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Esophageal and Esophagogastric Junction Cancers, Version 1.2015

Clinical Practice Guidelines in Oncology

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Abstract

Esophageal cancer is the sixth most common cause of cancer deaths worldwide. Adenocarcinoma is more common in North America and Western European countries, originating mostly in the lower third of the esophagus, which often involves the esophagogastric junction (EGJ). Recent randomized trials have shown that the addition of preoperative chemoradiation or perioperative chemotherapy to surgery significantly improves survival in patients with resectable cancer. Targeted therapies with trastuzumab and ramucirumab have produced encouraging results in the treatment of advanced or metastatic EGJ adenocarcinomas. Multidisciplinary team management is essential for patients with esophageal and EGJ cancers. This portion of the NCCN Guidelines for Esophageal and EGJ Cancers discusses management of locally advanced adenocarcinoma of the esophagus and EGJ. (J Natl Compr Canc Netw 2015;13:194–227)

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Overview

Upper gastrointestinal tract cancers originating in the esophagus, esophagogastric junction (EGJ), and

Please Note

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Disclosures for the NCCN Esophageal and Esophagogastric Junction Cancers Panel

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

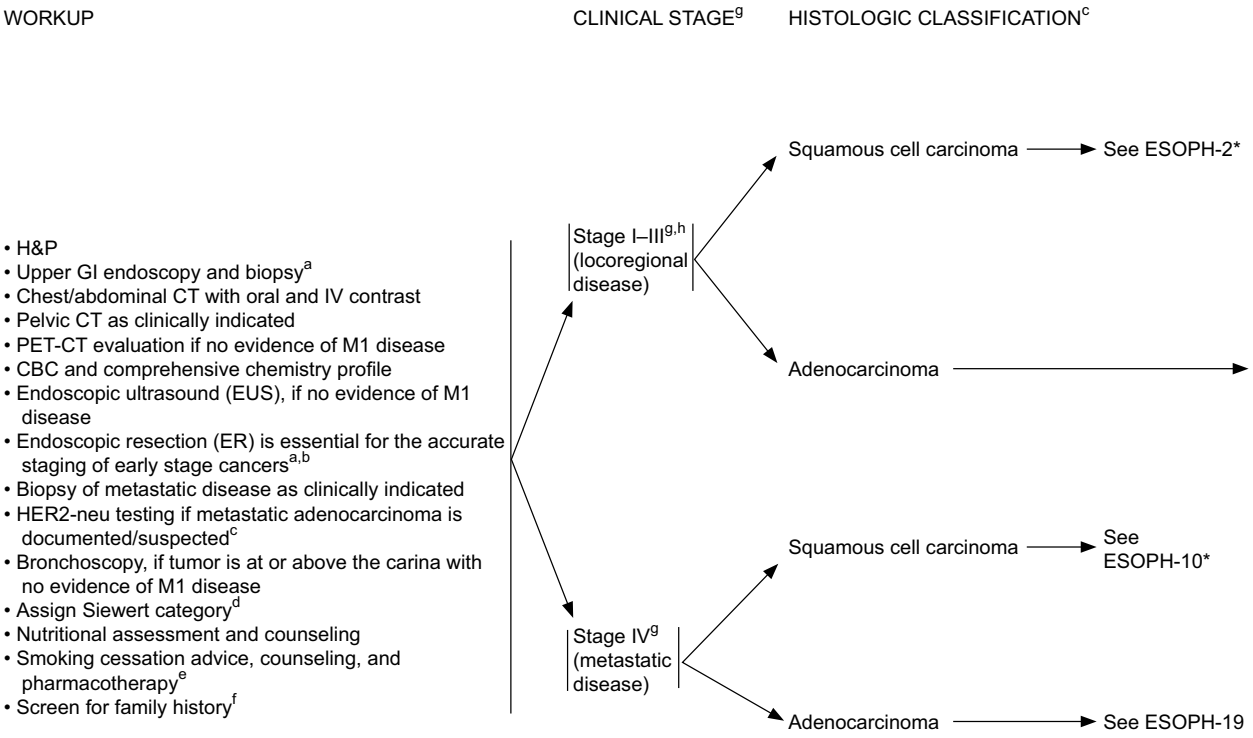
Individual disclosures for the NCCN Esophageal and Esophagogastric Junction Cancers Panel members can be found on page 227. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

stomach constitute a major health problem globally. Esophageal cancer is the sixth most common cause of cancer deaths worldwide, and is more common in men.[1] It is endemic in many parts of the world, particularly in developing nations, where it is the fourth most common cause of cancer death.[1] In 2014, an estimated 18,170 people were diagnosed with and 15,450 people died of esophageal cancer in the United States.[2] The incidence of esophageal cancer represents one of the widest variations, with a 60-fold difference between high- and low-incidence regions.[3] High-prevalence areas include Asia, southern and eastern Africa, and northern France.[4] In Western countries, the most common site of esophageal cancer is in the lower third of the esophagus, which often involves the EGJ.

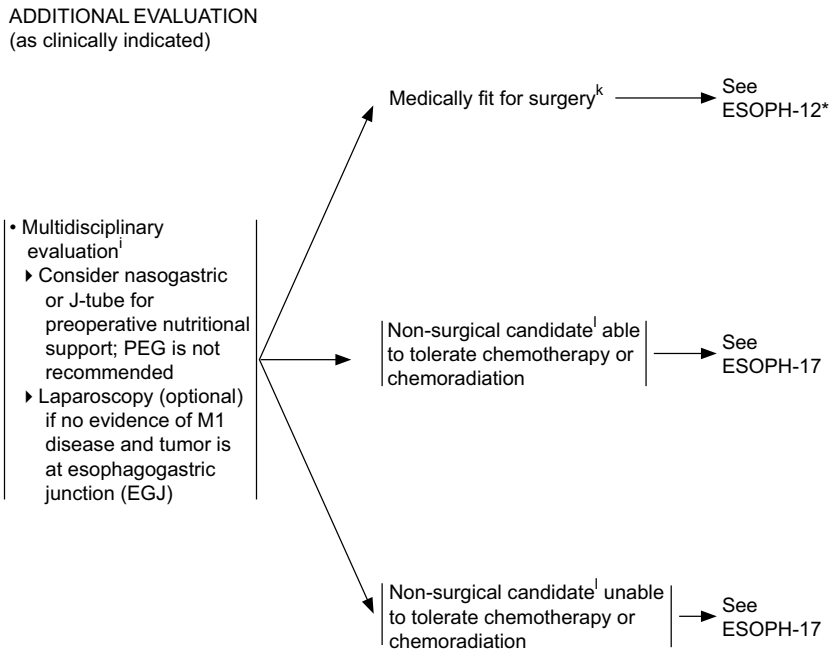
Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma,[5] both of which are more common in men. SCC is the most common histology in Eastern Europe and Asia, and adenocarcinoma is most common in North America and most Western European countries. SCCs have become increasingly less common in the West, accounting for less than 30% of all esophageal cancers in the United States and Western Europe. Adenocarcinoma is diagnosed predominantly in white men, for whom the incidence has dramatically increased. However, the overall incidence of adenocarcinoma is gradually increasing in men of all ethnic backgrounds and in women.[6] SCC seems to be more sensitive to chemotherapy, chemoradiation, and radiation therapy (RT) than adenocarcinoma, but the

Text cont. on page 211.



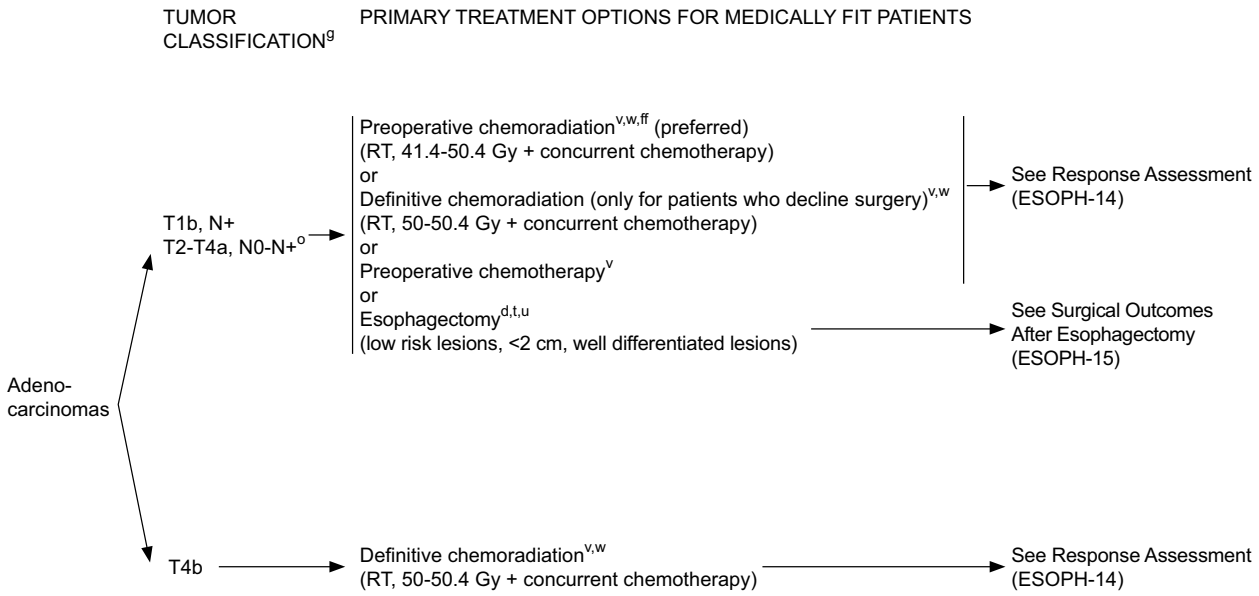
*Available online, in these guidelines, at NCCN.org.

[a]See Principles of Endoscopic Staging and Therapy (ESOPH-A*).
[b]ER may also be therapeutic for early stage cancers.
[c]See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B*).
[d]See Principles of Surgery ESOPH-C*.
[e]Smoking cessation guidelines are available from the Public Health Service at: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf
[f]See Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers (ESOPH-D*). Also see NCCN Clinical Practice Guidelines in Oncology for Colorectal Cancer Screening, Genetic/Familial High-Risk Assessement: Colorectal, and Genetic/Familial High-Risk Assessment: Breast and Ovarian, available at NCCN.org.
[g]See Staging (ST-1*) for tumor classification.
[h]Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.



*Available online, in these guideines, at NCCN.org.

[i]See Principles of Multidisciplinary Team Approach (ESOPH-E*).
[k]Medically able to tolerate major abdominal and/or thoracic surgery.
[l]Medically unfit patients or medically fit patients who decline surgery.



*Available online, in these guidelines, at NCCN.org.

[d]See Principles of Surgery (ESOPH-C*).
[g]See Staging (ST-1*) for tumor classification.
[o]Preclinical staging cannot establish the number of positive nodes.
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[ff]Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084)

ESOPH-13

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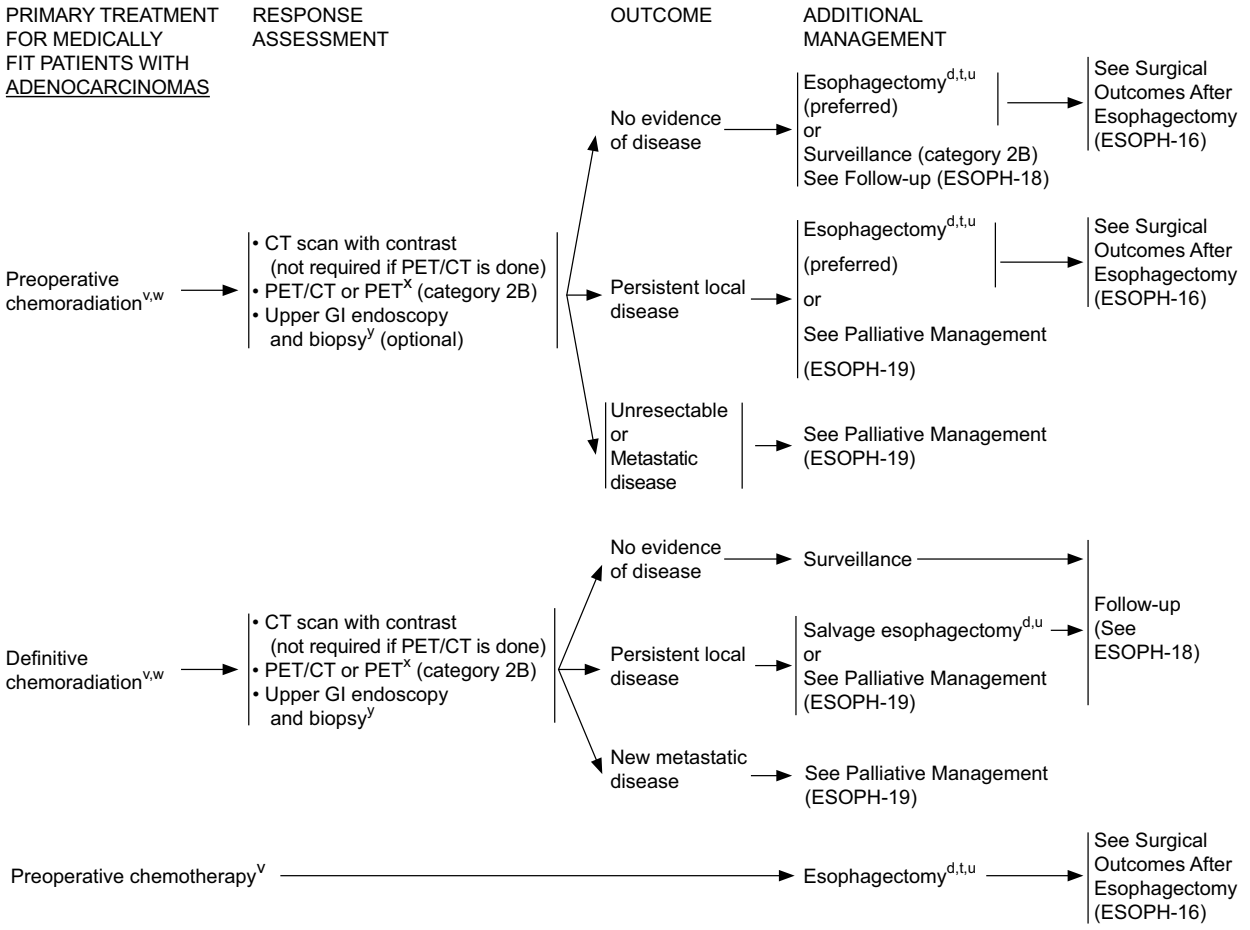
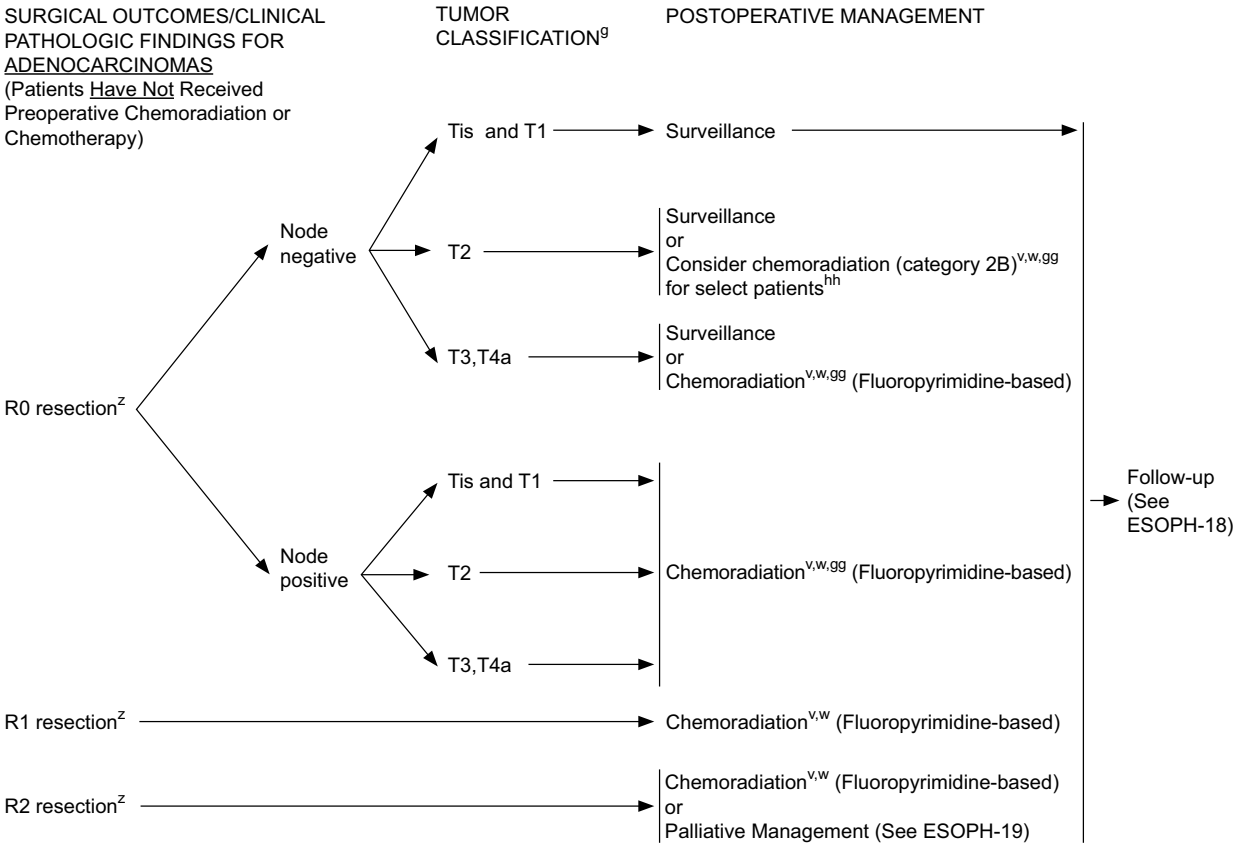


*Available online, in these guidelines, at NCCN.org.

[d]See Principles of Surgery (ESOPH-C*).
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[x]Assessment ≥5-6 weeks after completion of preoperative therapy.
[y]See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5*).

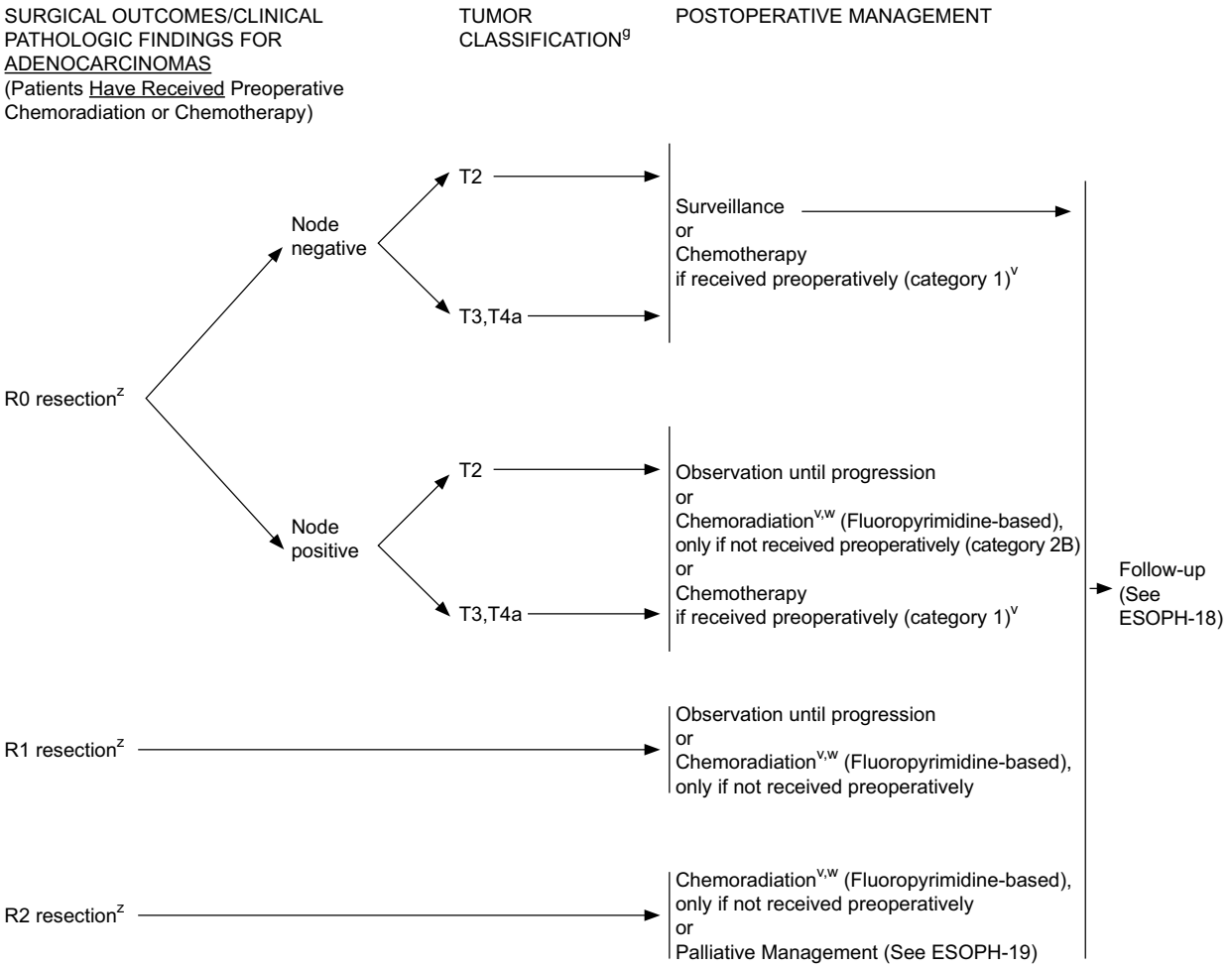
ESOPH-14



*Available online, in these guidelines, at NCCN.org.

[g]See Staging (ST-1*) for tumor classification.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[z]R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[gg]Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730. 5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy (ESOPH-F*).
[hh]Consider chemoradiation for patients with high risk lower esophagus or EGJ adenocarcinoma. High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, perineural invasion, or <50 years of age.

Esophageal and Esophagogastric Junction Cancers, Version 1.2015

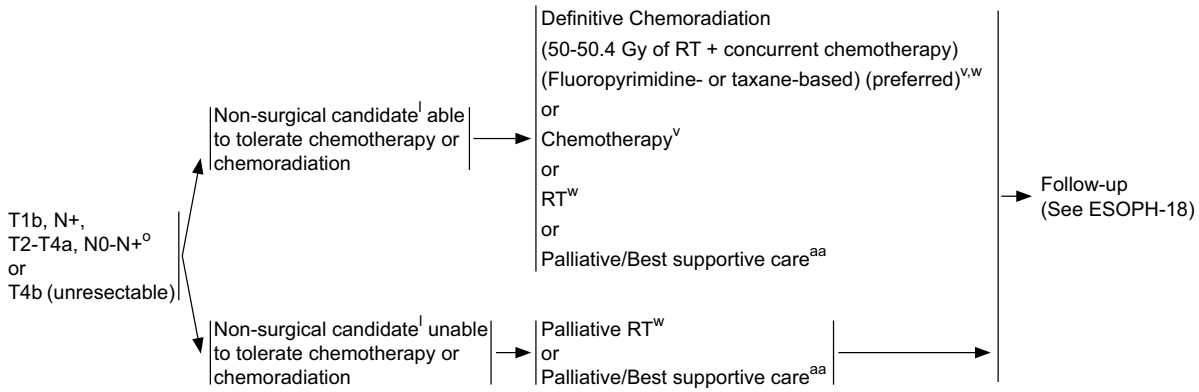


*Available online, in these guidelines, at NCCN.org.

[g]See Staging (ST-1*) for tumor classification.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[z]R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.

TUMOR CLASSIFICATION[g]
FOR PATIENTS WITH ADENOCARCINOMAS

MANAGEMENT OF NON-SURGICAL CANDIDATES[l]



*Available online, in these guidelines, at NCCN.org.

[g]See Staging (ST-1*) for tumor classification.
[l]Medically unfit patients or medically fit patients who decline surgery.
[o]Preclinical staging cannot establish the number of positive nodes.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[aa]See Principles of Palliative/Best Supportive Care (ESOPH-H*).

ESOPH-17

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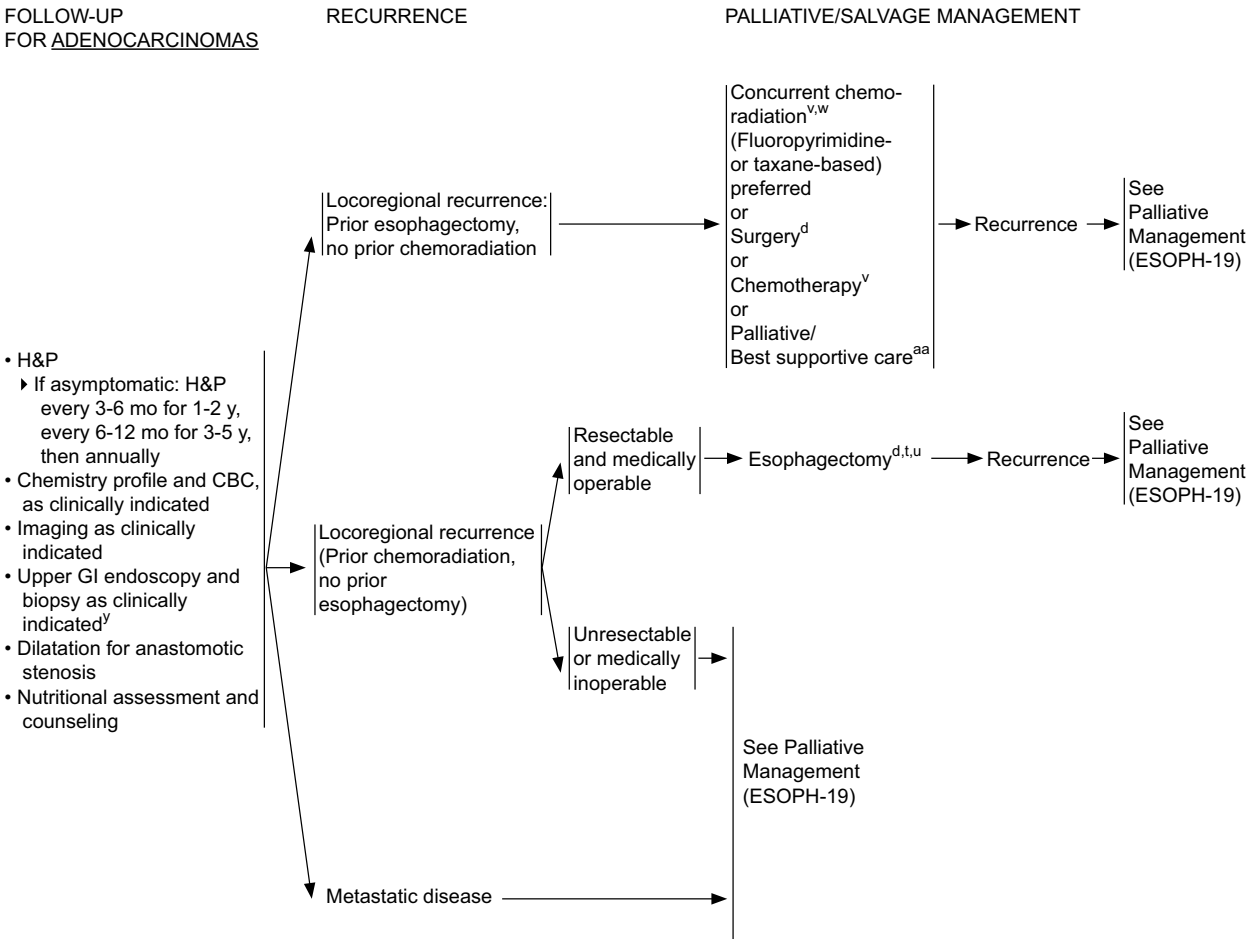
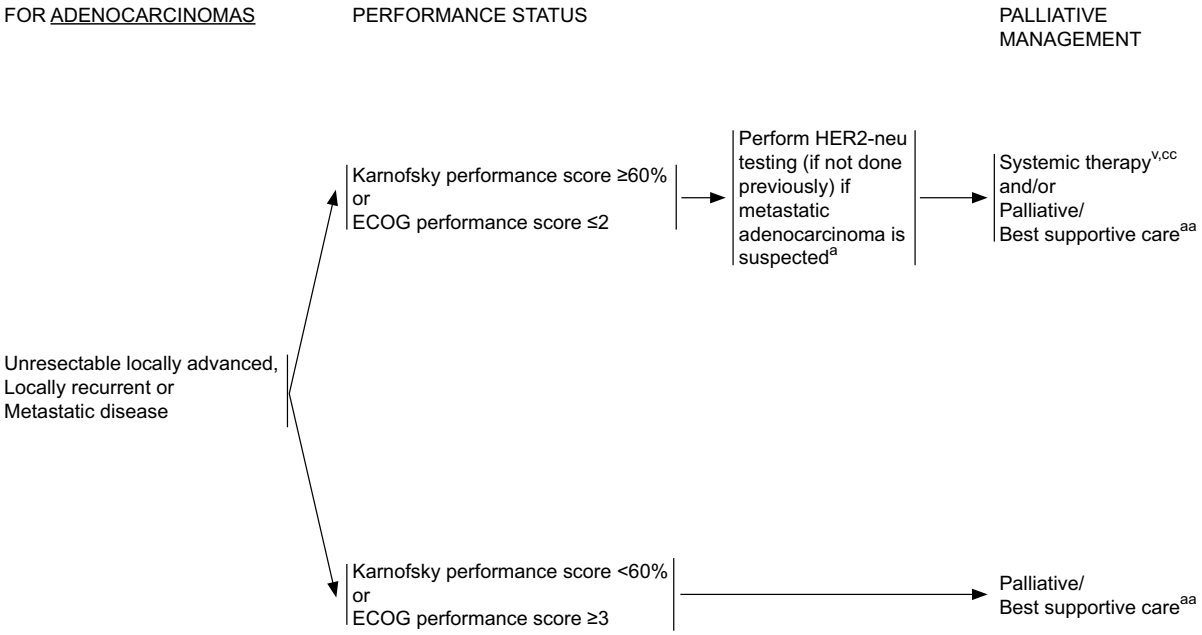


*Available online, in these guidelines, at NCCN.org.

[d]See Principles of Surgery (ESOPH-C*).
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v]See Principles of Systemic Therapy (ESOPH-F*).
[w]See Principles of Radiation Therapy (ESOPH-G*).
[y]See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5*).
[aa]See Principles of Palliative/Best Supportive Care (ESOPH-H*).



*Available online, in these guidelines, at NCCN.org.

Back to Follow-up and Recurrence (ESOPH-18)

[a]See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B*).
[v]See Principles of Systemic Therapy (ESOPH-F*).
[aa]See Principles of Palliative/Best Supportive Care (ESOPH-H*).
[dd]Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of Overexpression of HER2-neu in Esophageal and Esophagogastric Junction Cancers

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) or other in situ hybridization methods is recommended. The following criteria used in the ToGA trial[11] 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#
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

*The NCCN Guidelines Panel recommends that cases showing 2+ expression of HER2-neu by immunohistochemistry should be additionally examined by FISH or other in situ hybridization methods. Cases with 3+ overexpression by IHC or FISH-positive (HER2:CEP17 ≥2) are considered positive.

Reprinted and adapted from Bang YJ, 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.

[11]Bang YJ, 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.

PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) 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 (PS), comorbidities, and toxicity profile.
- For metastatic adenocarcinoma trastuzumab can be added to chemotherapy if tumor overexpresses HER2-neu.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising 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 fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusional fluorouracil is preferred over bolus fluorouracil.[1]
- Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.
- Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.[2] Perioperative chemotherapy is an alternative option[3,4]
- Induction chemotherapy may be appropriate as clinically indicated.
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.

[1]Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903-2909.
[2]van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.
[3]Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
[4]Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation:†
Infusional fluorouracil can be replaced with capecitabine
- Preferred Regimens:
  - Paclitaxel and carboplatin (category 1)[1]
  - Cisplatin and fluorouracil (category 1)[2,3]
  - Oxaliplatin and fluorouracil (category 1)[4,5]
- Other Regimens:
  - Irinotecan and cisplatin (category 2B)[6]
  - Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy:†
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
(3 cycles preoperative and 3 cycles postoperative):
- ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[8]
- ECF modifications[9]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine
- Fluorouracil and cisplatin (category 1)[10]

Definitive Chemoradiation:†
Infusional fluorouracil can be replaced with capecitabine
- Preferred Regimens:
  - Cisplatin and fluorouracil (category 1)[11]
  - Oxaliplatin and fluorouracil (category 1)[4,5]
  - Paclitaxel and carboplatin1 (category 2A)
- Other Regimens:
  - Cisplatin with docetaxel or paclitaxel[12-14]
  - Irinotecan and cisplatin (category 2B)[6]
  - Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Postoperative Chemoradiation:
- Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation[15]

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see (Discussion MS-33).

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

Systemic Therapy for Metastatic or Locally Advanced Cancer [where local therapy is not indicated]

- Trastuzumab can be added to chemotherapy for HER2-neu overexpressing adenocarcinoma
  [See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B; available online at NCCN.org)]
  - Combination with cisplatin and fluoropyrimidine (category 1 for first-line therapy)[16]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug cytoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
  - DCF (docetaxel, cisplatin and fluorouracil†) (category 1)[17]
  - DCF modifications
    - ◊ Docetaxel, cisplatin, and fluorouracil[18]
    - ◊ Docetaxel, oxaliplatin, and fluorouracil[19,†]
    - ◊ Docetaxel, carboplatin, and fluorouracil (category 2B)[20]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[21]
  - ECF modifications (category 1)[22]
    - ◊ Epirubicin, oxaliplatin, and fluorouracil
    - ◊ Epirubicin, cisplatin, and capecitabine
    - ◊ Epirubicin, oxaliplatin, and capecitabine
  - Fluorouracil† and irinotecan (category 1) [23]
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[24-27] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[25,28,29]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[30-32]
  - Docetaxel with cisplatin[33,34]
  - Docetaxel and irinotecan[35] (category 2B)
  - Fluoropyrimidine[26,36,37] (fluorouracil† or capecitabine)
  - Docetaxel[38,39]
  - Paclitaxel[40,41]

Second-Line Therapy

Dependent on prior therapy and performance status (PS):

- Preferred Regimens:
  - Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]
  - Docetaxel (category 1)[38,39]
  - Paclitaxel (category 1)[40,41,43]
  - Irinotecan (category 1)[43-46]
  - Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[47]
- Other Regimens:
  - Irinotecan and cisplatin[28,48]
  - Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine)[23,49] (category 2B)
  - Docetaxel and irinotecan[35] (category 2B)

Alternative regimens for consideration (category 2B):

- Mitomycin and irinotecan[50-52]
- Mitomycin and fluorouracil[53,†]

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see "Leucovorin Shortage," available online, in these guidelines, at NCCN.org [MS-33].

PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

[1]van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.
[2]Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092.
[3]Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-1168.
[4]Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-314.
[5]Khushalani NI, Leichman CG, Proulx G, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. J Clin Oncol 2002;20:2844-2850.
[6]Sharma R, Yang GY, Nava HR, et al. A single institution experience with neoadjuvant chemoradiation (CRT) with irinotecan (I) and cisplatin (C) in locally advanced esophageal carcinoma (LAEC) [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract e15619.
[7]Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol 2006;24:3953-3958.
[8]Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
[9]Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005;92:1976-1983.
[10]Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.
[11]Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174.
[12]Urba SG, Orringer MB, Ianettonni M, et al. Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. Cancer 2003;98:2177-2183.
[13]Li QQ, Liu MZ, Hu YH, et al. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. Dis Esophagus 2010;23:253-259.
[14]Day FL, Leong T, Ngan S, et al. Phase I trial of docetaxel, cisplatin and concurrent radical radiotherapy in locally advanced oesophageal cancer. Br J Cancer 2011;104:265-271.
[15]Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730.
[16]Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-697.
[17]Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.
[18]Shah MA, Jhawer M, Ilson DH, et al. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. J Clin Oncol 2011;29:868-874.
[19]Shankaran V, Mulcahy MF, Hochster HS, et al. Docetaxel, oxaliplatin, and 5-fluorouracil for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinomas: preliminary results of a phase II study [abstract]. Presented at the 2009 ASCO Gastrointestinal Cancers Symposium; January 15-17, 2009; San Francisco, California. Abstract 47.
[20]Elkerm YM, Elsaid A, Al-Batran S, Pauligk C. Final results of a phase II trial of docetaxel-carboplatin-FU in locally advanced gastric carcinoma [abstract]. Presented at the 2008 ASCO Gastrointestinal Cancers Symposium; January 25-27, 2008; Orlando, Florida. Abstract 38.
[21]Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20:1996-2004.
[22]Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
[23]Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. J Clin Onc 2014;32:3520-3526.
[24]Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009;20:1667-1673.
[25]Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.

[26]Bouche O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. J Clin Oncol 2004;22:4319-4328.
[27]Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009;20:666-673.
[28]Enzinger PC, Burtness B, Hollis D, et al. CALGB 80403/ECOG 1206: a randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 4006.
[29]Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 2012;48:518-526.
[30]Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000;6:316-323.
[31]Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998;78:511-514.
[32]Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol 2003;26:37-41.
[33]Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005;23:5660-5667.
[34]Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010;66:31-36.
[35]Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. Ann Oncol 2009;20:1242-1248.
[36]Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 2003;21:54-59.
[37]Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol 2004;15:1344-1347.
[38]Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007;24:407-412.
[39]Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78-86.
[40]Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994;86:1086-1091.
[41]Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898-902.
[42]Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;1224-1235.
[43]Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013;31:4438-4444.
[44]Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481-488.
[45]Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-2314.
[46]Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 2003;21:807-814.
[47]Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39.
[48]Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22-25.
[49]Leary A, Assersohn L, Cunningham D, et al. A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol 2009;64:455-462.
[50]Lustberg MB, Bekaii-Saab T, Young D, et al. Phase II randomized study of two regimens of sequentially administered mitomycin C and irinotecan in patients with unresectable esophageal and gastroesophageal adenocarcinoma. J Thorac Oncol 2010;5:713-718.
[51]Giuliani F, Molica S, Maiello E, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol 2005;28:581-585.
[52]Bamias A, Papamichael D, Syrigos K, Pavlidis N. Phase II study of irinotecan and mitomycin C in 5-fluorouracil-pretreated patients with advanced colorectal and gastric cancer. J Chemother 2003;15:275-281.
[53]Hofheinz RD, Hartung G, Samel S, et al. High-dose 5-fluorouracil/folinic acid in combination with three-weekly mitomycin C in the treatment of advanced gastric cancer. A phase II study. Onkologie 2002;25:255-260.

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Text cont. from page 195.

long-term outcome seems to be the same. Compared with SCC, adenocarcinoma may be associated with a better long-term prognosis after resection,[7] but more concrete data are needed. This portion of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers discusses the management of locally advanced adenocarcinoma of the esophagus and EGJ (to view the complete and most recent version of these guidelines, visit NCCN.org).

Staging

The TNM classification developed by the AJCC in 2002 was based on pathologic review of the surgical specimen in patients who underwent surgery as primary therapy. The revised 2010 AJCC staging classification is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) of 4627 patients treated with primary esophagectomy without preoperative or postoperative therapy.[8] In the data reported by the WECC, survival decreased with increasing depth of tumor invasion (pT), presence of regional lymph node metastases (pN), and distant metastases (pM).[9] Additionally, survival was somewhat worse for pT1b (submucosal) tumors than for pT1a (intramucosal) tumors, and for SCC than for adenocarcinomas.

The 2010 revised staging system includes separate stage groupings for SCC and adenocarcinoma, and is for esophageal and EGJ cancers, including cancer within the first 5 cm of the stomach that extends into the EGJ or distal thoracic esophagus.[8] However, this new classification may not work well for baseline clinical staging or for patients who underwent preoperative therapy. The 2010 classification has several other shortcomings, including inclusion of proximal 5 cm of the stomach; lack of guidance for regional resectable and unresectable cancer; the emphasis on the number of lymph nodes rather than their anatomic locations and significance; and lymph node size is not addressed.

Patient outcomes may correlate with clinical stage of the cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage (whether or not patient has received preoperative therapy). Although surgical pathology produces the most accurate staging, the advent of better imaging techniques has improved preclinical staging.[10] In North America and many western European countries, where screening programs for early detection of esophageal and EGJ cancers are not in use or practical because of low incidence, the 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, less than 60% of patients with locoregional cancer can undergo a curative resection, and approximately 70% to 80% of resected specimens harbor metastases in the regional lymph nodes. Thus, clinicians are often treating an advanced-stage, incurable cancer in newly diagnosed patients.

Esophagogastric Junction

In 1996, Siewert[11] classified the EGJ adenocarcinoma into 3 types based on the anatomic location of the tumor epicenter or the location of the tumor mass.[11] If the tumor epicenter 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. If the tumor epicenter or tumor mass is located within 1 cm proximal or 2 cm distal to the anatomic EGJ, the adenocarcinoma is classified as type II. If the tumor epicenter or more than 66% of the tumor mass is located more than 2 cm below the anatomic EGJ, the tumor is classified as type III.[11]

In 2000, the classification was slightly changed.[12] Siewert type I tumors were defined as adenocarcinoma of the distal esophagus with the tumor center located within 1 to 5 cm above the anatomic EGJ. Siewert type II tumors were defined as the true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ. Siewert type III was defined as the subcardial carcinoma with the tumor center between 2 to 5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below.

In the revised AJCC staging system, tumors with a midpoint in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extends into the EGJ or esophagus (Siewert types I and II) are classified as adenocarcinoma of the esophagus for staging purposes.[8] All other cancers with a midpoint in the stomach more than 5 cm distal to the EGJ or those within 5 cm of the EGJ but not extending into the EGJ or esophagus (Siewert type III) are staged using the gastric cancer staging system. This approach remains a subject of disagreement, some confusion, and debate. Based on thorough pre-

treatment staging, an individualized therapeutic approach may be preferred for specific patients and tumor locations. Therapeutic decisions may be refined according to the location of the individual tumor, nodal distribution, and specific requirements for local control.

Assessment of *HER2/neu* Overexpression

Human epidermal growth factor receptor 2 (*HER2*) gene and/or HER2 protein expression has been implicated in the development of gastric and EGJ adenocarcinomas.[13] *HER2/neu* amplification and overexpression are more frequent in adenocarcinoma of the esophagus (15%–30%) than SCC of the esophagus (5%–13%).[14–16] *HER2/neu* overexpression in esophagogastric cancer varies widely (2%–45%).[17] HER2/neu-positivity has been reported to be higher in patients with EGJ cancer than in those with gastric cancer.[18,19] In the ToGA trial, which evaluated the addition of trastuzumab to chemotherapy in patients with HER2/neu-positive advanced gastric cancer, HER2/neu-positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[20]

However, unlike in breast cancer, the prognostic significance of *HER2/neu* expression in patients with esophageal cancer is not clear. It has been shown that *HER2/neu* overexpression correlates with tumor invasion and lymph node metastasis, and therefore indicates a poor prognosis.[17] *HER2/neu* overexpression seems to be associated with poorer survival, especially in patients with SCC of the esophagus.[14]

Immunohistochemistry (IHC) is the most widely used, primary test for *HER2* overexpression assessment, and evaluates the membranous immunostaining of the tumor cells including intensity and the extent of staining and percentage of immunoreactive tumor cells, with scores ranging from 0 to 3+. Fluorescence in situ hybridization (FISH) is usually reserved for verifying results that are considered equivocal by IHC. These results are expressed as the ratio between the number of *HER2* gene copies and the number of chromosome 17 centromere (CEP17) within the nucleus, counted in at least 20 cancer cells (HER2:CEP17).

According to the HER2 scoring system for breast cancer proposed by ASCO and the College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, because of 2 major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it was reported that the application of this scoring system would not identify many patient with gastric cancer who could otherwise be candidates for anti-HER2 therapy.[21,22] Results from 2 separate series also showed that the HER2 scoring system for breast cancer identified a significantly lower percentage of patients with gastric cancer meeting the criteria for HER2-positivity by IHC (5.4% vs 11.0% in the ToGA trial).[23,24]

In 2008, Hoffmann et al[21] developed a modified 4-tier HER2 scoring system specific for gastric cancer using the assessment area cut-off of at least 10% stained tumor cells for resection specimens and omitting this area cut-off for biopsy specimens. In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[22] This modified HER2 scoring system was also used in the ToGA trial.[23]

HER2 testing is now recommended for all patients with metastatic EGJ adenocarcinoma at diagnosis. The NCCN Guidelines recommend that assessment of HER2 status should be performed first using IHC following the modified scoring system used in the ToGA trial[21,23] (see ESOPH-B, page 205).

Surgery

Surgery is a major component of treatment for resectable disease. A major development in surgical therapy for 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 shown that preoperative chemoradiation (CROSS study)[25] and perioperative chemotherapy (MAGIC trial; predominantly a gastric cancer trial with a small group of patients with lower esophageal and EGJ cancers)[26] significantly improved survival in patients with resectable esophageal and EGJ cancers.

All patients should be assessed for physiologic ability to undergo esophageal resection,[27] including

whether they are medically fit (ie, medically able to tolerate general anesthesia and major abdominal and/or thoracic surgery). Most patients with early-stage cancer can tolerate resection. For those 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 preoperative therapy followed by surgery. Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation.

Clinical staging using endoscopic ultrasound (EUS) with fine-needle aspiration (FNA), if indicated, with chest and abdomen CT scan, and PET scan (PET/CT preferred over PET alone) should be performed before surgery to assess resectability.[28] Patients with locally advanced cancer (T3 or N1) should have access to medical and radiation oncology consultations. 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.

Esophagectomy should be considered for all physiologically fit patients with localized, resectable, thoracic esophageal cancer (>5 cm from cricopharyngeus) and intra-abdominal esophageal or EGJ cancer. Esophagectomy should be performed in high-volume esophageal cancer centers by experienced surgeons.[29] Resection type is dictated by size, stage, and location of the primary tumor, as well as the surgeon's experience and the patient's preference. Cervical or cervicothoracic esophageal cancers less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Palliative esophagectomy can be considered for patients with cervical esophageal cancer who develop localized, resectable esophageal recurrence or untreatable stricture after definitive chemoradiation if there is no distant recurrence.[30]

The surgical approach for Siewert type I and II EGJ tumors is similar to that described previously. Siewert type III tumors are treated as gastric cancers, and the surgical approach is similar to that described in the NCCN Guidelines for Gastric Cancer[11,31,32] (to view the most recent version of these guidelines, visit NCCN.org). In some cases, additional esophageal resection may be necessary to obtain adequate surgical margins.

Laparoscopy may be useful in select patients for the detection of radiographically occult metastatic disease, especially in patients with Siewert type II or III tumors.[33] Positive peritoneal cytology in the absence of overt peritoneal metastases is associated with a poor prognosis in patients with EGJ adenocarcinoma.[34] Patients with advanced tumors, clinical stage T3 tumors, or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

Lymph node dissections (or *lymphadenectomy*) can be performed using the standard or extended (en bloc) technique. In a retrospective SEER analysis of 29,659 patients diagnosed with invasive esophageal cancer, patients who had more than 12 lymph nodes examined had a significant reduction in mortality compared with those who had no lymph node evaluation, and patients who had 30 or more lymph nodes examined had a significantly lower mortality than any other groups.[35] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[36,37] 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.[37] For patients undergoing esophagectomy without preoperative chemoradiation, these NCCN Guidelines for Esophageal and EGJ Cancers recommend that at least 15 lymph nodes should be removed for adequate nodal staging (to view the complete and most recent version, visit NCCN.org). The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.

Combined Modality Therapy

Combined modality therapy has been used for the treatment of esophageal and EGJ cancers because of the poor overall survival (OS) rates in patients treated with resection alone.[38]

Definitive Chemoradiation Therapy

Concurrent chemoradiation therapy versus RT, each without resection, was studied in the only random-

ized trial (RTOG 85-01) designed to deliver adequate doses of systemic chemotherapy with concurrent RT.[39,40] In this trial, patients with SCC or adenocarcinoma with clinical stage T1–3,N0–1,M0 received 4 cycles of 5-FU and cisplatin (CF),[39,40] and RT (50 Gy at 2 Gy/d) was given concurrently with day 1 of chemotherapy. The control arm was RT alone (64 Gy). 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 OS (27% vs none), with projected 8-year 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, which compared 2 different RT doses used with the same chemotherapy regimen (CF).[41] In this trial, 218 patients with either SCC (85%) or adenocarcinoma (15%) and clinical stage T1–4,N0–1,M0 were randomly assigned to a higher dose of RT (64.8 Gy) or the standard dose (50.4 Gy) with the same chemotherapy regimen (CF). No significant difference was observed in median survival (13 vs 18 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 RT arms, respectively.

The results of RTOG 85-01 and INT 0123 established definitive chemoradiation with CF using the RT dose of 50.4 Gy as the standard of care for patients with SCC or adenocarcinoma of the esophagus.

Recent reports have also confirmed the efficacy of definitive chemoradiation in patients with locally advanced esophageal cancer.[42–45] Definitive chemoradiation with docetaxel and cisplatin resulted in a high overall response rate in patients with SCC (98%; 71% complete response). At the median follow-up of 18 months, median OS time was 23 months.[42] The rate of locoregional progression-free survival (PFS), PFS, and 3-year OS rates were 60%, 29%, and 37%, respectively. Definitive chemoradiation with carboplatin and paclitaxel was also well tolerated resulting in superior OS, disease-specific survival, durable locoregional control, and palliation in approximately half of the patients with unresectable esophageal cancer.[43,44] In a recent randomized phase III trial, 267 patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to definitive chemoradiation with either FOLFOX4 (5-FU, leucovorin, and oxaliplatin) or CF.[45] Most patients had SCC, and the median follow-up was 25.3 months. Median PFS was 9.7 months in the FOLFOX4 arm and 9.4 in the 5-FU and cisplatin arm (P=.64).[45] Although definitive chemoradiation with FOLFOX was not associated with a PFS benefit compared with chemoradiation with CF, the investigators suggest that FOLFOX may be a more convenient option for patients with localized esophageal cancer who may not be candidates for surgery.

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational.[46] Results of 2 meta-analyses have shown that preoperative chemoradiation therapy plus surgery significantly reduced 3-year mortality and locoregional recurrence; preoperative chemoradiation therapy also downstaged the tumor when compared with surgery alone.[47,48] Another recent meta-analysis (1854 patients;12 randomized trials comparing preoperative chemoradiation vs surgery alone) showed a significant survival benefit for preoperative chemoradiation in patients with resectable adenocarcinoma of the esophagus.[49] In patients with locally advanced esophageal cancer, Swisher et al[50] reported that preoperative chemoradiation was associated with increased pathologic complete response (28% vs 4%) and 3-year OS (48% vs 29%) compared with preoperative chemotherapy. In a retrospective analysis of 363 patients with adenocarcinoma of the lower esophagus, OS after preoperative chemoradiation was significantly shorter for patients with Barrett esophagus compared with those without (32 vs 51 months, respectively).[51]

However, randomized trials comparing surgery alone with preoperative chemoradiation followed by surgery in patients with clinically resectable cancer have shown conflicting results.[25,52–58] Results from the multicenter, phase III, randomized CROSS study, the largest trial in its class, showed that preoperative chemoradiation with carboplatin and paclitaxel significantly improved OS and disease-free survival (DFS) compared with surgery alone in patients with resectable (T2–3,N0–1,M0) esophageal or EGJ cancers (368 patients;75% had adenocarcinoma and

23% had SCC).[25] The R0 resection rate was higher in the chemoradiation arm compared with the surgery alone arm (92% and 69%, respectively). Median survival was 49 months in the chemoradiation arm compared with 24 months in the surgery alone arm. The 1-, 2, 3-, and 5-year survival rates were 82%, 67%, 58%, and 47%, respectively, in the chemoradiation arm compared with 70%, 50%, 44%, and 34%, respectively, in the surgery alone arm. The pathologic complete response rate was higher in patients with SCC than in those with adenocarcinoma (49% and 23%, respectively; *P*=.008); histologic type was not a prognostic factor for survival. After a minimum follow-up of 24 months, the overall recurrence rate was 35% in the chemoradiation arm compared with 58% in the surgery arm. Preoperative chemoradiation significantly reduced locoregional recurrence from 34% to 14% (*P*<.001) and peritoneal carcinomatosis from 14% to 4% (*P*<.001).[59]

In contrast, the results of another phase III, randomized, controlled study (FFCD 9901) showed that preoperative chemoradiation therapy with CF did not improve the R0 resection rate and OS, but enhanced the postoperative mortality rate for patients with localized stage I or II esophageal cancer compared with surgery alone.[58] After a median follow-up of 93.6 months, the R0 resection rate was 93.8% for chemoradiation versus 92.1% for surgery alone (*P*=.749). The 3-year OS rates were 47.5% and 53.0%, respectively (*P*=.94), and the postoperative mortality rate was 11.1% for chemoradiation compared with 3.4% for surgery alone (*P*=.049).

The CALGB 9781 trial was a prospective randomized Intergroup trial that evaluated trimodality therapy versus surgery alone for the treatment of patients with stage I–III esophageal cancer.[60] The study fell short of its accrual goals with only 56 patients enrolled. Patients were randomized to undergo either surgery alone or receive concurrent chemoradiation therapy with CF; the median follow-up was 6 years. An intent-to-treat analysis showed a median survival of 4.5 versus 1.8 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 may be an appropriate standard of care for patients with localized esophageal cancer.

In a recent phase II randomized study, preoperative chemoradiation with CF did not show any survival benefit compared with preoperative chemotherapy in patients (n=75) with resectable adenocarcinoma of the esophagus and EGJ.[61] Median PFS was 26 and 14 months for chemotherapy and chemoradiation, respectively (*P*=.37). The corresponding median OS was 32 and 30 months, respectively (*P*=.83). However, the pathologic response rate (31% vs 8%; *P*=.01) and R1 resection rate (0% vs 11%; *P*=.04) favored chemoradiation therapy.

Postoperative Chemoradiation Therapy

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.[62] In this trial, 556 patients (20% had EGJ adenocarcinoma) with resected adenocarcinoma of the stomach or EGJ (stage IB–IV,M0 according to 1988 AJCC staging criteria) were randomly assigned to surgery plus postoperative chemoradiation (n=281; bolus 5-FU and leucovorin before and after concurrent chemoradiation with 5-FU and leucovorin) or surgery alone (n=275). The majority of patients had T3–T4 tumors (69%) and node-positive disease (85%), whereas only 31% of the patients had T1–T2 tumors and 14% had node-negative tumors. Surgery was not part of the trial protocol, but resection of all detectable disease was required for participation. Patients were eligible for the study only after recovery from surgery. Postoperative chemoradiation (offered to all patients with tumors ≥T1, with or without lymph node metastases) significantly improved OS and relapse free survival. Median OS was 27 and 36 months in the surgery-only and chemoradiation groups, respectively (*P*=.005). The chemoradiation group had better 3-year OS (50% vs 41%) and relapse-free survival rates (48% vs 31%) than the surgery-only group. A significant decrease was also seen in the chemoradiation group in local failure as the first site of failure (19% vs 29%). With more than 10 years of median follow-up, survival remains improved in patients with stage IB–IV,M0 gastric or EGJ adenocarcinoma treated with postoperative chemoradiation. No increases in late toxic effects were noted.[63]

Results of the INT-0116 trial have established postoperative chemoradiation therapy as a standard of care in patients with completely resected gastric

or EGJ adenocarcinoma who have not received preoperative therapy. However, the regimen used in this trial (bolus 5-FU and leucovorin before and after chemoradiation with the same combination) was associated with high rates of grade 3 or 4 hematologic and gastrointestinal toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group, only 64% of patients completed treatment and 17% discontinued treatment because of toxicity, and 3 patients died as a result of chemoradiation-related toxic effects, including pulmonary fibrosis, cardiac event, and myelosuppression.

Although the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric or EGJ adenocarcinoma, the recommended doses or schedule of chemotherapy agents used in the trial are no longer recommended because of concerns about toxicity. In retrospective analyses, the addition of postoperative chemoradiation has been associated with survival benefit in patients with lymph node–positive locoregional esophageal cancer.[64,65] Data from a more recent retrospective analysis also showed that postoperative chemoradiation according to the INT-0116 protocol resulted in improved DFS after curative resection in patients (n=211) with EGJ adenocarcinomas and positive lymph nodes who did not receive neoadjuvant chemotherapy.[66] The 3-year DFS rate after postoperative chemoradiation was 37% compared with 24% after surgery alone.

Alternative postoperative chemoradiation regimens have been evaluated by other investigators.[67,68] In a phase II nonrandomized trial that evaluated postoperative concurrent chemoradiation with CF in patients with poor-prognosis esophageal and EGJ adenocarcinoma, the projected rates of 4-year OS, freedom from recurrence, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively, for patients with lymph node–positive tumors (T3 or T4), which are better than the historical outcomes with surgery alone.[67] In the randomized Intergroup trial CALGB 80101, postoperative chemoradiation with epirubicin, cisplatin, and 5-FU (ECF) before and after 5-FU and RT did not improve survival compared with the INT-0116 regimen in patients who have undergone curative resection for gastric or EGJ adenocarcinoma.[68] The efficacy of postoperative chemoradiation compared with surgery alone has not been demonstrated in a randomized trial of patients with esophageal cancer.

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 either receive preoperative chemotherapy (CF) or surgery alone. Preliminary results did not show any survival benefit between the 2 groups.[69] Long-term results showed that 63% of patients treated with chemotherapy followed by surgery underwent complete resection (R0) compared with 59% treated with surgery alone.[70] Although preoperative chemotherapy decreased the incidence of R1 resection (4% vs 15% in the surgery-only group), there was no improvement in OS between the 2 groups.

In the MRC OEO2 trial, 802 patients with potentially resectable esophageal cancer were randomly assigned to either 2 cycles of preoperative 5-FU (1000 mg/m^2/d via continuous infusion for 4 days) and cisplatin (80 mg/m^2 on day 1) repeated every 21 days followed by surgery, or surgery alone.[71] However, this trial had several clinical methodology problems. Nearly 10% of patients received off-protocol preoperative RT, and patients accrued in China were excluded. At a short median follow-up time of 2 years, patients 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.[72] At a median follow-up of 6 years, DFS and OS 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 SCC and adenocarcinoma.[72]

Long-term results of another randomized trial also demonstrated that preoperative chemotherapy with a combination of etoposide and cisplatin significantly improved OS and DFS in patients (n=169) with SCC of the esophagus.[73] Median OS was 16 months for patients assigned to preoperative chemotherapy followed by surgery compared with 12 months for surgery alone; 5-year survival rates were 26% and 17%, respectively.

An individual, patient, data-based meta-analysis showed a small but significant OS and DFS benefit favoring preoperative chemotherapy over surgery alone.[74] The results of an updated meta-analysis, which included 1981 patients from 9 randomized trials comparing preoperative chemotherapy versus surgery alone, showed a survival benefit for preoperative chemotherapy in patients with resectable adenocarcinoma of the esophagus.[49]

Perioperative Chemotherapy

The Medical Research Council performed the first well-powered phase III trial (MAGIC trial) that evaluated perioperative chemotherapy for patients with resectable gastroesophageal cancer.[26] In this trial, 503 patients were randomized to receive either surgery alone or perioperative chemotherapy (preoperative and postoperative chemotherapy) with ECF and surgery. Patients were randomized before surgical intervention. Most (74%) of the patients had stomach cancer, whereas a small group of patients had adenocarcinoma of the lower esophagus (14%) and EGJ (11%). Most patients had T2 or higher tumors (12% had T1 tumors, 32% had T2 tumors, and 56% had T3–T4 tumors), and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5%, respectively). Perioperative chemotherapy significantly improved PFS (P<.001) and OS (P=.009). The 5-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

In a more recent FNCLCC/FFCD trial (N=224; 75% with adenocarcinoma of the lower esophagus or EGJ and 25% had gastric cancer), Ychou et al[75] reported that perioperative chemotherapy with 5CF significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer. At the median follow-up of 5.7 years, the 5-year OS rate was 38% for patients in the surgery plus perioperative chemotherapy group and 24% for those in the surgery-only group (P=.02); corresponding 5-year DFS rates were 34% and 19%, respectively. This trial was prematurely terminated because of low accrual.

The results of these 2 studies have established perioperative chemotherapy as another option for the standard of care for patients with resectable adenocarcinoma of the lower esophagus and EGJ.

Chemotherapy for Locally Advanced or Metastatic Cancer

Cisplatin is one of the most active chemotherapeutic agents, with a single-agent response rate consistently in the range of 20% or greater.[76] Several other agents including irinotecan,[77–79] docetaxel,[80,81] paclitaxel,[82,83] and etoposide[84] have also shown single-agent activity in patients with advanced or metastatic esophageal cancer. CF is the most investigated and most commonly used regimen for patients with esophageal cancer, resulting in response rates of 20% to 50%.

Cisplatin plus paclitaxel or docetaxel, with or without 5-FU, has also demonstrated activity in patients with locally advanced EGJ or metastatic esophageal cancers.[85–90] In a randomized multinational phase III study (V325), 445 untreated patients were randomized to receive either docetaxel, cisplatin, and 5-FU (DCF; every 3 weeks) or CF.[89] Most patients had advanced gastric cancer and 19% to 25% had EGJ cancer. At a median follow-up of 13.6 months, time to progression was significantly longer with DCF compared with CF (5.6 vs 3.7 months; P<.001). Median OS was significantly longer for DCF compared with CF (9.2 vs 8.6 months; P=.02), at a median follow-up time of 23.4 months; the overall confirmed response rate was also significantly higher with DCF than CF (37% and 25%, respectively; P=.01).[89] Various modifications of the DCF regimen with the intent to improve tolerability are being evaluated in clinical trials for patients with advanced esophagogastric cancer.[91–95]

The REAL-2 trial (30% of patients with esophageal cancer) was a randomized, multicenter, phase III study comparing capecitabine with 5-FU and oxaliplatin with cisplatin in 1002 patients with advanced esophagogastric cancer.[96] Patients with histologically confirmed adenocarcinoma, SCC, or undifferentiated cancer of the esophagus, EGJ, or stomach were randomized to receive 1 of 4 epirubicin-based regimens: ECF; epirubicin, oxaliplatin, and 5-FU (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 both as effective as CF 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-FU and capecitabine were not different.

Irinotecan-based combination regimens have also been evaluated in prospective studies as first-line therapy for patients with advanced or metastatic esophageal or EGJ cancers.[97–103] The results of a randomized phase III study (N=337) showed that irinotecan in combination with 5-FU (IF) and folinic acid was noninferior to CF in terms of PFS (estimated probabilities of PFS at 6 and 9 months were 38% and 20% for IF, respectively, vs 31% and 12%, respectively for CF) but not for OS (9.0 vs 8.7 months for CF) and time to treatment progression (5.0 vs. 4.2 months for CF; *P*=.018).[98] IF was associated with a more favorable toxicity profile. In a phase II study that evaluated 5-FU and folinic acid (AIO regimen) in combination with irinotecan in patients with locally advanced or metastatic esophageal cancer (adenocarcinoma or SCC), partial response was achieved in 33% of evaluable patients (n=19); 38% had stable disease and 8% had progressive disease.[99] Median survival was 20 and 10 months, respectively, for patients with adenocarcinoma and SCC. A more recent randomized phase III study (French Intergroup Study) compared 5-FU, leucovorin, and irinotecan (FOLFIRI) with ECF as first-line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[103] In this study, 416 patients (65% had gastric adenocarcinoma and 33% had EGJ adenocarcinoma) were randomized to receive either FOLFIRI or ECF. After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECX (5.1 vs 4.2 months; *P*=.008).[103] There were no significant differences in median PFS (5.3 vs 5.8 months; *P*=.96), median OS (9.5 vs 9.7 months; *P*=.95), or response rate (39.2% vs 37.8%). FOLFIRI was less toxic and better tolerated than ECF. The NCCN panel felt that FOLFIRI is an acceptable option for first-line therapy for patients with advanced or metastatic EGJ adenocarcinoma.

Irinotecan in combination with 5-FU or docetaxel or capecitabine has also demonstrated activity in patients with advanced or metastatic esophagogastric cancer that have progressed on platinum-based chemotherapy.[100,104,105]

Combination chemotherapy regimens containing oxaliplatin,[106,107] carboplatin,[108] mitomycin,[109] and gemcitabine[110,111] have also shown activity in patients with advanced or metastatic esophageal cancer. A phase III trial conducted by the German Study Group showed that the combination of 5-FU, leucovorin, and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend toward improved median PFS (5.8 vs 3.9 months) compared with 5-FU, leucovorin, and cisplatin (FLP) in patients with metastatic esophagogastric cancer.[107] However, no significant differences were seen in median OS (10.7 vs 8.8 months, respectively) between the FLO and FLP regimens. 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 PFS (6.0 vs 3.1 months), and an improved OS (13.9 vs 7.2 months) compared with FLP, respectively. Combination of carboplatin and paclitaxel was moderately active with a response rate of 43% in patients with advanced esophageal cancer.[108] However, 52% of patients had neutropenia (grade 3/4). In a prospective randomized study, the combination of mitomycin, cisplatin, and fluorouracil (protracted intravenous infusion) was equally efficient to ECF (protracted intravenous infusion) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.[109]

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.[112] Palliative chemotherapy is not known to provide any survival advantage, but it may improve the quality of life in patients with metastatic or unresectable esophageal cancer.[113] Adequately powered phase III studies are lacking.

Targeted Therapies

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.[23] In this trial, 594 patients with HER2/neu-positive (3+ on IHC- or FISH-positive [HER2:CEP17 ≥2]), locally advanced, recurrent, or metastatic gastric and EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (5-FU or capecitabine and cisplatin)

or chemotherapy alone.[23] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 and 17 months, respectively. There was a significant improvement in median OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in patients with *HER2/neu* overexpression or amplification (13.8 vs 11.0 months, respectively; *P*=.046). This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with HER2/neu-positive advanced or metastatic gastric and EGJ adenocarcinoma.

However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3+ or IHC 2+ and were FISH-positive. There was no significant survival benefit for patients whose tumors were IHC 0 or 1+ and were FISH-positive.[23] In the posthoc subgroup analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients with tumors that were IHC 2+ and FISH-positive or IHC 3+ (n=446; 16.0 vs 11.8 months; hazard ratio [HR], .65) compared with those with tumors that were IHC 0 or 1+ and FISH-positive (n=131; 10.0 vs 8.7 months; HR, 1.07).

Ramucirumab, a VEGFR-2 antibody, has shown promising results in the treatment of patients with previously treated advanced or metastatic gastric or EGJ cancers in phase III clinical trials.[114,115] An international, randomized, multicenter, placebo-controlled, phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[114] In this study, 355 patients were randomized to receive either ramucirumab (n=238; 178 patients with gastric cancer; 60 with EGJ adenocarcinoma) or placebo (n=117; 87 patients with gastric cancer; 30 with EGJ adenocarcinoma). Median OS was 5.2 months for patients treated with ramucirumab compared with 3.8 months for placebo (*P*=.047). Ramucirumab was associated with higher rates of hypertension than the placebo group (16% vs 8%), whereas rates of other adverse events were mostly similar between the 2 groups. In a more recent international phase III randomized trial (RAINBOW) that evaluated paclitaxel with or without ramucirumab in patients with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy, combination paclitaxel and ramucirumab resulted in significantly higher OS, PFS, and overall response rate compared with paclitaxel alone.[115] In this study, 665 patients were randomized to ramucirumab plus paclitaxel (n=330) or paclitaxel alone (n=335). Median OS was significantly longer for ramucirumab plus paclitaxel compared with paclitaxel alone (9.63 vs 7.36 months; *P*<.0001). The median PFS was 4.40 and 2.86 months, respectively, for the treatment groups. The overall response rate was 28% for ramucirumab plus paclitaxel compared with 16% for paclitaxel alone (*P*=.0001). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel.

Based on the results of these 2 studies, ramucirumab as single agent or in combination with paclitaxel was recently FDA approved for the treatment for patients with advanced EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy.

Treatment Guidelines

The management of patients with esophageal and EGJ cancers requires the expertise of several disciplines, including surgical, medical, and radiation oncology, and gastroenterology, radiology, and pathology. Additionally, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines are also desirable. Geneticists should be engaged when appropriate. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of any discipline taking care of patients with esophagogastric cancer. Optimally at each meeting, the panel encourages participation of all relevant disciplines. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient. (See "Principles of Multidisciplinary Team Approach for Esophagogastric Cancers," available online, in these guidelines, at NCCN.org [ESOPH-E]).

Workup

Patients who are newly diagnosed should undergo a complete history, physical examination, CBC and

chemistry profile, biopsy (to confirm histologic classification and metastatic cancer), and an endoscopy with biopsy of the entire upper gastrointestinal tract (ESOPH-1, page 196). If the cancer is located at or above the carina, bronchoscopy (including biopsy of any abnormality and cytology of the washings) should be performed. For patients in whom the upper gastrointestinal tract cannot be visualized, a double-contrast barium study of the upper gastrointestinal tract is optional. CT scan (with oral and intravenous contrast) of the chest and abdomen should also be performed. Pelvic CT should be obtained when clinically indicated. EUS and PET/CT evaluation is recommended if metastatic cancer is not evident. *HER2/neu* testing is recommended if metastatic disease is documented or suspected (see "Assessment of *HER2/neu* Overexpression," page 212). The NCCN Guidelines recommended assessment of Siewert tumor type as part of the initial workup in all patients with EGJ adenocarcinoma.[11,12] The NCCN Guidelines also recommend screening for family history of esophageal or EGJ cancers. Referral to a cancer genetics professional is recommended for those with a known high-risk syndrome associated with esophageal and EGJ cancers.

PET/CT scans are useful for the initial staging and evaluation of patients after chemoradiation before surgery for the detection of distant lymphatic and hematogenous metastases.[116–118] PET/CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer.[119] It has also been shown to be an independent predictor of OS in patients with nonmetastatic esophageal cancer.[120] Additionally, a recent study reported that combined PET/CT scans are more accurate than EUS-FNA and CT scan for predicting nodal status and complete response after neoadjuvant therapy in patients with esophageal cancer.[121] 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. A recent retrospective analysis involving patients with biopsy-proven esophageal cancer identified in a prospectively held database showed that the addition of PET/CT to standard staging led to changes in the multidisciplinary recommendations in 38.2% patients, improving the patient selection for radical treatment.[122]

Initial workup enables patients to be classified into 2 groups with the following characteristics: locoregional cancer (stages I–III) or metastatic cancer (stage IV).

Additional Evaluation

In patients with apparent locoregional cancer, additional evaluations may be needed 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 gastrostomy is not recommended. In patients with adenocarcinoma of the esophagus or EGJ, laparoscopic staging of the peritoneal cavity should be considered (optional) if there is no evidence of metastatic disease (M1).[33] 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 patients when colon interposition is planned.

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

- Medically fit patients
- Nonsurgical candidates able to tolerate chemotherapy or chemoradiation
- Nonsurgical candidates unable to tolerate chemotherapy or chemoradiation

Management of Locoregional Cancer in Medically Fit Patients

Primary Treatment: Primary treatment options for patients with T1b, N+ and those with locally advanced resectable tumors (T2-T4a, any regional N) include preoperative chemoradiation (preferred),[25] definitive chemoradiation (only for patients who decline surgery),[40,41,45] perioperative chemotherapy,[26] or esophagectomy (for patients with low-risk and well-differentiated lesions <2 cm; see ESOPH-13, page 198).

Definitive chemoradiation is the preferred treatment for patients with unresectable T4b tumors and occasionally can facilitate surgical resection in selected patients.[44]

Fluoropyrimidine- or taxane-based regimens are recommended for preoperative and definitive

chemoradiation. See "Principles of Systemic Therapy" for list of specific regimens (available online, in these guidelines, at NCCN.org).

Additional Treatment: Restaging (eg, with CT scan with contrast, if PET/CT is not performed; PET/CT or PET; upper gastrointestinal endoscopy with biopsy [optional after preoperative chemoradiation]) is recommended after completion of preoperative or definitive chemoradiation for all patients with SCC or adenocarcinoma. Response assessment with PET/CT or PET scan (category 2B) should be performed 5 to 6 weeks after completion of preoperative therapy (see ESOPH-14, page 199).

Adjuvant treatment options (after preoperative and definitive chemoradiation) are based on the outcome of response assessment. Esophagectomy is recommended for patients with no evidence of disease and for those with persistent local disease after preoperative chemoradiation. Alternatively, patients with no evidence of disease may be observed (category 2B) and those with persistent local disease can be managed with palliative therapy. Following definitive chemoradiation, patients with no evidence of disease can be observed and those with persistent local disease can be treated with esophagectomy or palliative therapy.

Esophagectomy is the preferred treatment option for all patients after preoperative chemotherapy for patients with adenocarcinoma.

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. The efficacy of postoperative treatment has not been established in randomized trials for patients with esophageal cancer. Available evidence for the use of postoperative chemoradiation (only for patients who have not received preoperative therapy) and perioperative chemotherapy for patients with adenocarcinoma of the distal esophagus or EGJ comes from prospective randomized clinical trials involving patients with gastric cancer that have included patients with adenocarcinoma of the distal esophagus or EGJ.[26,62]

For Patients Who Have Not Received Preoperative Therapy: No further treatment is necessary for patients with Tis and T1, N0 tumors if no residual disease is present at the surgical margins (R0 resection). Based on the results of the INT-0116 trial, the panel included postoperative fluoropyrimidine-based chemoradiation for all patients with T3–T4a tumors and node-positive T1–T2 tumors.[62,63] Given the lack of evidence from randomized clinical trials showing any survival benefit for postoperative chemoradiation for patients with T2, N0 tumors, postoperative chemoradiation is recommended (category 2B) only for selected patients with high-risk features (poorly differentiated or higher-grade cancer, lymphovascular invasion, neural invasion, or age <50 years) if no residual disease is present at the surgical margins (R0 resection).[123] Alternatively, patients with node-negative T2–T4a tumors can also be observed (see ESOPH-15, page 200).

The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer.[62,63] However, the panel does not recommend the doses or the schedule of chemotherapy agents as used in the INT-0116 trial because of concerns regarding toxicity. Instead, the panel recommends the use of fluoropyrimidine (infusional 5-FU or capecitabine) before and after fluoropyrimidine-based chemoradiation.

Patients with microscopic (R1 resection) or macroscopic residual disease with no distant metastatic disease (R2 resection) should be treated with fluoropyrimidine-based chemoradiation. Palliative therapy is an alternative option for patients with macroscopic residual disease.

For Patients Who Have Received Preoperative Therapy: Postoperative chemotherapy (category 1), if received preoperatively, is recommended for all patients (irrespective of the nodal status) if no residual disease is present at the surgical margins (R0 resection).[26] Observation is an option for patients who have not received preoperative chemotherapy. Alternatively, patients with node-positive adenocarcinoma could be treated with chemoradiation (category 2B), if not received preoperatively. However, this approach has not been evaluated in prospective studies.

Patients with microscopic (R1 resection) or macroscopic (R2 resection) residual disease should be treated with fluoropyrimidine-based chemoradiation if they have not received it preoperatively.

Alternatively, patients with microscopic residual disease (R1 resection) can be observed until progression, and patients with macroscopic residual disease (R2 resection) can be treated with palliative therapy.

Management of Locoregional Cancer in Nonsurgical Candidates

Fluoropyrimidine- or taxane-based definitive chemoradiation is the preferred treatment option for technically resectable locally advanced cancer (T2–T4a, any regional N) in nonsurgical candidates who are able to tolerate chemotherapy or chemoradiation. Alternatively, these patients can also be treated with chemotherapy or RT or best supportive care.

Palliative RT or best supportive care are the appropriate options for nonsurgical candidates who are unable to tolerate chemotherapy or chemoradiation (see ESOPH-17, page 202).

Follow-up After Resection or Definitive Chemoradiation

All patients should be followed 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. A CBC, multichannel serum chemistry evaluation, upper gastrointestinal endoscopy with biopsy, and imaging studies should be obtained as clinically indicated. In addition, some patients may require dilatation of an anastomotic or a chemoradiation-induced stricture. Nutritional assessment and counseling may be extremely valuable. *HER2/neu* testing should be performed if metastatic adenocarcinoma was present at diagnosis.

Management of Locally Advanced, Metastatic, or Recurrent Disease

Locoregional recurrence after esophagectomy can be treated with fluoropyrimidine- or taxane-based concurrent chemoradiation in patients who have not received prior chemoradiation (see ESOPH-18, page 203). Other options include best supportive care or surgery or chemotherapy. Selected patients with anastomotic recurrences can undergo re-resection.

When recurrence develops after chemoradiation therapy with no prior esophagectomy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable (see ESOPH-18, page 203). If both criteria are met, esophagectomy remains an option. When patients experience another recurrence after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described for locally advanced or metastatic cancer. Palliative therapy is recommended for medically unfit patients and those who develop an unresectable or metastatic recurrence.

Phase III trials for locally advanced or metastatic esophageal cancer have not been performed for many years. The survival benefit of second-line chemotherapy compared with best supportive care has been demonstrated in a small cohort of patients with lower esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma phase III trials.[124,125] In a randomized phase III study, second-line chemotherapy with irinotecan significantly prolonged OS compared with best supportive care in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n=40).[124] The study was closed prematurely because of poor accrual. Median survival was 4.0 months in the irinotecan arm compared with 2.4 months in the best supportive care–only arm. In a recent open-label, multicenter, phase III, randomized trial, the addition of docetaxel to active symptom control was associated with a survival benefit for patients with advanced, histologically confirmed adenocarcinoma of the esophagus, EGJ junction, or stomach that had progressed on or within 6 months of treatment with combination chemotherapy with platinum and fluoropyrimidine.[125] In this study, patients (n=168) with an ECOG performance status of 0–2 were randomly assigned to receive docetaxel plus active symptom control or active symptom control alone. After a median follow-up of 12 months, the median OS was 5.2 months for patients with the docetaxel group compared with 3.6 months for those in the active symptom control group (P=.01). Docetaxel was associated with higher incidence of grade 3/4 neutropenia, infection, and febrile neutropenia. However, disease-specific, health-related quality-of-life measures also showed benefits for docetaxel in reducing dysphagia and abdominal pain.

Docetaxel and irinotecan are included as options for second-line therapy for patients with locally advanced or metastatic disease. Other regimens included in the guidelines for patients with locally advanced or metastatic disease are derived from the

gastric adenocarcinoma phase III trials that have included patients with lower esophageal and/or EGJ cancer.

First-line therapy with 2-drug chemotherapy regimens is preferred for patients with advanced or metastatic disease. Three-drug regimens should be reserved for medically fit patients with good performance status and access to frequent toxicity evaluation. The selection of a second-line therapy regimen depends on prior therapy and performance status. The panel consensus was that no category 1 evidence supports any specific regimens as second-line or third-line therapy for patients with advanced or metastatic disease. This remains an active area of investigation.

Based on the results of the ToGA trial, the guidelines recommend trastuzumab with chemotherapy for patients with a tumor score of IHC 3+ and IHC 2+ with evidence of *HER2* amplification by FISH (HER2:CEP17 ratio ≥2).[23] Trastuzumab is not recommended for patients with a tumor score of IHC 0 or 1+. The use of trastuzumab in combination with an anthracycline is not recommended. Based on recent FDA approvals, the guidelines have included ramucirumab as a single agent or in combination with paclitaxel as options for second-line therapy in patients with advanced or metastatic esophageal or EGJ adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma).[114,115]

Best supportive care is always indicated for patients with locally advanced, metastatic, or recurrent disease. The decision to offer best supportive care alone or with chemotherapy is dependent on the patient's performance status (see ESOPH-19, page 204). Karnofsky Performance Status (KPS)[126,127] and ECOG Performance Status (ECOG PS)[128] are the 2 commonly used scales to assess the performance status of patients with cancer. Patients with a KPS score of 60 or lower or an ECOG PS score of 3 or higher should probably be offered best supportive care only. Patients with better performance status (KPS score ≥60 or an ECOG PS score ≤2) may be offered chemotherapy along with best supportive care. Further treatment after 2 sequential regimens depends on the patient's performance status and availability of clinical trials. See "Principles of Systemic Therapy" for a list of specific regimens (ESOPH-14, page 199).

Summary

Multidisciplinary team management is essential for patients with esophageal and EGJ cancers. Several advances have been made in staging procedures and therapeutic approaches. Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal and EGJ cancers. Trastuzumab plus chemotherapy is recommended for patients with HER2/neu-positive advanced or metastatic adenocarcinoma. Ramucirumab as a single agent or in combination with paclitaxel is included as option for second-line therapy for patients with advanced or metastatic adenocarcinoma. Best supportive care is an integral part of treatment, especially in patients with locally advanced or metastatic disease. The panel encourages patients to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
3. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. Int J Epidemiol 2001;30:1415–1425.
4. Pickens A, Orringer MB. Geographical distribution and racial disparity in esophageal cancer. Ann Thorac Surg 2003;76:S1367–1369.
5. Siewert JR, Katja O. Are squamous and adenocarcinomas of the esophagus the same disease? Semin Radiat Oncol 2007;17:38–44.
6. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white americans by sex, stage, and age. J Natl Cancer Inst 2008;100:1184–1187.
7. Siewert JR, Stein HJ, Feith M, et al. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360–367.
8. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th edition. New York, NY: Springer; 2010.
9. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. Dis Esophagus 2009;22:1–8.
10. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. Radiographics 2009;29:403–421.
11. Siewert JR. Carcinoma of the cardia: carcinoma of the gastroesophageal junction classification, pathology, and extent of resection. Dis Esophagus 1996;9:173–182.
12. Siewert JR, 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.
13. Hechtman JF, Polydorides AD. HER2/neu gene amplification and protein overexpression in gastric and gastroesophageal junction adenocarcinoma: a review of histopathology, diagnostic testing, and clinical implications. Arch Pathol Lab Med 2012;136:691–697.
14. Dreilich M, Wanders A, Brattstrom D, et al. HER-2 overexpression (3+) in patients with squamous cell esophageal carcinoma correlates with poorer survival. Dis Esophagus 2006;19:224–231.
15. Reichelt U, Duesedau P, Tsourlakis MC, et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol 2007;20:120–129.

16. Schoppmann SF, Jesch B, Friedrich J, et al. Expression of Her-2 in carcinomas of the esophagus. Am J Surg Pathol 2010;34:1868–1873.
17. Moelans CB, van Diest PJ, Milne AN, Offerhaus GJ. Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. Patholog Res Int 2011;2011:674182.
18. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008;19:1523–1529.
19. Tanner M, Hollmen M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005;16:273–278.
20. Bang Y, Chung H, Xu J, et al. Pathological features of advanced gastric cancer (GC): relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 4556.
21. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008;52:797–805.
22. Ruschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 2010;457:299–307.
23. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–697.
24. Barros-Silva JD, Leitao D, Afonso L, et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 2009;100:487–493.
25. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–2084.
26. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.
27. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 2006;24:4277–4284.
28. Krasna MJ, Reed CE, Jaklitsch MT, et al. Thoracoscopic staging of esophageal cancer: a prospective, multiinstitutional trial. Cancer and Leukemia Group B Thoracic Surgeons. Ann Thorac Surg 1995;60:1337–1340.
29. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–1137.
30. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123:175–183.
31. Rusch VW. Are cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several? Semin Oncol 2004;31:444–449.
32. Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophagogastric junction. Scand J Surg 2006;95:260–269.
33. de Graaf GW, Ayantunde AA, Parsons SL, et al. The role of staging laparoscopy in oesophagogastric cancers. Eur J Surg Oncol 2007;33:988–992.
34. Nath J, Moorthy K, Taniere P, et al. Peritoneal lavage cytology in patients with oesophagogastric adenocarcinoma. Br J Surg 2008;95:721–726.
35. Groth SS, Virnig BA, Whitson BA, et al. Determination of the minimum number of lymph nodes to examine to maximize survival in patients with esophageal carcinoma: data from the Surveillance Epidemiology and End Results database. J Thorac Cardiovasc Surg 2010;139:612–620.
36. Peyre CG, Hagen JA, DeMeester SR, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg 2008;248:979–985.
37. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg 2010;251:46–50.
38. Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. J Clin Oncol 2007;25:4110–4117.
39. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593–1598.
40. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623–1627.
41. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–1174.
42. Li QQ, Liu MZ, Hu YH, et al. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. Dis Esophagus 2010;23:253–259.
43. Ruppert BN, Watkins JM, Shirai K, et al. Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol 2010;33:346–352.
44. Meerten EV, van Rij C, Tesselaar ME, et al. Definitive concurrent chemoradiation (CRT) with weekly paclitaxel and carboplatin for patients (pts) with irresectable esophageal cancer: a phase II study [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract e14508.
45. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305–314.
46. Iyer R, Wilkinson N, Demmy T, Javle M. Controversies in the multimodality management of locally advanced esophageal cancer: evidence-based review of surgery alone and combined-modality therapy. Ann Surg Oncol 2004;11:665–673.
47. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185:538–543.
48. Fiorica F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. Gut 2004;53:925–930.
49. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681–692.
50. Swisher SG, Hofstetter W, Komaki R, et al. Improved long-term outcome with chemoradiotherapy strategies in esophageal cancer. Ann Thorac Surg 2010;90:892–898; discussion 898–899.
51. Cen P, Correa AM, Le JH, et al. Adenocarcinoma of the lower esophagus with Barrett's esophagus or without Barrett's esophagus: differences in patients' survival after preoperative chemoradiation. Dis Esophagus 2009;22:32–41.
52. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462–467.
53. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161–167.
54. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–313.
55. Bains MS, Stojadinovic A, Minsky B, et al. A phase II trial of preoperative combined-modality therapy for localized esophageal carcinoma: initial results. J Thorac Cardiovasc Surg 2002;124:270–277.
56. Kaklamanos IG, Walker GR, Ferry K, et al. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. Ann Surg Oncol 2003;10:754–761.
57. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659–668.
58. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416–2422.
59. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 2014;32:385–391.
60. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086–1092.
61. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for

adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 2011;47:354–360.

62. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–730.
63. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327–2333.
64. Bedard EL, Inculet RI, Malthaner RA, et al. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. Cancer 2001;91:2423–2430.
65. Rice TW, Adelstein DJ, Chidel MA, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. J Thorac Cardiovasc Surg 2003;126:1590–1596.
66. Kofoed SC, Muhic A, Baeksgaard L, et al. Survival after adjuvant chemoradiotherapy or surgery alone in resectable adenocarcinoma at the gastro-esophageal junction. Scand J Surg 2012;101:26–31.
67. Adelstein DJ, Rice TW, Rybicki LA, et al. Mature results from a phase II trial of postoperative concurrent chemoradiotherapy for poor prognosis cancer of the esophagus and gastroesophageal junction. J Thorac Oncol 2009;4:1264–1269.
68. Fuchs CS, Tepper JE, Niedzwiecki D, et al. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101[abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 4003.
69. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979–1984.
70. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol 2007;25:3719–3725.
71. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727–1733.
72. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–5067.
73. Boonstra JJ, Kok TC, Wijnhoven BP, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer 2011;11:181.
74. Thirion PG, Michiels S, Le Maitre A, et al. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in resectable oesophageal carcinoma [abstract]. J Clin Oncol 2007;25(Suppl 18):Abstract 4512.
75. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715–1721.
76. Leichman L, Berry BT. Experience with cisplatin in treatment regimens for esophageal cancer. Semin Oncol 1991;18:64–72.
77. Muhr-Wilkenshoff F, Hinkelbein W, Ohnesorge I, et al. A pilot study of irinotecan (CPT-11) as single-agent therapy in patients with locally advanced or metastatic esophageal carcinoma. Int J Colorectal Dis 2003;18:330–334.
78. Enzinger PC, Kulke MH, Clark JW, et al. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. Dig Dis Sci 2005;50:2218–2223.
79. Burkart C, Bokemeyer C, Klump B, et al. A phase II trial of weekly irinotecan in cisplatin-refractory esophageal cancer. Anticancer Res 2007;27:2845–2848.
80. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 2004;15:955–959.
81. Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007;24:407–412.
82. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994;86:1086–1091.
83. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898–902.
84. Harstrick A, Bokemeyer C, Preusser P, et al. Phase II study of single-agent etoposide in patients with metastatic squamous-cell carcinoma of the esophagus. Cancer Chemother Pharmacol 1992;29:321–322.
85. Ilson DH, Ajani J, Bhalla K, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998;16:1826–1834.
86. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998;78:511–514.
87. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000;6:316–323.
88. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005;23:5660–5667.
89. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991–4997.
90. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010;66:31–36.
91. Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19:1882–1887.
92. Shankaran V, Mulcahy MF, Hochster HS, et al. Docetaxel, oxaliplatin, and 5-fluorouracil for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinomas: preliminary results of a phase II study [abstract]. Presented at 2009 ASCO Gastrointestinal Cancers Symposium; January 15–17, 2009; San Francisco, California. Abstract 47.
93. Overman MJ, Kazmi SM, Jhamb J, et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010;116:1446–1453.
94. Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. Br J Cancer 2010;102:475–481.
95. Stein A, Arnold D, Thuss-Patience PC, et al. Docetaxel, oxaliplatin and capecitabine (TEX regimen) in patients with metastatic gastric or gastro-esophageal cancer: results of a multicenter phase I/II study. Acta Oncol 2014;53:392–398.
96. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36–46.
97. Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22–25.
98. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008;19:1450–1457.
99. Wolff K, Wein A, Reulbach U, et al. Weekly high-dose 5-fluorouracil as a 24-h infusion and sodium folinic acid (AIO regimen) plus irinotecan in patients with locally advanced nonresectable and metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus: a phase II trial. Anticancer Drugs 2009;20:165–173.
100. Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. Ann Oncol 2009;20:1242–1248.
101. Lustberg MB, Bekaii-Saab T, Young D, et al. Phase II randomized study of two regimens of sequentially administered mitomycin C and irinotecan in patients with unresectable esophageal and gastroesophageal adenocarcinoma. J Thorac Oncol 2010;5:713–718.
102. Moehler M, Kanzler S, Geissler M, et al. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic

adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2010;21:71–77.

103. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014;32:3520–3526.

104. Assersohn L, Brown G, Cunningham D, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol 2004;15:64–69.

105. Leary A, Assersohn L, Cunningham D, et al. A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol 2009;64:455–462.

106. Mauer AM, Kraut EH, Krauss SA, et al. Phase II trial of oxaliplatin, leucovorin and fluorouracil in patients with advanced carcinoma of the esophagus. Ann Oncol 2005;16:1320–1325.

107. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435–1442.

108. El-Rayes BF, Shields A, Zalupski M, et al. A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 2004;15:960–965.

109. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20:1996–2004.

110. Urba SG, Chansky K, VanVeldhuizen PJ, et al. Gemcitabine and cisplatin for patients with metastatic or recurrent esophageal carcinoma: a Southwest Oncology Group study. Invest New Drugs 2004;22:91–97.

111. Millar J, Scullin P, Morrison A, et al. Phase II study of gemcitabine and cisplatin in locally advanced/metastatic oesophageal cancer. Br J Cancer 2005;93:1112–1116.

112. Homs MY, van der Gaast A, Siersema PD, et al. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. Cochrane Database Syst Rev 2006:CD004063.

113. Shah MA, Schwartz GK. Treatment of metastatic esophagus and gastric cancer. Semin Oncol 2004;31:574–587.

114. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31–39.

115. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–1235.

116. van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 2004;22:3805–3812.

117. Rosenbaum S, Stergar H, Antoch G, et al. Staging and follow-up of gastrointestinal tumors with PET/CT. Abdominal Imaging 2006;31:25–35.

118. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated CT-PET in initial staging and response assessment after preoperative therapy. J Thorac Imaging 2006;21:137–145.

119. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202–3210.

120. Flamen P, Lerut T, Haustermans K, et al. Position of positron emission tomography and other imaging diagnostic modalities in esophageal cancer. Q J Nucl Med Mol Imaging 2004;48:96–108.

121. Cerfolio RJ, Bryant AS, Ohja B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1232–1241.

122. Blencowe NS, Whistance RN, Strong S, et al. Evaluating the role of fluorodeoxyglucose positron emission tomography-computed tomography in multi-disciplinary team recommendations for oesophago-gastric cancer. Br J Cancer 2013;109:1445–1450.

123. Du C, Zhou Y, Huang K, et al. Defining a high-risk subgroup of pathological T2N0 gastric cancer by prognostic risk stratification for adjuvant therapy. J Gastrointest Surg 2011;15:2153–2158.

124. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306–2314.

125. Ford HER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78–86.

126. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York Columbia University Press: New York, NY; 1949:199–205.

127. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187–193.

128. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.

Individual Disclosures of the NCCN Esophageal and Esophagogastric Junction Cancers

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Jaffer A. Ajani, MD	Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; ImClone Systems Incorporated; Novartis Pharmaceuticals Corporation; Ascenta Therapeutics, Inc.; Genta Incorporated; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Pharmaceuticals Co., Ltd.	Bristol-Myers Squibb Company; Eli Lilly and Company; and sanofi-aventis U.S.	None	None	9/30/14
Khaldoun Almhanna, MD, MPH	None	Eli Lilly and Company; and Genentech, Inc.	None	None	10/28/14
David J. Bentrem, MD	None	None	None	None	12/9/13
Stephen Besh, MD	None	None	None	None	9/17/14
Joseph Chao, MD	Cerulean Pharma Inc.	None	None	None	5/21/14
Thomas A. D`Amico, MD	None	Scanlan	None	None	10/5/12
Prajnan Das, MD, MS, MPH	None	None	None	None	11/7/14
Crystal S. Denlinger, MD	Bayer HealthCare; Genentech, Inc.; ImClone Systems Incorporated; MedImmune Inc.; OncoMed Pharmaceuticals; Astex Pharmaceuticals; Merrimack Pharmaceuticals; and Pfizer Inc.	Eli Lilly and Company	None	None	10/16/14
Paul Fanta, MD	None	None	None	None	7/28/14
Charles S. Fuchs, MD, MPH	Amgen Inc.; and Eli Lilly and Company	Amgen Inc.; Bayer HealthCare; Eli Lilly and Company; Genentech, Inc.; MedImmune Inc.; Acceleron Pharma, Inc.; Metamark Genetics, Inc.; Momenta Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Takeda Pharmaceuticals North America, Inc.	None	None	6/9/14
Hans Gerdes, MD	None	None	None	None	9/23/14
Robert E. Glasgow, MD	None	None	None	None	8/13/14
James A. Hayman, MD, MBA	None	None	None	None	1/20/15
Steven Hochwald, MD	None	Ethicon, Inc.	None	None	7/31/14
Wayne L. Hofstetter, MD	None	None	None	None	8/6/14
David H. Ilson, MD, PhD	Amgen Inc.; Bayer HealthCare; and Bristol-Myers Squibb Company	Amgen Inc.; Eli Lilly and Company; and Genentech, Inc.	None	None	1/14/14
Dawn Jaroszewski, MD	None	None	None	None	11/25/14
Kory Jasperson, MS, CGC	None	Guidepoint Global; and McKesson Health Solutions	None	None	12/2/14
Rajesh N. Keswani, MD	None	Boston Scientific; and Cook Medical	None	None	11/1/14
Lawrence R. Kleinberg, MD	None	None	None	None	9/4/14
W. Michael Korn, MD	None	Genentech, Inc.; Merrimack Pharmaceuticals	None	None	10/15/13
Stephen Leong, MD	Genentech, Inc.; and Pfizer Inc.	None	None	None	8/26/14
A. Craig Lockhart, MD, MHS	Amgen Inc.; Bayer HealthCare; Cephalon, Inc.; Daiichi- Sankyo Co.; Genentech, Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Allos Therapeutics, Inc.; Eli Lilly and Company; ImClone Systems Incorporated; Zenyaku Kogyo Co., Ltd.; Pfizer Inc.; and sanofi-aventis U.S.	None	None	None	10/10/13
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James A. Posey, MD	None	None	None	None	4/16/14
George A. Poultsides, MD	Stanford University	None	None	None	8/2/14
Aaron R. Sasson, MD	None	Genentech, Inc.; and Novartis Pharmaceuticals Corporation	None	None	1/10/14
Walter J. Scott, MD	None	None	Celgene Corporation; and Johnson & Johnson	None	8/12/14
Vivian E. Strong, MD	None	None	None	None	8/2/14
Thomas K. Varghese Jr, MD	None	None	None	None	8/21/14
Mary Kay Washington, MD, PhD	None	None	None	None	10/14/13
Christopher G. Willett, MD	None	None	None	None	6/6/14
Cameron D. Wright, MD	None	None	None	None	9/7/14
Debra Zelman, Esq	None	Debbie's Dream Foundation: Curing Stomach Cancer	None	None	5/8/14

Hema Sundar, PhD, has disclosed that her spouse is employed by Kashiv Pharma LLC. The remaining guidelines staff have no conflicts to disclose.