the abdominal incision, and the gastric conduit is drawn through the posterior mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be hazardous. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy.[62] In the largest population-based study that assessed outcomes after transthoracic and transhiatal esophagectomy for esophageal cancer, transhiatal esophagectomy offered an early survival advantage, but long-term survival was not different between the surgical approaches.[63]

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision through the eighth intercostal space.[64] The stomach is mobilized for use as the conduit as described previously, and esophagectomy is accomplished through the left thoracotomy. Esophagogastric anastomosis is performed in the left chest, usually just superior to the inferior pulmonary vein, although it may be performed higher if the conduit is tunneled under the aortic arch. This approach may be used for lesions in the distal esophagus.[64]

Minimally invasive esophagectomy (MIE) strategies include numerous techniques, including minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy and limited thoracotomy or thoracoscopy) and minimally invasive McKeown esophagogastrectomy (thoracoscopy, limited laparotomy or laparoscopy, and cervical incision). MIE strategies may be associated with decreased morbidity and shorter recovery times. In a study of MIE (mainly using thoracoscopic mobilization) in 222 patients, the mortality rate was only 1.4% and hospital stay was only 7 days, which is less than most open procedures; only 16 patients (7.2%) required conversion to an open procedure.[65] However, importantly, 62% of their patients had early-stage disease. A recent report involving 56 patients also showed that MIE was comparable to open esophagectomy, but the use of neoadjuvant treatment slightly increased the surgical mortality from 1.5% to 1.8%.[66] No randomized trials have assessed whether MIE improves outcomes compared with open procedures.

Even among minimally invasive thoracic surgeons, open esophagectomy may still be preferred in certain settings, including in patients with previous abdominal surgery, for large and bulky tumors, when concerns exist that the gastric conduit may not be useable, and when there is difficulty with lymph node dissection. In the absence of prospective trials with longer follow-up, MIE remains investigational and is an evolving treatment option for patients with esophageal cancer.[67,68] Open surgery should remain the standard for many patients. MIE may be useful for older patients.[69]

Principles of Surgery

Patients with locally advanced disease should have access to medical and radiation oncology consults. Patients with Tis or T1a tumors should be given the option of EMR. Esophageal resection, EMR, and other ablative techniques should be performed in high-volume esophageal cancer centers by experienced surgeons and endoscopists.[70] Patients with tumors in the submucosa (T1b) or deeper may be treated with esophagectomy. Patients with T1

through T3 tumors (stage I or II disease) are considered to be potentially resectable, even in the presence of regional nodal metastases, although patients with bulky, multistation nodal involvement have poor overall survival. Selected patients with stage III disease also may be resectable. T4 tumors with involvement of pericardium, pleura, or diaphragm may be resectable. EGJ tumors with supraclavicular lymph node involvement; stage IV tumors with distant metastases, including nonregional lymph node involvement; and T4 tumors with involvement of heart, great vessels, trachea, or adjacent organs, including liver, pancreas, lung, and spleen, are considered unresectable.

Surgical resection for esophageal cancer is usually performed with a curative intent, but it may be included as a component of palliative care. Selecting patients for surgery involves assessing whether they are medically fit (medically able to tolerate general anesthesia and major abdominal and/or thoracic surgery). Most patients with early-stage cancer can tolerate resection. Palliative resections should be avoided in patients with clearly unresectable or advanced cancer with comorbidities, including severe cardiac and pulmonary disease. These patients may benefit from noninvasive palliative interventions.

All patients should be assessed for physiologic ability to undergo esophageal resection.[71] Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation. Pretreatment nutritional support should be considered for patients with significant dysphagia and weight loss to support them during induction chemoradiation. Enteral nutrition is the best option, and a jejunostomy feeding tube is preferred over a gastrostomy feeding tube or percutaneous endoscopic gastrostomy tube.

Esophageal resection should be considered for all physiologically fit patients with localized resectable thoracic esophageal cancer in the thorax (> 5 cm from cricopharyngeus) and intra-abdominal esophagus or EGJ cancer. Cervical or cervicothoracic esophageal carcinomas less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Salvage esophagectomy can be considered for patients who develop localized, resectable esophageal recurrence after definitive chemoradiation if no distant recurrence is present.[72]

Clinical staging using EUS (with fine needle aspiration [FNA], if indicated), chest and abdomen CT scan, and PET scan (integrated PET/CT preferred over PET alone) should be performed before surgery to assess resectability.[73] Evaluation of patients for resectability using laparoscopy, including intraperitoneal lavage for cytology, should be considered, especially for patients with large tumors involving the EGJ.

Lymph node dissections can be performed using the standard or extended (en bloc) technique.[74] In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the SEER database, overall and disease-free survivals were significantly longer in patients who had 11 or more lymph nodes examined.[75] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[76,77] A recent report from the WECC database, which analyzed 4627 patients who had esophagectomy alone, also suggested that a greater extent of lymphadenectomy was associated with increased survival for all patients with pN0M0 moderately and poorly differentiated cancers and all node-positive (pN+) cancers.[77] In patients undergoing esophagectomy without preoperative chemoradiation, the NCCN Guidelines recommend that at least 15 lymph nodes should be removed for adequate nodal staging. The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.

Endoscopic Therapies

EMR and endoscopic ablation procedures (cryoablation, radiofrequency ablation [RFA], and photodynamic therapy [PDT]) are used as alternatives to surgical resection in the treatment of patients with HGD and Barrett's esophagus.

EMR represents a major advance in minimally invasive approaches to treatment of the gastrointestinal tract. EMR is used widely for treating superficial early SCC of the esophagus in Japan and is gaining acceptance in the Western countries for the treatment of Barrett's esophagus and superficial adenocarcinomas.[78–81] Although EMR of visible lesions suspicious for malignancy is effective, it is also associated with a high rate of recurrence. Complete Barrett's eradication EMR has been shown to be a highly effective long-term treatment for patients with Barrett's esophagus and HGD.[82–86] Diagnostic EMR has been

reported to accurately determine the depth of tumor invasion, and therefore influence surgical planning before surgical resection.[87]

PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett's esophagus and HGD.[88,89] However, more recently, the use of PDT as an endoscopic therapy for esophageal cancers is losing popularity because of long-term consequences. Balloon-based RFA induces complete remissions in most patients with Barrett's esophagus with or without HGD.[90] Endoscopic cryoablation has also been reported to be a safe and well-tolerated therapy for patients with Barrett's esophagus with HGD and early-stage esophageal cancers.[91,92]

Although no randomized studies have compared EMR and endoscopic ablation procedures with other surgical techniques for gastrointestinal cancers, retrospective studies show that EMR and other endoscopic ablation procedures are effective therapeutic options for selected patients with Barrett's esophagus and superficial esophageal cancer.[93] These procedures are best performed in centers with experienced physicians.

Principles of Endoscopy

Endoscopy has become an important tool in the diagnosis, staging, treatment, and surveillance of patients with esophageal cancer. Most endoscopy procedures are performed with conscious sedation or monitored anesthesia provided by the endoscopist, a nurse, a nurse anesthetist, or an anesthesiologist. Some patients who are at risk for aspiration during endoscopy may require general anesthesia.

Diagnosis: Diagnostic endoscopies are performed to determine the presence and location of esophageal cancer and to biopsy any suspicious lesions. Multiple biopsies (6–8) using standard-size endoscopy forceps should be performed to provide sufficient material for histologic interpretation. Larger forceps are recommended during surveillance endoscopy of Barrett's esophagus for the detection of dysplasia.[94] Cytologic brushings or washings are rarely adequate in the initial diagnosis but can be useful in confirming persistent disease after treatment.

The location of the tumor relative to the teeth and EGJ, degree of obstruction, tumor length, and extent of circumferential involvement of the tumor should be carefully recorded to assist with treatment planning. Esophageal tumor length, as assessed with preoperative endoscopy, has been identified as an independent predictor of long-term survival in patients with adenocarcinoma of the esophagus.[95] The 5-year survival rate was significantly higher for patients with a tumor length of 2 cm or less (78% vs. 29% of those with a tumor length > 2 cm).

EMR of focal nodules can be performed in early-stage disease to accurately stage the tumor, as well as determine the degree of differentiation and extent of vascular and/or lymphatic invasion.[96,97] High-resolution endoscopy and narrow-band imaging may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[98,99]

Staging: EUS provides accurate initial staging of locoregional esophageal cancer. EUS performed before any treatment provides evidence of depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and occasionally signs of distant spread, such as lesions in surrounding organs (M).[100,101] Mediastinal and perigastric lymph nodes are readily identified with EUS, and identification of enlarged, hypoechoic (dark), homogeneous, well-circumscribed, rounded structures in these areas indicates the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but is also confirmed with FNA biopsy for cytology assessment.[102]

The combined use of EUS and FNA (EUS/FNA) has greater accuracy than EUS alone in evaluating lymph node metastasis, especially in celiac lymph nodes.[103,104] In a study conducted by the Mayo Clinic comparing the performance characteristics of CT, EUS, and EUS/FNA for preoperative nodal staging in 125 patients with esophageal cancer, EUS/FNA was more sensitive than CT (83% vs. 29%) and more accurate than CT (87% vs. 51%) or EUS (87% vs. 74%) for nodal staging.[105]

Obstructing tumors may increase the risk of perforation during staging EUS. The use of wire-guided EUS probes, or mini probes, may permit EUS staging with a lower risk. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate, but the risk of perforation increases after dilation. FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. Review of CT and PET scans before performing EUS is recommended to en-

able familiarity with the nodal distribution for a possible FNA biopsy.

Treatment: The goal of EMR and/or ablation is the complete removal of Barrett's esophagus and eradication of the malignancy. Indications for therapeutic EMR for esophageal cancer include HGD or carcinoma in situ (Tis) and well-differentiated to moderately differentiated lesions confined to the mucosa (T1a) without evidence of lymphovascular invasion or lymph node metastases. Esophagectomy for Tis or T1a tumors should be reserved for unsuccessful EMR. All focal nodules should be resected rather than ablated. Tis or HGD must be fully characterized, including evaluating the presence of nodularity and lateral spread and ruling out multifocal disease. In the setting of carcinoma, EUS staging is recommended before proceeding with EMR.[96] Ablative therapy of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed after EMR.

Long-term palliation of dysphagia can be achieved with endoscopic tumor ablation using Nd:YAG laser, PDT, and cryotherapy, or endoscopic- and radiographic-assisted insertion of expandable metal or plastic stents.[106,107] Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic- or radiographic-assisted placement of feeding gastrostomy or jejunostomy. The placement of a gastrostomy in the preoperative setting may compromise the gastric vasculature, thereby interfering with the creation of the gastric conduit in the reconstruction during esophagectomy, and should be avoided.

Posttreatment Surveillance: Assessment with endoscopy with biopsy and brushings should be performed 5 to 6 weeks after completion of preoperative therapy. EUS performed after chemotherapy or radiotherapy has a reduced ability to accurately determine the current stage of disease.[108] Similarly, biopsies performed after chemotherapy or radiotherapy may not accurately diagnose the presence of residual disease.[109]

Endoscopic surveillance after definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS performed in conjunction with endoscopy examinations has a high sensitivity for recurrent disease.[110] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

Endoscopic surveillance after ablative therapy or EMR of early esophageal cancer should continue after completion of treatment. Biopsies of the neosquamous mucosa are recommended even in the absence of mucosal abnormalities, because dysplasia may occasionally be present beneath the squamous mucosa. Endoscopic surveillance should also include a search for the presence of Barrett's esophagus and 4-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent HGD and low-grade dysplasia (LGD) using RFA or cryoablation should be considered. Ablation of nondysplastic Barrett's esophagus is not recommended.

Barrett's Esophagus

Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[23] Patients with Barrett's esophagus are at a greater risk of developing esophageal adenocarcinoma than the general population, and the risk of malignancy increases with the development of LGD and HGD.[21] The 5-year cumulative incidence of cancer was 4% for patients with LGD compared with 59% for those with HGD.[111] Age, male sex, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with the progression of Barrett's esophagus to adenocarcinoma of the esophagus.[24,25,112] Biomarkers such as aneuploidy and p53 loss of heterozygosity have been associated with increased risk of progression to HGD and/or adenocarcinoma of the esophagus.[112] These preliminary results warrant further prospective evaluation as predictors of risk for the development of HGD and esophageal adenocarcinoma in patients with Barrett's esophagus.

Endoscopy is performed on patients with severe symptoms of GERD, especially those with a family history of Barrett's esophagus or esophageal cancer. The location, length, and circumferential involvement should be characterized in accordance with the Prague classification[113] and mucosal nodules should be carefully documented.

Medical management of patients with Barrett's esophagus continues to evolve and is based on the symptomatic control of gastroesophageal reflux using histamine receptor antagonists or proton pump inhibitors. Surgical resection has been the preferred

treatment for patients with Barrett's esophagus and HGD. Many alternatives to surgical resection are being investigated. Alternative strategies for patients with Barrett's esophagus and HGD include EMR and endoscopic ablation with PDT, RFA, or cryoablation.[114] For patients with metaplasia or LGD, acid reflux is controlled with histamine receptor antagonists or proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole).

Endoscopic surveillance is performed to evaluate the progression from metaplasia to LGD, HGD, or adenocarcinoma. However, controversy exists when recommending a surveillance schedule for patients with Barrett's esophagus. Dysplasia of any grade discovered during surveillance should be confirmed by an expert pathologist. The updated guidelines from the American College of Gastroenterology recommend endoscopic surveillance every 3 years for patients without dysplasia on 2 consecutive endoscopies with biopsies within a year.[32] If the finding is LGD, endoscopy within 6 months is warranted to ensure that no HGD is present in the esophagus. Follow-up endoscopy is recommended annually until no dysplasia is detected on 2 consecutive endoscopies with biopsies. If HGD is discovered during surveillance, a subsequent endoscopy within 3 months is recommended to rule out adenocarcinoma of the esophagus. Follow-up endoscopy every 3 months is recommended thereafter.[32] For patients who are at high risk for cancer or who refuse EMR, continued surveillance every 3 months is an option if definitive therapy would be offered for those who develop adenocarcinoma.

Radiation Therapy

Several historical series have reported results of using external beam radiotherapy alone. Most of these series included patients with unfavorable features, such as those with clinical T4 cancer and those who were not expected to withstand surgery. Overall, the 5-year survival rate for patients treated with conventional doses of radiotherapy alone is 0% to 10%.[115–117] Shi et al.[118] reported a 33% 5-year survival rate with the use of late-course accelerated fractionation to a total dose of 68.4 Gy. However, in the Radiation Therapy Oncology Group (RTOG) 85-01 trial in which patients in the radiotherapy alone arm received 64 Gy at 2 Gy/d with conventional techniques, all patients died of cancer by 3 years.[119,120] Therefore, the panel recommends that radiotherapy alone generally be reserved for palliation or for patients who are medically unable to undergo chemotherapy.

Alternative radiation approaches, such as hypoxic cell sensitizers and hyperfractionation, have not resulted in a clear survival advantage. Experience with intraoperative radiation as an alternative to external beam radiation is limited.[121–125] Intensity-modulated radiation therapy (IMRT) is currently being investigated. Retrospective planning studies comparing three-dimensional (3D) conformal versus IMRT treatment plans for esophagus cancer have generally shown superior dose conformity and homogeneity with IMRT and reduction of radiation dose to the lungs and heart.

In the adjuvant setting, randomized trials do not show a survival advantage for preoperative or postoperative radiotherapy alone.[126–128] A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative radiation.[129]

Principles of Radiation Therapy

Radiotherapy (definitive, preoperative, postoperative, or palliative) can be an integral part of treatment for esophageal cancer. The panel recommends a dose range of 45 to 50.4 Gy delivered in fractions of 1.8 to 2 Gy/d. The panel recommends a multidisciplinary team, which should include medical, radiation, and surgical oncologists; radiologists; gastroenterologists; and pathologists. The panel encourages the use of CT simulation and 3D treatment planning. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid target localization. Use of immobilization device is strongly recommended for reproducibility.

The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified with imaging studies such as CT scan, barium swallow, EUS, and PET/CT scans. The clinical tumor volume (CTV) should include the areas at risk for microscopic disease. The planning target volume (PTV) should include the tumor plus a cephalad and caudal margin of 5 cm, and a radial margin of 1.5 to 2 cm. Every effort should be made to reduce unnecessary radiation doses to vital organs, such as liver, kidneys, spinal cord, heart (especially the left ventricle), and lungs. Lung dose volume histogram (DVH) parameters should be considered as

predictors of pulmonary complications in patients with esophageal cancer. Optimal criteria for DVH parameters are being actively developed in NCCN Member Institutions.

Custom blocking is necessary to limit the volume of normal organs receiving high radiotherapy doses (< 30 Gy to 60% of liver), kidneys (< 20 Gy to at least 60% of one kidney), spinal cord (< 45 Gy), heart (< 50 Gy to 30% of heart and effort should be made to keep the left ventricle doses to a minimum), and lungs (≥ 20 Gy to 20% and ≥ 10 Gy to 40% to reduce incidence of postoperative pulmonary complications). These guidelines may be exceeded as needed to achieve other important planning goals, and as further information becomes available. IMRT may be appropriate in selected cases to reduce the dose to normal structures, such as heart and lungs. In designing IMRT plans for structures such as the lungs, attention should be given to the volume receiving low to moderate doses, and the volume receiving high doses.

Close patient monitoring and aggressive supportive care are essential during radiation treatment. Management of acute toxicities is necessary to avoid treatment interruptions or dose reductions. Antiemetics should be given on a prophylactic basis when appropriate. Antacid and antidiarrheal medications may be prescribed when needed. If the caloric intake is inadequate, oral and/or enteral nutrition should be considered. Feeding jejunostomies or nasogastric feeding tubes may be placed if clinically indicated. Adequate enteral and/or intravenous hydration is necessary throughout chemoradiation and early recovery.

Brachytherapy

Brachytherapy alone is a palliative modality and results in a local control rate of 25% to 35% and a median survival of approximately 5 months. In the randomized trial from Sur et al.,[130] no significant difference was seen in local control or survival with high-dose brachytherapy compared with external beam. In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 combined modality regimen (5-fluorouracil and cisplatin with 50 Gy of external beam radiotherapy) followed by an intraluminal boost.[131] Local failure was 27%, and acute toxicity included 58% of patients with grade 3 toxicity, 26% with grade 4, and 8% with grade 5. The cumulative incidence of fistula was 18% per year, and the crude incidence was 14%. Therefore, the additional benefit of adding intraluminal brachytherapy to radiation or combined modality therapy, although reasonable, remains unclear.

Combined Modality Treatments: Concomitant Chemotherapy and Radiation Therapy

Multiple modalities have been used for the treatment of esophageal cancer because of the overall poor survival rates of patients who have been treated with resection alone.[132] Concomitant chemoradiation therapy versus radiotherapy, each without resection, was studied in the only randomized trial (RTOG 85-01) designed to deliver adequate doses of systemic chemotherapy with concurrent radiotherapy.[133]

Definitive Chemoradiation Therapy

In the RTOG 85-01 trial, patients with SCC or adenocarcinoma received 4 cycles of 5-fluorouracil and cisplatin.[120,133] Radiotherapy (50 Gy at 2 Gy/d) was given concurrently with day 1 of chemotherapy. The control arm was radiotherapy alone, albeit a higher dose (64 Gy) than in the combined modality therapy arm. Patients who were randomly assigned to receive combined modality therapy showed a significant improvement in both median survival (14 vs. 9 months) and 5-year overall survival (27% vs. none) with projected 8- and 10-year survival rates of 22% and 20%, respectively. The incidence of local failure as the first site of failure (defined as local persistence plus recurrence) was also lower in the combined modality arm (47% vs. 65%).

The INT 0123 trial was the follow-up trial to RTOG 85-01, comparing 2 different radiotherapy doses used with the same chemotherapy regimen (5-fluorouracil and cisplatin).[134] In this trial, 218 patients with either SCC (85%) or adenocarcinoma (15%) were randomly assigned to a higher dose (64.8 Gy) of radiotherapy or the standard dose of 50.4 Gy. No significant difference was observed in median survival (13.0 vs. 18.1 months), 2-year survival (31% vs. 40%), and locoregional failure or locoregional persistence of cancer (56% vs. 52%) between the high-dose and standard-dose radiotherapy arms.

After the results of these studies, definitive chemoradiation therapy with 5-fluorouracil and cisplatin using the radiotherapy dose of 50.4 Gy was established as the standard of care for patients with esophageal cancer.

Recent reports have also confirmed the efficacy of definitive chemoradiation with cisplatin- or fluoropyrimidine-based chemotherapy.[135–139] Definitive chemoradiation therapy with docetaxel and cisplatin in SCC was associated with high overall response rates (98%; 71% complete response) in patients with SCC; during the median follow-up time of 18 months, the median overall survival was 23 months.[135] The rates of locoregional progression-free survival, progression-free survival, and overall survival in 3 years were 60%, 29%, and 37%, respectively. Definitive chemoradiation with carboplatin and paclitaxel was also well-tolerated, resulting in superior overall and disease-specific survivals compared with cisplatin and irinotecan in patients with locally advanced esophageal cancer.[136] In a retrospective study, definitive chemoradiation was also beneficial for patients with adenocarcinoma of the esophagus, with a median survival of 21 months; 2-, 3-, and 5-year survival rates were 44%, 33%, and 19.5%, respectively.[137] In a recent randomized phase II trial, patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to chemoradiation therapy with either FOLFOX 4 (5-fluorouracil, leucovorin, and oxaliplatin) or 5-fluorouracil and cisplatin.[138] Most patients had SCC. The endoscopic complete response rate was 45% for the FOLFOX arm and 29% for the 5-fluorouracil and cisplatin arm. Median times to progression were 15 and 9 months, respectively. Median overall survival (23 vs. 15 months) was better with FOLFOX 4. This study is continuing as a phase III trial. The results of another phase II study also showed that concurrent chemoradiation with paclitaxel and carboplatin as definitive treatment resulted in durable locoregional control and palliation in approximately half of the patients with unresectable esophageal cancer.[139] Median overall and disease-free survivals were 17 and 9 months, respectively.

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational.[140] The results of 2 meta-analyses showed that preoperative chemoradiation therapy plus surgery significantly reduced 3-year mortality and locoregional recurrence, and preoperative chemoradiation therapy also downstaged the tumor when compared with surgery alone.[141,142] In another retrospective analysis of 363 patients with adenocarcinoma of the lower esophagus, the overall survival after preoperative chemoradiation was significantly shorter for patients with Barrett's esophagus compared with those without Barrett's esophagus (32 vs. 51 months, respectively).[143] Another recent meta-analysis (1209 patients; 10 randomized comparisons of preoperative chemoradiation vs. surgery alone), showed a significant survival benefit for preoperative chemoradiation in patients with resectable adenocarcinoma of the esophagus.[144] Recently, Swisher et al.[145] also reported that preoperative chemoradiation was associated with increased pathologic complete response (28% vs. 4%) and overall survival (3 years, 48% vs. 29%) compared with preoperative chemotherapy in patients with locally advanced esophageal cancer.

In a phase III study, Stahl et al.[146] compared preoperative chemotherapy (cisplatin, fluorouracil, and leucovorin) with chemoradiation therapy using the same regimen in 119 patients with locally advanced adenocarcinoma of the EGJ. Patients with locally advanced adenocarcinoma of the lower esophagus or gastroesophageal junction were randomized between 2 treatment groups: chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiotherapy followed by surgery (arm B). Patients in arm B had a significantly higher probability of showing pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection. Preoperative chemoradiation therapy improved the 3-year survival rate from 27.7% to 47.4%. Although the study was closed prematurely because of low accrual and statistical significance was not achieved, a trend was seen toward a survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the EGJ.

Preoperative chemoradiation therapy using 2-drug combination regimens, including paclitaxel, docetaxel, or irinotecan with oxaliplatin or cisplatin, 5-fluorouracil, or capecitabine has also been shown to be promising for localized esophageal cancer or EGJ adenocarcinoma in nonrandomized phase I and II studies.[147–163] In a recent phase I/II study, preoperative chemoradiation with a three drug regimen comprising of docetaxel, oxaliplatin, and capecitabine was safe and effective in patients with locoregional disease.[164] At a median follow-up of 116 weeks, median disease-

free and overall survivals were 16 and 24 months, respectively. The 2-year disease-free and overall survival rates were 45% and 52%, respectively.

However, randomized trials comparing preoperative chemoradiation therapy with surgery alone in patients with clinically resectable cancer have shown conflicting results.[165–173] Results from a recent multicenter phase III randomized trial (CROSS study) showed that preoperative chemoradiation therapy with carboplatin and paclitaxel improved overall survival compared with surgery alone in patients with resectable (T2–3, N0–1, M0) esophageal or EGJ cancers.[174] The reported rate of R0 resection was higher in the chemoradiation arm than in the surgery-alone arm (92% and 65%, respectively). The overall survival was significantly better for patients treated with chemoradiation. Median survival was 49 months in the chemoradiation arm compared with 26 months in the surgery alone arm. The 1-, 2-, and 3-year survival rates were 82%, 67%, and 59%, respectively, in the chemoradiation arm and 70%, 52%, and 48%, respectively, in the surgery alone arm. In contrast to the results of the CROSS study, the results of an interim analysis of another phase III randomized controlled study (FFCD 9901) showed that preoperative chemoradiation therapy with cisplatin and fluorouracil did not improve overall survival but enhanced the postoperative mortality rate for patients with localized stage I or II esophageal cancer compared with surgery alone.[175] Full publications of these data are awaited.

The CALGB 9781 trial was a prospective randomized Intergroup trial comparing trimodality therapy with surgery alone for the treatment of stage I through III esophageal cancer.[52] The study fell short of its accrual goals, with only 56 patients enrolled. Those patients were randomized to undergo either surgery alone or concurrent chemoradiation therapy with cisplatin and 5-fluorouracil. Median follow-up was 6 years. An intent-to-treat analysis showed a median survival of 4.5 versus 8 years, favoring trimodality therapy. Patients receiving trimodality therapy also had a significantly better 5-year survival rate (39% vs. 16%). Although the accrual rate was low, the observed difference in survival was significant, and this study showed that trimodality therapy might be an appropriate standard of care for patients with localized esophageal cancer.

The effect of adding surgery to chemoradiation therapy in patients with locally advanced SCC of the esophagus has been evaluated in randomized trials.[176,177] Stahl et al.[176] randomized 172 patients to either induction chemotherapy followed by chemoradiation therapy and surgery or induction chemotherapy followed by chemoradiation therapy. Two-year progression-free survival rates were better in the surgery group than in the chemoradiation therapy group (64.3% vs. 40.7%). However, no difference was seen in overall survival. The surgery group had significantly higher treatment-related mortality than the chemoradiation therapy group (12.8% vs. 3.5%, respectively). Long-term results with a median follow-up of 10 years also showed no clear difference in survival between the groups.[178] The Stahl trial was prematurely terminated because of lack of accrual. Bedenne et al.[177] (FFCD 9102 trial) also showed that adding surgery to chemoradiation provided no benefit compared with treatment with additional chemoradiation, especially in patients with locally advanced SCC of the esophagus who experience response to initial chemoradiation therapy. However, this trial had a suboptimal design and low number of patients.

Postoperative Chemoradiation Therapy

In retrospective analyses, the addition of postoperative chemoradiation has been associated with survival benefit in patients with locoregional esophageal cancer.[179,180] In a phase II nonrandomized trial evaluating postoperative concurrent chemoradiation with cisplatin and 5-fluorouracil in patients with poor-prognosis esophageal and EGJ cancers, the projected rates of 4-year overall survival, freedom from recurrence, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively, for patients with node-positive (T3 or T4) tumors, which are better than those of the historical outcomes with surgery alone.[181] However, the efficacy of postoperative chemoradiation has not been compared with surgery alone in a randomized trial involving patients with esophageal cancer.

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[182] This study randomly assigned 556 patients with resected adenocarcinoma of the stomach or EGJ (stage IB–IV, M0 according to 1988 AJCC staging criteria) to surgery plus postoperative chemoradiation (5-fluorouracil and leucovorin before and after

concurrent chemoradiation with 5-fluorouracil and leucovorin) or surgery alone. In this trial, 20% of patients had EGJ adenocarcinoma. Median overall survival in the surgery-only group was 27 months, compared with 36 months in the chemoradiation group. The hazard ratio for death was 1.35. The chemoradiation group had better 3-year survival rates (50% vs. 41%) and 3-year relapse-free survival rates (48% vs. 31%) than the surgery-only group. Postoperative chemoradiation therapy significantly improved overall and relapse-free survival for all patients at high risk for recurrence of adenocarcinoma of the stomach or EGJ. Resection of all detectable disease was required for participation in the trial. With more than 10 years of median follow-up, survival remains improved in patients with stage IB through IV (M0) gastric cancer treated with postoperative chemoradiation. No increases in late toxic effects were noted.[183] Surgery was not part of this protocol, and patients were eligible for the study only after recovery from surgery. One major criticism of this trial is that 54% of patients had a D0 resection (with suboptimal dissection of N1 lymph nodes), 36% of patients had a D1 resection, and only 10% of patients had a D2 dissection. D2 lymph node dissection was not recommended and patients were not excluded based on the extent of lymphadenectomy. Nevertheless, the results of this study have established postoperative chemoradiation as a reasonable option for patients EGJ adenocarcinoma.

Chemotherapy

Preoperative Chemotherapy

Chemotherapy alone has been investigated in the preoperative setting. The RTOG 8911 (Intergroup 0113) trial randomized patients with potentially resectable esophageal cancer of both histologic types to undergo either preoperative chemotherapy (5-fluorouracil plus cisplatin) or surgery alone. The preliminary results of this study did not show any survival benefit between the groups.[184] Long-term results of this study showed that 63% of patients treated with chemotherapy followed by surgery underwent complete resection (R0) compared with 59% of patients treated with surgery alone.[185] Although preoperative chemotherapy decreased the incidence of R1 resection (4% vs. 15% in the surgery-only group), no improvement was seen in overall survival between the groups.

The Medical Research Council (MRC) published their trial (MRC OEO2), which involved 802 patients with potentially resectable esophageal cancer.[186] In this trial, patients were randomly assigned to receive either 2 cycles of preoperative 5-fluorouracil (1000 mg/m^2 per day through continuous infusion for 4 days) and cisplatin (80 mg/m^2 on day 1) repeated every 21 days followed by surgery, or surgery alone. However, this trial had several clinical methodology problems. Nearly 10% of patients received off-protocol preoperative radiotherapy, and patients accrued in China were excluded. At a short median follow-up time of 2 years, the group treated with preoperative chemotherapy had a 3.5-month survival time advantage (16.8 vs. 13.3 months). Long-term follow-up confirmed that preoperative chemotherapy improves survival in patients with resectable esophageal cancer.[187] At a median follow-up of 6 years, disease-free and overall survivals were significantly longer for the preoperative chemotherapy group. The difference in survival favoring the preoperative chemotherapy group (23% vs. 17% for surgery) was consistent in patients with adenocarcinoma and SCC.[187] However, the 2 large histologic subtypes (SCC and adenocarcinoma) that constituted more than 97% of total patients analyzed showed no treatment effect, suggesting limited or no benefit from preoperative chemotherapy.

The phase III study conducted by the French Study group (FNLCC ACCORD07-FFCD 9703) compared preoperative chemotherapy (5-fluorouracil and cisplatin) with surgery alone in patients with adenocarcinoma of the stomach and lower esophagus.[188] This study randomized 224 patients to either surgery alone and preoperative chemotherapy (5-fluorouracil and cisplatin) followed by surgery. Postoperative 5-fluorouracil and cisplatin was recommended for patients experiencing response to preoperative 5-fluorouracil and cisplatin. At a median follow-up of 5.7 years, 3- and 5-year disease-free survival rates were 40% and 34%, respectively, for patients who received preoperative 5-fluorouracil and cisplatin compared with 25% and 21%, respectively, for those treated with surgery alone. The preoperative chemotherapy group also had better 3- and 5-year overall survival rates (48% and 38%, respectively) than the surgery-alone group (35% and 24%, respectively). This trial was prematurely terminated because of low accrual.

A meta-analysis based on individual patient data showed a small but significant overall and disease-free survival benefit favoring preoperative chemotherapy over surgery alone. A 4% increase in 5-year overall and disease-free survivals favored the preoperative chemotherapy group.[189]

Perioperative Chemotherapy

The British MRC performed the first well-powered phase III trial (MAGIC trial) for perioperative chemotherapy.[51] This trial evaluated the effect of perioperative chemotherapy with the ECF (epirubicin, cisplatin, and 5-fluorouracil) regimen given before and after surgery in resectable gastroesophageal cancer. Most (74%) of the patients had stomach cancer, whereas a small group of patients had adenocarcinoma of the lower esophagus (14%) and EGJ (11%). The perioperative chemotherapy group had a greater proportion of pathologic T1 and T2 tumors (51.7%) than the surgery group (36.8%). Five-year survival rates were 36% among those who underwent perioperative chemotherapy and 23% in the surgery group. Perioperative chemotherapy with the ECF regimen significantly improved progression-free and overall survival in patients with operable gastric and lower esophageal adenocarcinomas.

Chemotherapy for Advanced Disease

Combination chemotherapy for metastatic esophageal cancer continues to evolve and patients with advanced adenocarcinoma of the esophagus and EGJ can be treated using the regimens included in the gastric cancer guidelines for advanced gastric cancer. Compared with adenocarcinoma, SCC seems to be more sensitive to chemotherapy, chemoradiation, and radiotherapy, but the long-term outcome seems to be the same. In randomized clinical trials, no consistent benefit was seen for any specific chemotherapy regimen, and chemotherapy showed no survival benefit compared with best supportive care for patients with advanced esophageal cancer.[190] Adequately powered phase III studies are lacking. Palliative chemotherapy is not known to provide any survival advantage, but it may improve quality of life in patients with metastatic or unresectable esophageal cancer.[191]

Cisplatin is one of the most active agents, with a single-agent response rate consistently in the range of 20% or greater.[192] Newer agents such as irinotecan,[193–195] docetaxel,[196,197] paclitaxel,[198–200] and etoposide[201] have also shown activity as single agents in advanced esophageal cancer.

Cisplatin plus fluorouracil is the most investigated and most commonly used regimen for patients with esophageal cancer. Reported response rates to this combination vary between 20% and 50%. Cisplatin has also been evaluated in combination with taxanes, irinotecan, mitomycin, and gemcitabine. Cisplatin plus paclitaxel[202–204] or docetaxel,[205–207] with or without 5-fluorouracil, has shown activity in patients with locally advanced EGJ or metastatic esophageal cancer. In a multicenter phase II study, docetaxel plus cisplatin combination chemotherapy induced an objective response rate of 33% in patients with metastatic SCC; median and progression-free survival were 8 and 5 months, respectively.[207] In a randomized multinational phase III study (V325), 445 untreated patients were randomized to receive either docetaxel, cisplatin, and fluorouracil (DCF; every 3 weeks) or the combination of cisplatin and fluorouracil.[206] Most patients had advanced gastric cancer, and 19% to 25% of patients had EGJ cancer. Time to progression was significantly longer for DCF compared with cisplatin and fluorouracil (5.6 vs. 3.7 months). Various modifications of the DCF regimen with the intent to improve tolerability are being evaluated in clinical trials for patients with advanced esophagogastric cancer.[208–213] The combination of cisplatin with irinotecan is active, particularly against SCC of the esophagus.[214] In a prospective randomized study, the combination of mitomycin, cisplatin, and protracted intravenous infusion of fluorouracil (PVI 5-FU) was equally efficient to the combination of epirubicin, cisplatin, and PVI 5-FU (ECF) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.[215] Cisplatin in combination with gemcitabine has shown significant activity in phase II studies in patients with metastatic and advanced esophageal cancer.[216,217]

Capecitabine is an orally administered fluoropyrimidine that is converted to 5-fluorouracil preferentially in the tumor tissue. It has been evaluated in combination with other agents in advanced esophagogastric cancers.[218] The REAL-2 trial (30% of patients with esophageal cancer) was a randomized multicenter phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in

1002 patients with advanced esophagogastric cancer.[219] Patients with histologically confirmed adenocarcinoma, SCC, or undifferentiated cancer of the esophagus, EGJ, or stomach were randomized to receive 1 of the 4 epirubicin-based regimens (ECF, epirubicin, oxaliplatin, 5-fluorouracil [EOF]; epirubicin, cisplatin, and capecitabine [ECX]; and epirubicin, oxaliplatin, and capecitabine [EOX]). Median follow-up was 17.1 months. Results from this study suggest that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated advanced esophagogastric cancer. Compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy. The toxic effects from 5-fluorouracil and capecitabine were not different.

In phase II studies, non–cisplatin-containing regimens have shown activity in patients with advanced esophageal cancer. The combination of 5-fluorouracil, leucovorin, and irinotecan was found to be active in primary refractory or untreated locally advanced esophagogastric cancer and in patients with locally advanced unresectable and metastatic adenocarcinoma and SCC of the esophagus.[220–223] In patients with locally advanced or metastatic esophageal cancer, 33% of evaluable patients experienced partial response (n = 19), 38% had stable disease, and 8% had progressive disease.[221] Median survivals were 20 and 10 months, respectively, for patients with adenocarcinoma and SCC. Capecitabine in combination with irinotecan was active in patients with metastatic esophagogastric cancer that has progressed on platinum-based chemotherapy.[224] The results of a recent randomized study also showed that capecitabine and irinotecan was comparable in efficacy and activity to cisplatin and irinotecan.[225] Irinotecan in combination with docetaxel also has shown promising activity in patients (chemotherapy-naïve and pretreated) with unresectable or metastatic SCC or adenocarcinoma of the esophagus.[226] Among chemotherapy-naïve patients, the overall response rate was 31% (4% complete response and 27% partial response). Median time to progression was similar in both chemotherapy-naïve and pretreated patients (4 and 3.5 months, respectively) and the median survival was 9 and 11 months, respectively. Mitomycin and irinotecan combination was also effective in patients with advanced esophageal or EGJ adenocarcinoma.[227]

The combination of carboplatin and paclitaxel regimen was moderately active with a response rate of 43% in patients with advanced esophageal cancer.[228] However, 52% of patients had neutropenia (grade 3–4). Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin, and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend towards improved median progression-free survival (5.8 vs. 3.9 months) compared with fluorouracil, leucovorin, and cisplatin (FLP) in patients with metastatic gastroesophageal cancer.[229] However, no significant differences were seen in median overall survival (10.7 vs. 8.8 months, respectively) between the FLO and FLP. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs. 16.7%), time to treatment failure (5.4 vs. 2.3 months), and progression-free survival (6.0 vs. 3.1 months), and an improved overall survival (13.9 vs. 7.2 months) compared with FLP, respectively. The combination of gemcitabine, fluorouracil, and leucovorin has also shown activity in patients with locally advanced or metastatic SCC or adenocarcinoma.[230,231]

Targeted Therapies

The overexpression of EGFR, vascular endothelial growth factor receptor (VEGFR) and HER2-neu has been associated with poor prognosis in patients with gastric and esophageal cancers. In clinical trials, EGFR inhibitors, including cetuximab and erlotinib, trastuzumab (anti-HER2 antibody), and bevacizumab (anti-VEGFR antibody), have been evaluated in the treatment of patients with advanced esophageal cancer and EGJ adenocarcinoma.[232]

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-neu–positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[49] The results of this study confirmed that trastuzumab plus standard chemotherapy is superior to chemotherapy alone in patients with HER2-neu–positive advanced gastric and EGJ adenocarcinoma. In this study, 594 patients with HER2-neu–positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive

trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) or chemotherapy alone. Median follow-up was 19 months in the trastuzumab plus chemotherapy group and 17 months in the chemotherapy-alone group. A significant improvement was seen in the median overall survival with the addition of trastuzumab to chemotherapy compared with chemotherapy alone (14 vs. 11 months, respectively). Safety profiles were similar, with no unexpected adverse events in the trastuzumab group, and no difference was seen in symptomatic congestive heart failure between the arms. This establishes trastuzumab plus chemotherapy as a new standard of care for the treatment of patients with HER2-expressing advanced gastric and EGJ adenocarcinoma.

The safety and efficacy of cetuximab,[233–238] erlotinib[239–241] and bevacizumab[242,243] have been evaluated in multiple phase II studies. Ongoing trials are evaluating the efficacy and safety of the agents mentioned earlier in combination with chemotherapy for the treatment of patients with advanced esophageal and EGJ cancers.

Treatment Guidelines

The management of esophageal and EGJ cancers requires the expertise of several disciplines, which may include surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, 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 any discipline caring for patients with esophagogastric cancer. Optimally at each meeting, the panel encourages all relevant disciplines to participate. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient (see page 846).

Workup

Newly diagnosed patients should undergo a complete history, physical examination, and endoscopy with biopsy of the entire upper gastrointestinal tract. Histologic confirmation of cancer is required. For patients in whom the upper gastrointestinal tract cannot be visualized, a double-contrast barium study of the upper gastrointestinal tract is optional. A CBC, multichannel serum chemistry analysis, coagulation studies, and CT scan (with oral and intravenous contrast) of the chest and abdomen should also be performed. Pelvic CT should be obtained when clinically indicated. At this point, if metastatic cancer is not evident, EUS with FNA is recommended if indicated. *HER2-neu* testing is recommended if metastatic disease is documented or suspected (see page 844 for assessment of *HER2-neu* overexpression). If the cancer is located at or above the cardia, bronchoscopy (including biopsy of any abnormality and cytology of the washings) should be performed. In addition, if the cancer is located at the EGJ, laparoscopic staging of the peritoneal cavity is optional.[244] Suspicions for metastatic cancer should be confirmed with biopsy. The revised staging system for esophageal and EGJ cancers includes tumors within the first 5 cm of the stomach that extend into the EGJ or distal thoracic esophagus. The guidelines recommended assessment of Siewart category as part of initial workup.

Combined PET/CT imaging has many advantages over PET scan alone and significantly improves the diagnostic accuracy.[245] PET/CT scans are useful in the initial staging and evaluation of patients after chemoradiation before surgical resection,[246] and may be useful for detecting distant lymphatic and hematogenous metastases.[247] PET/CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer.[248] It was also shown to be an independent predictor of overall survival in patients with nonmetastatic esophageal cancer.[249] In addition, a recent study in patients with esophageal cancer reported that combined PET/CT scans are more accurate than EUS with FNA and CT for predicting nodal status and complete response after neoadjuvant therapy.[250] When used alone, PET/CT and CT suggest targets for biopsy; however, false-positive results are common. Combined PET/CT scans are emerging and seem to be useful for restaging patients and monitoring response to primary therapy. Additional studies are needed to assess the efficacy of combined PET/CT scan in esophageal cancer. PET evaluation is preferred if no evidence of metastatic disease is present (PET/CT is preferred over PET scan).

Additional Evaluation

In patients with apparent locoregional cancer, additional evaluations may be warranted to assess their medical condition and feasibility of resection,

especially for patients with celiac-positive disease. These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. Nasoduodenal or jejunostomy tube should be considered for preoperative nutritional support. Percutaneous endoscopic gastronomy is not recommended. Moreover, evaluation of the colon using barium radiograph or colonoscopy may be warranted if colon interposition is planned as part of the surgical procedure. A superior mesenteric artery angiogram should be considered only in selected cases when colon interposition is planned.

Initial workup enables patients to be classified into either those with locoregional cancer (stages I–III) or metastatic cancer (stage IV).

Patients with locoregional cancer are further classified into the following groups after additional evaluation:

- Medically fit with resectable disease
- Medically unfit for surgery; surgery not elected and patient medically able to tolerate chemoradiation; or unresectable disease (T4)
- Medically unfit for surgery and patient unable to tolerate chemoradiation

Primary Treatment for Medically Fit Patients

EMR or ablation is the primary treatment option for patients with Tis tumors, whereas those with T1a tumors should be treated with EMR and ablation or esophagectomy. Ablation may not be needed for squamous lesions that are completely excised. For patients with tumors that are T1b, any N, esophagectomy is the preferred treatment option for those with resectable noncervical cancer, whereas chemoradiation is the preferred modality for those with cervical cancer.

Primary treatment options for patients with locally advanced resectable disease (T2 or higher, any N tumors) include preoperative chemoradiation, definitive chemoradiation (preferred for cervical cancer), rarely preoperative chemotherapy (for adenocarcinoma of the distal esophagus or EGJ), or esophagectomy. Preoperative chemoradiation is preferred over preoperative chemotherapy for patients with adenocarcinoma of the distal esophagus or EGJ.[145,146,174] In randomized trials, definitive chemoradiation therapy has been shown to be the curative approach for patients with SCC of the esophagus, whereas its role is not established in patients with adenocarcinoma.[132] Although definitive chemoradiation is an option for patients with SCC, surgery is the preferred treatment for patients with adenocarcinoma. Fluoropyrimidine- or taxane-based regimens are recommended for preoperative and definitive chemoradiation (see page 850 for list of specific regimens). Note: The complete list of dosing schedules is not published in this issue of *JNCCN*. To view the complete list, visit the NCCN Web site at www.NCCN.org.

Response Assessment and Additional Treatment

The prognostic value of metabolic response defined by PET scan after neoadjuvant chemotherapy was confirmed in a prospective phase II (MUNICON-II) study in patients with advanced esophageal adenocarcinoma.[251,252] PET scan has also been shown to predict histopathologic complete response and outcome after definitive chemoradiation or preoperative chemoradiation in patients with locally advanced esophageal cancer.[253–258] However, other studies have shown conflicting results.[259–264] Swisher et al.[254] also showed that a postchemoradiation 18-fluorodeoxyglucose (FDG) uptake value of 4 or less was found to be the only preoperative factor to correlate with decreased survival. The 2-year survival rate was 60% for patients with a postchemoradiation FDG uptake of less than 4 and 34% for those with an FDG uptake of 4 or more. In a prospective multicenter study (SAKK 75/02), a decrease in the FDG uptake of less than 40% was prospectively hypothesized as a predictor of histopathologic nonresponse after chemoradiation therapy.[261] However, PET scans could not distinguish patients with microscopic residual disease and complete pathologic response[254,261] and its accuracy in detecting nonresponders was very low.[264] In patients undergoing preoperative or definitive chemoradiation therapy, CT scan with contrast or PET/CT scan can be considered before surgery or initiation of postoperative treatment. However, PET scans should not be used to select patients for surgery after preoperative chemoradiation.

Esophagectomy is the preferred treatment option for all patients after preoperative chemotherapy, whereas those who underwent preoperative or definitive chemoradiation should undergo restaging (PET/CT or PET, upper gastrointestinal endoscopy, or CT scan with contrast if PET/CT is not performed) after completion of primary treatment. After definitive chemoradiation, patients with no evidence of disease can be observed and those with

persistent local disease can be treated with salvage esophagectomy or palliative therapy. Esophagectomy is the preferred treatment option for patients with no evidence of disease and those with persistent local disease after preoperative chemoradiation. Alternatively, patients, particularly those with SCC, with no evidence of disease may be observed (category 2B) and those with persistent local disease can be given palliative therapy. Patients with unresectable or metastatic disease after definitive or preoperative chemoradiation should be considered for palliative therapy, depending on their performance status.

Postoperative Treatment

Postoperative treatment is based on the surgical margins, nodal status, and histology. Among patients who have not undergone preoperative therapy (T1b, any N, noncervical cancer and T2 or higher, any N) and have no residual disease at surgical margins (R0 resection), fluoropyrimidine-based chemoradiation is recommended for all with adenocarcinoma of the esophagus or EGJ, except those with node-negative adenocarcinoma (T1–T2, N0 tumors). Alternatively, patients with node-positive adenocarcinoma of the proximal or mid esophagus and node-negative adenocarcinoma (T3, N0 tumors) can undergo observation. No further treatment is necessary for those with SCC, irrespective of their nodal status, if they have no residual disease at the surgical margins. Patients with microscopic (R1 resection) or macroscopic residual disease with no distant disease (R2 resection) should be treated with fluoropyrimidine-based chemoradiation. Palliative therapy is an alternative option for patients with macroscopic residual disease.

Among patients who have undergone preoperative therapy (T2 or higher, any N), no further treatment is necessary for those with SCC (irrespective of their nodal status), node-negative adenocarcinoma (T2–3, N0 tumors), and node-positive adenocarcinoma of proximal or mid esophagus if they have no residual disease at the surgical margins (R0 resection). Based on the results of the Intergroup trial INT-0116, patients with adenocarcinoma of the EGJ and selected patients with adenocarcinoma of the esophagus may undergo postoperative chemoradiation if they have no evidence of metastases. The guidelines recommend fluoropyrimidine-based chemoradiation as an option for patients with node-negative adenocarcinoma (T3, N0 tumors), node-positive adenocarcinoma of proximal or mid esophagus, and adenocarcinoma of the distal esophagus and EGJ (category 1). Postoperative chemoradiation is recommended only if it was not received preoperatively. Postoperative chemotherapy is recommended for patients who were treated with preoperative chemotherapy (category 1). Based on the results of the MAGIC trial, perioperative chemotherapy with the ECF regimen or its modifications is recommended for patients with completely resected node-negative adenocarcinoma (T2–T3, N0) or node-positive adenocarcinoma of the distal esophagus or EGJ.[51]

Patients with microscopic (R1 resection) or macroscopic residual disease with no distant disease (R2 resection) should be treated with fluoropyrimidine-based chemoradiation if they have not received preoperative chemoradiation. Palliative therapy is an alternative option for patients with macroscopic residual disease.

Primary Treatment for Medically Unfit Patients

EMR or ablation is recommended for patients with Tis tumors, whereas those with T1a tumors should be treated with EMR and ablation. Fluoropyrimidine- or taxane-based concurrent chemoradiation is the preferred treatment option for all other patients with technically resectable cancer who are medically unfit for surgery, or those who choose not to undergo surgery and are medically able to tolerate chemotherapy. Alternatively, these patients can also be treated with chemotherapy, radiotherapy, or best supportive care. Palliative radiotherapy or best supportive care are the appropriate options for patients medically unfit for surgery and are unable to tolerate chemotherapy.

Unresectable or Nonmetastatic Disease

In patients with advanced unresectable esophageal cancer (T4), chemoradiation may be appropriate and occasionally can facilitate surgical resection in selected cases. Fluoropyrimidine- or taxane-based concurrent chemoradiation is the preferred treatment for patients with unresectable T4 tumors. Chemotherapy, radiotherapy, or best supportive care are also reasonable alternatives for this group of patients.

Follow-Up After Resection or Definitive Chemoradiation

All patients should be followed up systematically. For asymptomatic patients, follow-up should include a complete history and physical examination

every 3 to 6 months for 1 to 2 years, then every 6 to 12 months for 3 to 5 years, and annually thereafter. CBC, multichannel serum chemistry evaluation, upper gastrointestinal endoscopy with biopsy, and imaging studies should be obtained as clinically indicated. Patients with Tis or T1a tumors who undergo EMR should undergo endoscopic surveillance every 3 months for 1 year and then annually. In addition, some patients may require dilatation of an anastomotic or a chemoradiation-induced stricture. Nutritional counseling may be extremely valuable.[265]

Recurrent and Metastatic Esophageal Cancer

Treatment for recurrent disease can range from aggressive intervention with curative intent in patients with locoregional relapse to therapy intended strictly for palliation in patients for whom cure is not a possibility. Local or regional recurrence after esophagectomy can be treated with fluoropyrimidine- or taxane-based concurrent chemoradiation in patients who have not undergone prior chemoradiation. Other options include best supportive care, surgery, or chemotherapy. Selected patients with anastomotic recurrences can undergo reresection. When recurrence develops after chemoradiation therapy with no prior esophagectomy, clinicians should determine whether patients are medically fit for surgery and if the relapse is resectable. If both criteria are met, esophagectomy remains an option. When patients experience another relapse after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described for metastatic disease. Palliative therapy is also recommended for medically unfit patients and those who develop an unresectable recurrence.

Best supportive care is the appropriate treatment option for patients with metastatic cancer. Patients' performance status should determine whether chemotherapy is added to best supportive care. Several scales are available to measure performance status in patients with cancer, with the Karnofsky Performance Status scale (KPS) and the ECOG Performance Status Scale (ECOG PS) the most commonly used.[266,267] The KPS is an ordered scale with 11 levels (0–100), and the general functioning and survival of a patient is assessed based on their health status (activity, work, and self-care). Low Karnofsky scores are associated with poor survival and more serious illnesses (www.hospicepatients.org/karnofsky.html). ECOG PS is a 5-point scale (0–5) based on the level of symptom interference with normal activity. Patients with higher levels are considered to have poor performance status (www.ecog.org/general/perf_stat.html).

Patients with a KPS of 60 or less or an ECOG PS of 3 or more should probably be offered best supportive care. Patients with better performance status (KPS ≥ 60, or an ECOG PS ≤ 2) may be offered chemotherapy along with best supportive care. Further treatment after 2 sequential regimens depends on the performance status and availability of clinical trials.

Phase III trials for metastatic esophageal cancer have not been performed for many years. The regimens listed in the guidelines are derived from the gastric adenocarcinoma phase III trials that have included patients with lower esophageal and/or EGJ cancer. Some of the regimens listed in the guidelines are based on institutional preferences that have support only from phase II studies. Two-drug regimens or single agents are preferred. Three-drug regimens should be reserved for medically fit patients with good performance status and access to frequent toxicity evaluation. DCF modifications are preferred over DCF. The use of trastuzumab in combination with an anthracycline is not recommended. Leucovorin can be used with certain infusional 5-fluorouracil–based regimens. The following regimens are listed in the guidelines for metastatic or locally advanced esophageal or EGJ cancers (see page 851 for list of specific regimens).

First-Line Therapy:

- DCF or its modifications (category 1 for docetaxel, cisplatin, and fluorouracil; category 2B for docetaxel, carboplatin, and fluorouracil; category 2A for all other combinations)
- ECF or its modifications (category 1)
- Fluoropyrimidine- or taxane-based regimens, single-agent or combination therapy (category 1 for combination of fluoropyrimidine and cisplatin; category 2A for all other regimens)
- Trastuzumab with chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients who are HER2-neu–positive, as determined by a standardized method

Second-Line Therapy:

- Trastuzumab with chemotherapy (category 1 for combination with cisplatin and fluoropy-

rimidine; category 2B for combination with other chemotherapy agents) for patients who are HER2-neu–positive, if not used as first-line therapy
- Docetaxel or paclitaxel (category 2B)
- Irinotecan-based single-agent or combination therapy (category 2B)

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin for all doses in all patients, because lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[268–270] Finally, if none of these options are available, treatment without leucovorin would be reasonable. For patients who tolerate this approach without grade II or higher toxicity, a modest increase in fluorouracil dose (in the range of 10%) may be considered.

Best Supportive Care

The goal of best supportive care is to prevent and relieve suffering and improve quality of life for patients and their caregivers regardless of disease stage. In patients with unresectable or locally advanced cancer, palliative interventions provide symptomatic relief and may result in significant prolongation of life, improvement in nutritional status, the sensation of well-being, and overall quality of life.

Dysphagia: Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Assessing the severity of the disease and swallowing impairment is essential to initiate appropriate interventions for long-term palliation of dysphagia in patients with esophageal cancer. Available palliative methods for the management of dysphagia include endoscopic lumen restoration or enhancement, placement of permanent or temporary self-expanding metal stents (SEMS), radiotherapy, brachytherapy, chemotherapy, and surgery.

Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Single-dose brachytherapy was associated with fewer complications and better long-term relief of dysphagia compared with metal stents.[271] Temporary placement of SEMS with concurrent radiotherapy was found to be beneficial for increasing survival rates compared with permanent stent placement.[272] SEMS is the preferred treatment for patients with tracheoesophageal fistula and those who are not candidates for chemoradiation or who failed to experience adequate palliation with this therapy.[273] Membrane-covered stents have significantly better palliation than conventional bare metal stents because of a decreased rate of tumor ingrowth, which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[107] Treatment options for the management of dysphagia should be individualized. A multimodality interdisciplinary approach is strongly encouraged.

For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, external beam radiotherapy, chemotherapy, or surgery. Surgical or radiologic placement of jejunostomy or gastronomy tubes may be necessary to provide adequate hydration and nutrition, if endoscopic lumen restoration is not undertaken or is unsuccessful. Brachytherapy may be considered instead of radiotherapy if the lumen can be restored using appropriate applicators during the delivery of brachytherapy to decrease excessive dose on mucosal surfaces. Brachytherapy should only be performed by practitioners experienced in delivering esophageal brachytherapy. For patients with severe esophageal obstruction (those able to swallow liquids only), options include endoscopic lumen enhancement (wire-guided or balloon dilation), endoscopy- or fluoroscopy-guided placement of covered expandable metal stents, or another measure described earlier. Although data suggest a lower migration and reobstruction rate with the larger diameter, it may be associated with a higher risk of stent-related complications.[274]

Pain: Patients experiencing tumor-related pain should be assessed and treated according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Severe uncontrolled pain after stent placement should be treated with its immediate removal.

Bleeding: Bleeding in patients with esophageal cancer may be secondary to tumor-related aortoesophageal fistulization. Surgery or external beam radiotherapy and/or endoscopic therapy may be indicated in patients with brisk bleeding from the cancer. Bleeding that occurs primarily from the tumor surface may be controlled with endoscopic electrocoagulation techniques, such as bipolar electrocoagulation or argon plasma coagulation.

Nausea/Vomiting: Patients experiencing nausea and vomiting should be treated according to the NCCN Guidelines for Antiemesis (to view the most recent version of these guidelines, visit the NCCN Web site at www.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

Esophageal cancer is a major health hazard in many parts of the world. Several advances have been made in staging procedures and therapeutic approaches. Unfortunately, esophageal cancer is often diagnosed late; therefore, most therapeutic approaches are palliative. Multidisciplinary team management is essential for treating patients with esophageal cancer.

Adenocarcinoma and SCC are the 2 major types of esophageal cancer. SCC is most common in the endemic regions of the world, whereas adenocarcinoma is most common in nonendemic regions. Tobacco and alcohol abuse are major risk factors for SCC, whereas the use of tobacco is a moderate established risk factor for adenocarcinoma. Barrett's esophagus, obesity, and GERD seem to be the major risk factors for development of adenocarcinoma of the esophagus or EGJ.

EMR or ablation is the primary treatment option for medically fit patients with Tis tumors, whereas those with T1a tumors should be treated with EMR and ablation or esophagectomy. Esophagectomy is the preferred primary treatment option for medically fit patients with resectable noncervical cancer (T1b, any N), whereas chemoradiation is the preferred modality for those with cervical cancer. In medically fit patients with locally advanced resectable disease (T2 or higher, any N tumors), primary treatment options include preoperative chemoradiation (preferred for adenocarcinoma of the distal esophagus or EGJ), definitive chemoradiation (preferred for cervical cancer), rarely preoperative chemotherapy (for adenocarcinoma of the distal esophagus or EGJ), or esophagectomy.

Postoperative treatment is based on histology, surgical margins, and nodal status. Among patients with SCC (irrespective of their nodal status), node-negative adenocarcinoma (T2–3, N0 tumors), and node-positive adenocarcinoma of proximal or mid esophagus, no further treatment is necessary if they have no residual disease at the surgical margins (R0 resection). Fluoropyrimidine-based chemoradiation is recommended for patients with node-negative adenocarcinoma (T2–3, N0 tumors), node-positive adenocarcinoma of proximal or mid esophagus, and adenocarcinoma of the distal esophagus and EGJ. Postoperative chemotherapy is recommended (only if preoperative chemotherapy was given) for patients with completely resected node-negative adenocarcinoma (T2–T3, N0) and node-positive adenocarcinoma of the lower esophagus and EGJ. All patients with residual disease at surgical margins (R1 and R2 resections) may be treated with fluoropyrimidine-based chemoradiation.

Fluoropyrimidine- or taxane-based concurrent chemoradiation is recommended for unresectable disease, for patients with technically resectable disease who choose not to undergo surgery, and for those medically unfit for surgery and able to tolerate chemotherapy.

Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal and gastroesophageal junction cancers. Based on the results of the ToGA trial, the NCCN panel has included trastuzumab plus chemotherapy as a new treatment option for patients with HER2-neu–positive advanced EGJ adenocarcinoma. HER2-neu testing is recommended if metastatic disease is documented or suspected. The efficacy of VEGFR and EGFR inhibitors in combination with chemotherapy for patients with advanced EGJ cancers is being evaluated in ongoing randomized phase III trials.

Best supportive care is an integral part of treatment, especially in patients with locally advanced disease. Assessing disease severity and related symptoms is essential to initiate appropriate palliative interventions that will prevent and relieve suffering and improve quality of life for patients and their

caregivers. Metastatic disease in patients with good performance status can be treated with chemotherapy plus best supportive care, whereas best supportive care is recommended for those with poor performance status. Endoscopic palliation of esophageal cancer has improved substantially because of improving technology.

These guidelines emphasize that considerable advances have been made in the treatment of locoregional esophageal cancer. Novel therapeutic modalities, such as targeted therapies, vaccines, gene therapy, and antiangiogenic agents, are being studied in clinical trials for patients with esophageal cancer. The panel encourages patients with esophageal cancer to participate in well-designed clinical trials to enable further advances.

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Individual Disclosures of the NCCN Esophageal and Esophagogastric Junction Cancers Panel Members

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Jaffer A. Ajani, MD	Bayer HealthCare; ImClone Systems Incorporated; Ascenta Therapeutics; Genta, Incorporated; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	Bristol-Myers Squibb Company; and sanofi-aventis U.S.	None	None	8/5/09
James S. Barthel, MD	None	None	Merit Medical Endotek	None	3/29/11
David J. Bentrem, MD	None	None	None	None	9/21/10
Thomas A. D'Amico, MD	None	Covidien AG; and Scanlan	None	None	9/21/10
Prajnan Das, MD, MS, MPH	None	None	None	None	9/20/10
Crystal S. Denlinger, MD	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; Chugai Pharmaceuticals; Merrimack Pharmaceuticals; and Roche Laboratories, Inc.	Vicus Pharmaceuticals	None	None	4/1/11
Charles S. Fuchs, MD, MPH	Amgen Inc.; and ImClone Systems Incorporated	Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Genentech, Inc.; Genomic Health, Inc.; GlaxoSmithKline; ImClone Systems Incorporated; Merck & Co., Inc.; Alnylam Pharmaceuticals, Inc.; Mersana Therapeutics, Inc.; and Roche Laboratories, Inc.	None	None	5/2/11
Hans Gerdes, MD	None	None	None	None	10/6/09
Robert E. Glasgow, MD	None	None	None	None	2/24/10
James A. Hayman, MD, MBA	None	None	None	None	2/28/11
Wayne L. Hofstetter, MD	None	None	None	None	7/19/10
David H. Ilson, MD, PhD	None	None	None	None	9/3/10
Rajesh N. Keswani, MD	None	None	None	None	11/20/09
Lawrence R. Kleinberg, MD	None	None	None	None	12/7/09
W. Michael Korn, MD	None	Celgene Corporation; and Daiichi- Sankyo Co.	None	None	9/15/10
A. Craig Lockhart, MD, MHS	Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Eli Lilly/ImClone; Zenyaku; and sanofi-aventis U.S.	None	None	None	9/20/10
Mary F. Mulcahy, MD	None	None	None	None	12/21/09
Mark B. Orringer, MD	None	None	None	None	9/28/09
Raymond U. Osarogiagbon, MD	Bristol-Myers Squibb Company; Eli Lilly and Company; OSI Pharmaceuticals, Inc.; and sanofi-aventis U.S.	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	None	None	4/19/10
James A. Posey, MD	None	None	None	None	4/16/10
Aaron R. Sasson, MD	None	None	None	None	11/19/09
Walter J. Scott, MD	None	None	Johnson & Johnson	None	3/16/11
Stephen Shibata, MD	None	Genentech, Inc.; and sanofi-aventis U.S.	None	None	9/28/09
Vivian E. M. Strong, MD	None	None	None	None	10/2/09
Thomas K. Varghese, Jr., MD	None	None	None	None	7/9/10
Graham Warren, MD, PhD	None	None	None	None	11/29/10
Mary Kay Washington, MD, PhD	None	Genentech, Inc.	None	None	7/26/10
Christopher Willett, MD	None	None	None	None	11/17/09
Cameron D. Wright, MD	None	None	None	None	7/6/09

The NCCN guidelines staff have no conflicts to disclose.

