National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Esophageal and Esophagogastric Junction Cancers

Version 2.2022 — February 11, 2022

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Esophageal and Esophagogastric Junction Cancers

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¤ Gastroenterology
Δ Genetics
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial.
Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2022 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 1.2022 include:

MS-1

- The Discussion has been updated to reflect the changes in the algorithm.

Updates in Version 1.2022 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 4.2021 include:

Squamous Cell Carcinoma and Adenocarcinoma

ESOPH-1

- Workup
  - 10th bullet revised: "~~MSI by PCR/MMR by IHC,~~ Microsatellite *instability* (MSI) and PD-L1...."
  - 12th bullet revised: ~~If sufficient tissue is available after the above testing has been completed,~~ *N*ext-generation sequencing (NGS) may be considered
  - New bullet added: If anemia is suspected, See NCCN Guidelines for Hematopoietic Growth Factors

ESOPH-3 and ESOPH-8, ESOPH-12, and ESOPH-17

- Primary Treatment Options for Medically Fit Patients
  - pTis: The list of preferred endoscopic therapies was reordered. "ER followed by ablation" moved up to be second in the list of options. Previously it was listed last. A similar change was also made to the endoscopic therapy options on the pages noted above.

ESOPH-10 and ESOPH-19

- Unresectable locally advanced, Locally recurrent, or Metastatic disease; Third column revised: Perform ~~MSI by PCR/MMR by IHC~~ *microsatellite* and PD-L1 testing (if not done previously) if metastatic ~~squamous cell carcinoma~~ *cancer* is suspected
- Bullet revised: ~~If sufficient tissue is available after the above testing has been completed,~~ NGS may be considered *via validated assay*

Adenocarcinoma

ESOPH-15

- Postoperative Management for Patients Who Have Not Received Preoperative Chemoradiation or Chemotherapy
  - R0 resection;
    - ◊ Node negative; pT3, pT4a: Chemotherapy was added as an option
    - ◊ Node positive (Any T): Surveillance added as an option.

Squamous Cell Carcinoma and Adenocarcinoma

ESOPH-B Principles of Pathologic Review and Biomarker Testing

3 of 6

- Assessment of Overexpression or Amplification of HER2 in Esophageal and Esophagogastric Junction Cancers
  - Revised: "... a traditional biopsy. ~~It should be noted that NGS has several inherent limitations and thus whenever possible,~~ The use of ~~gold-standard assays (~~IHC/ISH~~)~~ should be ~~performed~~ *considered* first*, followed by* ~~and if sufficient tissue is available, additional~~ NGS testing ~~may be considered~~ *as appropriate*. ~~Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic esophageal/EGJ adenocarcinoma~~."

4 of 6

- Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing
  - Revised: "Testing for MSI by polymerase chain reaction (PCR)*/NGS* or MMR... in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines. ~~MMR or MSI~~ *T*esting ~~may~~ *should* be performed only in CLIA-approved laboratories..."
  - Footnote l revised: PCR*/NGS* for MSI and IHC for MMR proteins measure..."

5 of 6

- Next-Generation Sequencing (NGS):
  - Revised: At present, ~~three~~ *several* targeted therapeutic agents, trastuzumab, ~~ramucirumab, and~~ pembrolizumab*/nivolumab*, *and entrectinib/larotrectinib,* have been approved by the FDA for use in esophageal and EGJ cancers. Trastuzumab is based on testing for HER2 ~~positivity~~ *overexpression*. Pembrolizumab*/nivolumab* ~~is~~ *are* based on testing for MSI by ~~PCR/MMR~~ *PCR or NGS/MMR* by IHC, PD-L1 *immunohistochemical* expression, by CPS or high tumor mutational burden (TMB) by NGS...In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI *status*, MMR ~~mutations~~ *deficiency*, TMB, and *NTRK* gene fusions. ~~It should be noted that NGS has several inherent limitations and thus whenever possible,~~ The use of ~~gold-standard assays (~~IHC/~~FISH~~ ISH/ targeted PCR~~)~~ should be ~~performed~~ *considered* first ~~and if sufficient tissue is available, additional~~ *followed by* NGS testing ~~may be considered~~ *as appropriate*.

Continued

UPDATES

Squamous Cell Carcinoma and Adenocarcinoma

ESOPH-B Principles of Pathologic Review and Biomarker Testing (continued)

5 of 6

- **Liquid Biopsy**
  - **"...Liquid biopsy is being used more frequently in patients with advanced disease*, particularly those* who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers ~~and are~~ *who may be* unable to undergo a traditional biopsy *or for disease progression monitoring*, testing using a validated NGS-based comprehensive genomic profiling assay....**

ESOPH-D Principles of Genetic Risk Assessment

- **Criteria for Further Risk Evaluation for High-Risk Syndromes**
  - **New bullet added: The most efficient strategy to identify a causative gene mutation in a family is to test a close relative with cancer. If the relative is either unwilling or unavailable for testing, then consider testing of an unaffected relative. A detailed discussion of genetic counseling and testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**

Principles of Systemic Therapy

ESOPH-F 1 of 17

- **4th bullet revised: "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.~~ *The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations*.**

Principles of Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease

ESOPH-F 3 of 17

- **First-line Therapy; Preferred Regimens; HER2 overexpression negative; Revised as follows**
  - **Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma only (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS ~~1-4~~ <*5*)**
  - **Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS ~~1-9~~ <*10*)**
  - **Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS ~~1-9~~ <*10*)**
  - **Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin ~~for adenocarcinoma or squamous cell carcinoma~~**
  - **Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin ~~for adenocarcinoma or squamous cell carcinoma~~**

ESOPH-F 4 of 17

- **Second-line or Subsequent Therapy; Useful in Certain Circumstances: *Dostarlimab-gxly for MSI-H or dMMR tumors* was added as an option.**
- **Footnote k is new: For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.**

Continued
UPDATES

Squamous Cell Carcinoma and Adenocarcinoma

Principles of Systemic Therapy-Regimens and Dosing Schedules

ESOPH-F 5 of 17

- **Preoperative Chemoradiation; Other Recommended Regimens**
  Irinotecan and cisplatin dosing was clarified as *cycled every 35 days*. (Also for ESOPH-F 7 of 17)

ESOPH-F 6 of 17

- **Perioperative Chemotherapy (Only for adenocarcinoma of the thoracic esophagus or EGJ)**
  - **Preferred Regimens: Dose schedule revised for Fluoropyrimidine and oxaliplatin: ~~3~~ *4* cycles preoperative and ~~3~~ *4* cycles postoperative**

ESOPH-F 8 of 17

- **Postoperative chemoradiation (only for EGJ adenocarcinoma): Dosing for Fluorouracil and Capecitabine were revised to include the following statement, *For cycles after chemoradiation, begin chemotherapy 1 month after chemoradiation*.**

ESOPH-F 12 of 17

- **First-Line Therapy; Other Recommended Regimens**
  - **Dosing revised for "Paclitaxel with or without cisplatin or carboplatin"**
    - **Paclitaxel 135–200 mg/m² IV on Day 1**
      Cisplatin 75 mg/m² IV on Day ~~2~~ *1*
      Cycled every 21 days
    - **Paclitaxel 80 mg/m² IV ~~on Day 1~~ weekly**
      Cycled every 28 days

ESOPH-F 14 of 17

- **Second-line or Subsequent Therapy; Useful in Certain Circumstances; Dosing was added for:**
  Dostarlimab-gxly
  (for MSI-H/dMMR tumors)
  Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1,000 mg IV every 6 weeks

Principles of Systemic Therapy-References

ESOPH-F 15 of 17 to ESOPH-F 17 of 17

- **References were updated.**
- **Reference for Dostarlimab-gxly was added: Berton D, Banerjee SN, Curigliano G, et al. Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability–high tumors: A combined analysis of two cohorts in the GARNET study. J Clin Oncol 2021;39(15_suppl):Abstract 2564.**

ESOPH-G Principles of Radiation

ESOPH-G 1 of 5

- **Simulation and Treatment Planning; 1st bullet revised: CT simulation and conformal treatment planning should be used *with either 3D conformal radiation or* intensity-modulated radiation therapy (IMRT). ~~or~~ *P*roton beam therapy is appropriate in clinical settings where reduction in dose to organs at risk (eg, heart, lungs) is required that cannot be achieved by 3-D techniques*, ideally within a clinical trial or registry study.***

ESOPH-G 3 of 5

- **Normal Tissue Tolerance Dose-Limits: This section was extensively revised.**

ESOPH-G 4 of 5

- **RT Dosing revised as follows**
  - **Preoperative RT: 41.4–50.4 Gy (1.8–2.0 Gy/day) *(total 23–28 fractions)***
  - **Postoperative RT: 45–50.4 Gy (1.8–2.0 Gy/day) *(total 25–28 fractions)***
  - **Definitive RT: 50–50.4 Gy (1.8–2.0 Gy/day) *(total 25–28 fractions)***
    - **Sub-bullet removed: Higher doses may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned.**
- **Footnote removed: Published studies have reported radiation doses from 60–66 Gy (1.8–2.0 Gy/day). However, there is no randomized evidence to support any benefit or detriment of this dose range over 50–50.4 Gy (1.8–2.0 Gy/day).**

ESOPH-G 5 of 5

- **References were updated.**

Continued

UPDATES

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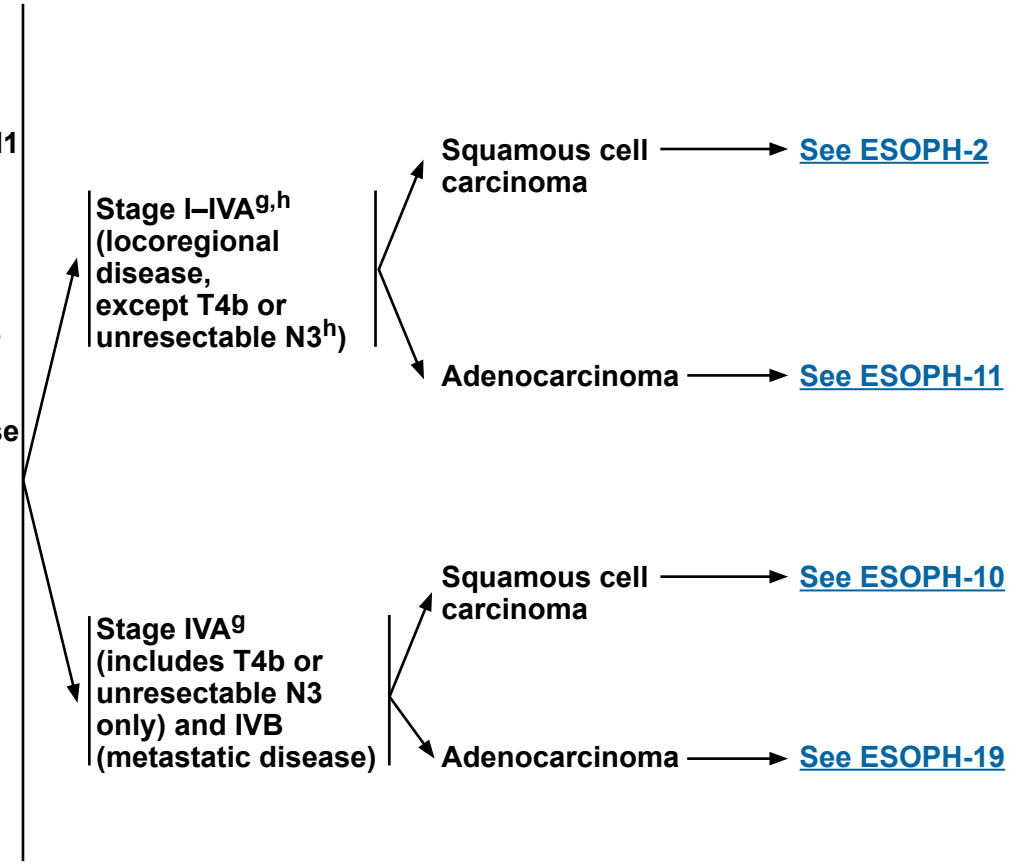
WORKUP

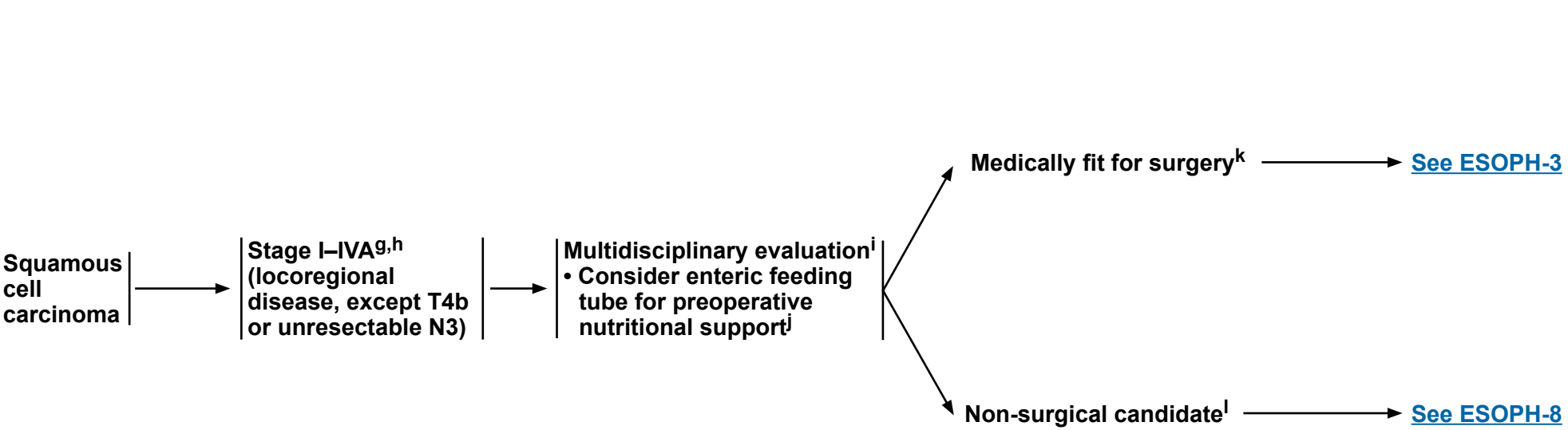
- H&P
- Upper GI endoscopy and biopsy[a]
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT with contrast as clinically indicated
- FDG-PET/CT evaluation (skull base to mid-thigh) if no evidence of M1 disease
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS), if no evidence of M1 unresectable disease
- Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b).[a,b] Early-stage cancers can best be diagnosed by ER
- Biopsy of metastatic disease as clinically indicated
- Microsatellite instability (MSI) and PD-L1 testing if metastatic disease is documented/suspected[c]
- HER2 testing if metastatic adenocarcinoma is documented/suspected[c]
- Next-generation sequencing (NGS) may be considered[c]
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category[d]
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated[e]
- Screen for family history[f]
- If anemia is suspected, See NCCN Guidelines for Hematopoietic Growth Factors

CLINICAL STAGE[g] / HISTOLOGIC CLASSIFICATION[c]



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

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



[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the EGJ/distal esophagus may still be considered for combined modality therapy.
[i] See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[j] Percutaneous gastrostomy tube may be considered for patients with cervical esophageal tumors receiving definitive chemoradiation or for patients with marginally resectable disease. Multidisciplinary expertise is recommended prior to placement of percutaneous gastrostomy tube. The approach, timing, and location of the feeding tube should be discussed with the surgeon prior to its placement.
[k] Medically able to tolerate major surgery.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.

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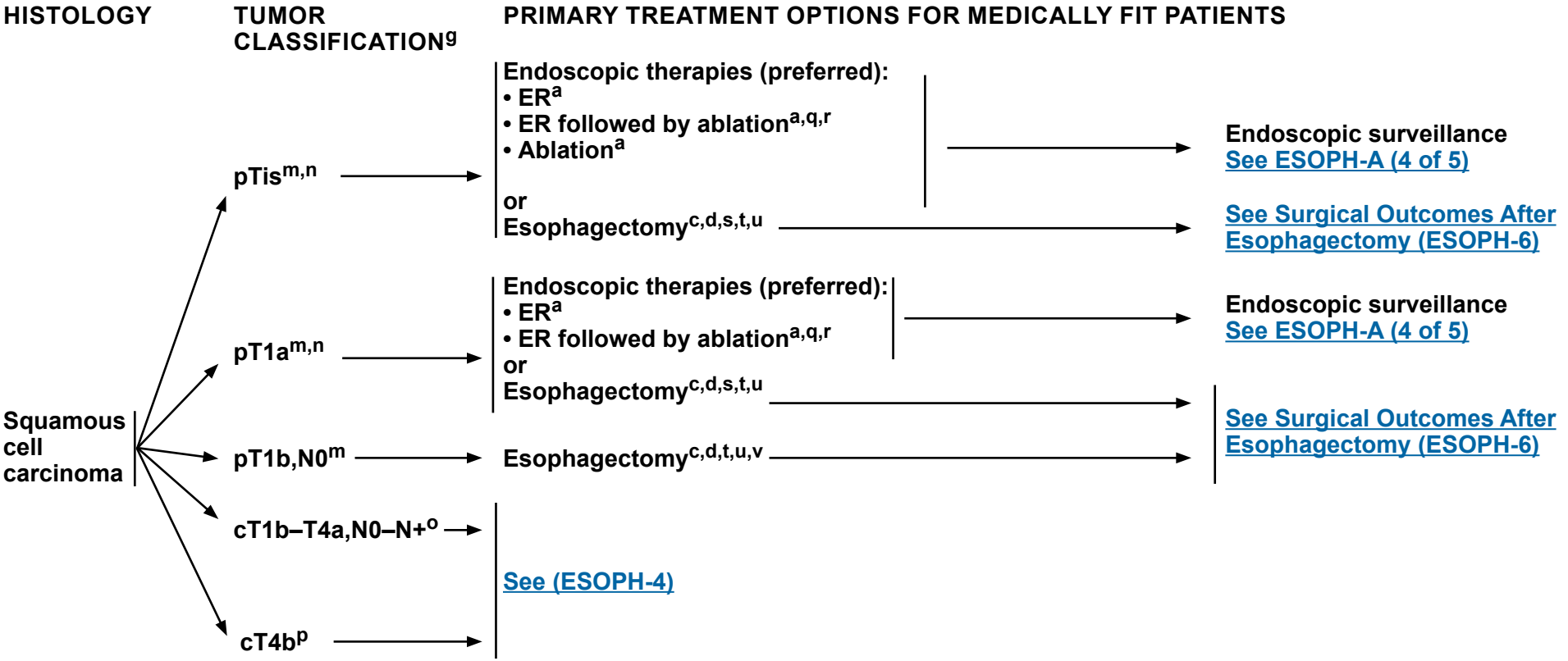

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[m] pTis, pT1a, and pT1b tumor classifications are defined by pathology of the diagnostic ER specimen. See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] For select patients, consider endoluminal stenting when appropriate. See Principles of Palliative/Best Supportive Care (ESOPH-H).
[q] For pTis and pT1a the level of evidence for ablation of SCC after ER is low. However, additional ablation may be needed if there is multifocal high-grade dysplasia (HGD)/carcinoma in situ. Ablation may not be needed if all lesions are completely excised. For references, See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[r] ER followed by ablation may be used to completely eliminate residual dysplasia.
[s] Esophagectomy is indicated for patients with extensive carcinoma in situ (pTis or HGD) or pT1a, especially nodular disease that is not adequately controlled by ablation or ER followed by ablation.
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] Definitive chemoradiation may be an appropriate option for patients who decline surgery; see (ESOPH-8).

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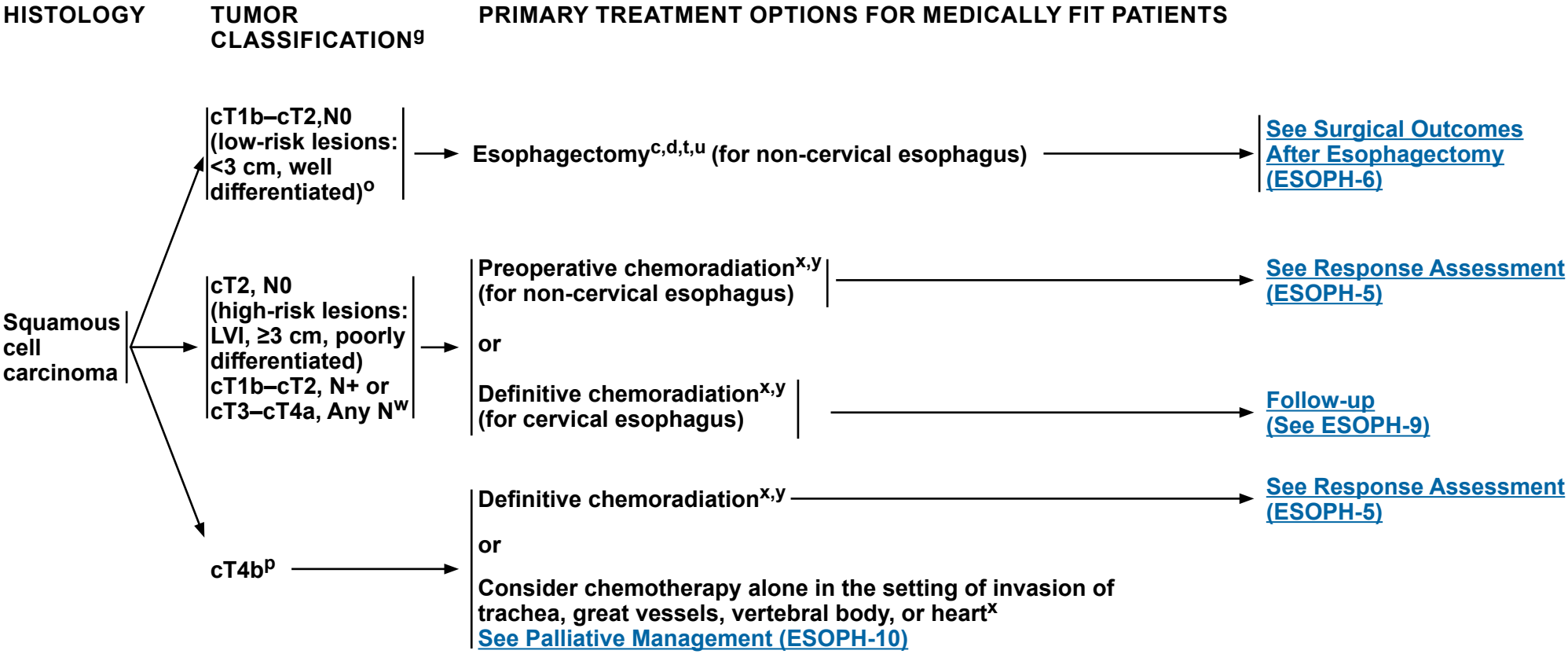

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] For select patients, consider endoluminal stenting when appropriate. See Principles of Palliative/Best Supportive Care (ESOPH-H).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[w] Histologic confirmation of suspected positve node is desirable.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).

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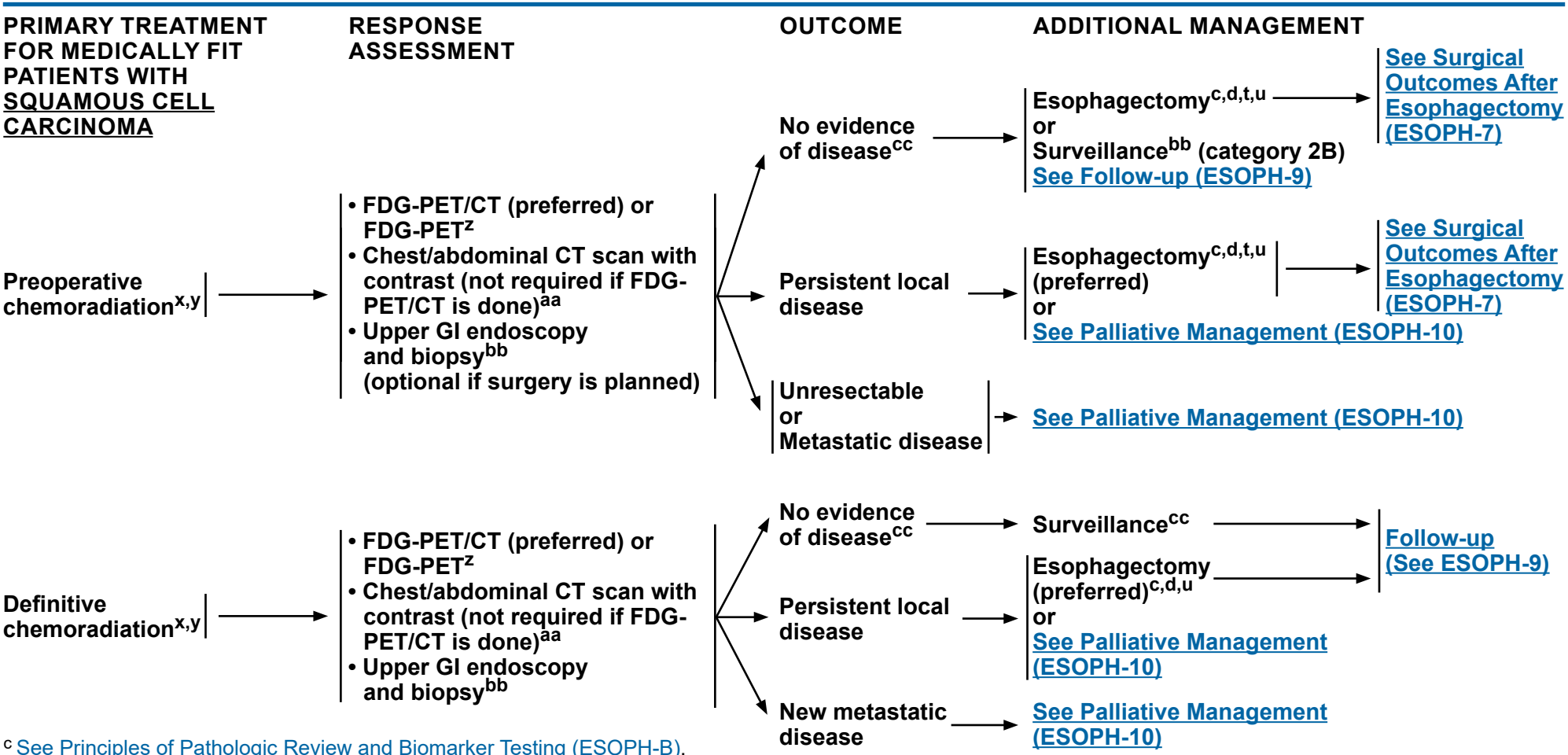

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[z] Assessment ≥5–8 weeks after completion of preoperative therapy.
[aa] Pelvic CT if clinically indicated.
[bb] See Post-Treatment Surveillance–Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[cc] If surgery is not being considered for management, upper GI endoscopy and biopsy should be done.

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Not Received Preoperative Chemoradiation)	TUMOR CLASSIFICATION[g]	POSTOPERATIVE MANAGEMENT	
R0 resection[dd]	p Any T, Any N	Surveillance	Follow-up (See ESOPH-9)
R1 resection[dd]		Chemoradiation[x,y] (Fluoropyrimidine-based)	
R2 resection[dd]		Chemoradiation[x,y] (Fluoropyrimidine-based) or Palliative management (See ESOPH-10)	

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

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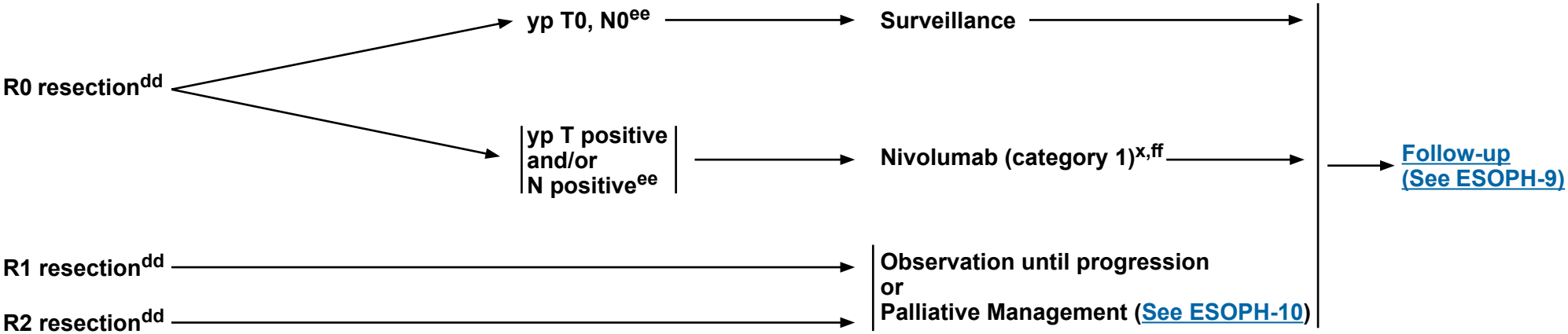
SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g,dd]

POSTOPERATIVE MANAGEMENT



g See Staging (ST-1) for tumor classification.
x See Principles of Systemic Therapy (ESOPH-F).
dd R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
ee The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.
ff See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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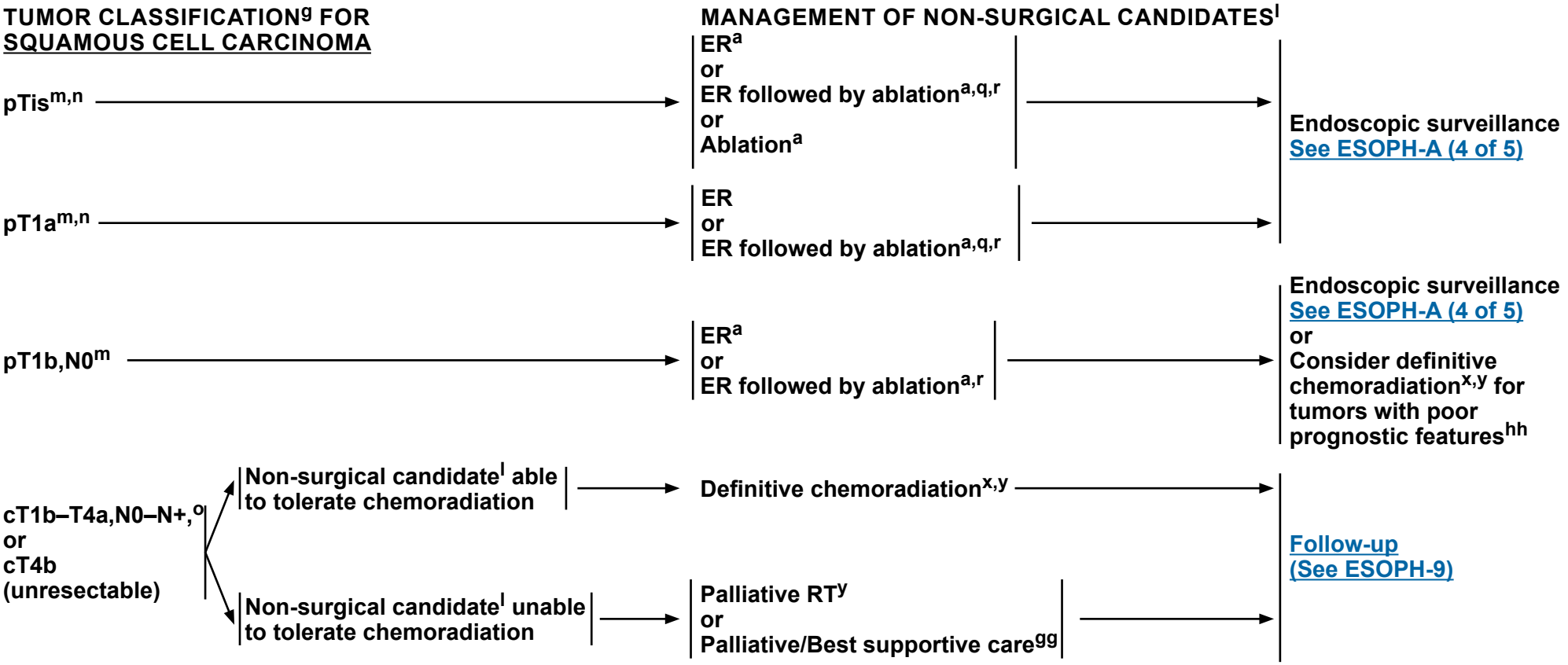

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[g] See Staging (ST-1) for tumor classification.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[m] pTis, pT1a, and pT1b tumor classification are defined by pathology of the diagnostic ER specimen. See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o] Preclinical staging cannot establish the number of positive nodes.
[q] For pTis and pT1a, the level of evidence for ablation of SCC after ER is low. However, additional ablation may be needed if there is multifocal HGD/carcinoma in situ. Ablation may not be needed if all lesions are completely excised. For references, See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[r] ER followed by ablation may be used to completely eliminate residual dysplasia.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[hh] Poor prognostic features include lymphovascular invasion (LVI), poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2 cm or more.

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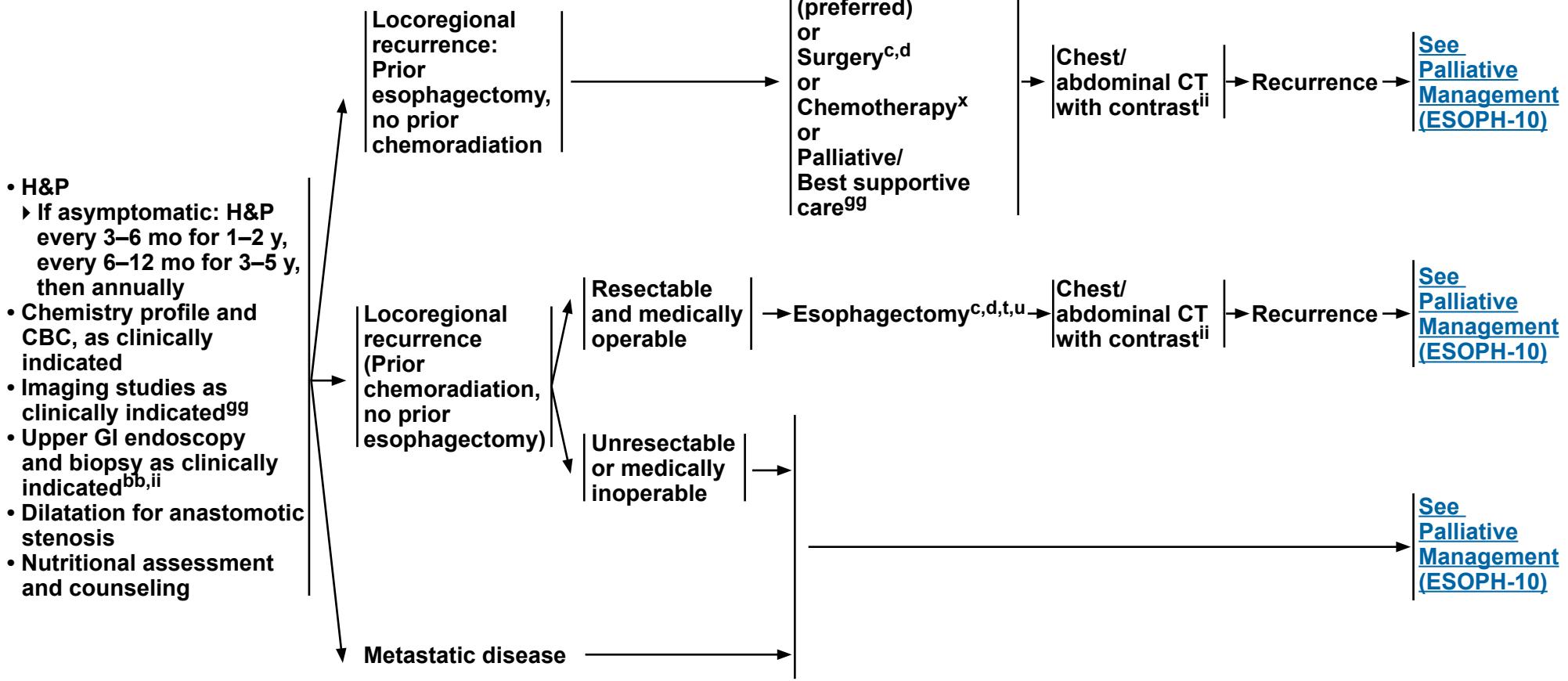
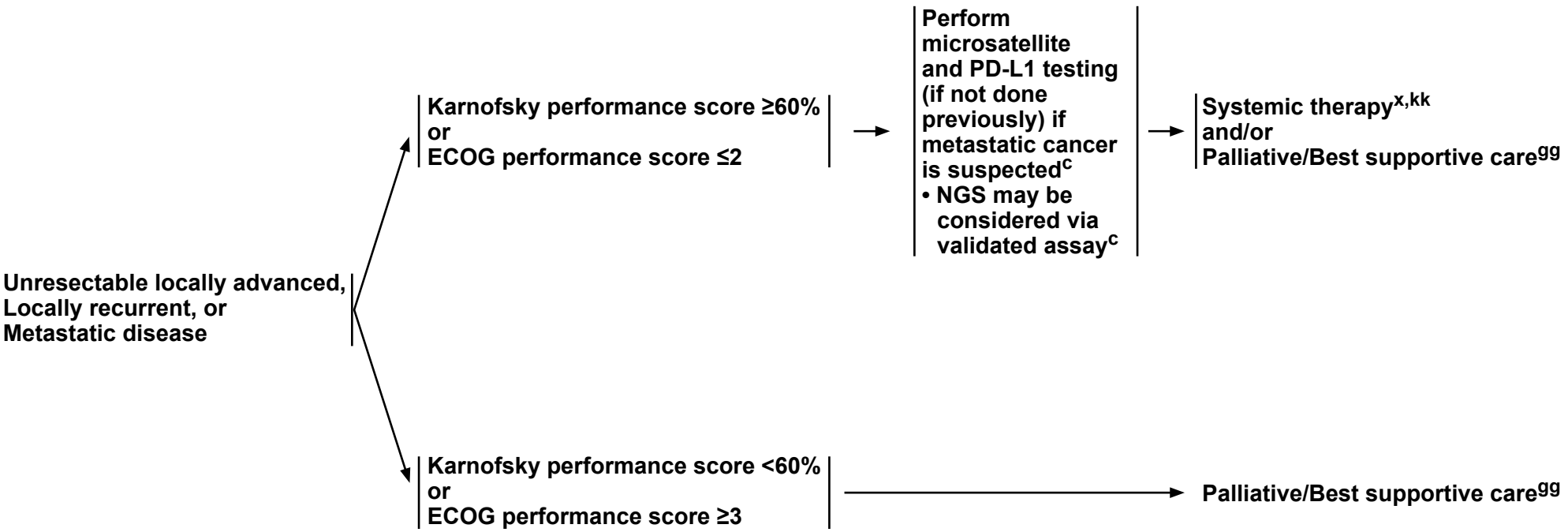
FOLLOW-UP/SURVEILLANCE FOR SQUAMOUS CELL CARCINOMA[ii,jj]



[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[bb] See Post-Treatment Surveillance–Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[ii] See Principles of Surveillance (ESOPH-I).
[jj] See Principles of Survivorship (ESOPH-J).

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

FOR SQUAMOUS CELL CARCINOMA



[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[x] See Principles of Systemic Therapy (ESOPH-F).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[kk] Further treatment after two sequential regimens should be dependent on performance status and availability of clinical trials.

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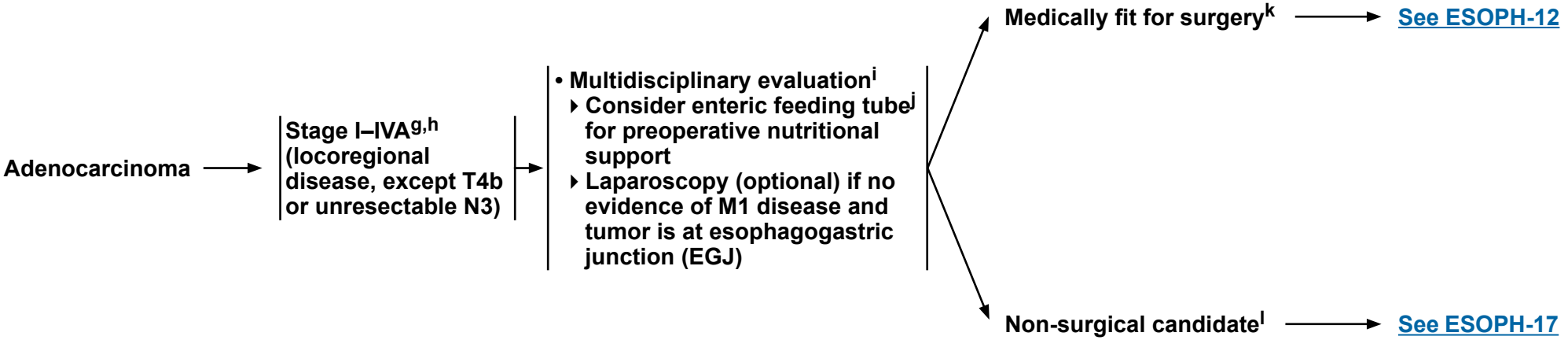
Back to Follow-up and Recurrence (ESOPH-9)



[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the EGJ/distal esophagus may still be considered for combined modality therapy.
[i] See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[j] Percutaneous gastrostomy tube may be considered for patients with cervical esophageal tumors receiving definitive chemoradiation or for patients with marginally resectable disease. Multidisciplinary expertise is recommended prior to placement of percutaneous gastrostomy tube. The approach, timing, and location of the feeding tube should be discussed with the surgeon prior to its placement.
[k] Medically able to tolerate major surgery.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.

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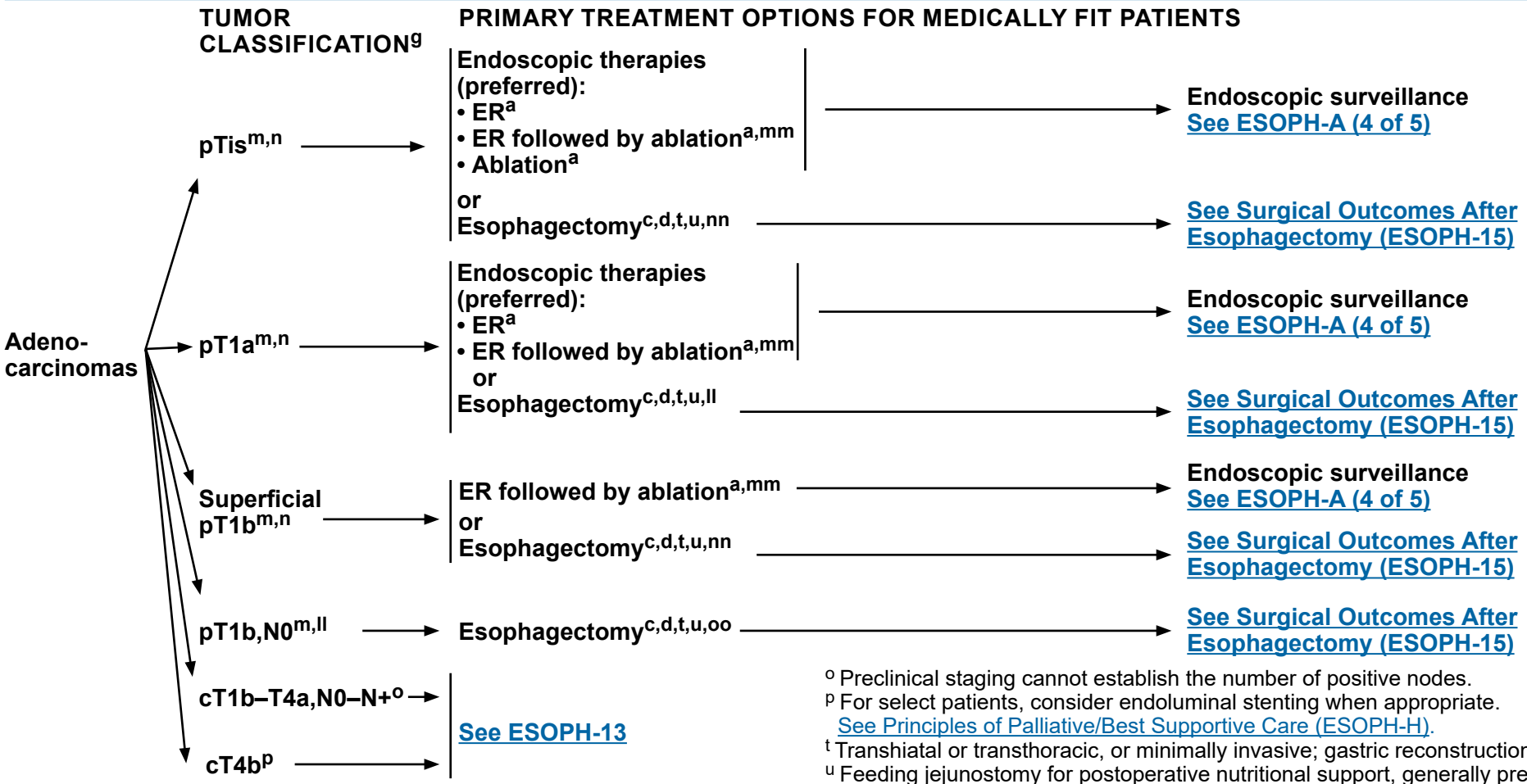

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[m] pTis, pT1a, superficial pT1b, pT1b, N0 tumor classifications are defined by pathology of the diagnostic ER specimen See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] For select patients, consider endoluminal stenting when appropriate. See Principles of Palliative/Best Supportive Care (ESOPH-H).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[ll] Diagnostic ER can be considered to confirm the pathologic staging and for treatment in select patients.
[mm] ER followed by ablation to completely eliminate residual dysplasia or Barrett epithelium.
[nn] Esophagectomy is indicated for patients with extensive carcinoma in situ (pTis or HGD), pT1a, or superficial pT1b, especially nodular disease that is not adequately controlled by ablation or ER followed by ablation.
[oo] Definitive chemoradiation may be an appropriate option for patients who decline surgery, see (ESOPH-17).

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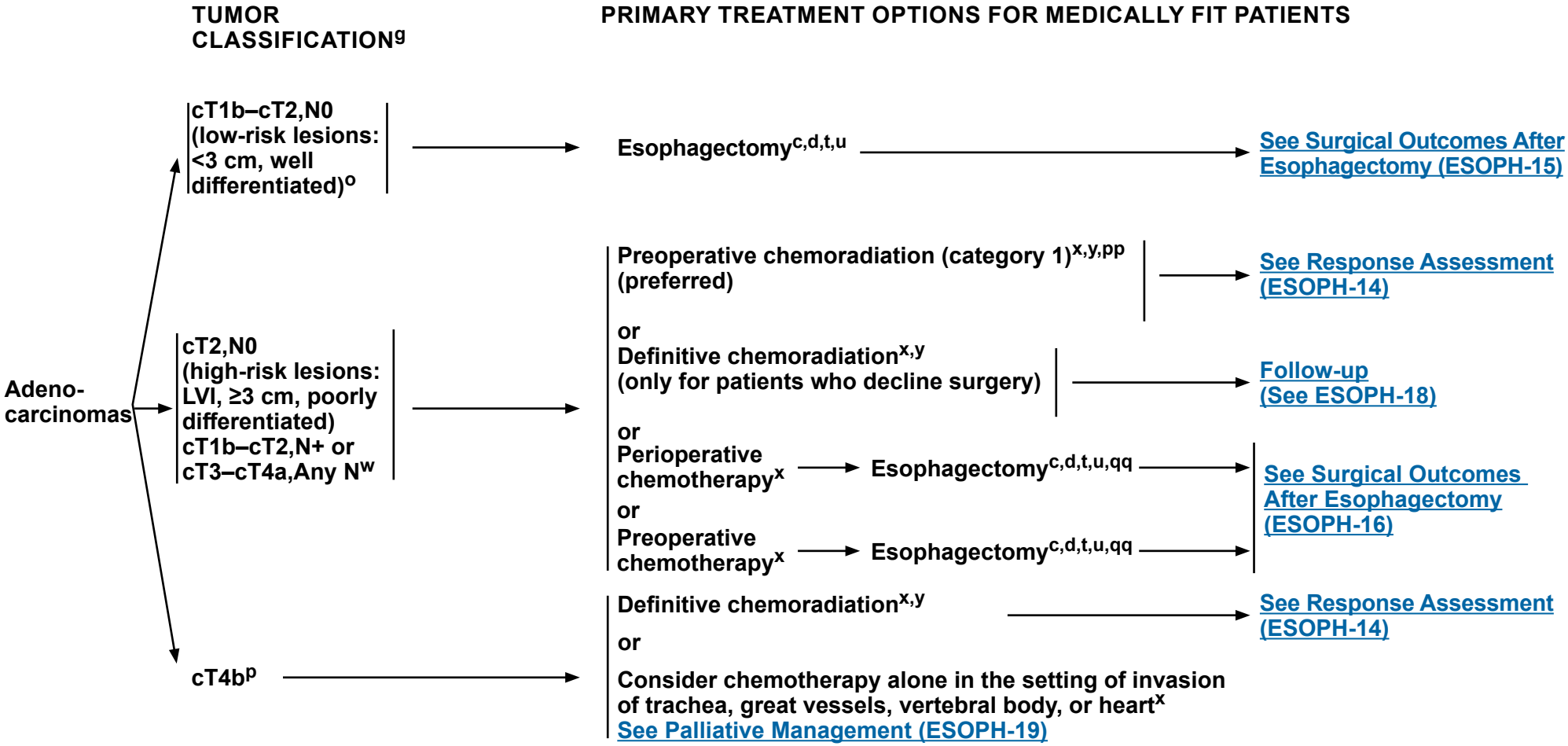

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] For select patients, consider endoluminal stenting when appropriate. See Principles of Palliative/Best Supportive Care (ESOPH-H).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[w] Histologic confirmation of suspected positve node is desirable.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[pp] Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ (van Hagen P, et al. N Engl J Med 2012;366:2074-2084).
[qq] Repeat multidisciplinary consultation is recommended before proceeding to surgery for post-neoadjuvant T4a and bulky multiple nodal station N3.

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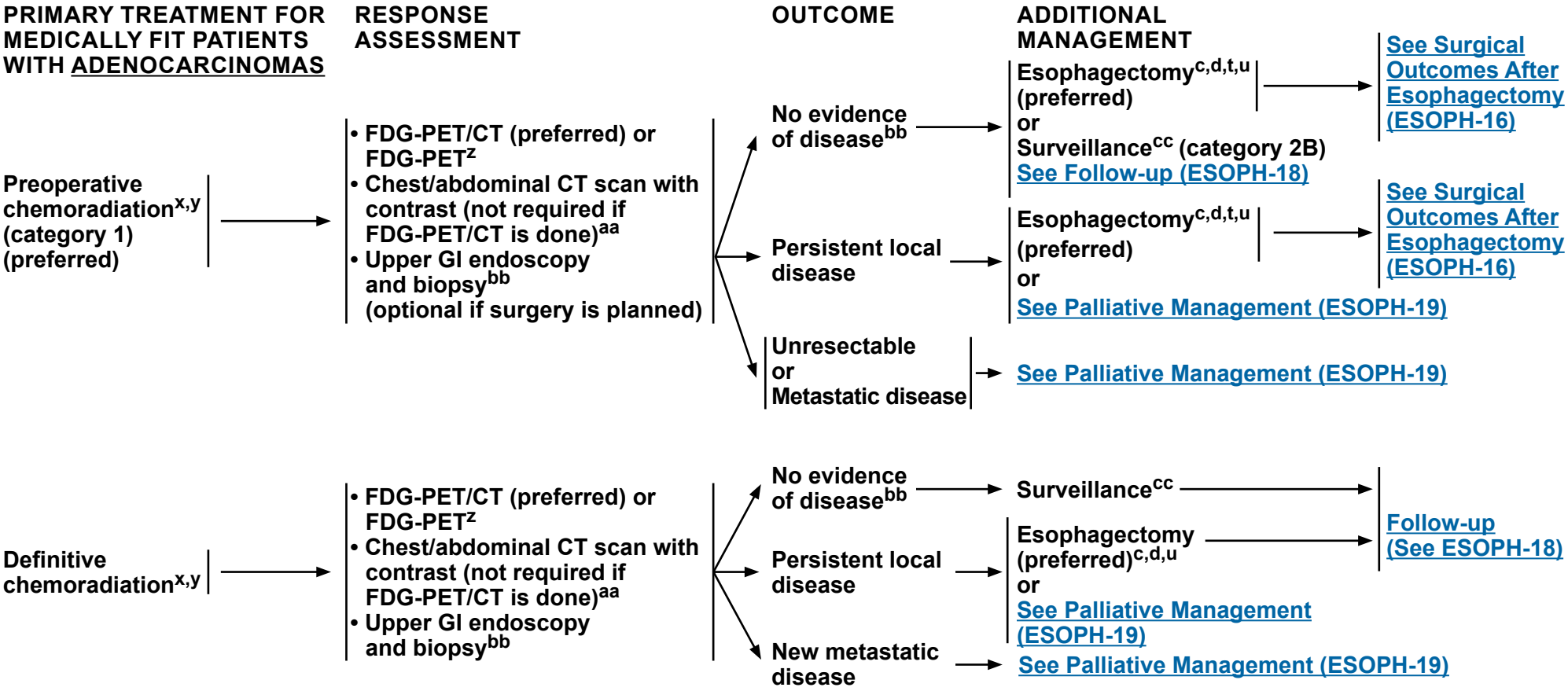

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[z] Assessment ≥5–8 weeks after completion of preoperative therapy.
[aa] Pelvic CT if clinically indicated.
[bb] See Post-Treatment Surveillance–Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[cc] If surgery is not being considered for management, upper GI endoscopy and biopsy should be done.

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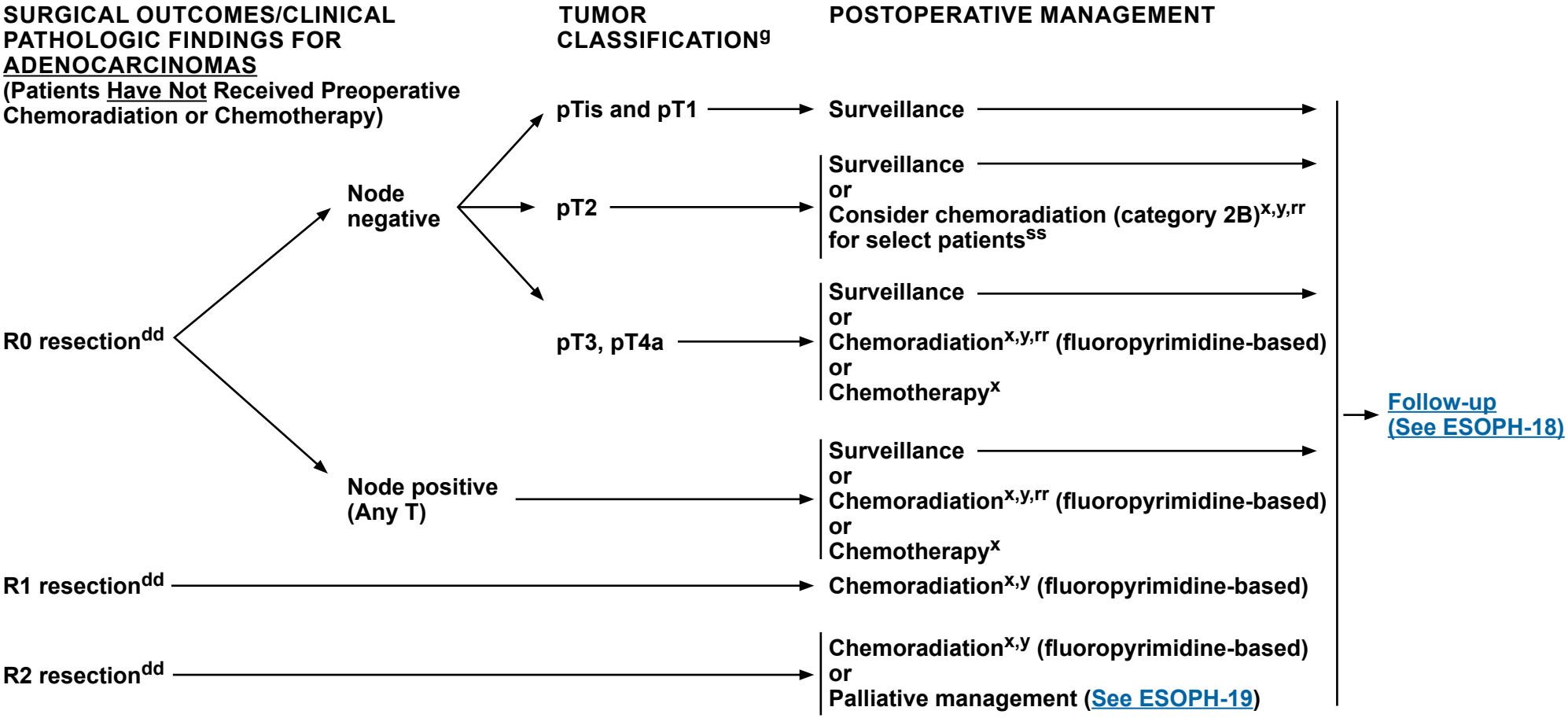

g See Staging (ST-1) for tumor classification.
x See Principles of Systemic Therapy (ESOPH-F).
y See Principles of Radiation Therapy (ESOPH-G).
dd R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
rr Smalley SR, et al. J Clin Oncol 2012;30:2327-2333. See Principles of Systemic Therapy (ESOPH-F).
ss Consider chemoradiation for patients with high-risk lower esophagus or EGJ adenocarcinoma. High-risk features include poorly differentiated or higher grade cancer, LVI, perineural invasion, or <50 years of age.

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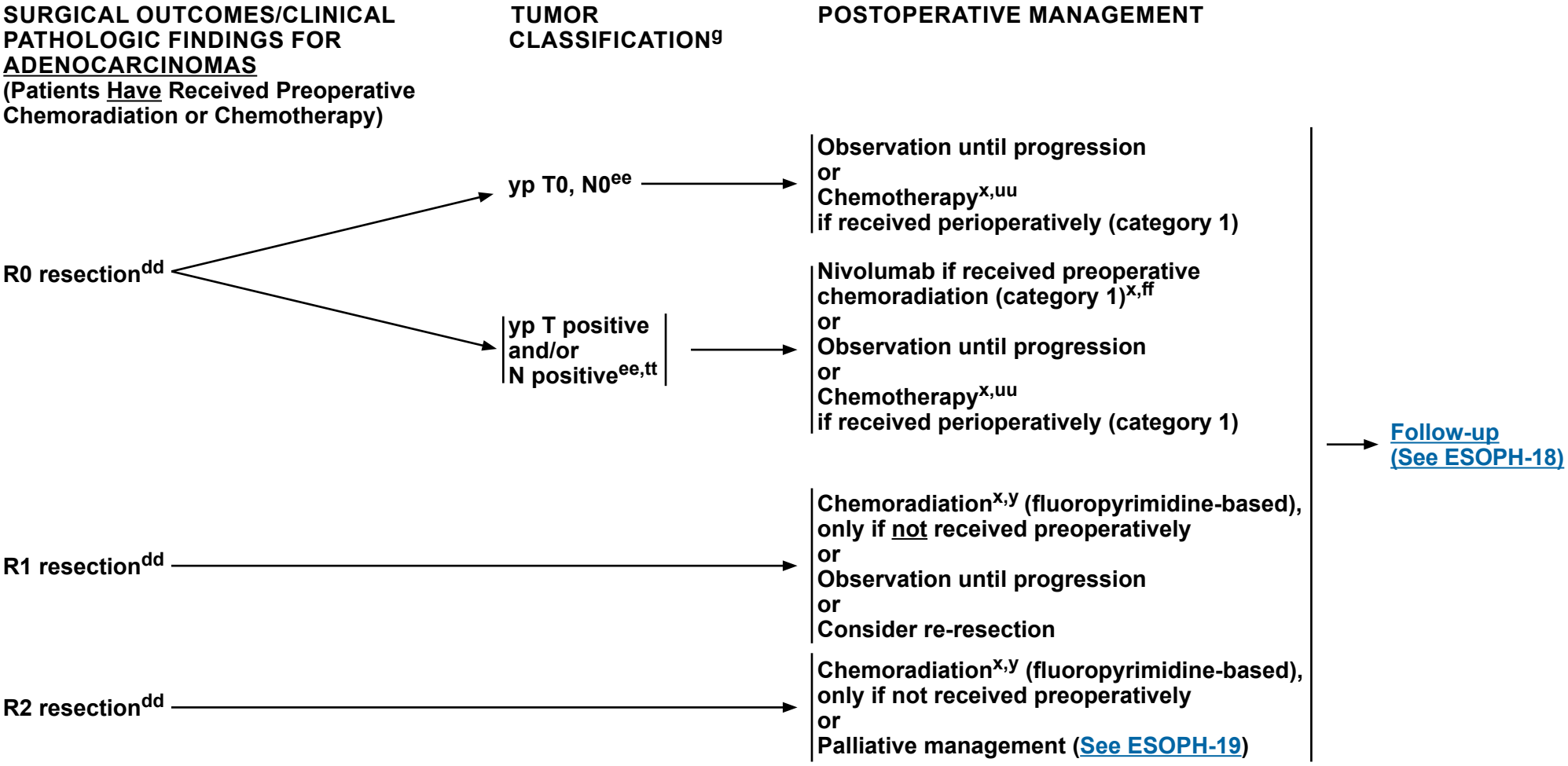

g See Staging (ST-1) for tumor classification.
x See Principles of Systemic Therapy (ESOPH-F).
y See Principles of Radiation Therapy (ESOPH-G).
dd R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
ee The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.
ff See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
tt Based on current data, adjuvant chemoradiation is not recommended for high-risk patients.
uu Al-Batran SE, et al. Lancet 2019;393:1948-1957.

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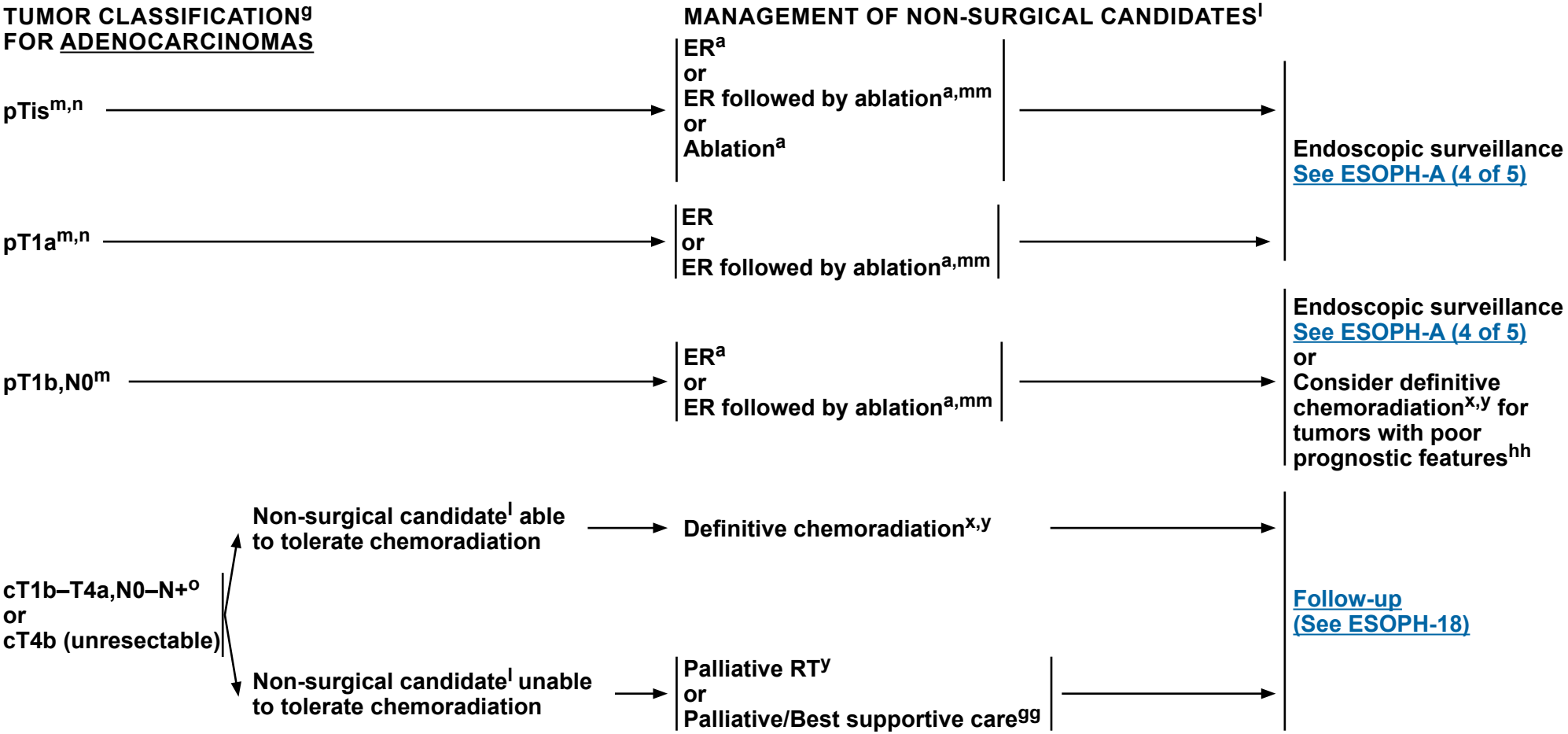

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[g] See Staging (ST-1) for tumor classification.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[m] pTis, pT1a, and pT1b tumor classification are defined by pathology of the diagnostic ER specimen See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o] Preclinical staging cannot establish the number of positive nodes.
[x] See Principles of Systemic Therapy (ESOPH-F).
[y] See Principles of Radiation Therapy (ESOPH-G).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[hh] Poor prognostic features include LVI, poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2 cm or more.
[mm] ER followed by ablation may be used to completely eliminate residual dysplasia or Barrett epithelium.

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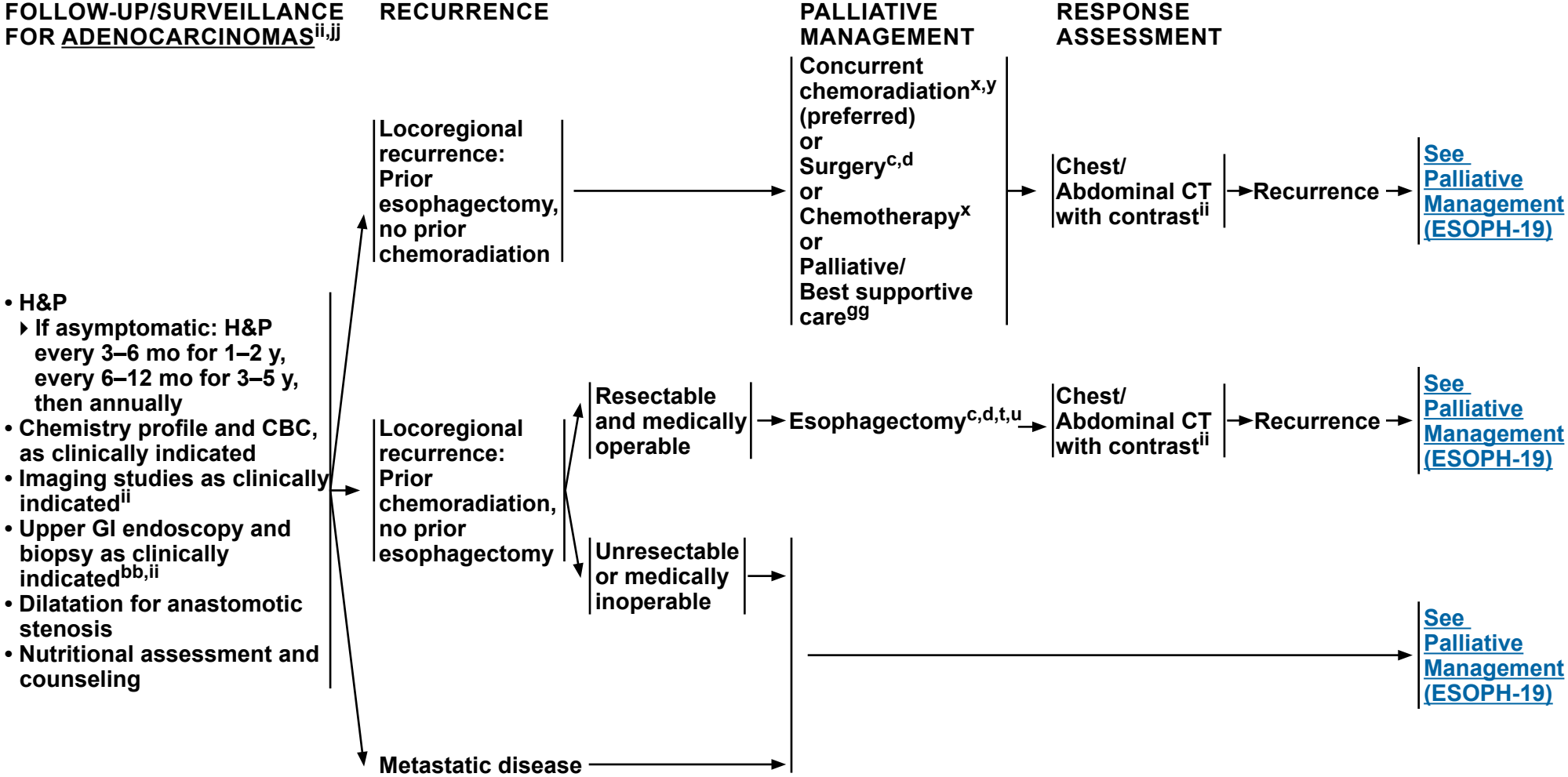

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[x] See Principles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

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

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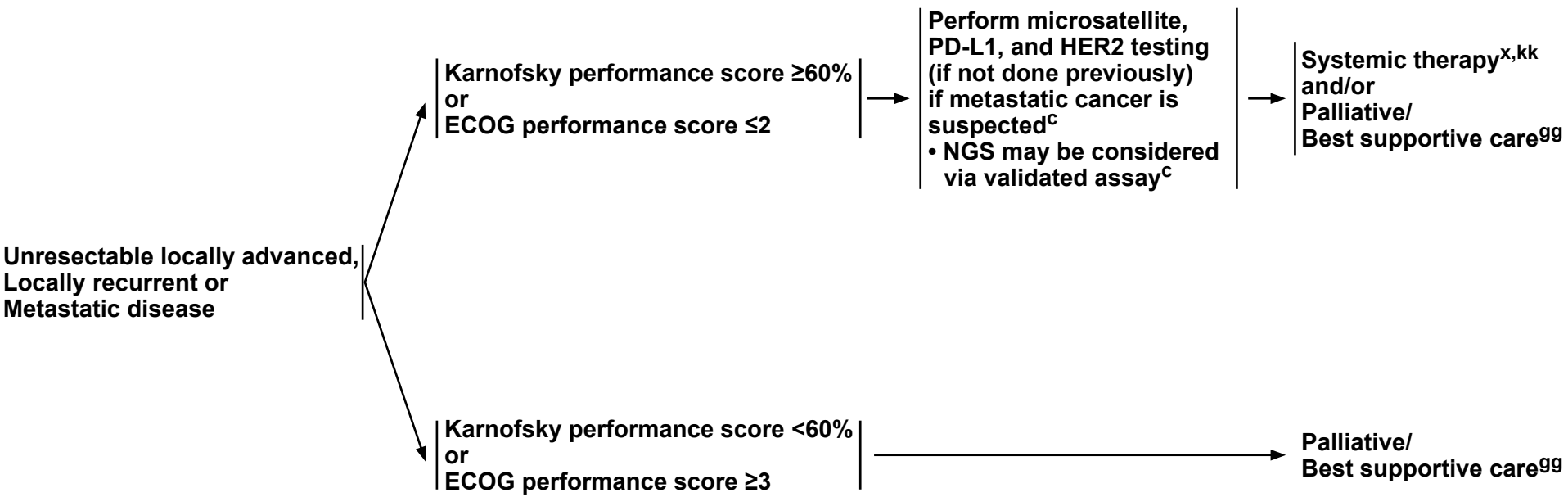
FOR ADENOCARCINOMAS



[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[x] See Principles of Systemic Therapy (ESOPH-F).
[gg] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[kk] Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

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

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

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

Diagnosis

- **Diagnostic and surveillance endoscopies are performed with the goal of determining the presence and location of esophageal neoplasia and to biopsy any suspicious lesions. Thus, an adequate endoscopic exam addresses both of these components.**
- **The location of the tumor relative to the teeth and EGJ, the length of the tumor, the extent of circumferential involvement, and the degree of obstruction should be carefully recorded to assist with treatment planning. If present, the location, length, and circumferential extent of Barrett esophagus should be characterized in accordance with the Prague criteria,[1] and mucosal nodules should be carefully documented.**
- **High-resolution endoscopic imaging and narrow-band imaging are presently available and may enhance visualization during endoscopy, with improved detection of lesions in Barrett and non-Barrett esophagus and stomach.[2]**
- **Multiple biopsies, six to eight, using standard size endoscopy forceps should be performed to provide sufficient material for histologic interpretation.[3] Larger forceps are recommended during surveillance endoscopy of Barrett esophagus for the detection of dysplasia.[4]**
- **Endoscopic resection (ER) of focal nodules should be performed in the setting of early-stage disease to provide accurate depth of invasion, degree of differentiation, and the presence of vascular and/or lymphatic invasion.[5] ER should be considered in the evaluation of areas of Barrett esophagus associated with high-grade dysplasia (HGD) and also patches of squamous cell dysplasia, specifically focusing on areas of nodularity or ulceration. Pathologists should be asked to provide an assessment of the depth of tumor infiltration into the lamina propria, muscularis mucosa, and submucosa; invasion of vascular structures and nerves; and the presence of tumor or dysplastic cells at the lateral and deep margins. ER may be fully therapeutic when a lesion is fully removed and histopathologic assessment demonstrates extension no deeper than the superficial submucosa and negative deep margins; however, patients with poorly differentiated tumors, deep submucosal invasion, and/or lymphovascular invasion (LVI) are at significantly higher risk of lymph node involvement.[6,7,8]**
- **Cytologic brushings or washings are rarely adequate in the initial diagnosis.**

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Continued
References

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Staging

- **EUS performed prior to any treatment is important in the initial clinical staging of neoplastic disease. Careful attention to ultrasound images provides evidence of depth of tumor invasion (T designation), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N designation), and occasionally signs of distant spread, such as lesions in surrounding organs (M designation).9**
- **Hypoechoic (dark) expansion of the esophageal wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal esophageal wall corresponding with greater depths of tumor penetration, correlating with higher T-categories. A dark expansion of layers 1–3 corresponds with infiltration of the superficial and deep mucosa plus the submucosal, T1 disease. Isolated thickening of the mucosal layer alone may be difficult to appreciate resulting in loss of sensitivity of EUS for superficial disease. Similarly, standard EUS scopes, with 7.5–12 MHz frequency transducers, may lack the resolution to accurately distinguish the penetration of the tumor through the muscularis mucosa, or superficial from deep penetration of the submucosa.[9,10] A dark expansion of layers 1–4 correlates with penetration into the muscularis propria, T2 disease, and expansion beyond the smooth outer border of the muscularis propria correlates with invasion of the adventitia, T3 disease. Loss of a bright tissue plane between the area of tumor and surrounding structures such as the pleura, diaphragm, and pericardium correlates with T4a disease, while invasion of surrounding structures such as the trachea, aorta, lungs, heart, liver, or pancreas correlates with T4b disease.**
- **For small, nodular lesions ≤2 cm, ER is encouraged as it provides a more accurate depth of invasion than the results of EUS.[10] A decision to proceed to further therapy such as resection or ablation, or to consider the ER completely therapeutic would depend on the final pathologic assessment of the resection specimen.**
- **Mediastinal and perigastric lymph nodes are readily seen by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well-circumscribed, rounded structures in these areas correlates with the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but is also confirmed with the use of fine-needle aspiration (FNA) biopsy for cytology assessment.[11] FNA of suspicious lymph nodes should be performed if it can be performed without traversing an area of primary tumor or major blood vessels, and if it will impact treatment decisions. The pre-procedure review of CT and FDG-PET scans is recommended, when available, prior to esophagogastroduodenoscopy (EGD)/EUS, to become fully familiar with the nodal distribution for possible FNA.**
- **Obstructing tumors may increase the risk of perforation while performing staging EUS exams. The use of wire-guided EUS probes, or miniprobes, may permit EUS staging with a lower risk of perforation. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate, but there is increased risk of perforation after dilation.**

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Continued
References

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Primary Treatment

- **The goal of endoscopic therapy [by endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and/or ablation] is the complete removal or eradication of early-stage disease (pTis, pT1a, selected superficial pT1b without LVI) and pre-neoplastic tissue (Barrett esophagus).**
- **Early-stage disease, Tis, also known as HGD, needs to be fully characterized, including evaluating presence of nodularity, lateral spread, and ruling out multifocal disease, as well as ruling out lymph node metastases by EUS in select higher risk cases. This is important to permit decisions on endoscopic therapy with ablative methods such as radiofrequency ablation (RFA), cryoablation, photodynamic therapy (PDT), and/or ER.[12-15] Areas of nodularity or ulceration should be resected rather than ablated. Completely flat, small lesions (≤2 cm) of squamous cell HGD/Tis (carcinoma in situ) and Barrett esophagus associated with flat HGD should be treated by ER as it provides more accurate histologic assessment of the lesion. Larger flat lesions (>2 cm) can be treated effectively by ER, but this is associated with greater risk of complications. Such lesions can be effectively treated by ablation alone, but there are very limited data on treating squamous cell HGD by ablation alone.[12,13,16-19]**
- **Lesions that are found to be pathologically limited to the lamina propria or muscularis mucosae (pT1a), or the superficial submucosa (pT1b), in the absence of evidence of lymph node metastases, LVI, or poor differentiation grade can be treated with full ER.[20-22] However, a thorough and detailed discussion regarding comparative risk of esophagectomy versus potential for concurrent nodal disease should be undertaken, preferably between patient and surgeon, especially in cases with larger tumors or deeper invasion. Ablative therapy of residual Barrett esophagus should be performed following ER.[17] Complete eradication of Barrett esophagus can also be performed with more aggressive application of EMR (widefield EMR) or ESD at the initial intervention, if necessary to completely resect an area of superficial tumor or mucosal nodularity ≤2 cm in maximal dimension.[23]**
- **The level of evidence for ablation of squamous cell carcinoma (SCC) after ER is low. However, additional ablation may be needed if there is multifocal HGD/carcinoma in situ elsewhere in the esophagus. Ablation may not be needed for lesions that are completely excised.[16,24,25]**
- **Endoscopic therapy is considered "preferred" for patients with limited early-stage disease (Tis and T1a, ≤2 cm, and well or moderately differentiated carcinoma), because the risk of harboring lymph node metastases, local or distant recurrence, and death from esophageal cancer is low following endoscopic therapy.[17]**

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Continued
References

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Treatment of Symptoms

- Esophageal dilation can be performed with the use of dilating balloons or bougies to temporarily relieve obstruction from tumors, or treatment-related strictures. Caution should be exercised to avoid overdilation, to minimize the risk of perforation.
- Long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG laser, PDT and cryoablation, or endoscopic and radiographic-assisted insertion of expandable metal or plastic stents.[26,27]
- Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic or radiographic-assisted placement of feeding gastrostomy or jejunostomy. The placement of a gastrostomy in the preoperative setting may compromise the gastric vasculature, thereby interfering with the creation of the gastric conduit in the reconstruction during esophagectomy and should be avoided.

Post-Treatment Surveillance

- Consider deferring assessment endoscopy with biopsy to 6 weeks or later after completion of preoperative therapy in patients whom avoidance of surgery is being considered.[28]
- EUS exams performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the present stage of disease.[29] Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.[28]
- Endoscopic surveillance following definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging.
- Endoscopic surveillance after ablative therapy or ER of early-stage esophageal cancer should continue after completion of treatment (See ESOPH-I). Biopsies should be taken of the neosquamous mucosa even in the absence of mucosal abnormalities as dysplasia may occasionally be present beneath the squamous mucosa.
- Endoscopic surveillance should also include a search for the presence of Barrett esophagus and four-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent high-grade and low-grade dysplasia using RFA or cryoablation should be considered.
- Patients who have received therapeutic ER should have endoscopic surveillance (See ESOPH-I).

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References

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY
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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Table 1 Pathologic Review

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

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Treatment Response

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

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

Table 2[h]

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

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Overexpression or Amplification of HER2 in Esophageal and Esophagogastric Junction Cancers

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

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

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

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

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

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

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

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

  - **MMR Interpretation**
    - ◊ **No loss of nuclear expression of MMR proteins: No evidence of dMMR (low probability of MSI-H)**
    - ◊ **Loss of nuclear expression of one or more MMR proteins: dMMR**

  - **MSI Interpretation**
    - ◊ **MSI-stable (MSS)**
    - ◊ **MSI-low (MSI-L)**
      - **1%–29% of the markers exhibit instability**
      - **1 of the 5 National Cancer Institute (NCI) or mononucleotide markers exhibits instability**
    - ◊ **MSI-H**
      - **≥30% of the markers exhibit instability**
      - **2 or more of the 5 NCI or mononucleotide markers exhibit instability**

PD-L1 Testing

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

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

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

Liquid Biopsy[14,15]

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

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

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PRINCIPLES OF SURGERY

- Prior to surgery, clinical staging should be performed to assess resectability with CT scan of the chest and abdomen, whole body FDG-PET (integrated FDG-PET/CT is preferred), and EUS.
- Prior to starting therapy all patients should be assessed by an esophageal surgeon for physiologic ability to undergo esophageal resection.[1] Esophageal resection should be considered for all physiologically fit patients with resectable esophageal cancer (>5 cm from cricopharyngeus).
- Siewert Classification
  - Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJ.[2,3]
    - ◊ Siewert Type I: adenocarcinoma of the lower esophagus with the epicenter located within 1 cm to 5 cm above the anatomic EGJ.
    - ◊ Siewert Type II: true carcinoma of the cardia with the tumor epicenter within 1 cm above and 2 cm below the EGJ.
    - ◊ Siewert Type III: subcardial carcinoma with the tumor epicenter between 2 cm and 5 cm below the EGJ, which infiltrates the EGJ and lower esophagus from below.
  - The treatment of Siewert types I and II is as described in the NCCN Guidelines for Esophageal and EGJ Cancers, and a variety of surgical approaches may be employed.
  - Siewert type III lesions are considered gastric cancers, and thus the NCCN Guidelines for Gastric Cancer should be followed. In some cases additional esophageal resection may be needed in order to obtain adequate margins.[2,4,5]
- Laparoscopy may be useful in select patients in detecting radiographically occult metastatic disease, especially in patients with Siewert II and III tumors.[1]
- Positive peritoneal cytology (performed in the absence of visible peritoneal implants) is associated with poor prognosis and is defined as M1 disease. In patients with advanced tumors, clinical T3 or N+ disease should be considered for laparoscopic staging with peritoneal washings.
- Cervical or cervicothoracic esophageal carcinomas <5 cm from the cricopharyngeus should be treated with definitive chemoradiation.
- Resectable esophageal or EGJ cancer:
  - T1a tumors, defined as tumors involving the mucosa but not invading the submucosa, may be considered for EMR + ablation or esophagectomy in experienced centers.[6-10]
  - Tumors in the submucosa (T1b) or deeper may be treated with esophagectomy.
  - T1–T3 tumors are resectable even with regional nodal metastases (N+), although bulky; multi-station lymphatic involvement is a relative contraindication to surgery, to be considered in conjunction with age and performance status.
  - T4a tumors with involvement of pericardium, pleura, or diaphragm are resectable.
- Unresectable esophageal cancer:
  - cT4b tumors with involvement of the heart, great vessels, trachea, or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
  - Most patients with multi-station, bulky lymphadenopathy should be considered unresectable, although lymph node involvement should be considered in conjunction with other factors, including age, performance status, and response to therapy.
  - Patients with EGJ and supraclavicular lymph node involvement should be considered unresectable.
  - Patients with distant (including nonregional lymph nodes) metastases (stage IV) are unresectable.

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PRINCIPLES OF SURGERY

- The type of esophageal resection is dictated by the location of the tumor, the available choices for conduit, as well as by the surgeon's experience and preference and the patient's preference.
- In patients who are unable to swallow well enough to maintain nutrition during induction therapy, esophageal dilatation or a feeding jejunostomy tube (J-tube) are preferred to a gastrostomy (which may compromise the integrity of gastric conduit for reconstruction).

- Acceptable operative approaches for resectable esophageal or EGJ cancer:
  - Ivor Lewis esophagogastrectomy (laparotomy + right thoracotomy)
  - McKeown esophagogastrectomy (right thoracotomy + laparotomy + cervical anastomosis)
  - Minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy + limited right thoracotomy)[11,12]
  - Minimally invasive McKeown esophagogastrectomy (right thoracoscopy + limited laparotomy/laparoscopy + cervical anastomosis)
  - Transhiatal esophagogastrectomy (laparotomy + cervical anastomosis)
  - Robotic minimally invasive esophagogastrectomy
  - Left transthoracic or thoracoabdominal approaches with anastomosis in chest or neck

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

- Acceptable lymph node dissections:[13]
  - Standard
  - Extended (en-bloc)

- In patients undergoing esophagectomy without induction chemoradiation, at least 15 lymph nodes should be removed and assessed to achieve adequate nodal staging. The optimum number of nodes after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.[14]

- Patients who develop localized, resectable esophageal cancer after definitive chemoradiation can be considered for esophagectomy if they do not have distant recurrence.[15]

- Patients with potentially resectable esophageal cancer should undergo multidisciplinary review. Esophageal resection, EMR, and other ablative techniques should be performed in high-volume esophageal centers by experienced surgeons and endoscopists.[16]

References

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PRINCIPLES OF GENETIC RISK ASSESSMENT FOR ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION (EGJ) CANCERS

Criteria for Further Risk Evaluation for High-Risk Syndromes:

- **Referral to a cancer genetics professional is recommended for an individual with a known high-risk syndrome associated with esophageal and EGJ cancers.**
- **Although early age of onset, multiple family members with the same or related cancer, and individuals with multiple primary cancers are all signs of hereditary cancer, specific referral guidelines for esophageal and EGJ cancers risk assessment are not possible at this time.**
- **The most efficient strategy to identify a causative gene mutation in a family is to test a close relative with cancer. If the relative is either unwilling or unavailable for testing, then consider testing of an unaffected relative. A detailed discussion of genetic counseling and testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.**

Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Esophageal and EGJ Cancers

- **Esophageal Cancer, Tylosis with Non-epidermolytic Palmoplantar Keratoderma (PPK), and Howel-Evans Syndrome[1,2]**
  - **Tylosis with esophageal cancer (TEC) is a very rare condition with an autosomal dominant pattern of inheritance and is caused by germline mutations in the *RHBDF2* gene. Individuals with germline *RHBDF2* mutations have an increased risk for SCC of the esophagus. PPK is divided into diffuse, punctate, or focal patterns of skin thickening on palms and soles. The non-epidermolytic PPK is associated with high risk of SCC of the middle and distal esophagus.**
- **Familial Barrett Esophagus[3]**
  - **Familial Barrett esophagus (FBE) includes adenocarcinoma of the esophagus and EGJ. Development of Barrett esophagus is strongly associated with gastroesophageal reflux disease (GERD). FBE may be associated with one or more autosomally inherited dominant susceptibility alleles. Several candidate genes have been identified, but not validated.**
- **Bloom Syndrome [4]**
  - **Bloom syndrome (BS) is characterized by mutations of the *BLM* gene at 15q26.1 and is associated with strikingly elevated sister chromatid exchange rates in all cells. Chromosomal quadraradials with breakage may be used to diagnose individuals with BS who often are affected by acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or lymphoid neoplasms at an early age, but then also cancers affecting many organs including the SCC of the esophagus after 20 years of age.**
- **Fanconi Anemia[1,2]**
  - **The genes involved in Fanconi anemia (FA) include FA complementation groups A–E, with FA-A (FANCA) located at 16q24.3; FA-B (FANCB), unknown; FA-C (FANCC) at 9q22.3; FA-D (FANCD) at 3p26–p22; and FA-E (FANCE), unknown. Mutations in FANCA and FANCC have been identified. Individuals are identified by pancytopenia and chromosome breakage and hematologic abnormalities, including anemia, bleeding, and easy bruising. Increased frequency of SCC of the esophagus as well as other squamous epithelium is observed. Karyotyping does not identify individuals with FA, but enhanced chromosome breakage with mitomycin C can identify homozygotes but not heterozygotes.**

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PRINCIPLES OF GENETIC RISK ASSESSMENT FOR ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION (EGJ) CANCERS

Screening Recommendations

Screening upper endoscopy with biopsies should be considered for patients who have the hereditary cancer predisposition syndromes as indicated below.

Syndrome	Gene(s)	Inheritance Pattern	Screening Recommendations
Esophageal cancer, tylosis with non-epidermolytic palmoplantar keratosis (PPK) and Howel-Evans syndrome[1,2]	*RHBDF2*	Autosomal dominant	Screening by upper gastrointestinal endoscopy is recommended in family members with tylosis after 20 years of age.
Familial Barrett esophagus (FBE)[3]	Candidate genes have not been validated	Autosomal dominant	• Potential family history of Barrett esophagus, esophageal adenocarcinoma, or EGJ adenocarcinoma should be determined for patients presenting with GERD, especially Caucasian males older than 40 years of age. • Screening for Barrett esophagus by upper gastrointestinal endoscopy is recommended in family members with FBE after 40 years of age, especially if the individual has a history of GERD.
Bloom syndrome (BS)[4]	*BLM/RECQL3*	Autosomal recessive	Screening for GERD with or without endoscopy to screen for early cancer after 20 years of age may be considered.
Fanconi anemia (FA)[1,2]	*FANCD1, BRCA2, FANCN (PALB2)*	Autosomal recessive	Endoscopy of the esophagus may be considered as a screening strategy in individuals identified with FA.

[1] Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Natl Cancer Inst 1998;90:1039-1071.
[2] Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008:1-93.
[3] Sun X, Elston R, Barnholtz-Sloan J, et al. A segregation analysis of Barrett's esophagus and associated adenocarcinomas. Cancer Epidemiol Biomarkers Prev 2010;19:666-674.
[4] Ellis NA, German J. Molecular genetics of Bloom's syndrome. Hum Mol Genet 1996;5 Spec No:1457-1463.

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

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

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

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

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

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

PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and EGJ adenocarcinoma, SCC 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.**
- **Trastuzumab[a] should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.**
- **Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising efficacy.[1]**
- **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.**
- **Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.[2] Perioperative chemotherapy is an alternative option for distal esophagus and EGJ.[3,4]**
- **In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.**

Footnotes

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

References

[1] 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.

[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] Ychou M, Boige V, Pignon J-P, 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.

[4] Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019; 393:1948-1957.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- 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)

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]
- Fluoropyrimidine and oxaliplatin[b,d]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Postoperative Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,16]
- Fluorouracil[b] and oxaliplatin[f]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

- Fluorouracil and cisplatin (category 2B)[10]

Postoperative Chemoradiation

- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[17]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[c] Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[d] The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] Cisplatin may not be used interchangeably with oxaliplatin in this setting.

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.

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

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

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

First-Line Therapy

- **Oxaliplatin is generally preferred over cisplatin due to lower toxicity.**

Preferred Regimens

- **HER2 overexpression positive adenocarcinoma[g]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]**
- **HER2 overexpression negative[g]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma only (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,h,19]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,20]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,20]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26]**

Other Recommended Regimens

- **HER2 overexpression positive adenocarcinoma[g]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,27]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,27]**
- **Fluorouracil[b,i] and irinotecan[j,28]**
- **Paclitaxel with or without cisplatin or carboplatin [j,29-33]**
- **Docetaxel with or without cisplatin [j,34-37]**
- **Fluoropyrimidine [j,25,38,39] (fluorouracil[b] or capecitabine)**
- **Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,40,41]**
- **Docetaxel, carboplatin, and fluorouracil (category 2B)[j,42]**

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

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

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

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

Second-Line or Subsequent Therapy
- **Dependent on prior therapy and PS**

Preferred Regimens
- **Nivolumab for esophageal squamous cell carcinoma (category 1)[e,h,43]**
- **Pembrolizumab[e,h]**
  - **For second-line therapy for esophageal squamous cell carcinoma with PD-L1 expression levels by CPS of ≥10 (category 1)[44]**
- **Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[45]**
- **Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[46]**
- **Docetaxel (category 1)[36,37]**
- **Paclitaxel (category 1)[31,33,47]**
- **Irinotecan (category 1)[47-50]**
- **Fluorouracil[b,i] and irinotecan[48,51,52]**
- **Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[53]**

Other Recommended Regimens
- **Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[54]**
- **Irinotecan and cisplatin[22,55]**
- **Fluorouracil and irinotecan + ramucirumab for adenocarcinoma[b,i,56]**
- **Irinotecan and ramucirumab for adenocarcinoma[57]**
- **Docetaxel and irinotecan (category 2B)[58]**

Useful in Certain Circumstances
- **Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[59,60]**
- **Pembrolizumab[e,h] for MSI-H or dMMR tumors[61-63]**
- **Pembrolizumab[e,h] for TMB high (≥10 mutations/megabase) tumors[64]**
- **Dostarlimab-gxly[e,h,k,65] for MSI-H or dMMR tumors**

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

PREOPERATIVE CHEMORADIATION

PREFERRED REGIMENS

Paclitaxel and carboplatin
Paclitaxel 50 mg/m² IV on Day 1
Carboplatin AUC 2 IV on Day 1
Weekly for 5 weeks[1]

Fluorouracil[b] and oxaliplatin
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation[2,m]

Fluorouracil 300 mg/m² IV continuous infusion over 24 hours daily for 4 days (over 96 hours) weekly
Oxaliplatin 85 mg/m2 IV over 2 hours on Day 1
Cycled every 14 days for 3 cycles with radiation[66]

Capecitabine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID on Days 1–5 weekly for 5 weeks[67]

OTHER RECOMMENDED REGIMENS

Fluorouracil and cisplatin
Cisplatin 75–100 mg/m² IV on Days 1 and 29
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4 and 29–32
35-day cycle[4]

Cisplatin 15 mg/m² IV daily on Days 1–5
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for 2 cycles[5]

Capecitabine and cisplatin
Cisplatin 30 mg/m² IV on Day 1
Capecitabine 800 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[68]

Irinotecan and cisplatin
Irinotecan 65 mg/m² IV on Days 1, 8, 22, and 29
Cisplatin 30 mg/m² IV on Days 1, 8, 22, and 29[6]
cycled every 35 days

OTHER RECOMMENDED REGIMENS–continued

Paclitaxel and fluoropyrimidine
Paclitaxel 45–50 mg/m² IV on Day 1 weekly
Fluorouracil 300 mg/m² IV continuous infusion daily on Days 1–5
Weekly for 5 weeks[7]

Paclitaxel 45–50 mg/m² IV on Day 1
Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[7]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.
[m] This regimen can be individualized and/or attenuated on a patient basis.

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.

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

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

PERIOPERATIVE CHEMOTHERAPY (Only for adenocarcinoma of the thoracic esophagus or EGJ)

PREFERRED REGIMENS

Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[b]
(4 cycles preoperative and 4 cycles postoperative)
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Leucovorin 200 mg/m² IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Docetaxel 50 mg/m² IV on Day 1
Cycled every 14 days[8]

Fluoropyrimidine and oxaliplatin[b]
(4 cycles preoperative and 4 cycles postoperative)
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Oxaliplatin 85 mg/m² IV on Day 1[b]
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[21]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[23]

OTHER RECOMMENDED REGIMENS

Fluorouracil and cisplatin
(4 cycles preoperative and 4 cycles postoperative)
Fluorouracil 2000 mg/m² IV continuous infusion over 48 hours on Days 1–2
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days

PREOPERATIVE CHEMOTHERAPY

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Fluorouracil and cisplatin
Fluorouracil 1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cisplatin 80 mg/m² IV on Day 1
Cycled every 21 days for 2 cycles preoperatively[10]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

DEFINITIVE CHEMORADIATION (NON-SURGICAL)

PREFERRED REGIMENS

Paclitaxel and carboplatin
Paclitaxel 50 mg/m² IV on Day 1
Carboplatin AUC 2 IV on Day 1
Weekly for 5 weeks[1]

Fluorouracil and oxaliplatin[b]
Oxaliplatin 85 mg/m² IV
on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m² IV daily on Days 1–33[3]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation
followed by 3 cycles without radiation[2]

Capecitabine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29
for 3 doses
Capecitabine 625 mg/m² PO BID
on Days 1–5 weekly for 5 weeks[67]

Fluorouracil and cisplatin
Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous
infusion
over 24 hours daily on Days 1–4
Cycled every 28 days for 2 cycles with radiation
followed by 2 cycles without radiation[11]

Capecitabine and cisplatin
Cisplatin 30 mg/m² IV on Day 1
Capecitabine 800 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[68]

OTHER RECOMMENDED REGIMENS

Taxane and cisplatin
Paclitaxel 60 mg/m² IV
on Days 1, 8, 15, and 22
Cisplatin 75 mg/m² IV on Day 1
Given for 1 cycle[12]

Docetaxel 60 mg/m² IV on Days 1 and 22
Cisplatin 60–80 mg/m² IV on Days 1 and 22
Given for 1 cycle[13]

Docetaxel 20–30 mg/m² IV on Day 1
Cisplatin 20–30 mg/m² IV on Day 1
Weekly for 5 weeks[14]

Irinotecan and cisplatin
Irinotecan 65 mg/m² IV
on Days 1, 8, 22, and 29
Cisplatin 30 mg/m² IV
on Days 1, 8, 22, and 29
cycled every 35 days[6]

OTHER RECOMMENDED REGIMENS–continued

Paclitaxel and fluoropyrimidine
Paclitaxel 45–50 mg/m² IV on Day 1 weekly
Fluorouracil 300 mg/m² IV continuous infusion
daily on Days 1–5
Weekly for 5 weeks[7]

Paclitaxel 45–50 mg/m² IV on Day 1
Capecitabine 625–825 mg/m² PO BID
on Days 1–5
Weekly for 5 weeks[7]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.

[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

POSTOPERATIVE THERAPY
PREFERRED
Nivolumab[e]
Nivolumab 240 mg IV every 14 days for 16 weeks
followed by Nivolumab 480 mg every 28 days
Maximum treatment duration of 1 year[15]

OTHER RECOMMENDED REGIMENS
Capecitabine and oxaliplatin
Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[16]

Fluorouracil and oxaliplatin[b]
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion
over 24 hours on Day 1
Cycled every 14 days[21]

POSTOPERATIVE CHEMORADIATION
(Only for EGJ adenocarcinoma)
THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[17,69] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE DOSES AND SCHEDULE OF CYTOTOXIC AGENTS SPECIFIED IN THIS TRIAL DUE TO CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:
Fluorouracil[b]
2 cycles before and 4 cycles after chemoradiation. For cycles after chemoradiation, begin chemotherapy 1 month after chemoradiation.
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days

With radiation
Fluorouracil 200–250 mg/m² IV continuous infusion
over 24 hours daily on Days 1–5
Weekly for 5 weeks[70]

Capecitabine
1 cycle before and 2 cycles after chemoradiation. For cycles after chemoradiation, begin chemotherapy 1 month after chemoradiation.
Capecitabine 750–1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[71]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[72]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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

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

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY

Trastuzumab[a] with chemotherapy
(See ESOPH-F [3 of 16] for list of regimens)
Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then Trastuzumab 6 mg/kg IV every 21 days[18]
or
Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Fluoropyrimidine and oxaliplatin[b]
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[21]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[23]

Capecitabine 625 mg/m² PO BID on Days 1–14[n]
Oxaliplatin 85 mg/m² IV on Day 1
Cycled every 21 days[73]

PREFERRED REGIMENS–continued

Fluoropyrimidine and cisplatin[b]
Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days[24]

Cisplatin 50 mg/m² IV daily on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days[21,25]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[26]

PREFERRED REGIMENS–continued

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab[b,e,i]
(for adenocarcinoma only)
Nivolumab 360 mg IV on Day 1
Capecitabine 1000 mg/m² PO BID every Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[19]

Nivolumab 240 mg IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[19]

The First-line Therapy list of "Preferred Regimens" continues on the next page (ESOPH-F 10 of 16)

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[k] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.
[n] Based on consensus opinion, the panel revised the doses and schedule studied in level C of the GO2 trial.

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY

PREFERRED REGIMENS–continued

Fluoropyrimidine (fluorouracil[b], or capecitabine), oxaliplatin, and pembrolizumab[e,i]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Capecitabine 1000 mg/m² PO BID every Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days for up to 6 cycles (total 18 weeks)

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days for up to 9 cycles
(total 18 weeks)

Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab[e,i]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Cisplatin 80 mg/m² IV on Day 1
Fluorouracil 800 mg/m² IV
continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for up to 6 cycles[20]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Cisplatin 80mg/m² IV on Day 1
Capecitabine 1,000 mg/m² PO twice daily on Days 1–14
Cycled every 21 days for a up of 6 cycles
(total of 18 weeks)

[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY-continued

OTHER RECOMMENDED REGIMENS

Trastuzumab[a] and pembrolizumab[e] with fluoropyrimidine and oxaliplatin or cisplatin (only for HER2 overexpression positive adenocarcinoma)

Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then Trastuzumab 6 mg/kg IV every 21 days[18]
or
Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

Pembrolizumab 200 mg IV on Day 1 Cycled every 3 weeks
or
Pembrolizumab 400 mg IV on Day 1 Cycled every 6 weeks[27]

OTHER RECOMMENDED REGIMENS–continued

Fluoropyrimidine and oxaliplatin[b]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[21]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[23]

Capecitabine 625 mg/m² PO BID on Days 1–14[n]
Oxaliplatin 85 mg/m² IV on Day 1
Cycled every 21 days[73]

OTHER RECOMMENDED REGIMENS–continued

Fluoropyrimidine and cisplatin[b]

Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days[24]

Cisplatin 50 mg/m² IV daily on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days[21,25]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[26]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.
[n] Based on consensus opinion, the panel revised the doses and schedule studied in level C of the GO2 trial.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY–continued
OTHER RECOMMENDED REGIMENS–continued

Fluorouracil and irinotecan[b]

Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[28]

Irinotecan 80 mg/m² IV on Day 1
Leucovorin 500 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[73]

Paclitaxel with or without cisplatin or carboplatin

Paclitaxel 135–200 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 1
Cycled every 21 days[29]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[30]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[31]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[32]

Paclitaxel 80 mg/m² IV weekly
Cycled every 28 days[33]

OTHER RECOMMENDED REGIMENS–continued

Docetaxel with or without cisplatin

Docetaxel 70–85 mg/m² IV on Day 1
Cisplatin 70–75 mg/m² IV on Day 1
Cycled every 21 days[34,35]

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[36,37]

Fluoropyrimidine[b]

Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[25]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[38]

Capecitabine 1000–1250 mg/m² PO BID on Days 1–14
Cycled every 21 days[39]

OTHER RECOMMENDED REGIMENS–continued

Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b]

Docetaxel 40 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV on Day 1
Fluorouracil 1000 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cisplatin 40 mg/m² IV on Day 3
Cycled every 14 days[40]

Docetaxel 50 mg/m² IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[41]

Docetaxel, carboplatin, and fluorouracil

Docetaxel 75 mg/m² IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1–3
Cycled every 21 days[42]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.

[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

SECOND-LINE AND SUBSEQUENT THERAPY

PREFERRED REGIMENS

Nivolumab[e,i]
(for second-line therapy for esophageal squamous cell carcinoma)
Nivolumab 240 mg IV on Day 1
Cycled every 14 days[43]
or
Nivolumab 480 mg IV on Day 1
Cycled every 28 days

Pembrolizumab[e,i]
(second-line therapy for esophageal squamous cell carcinoma with PD-L1 expression levels by CPS of ≥10)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[44]

Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks[75]

PREFERRED REGIMENS–continued

Ramucirumab and paclitaxel
(for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m² on Days 1, 8, and 15
Cycled every 28 days[45]

Fam-trastuzumab deruxtecan-nxki
(for HER2 overexpression positive adenocarcinoma)
6.4 mg/kg IV on Day 1
cycled every 21 days[o,46]

Taxane
Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[36,37]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[32]

Paclitaxel 80 mg/m² IV weekly
Cycled every 28 days[33]

Paclitaxel 80 mg/m² IV on Days 1, 8, 15
Cycled every 28 days[47]

PREFERRED REGIMENS–continued

Irinotecan
Irinotecan 250–350 mg/m² IV on Day 1
Cycled every 21 days[49]

Irinotecan 150–180 mg/m² IV on Day 1
Cycled every 14 days[47,48]

Irinotecan 125 mg/m² IV on Days 1 and 8
Cycled every 21 days[50]

Fluorouracil and irinotecan[b]
Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[48]

Trifluridine and tipiracil (for third-line or subsequent therapy for EGJ adenocarcinoma)
Trifluridine and tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose
(based on the trifluridine component)
PO twice daily on Days 1–5 and 8–12
Repeat every 28 days[53]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.
[o] Fam-trastuzumab deruxtecan-nxki is approved for metastatic HER2-positive breast cancer at a different dose of 5.4 mg/kg IV on Day 1, cycled every 21 days.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[l]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

SECOND-LINE AND SUBSEQUENT THERAPY

OTHER RECOMMENDED REGIMENS

Ramucirumab (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[54]

Irinotecan and cisplatin
Irinotecan 65 mg/m^2 IV on Days 1 and 8
Cisplatin 25–30 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[22,55]

Fluorouracil and irinotecan + ramucirumab[b]
(only for adenocarcinoma)
Ramucirumab 8 mg/kg IV on Day 1
Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IV Push on Day 1
Fluorouracil 1,200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[76]

Irinotecan and ramucirumab
Irinotecan 150 mg/m2 IV on Day 1
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[57]

Docetaxel and irinotecan
Docetaxel 35 mg/m^2 IV on Days 1 and 8
Irinotecan 50 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[58]

USEFUL IN CERTAIN CIRCUMSTANCES

Entrectinib or Larotrectinib
(For *NTRK* gene fusion-positive tumors)
Entrectinib 600 mg PO once daily[59]
or
Larotrectinib 100 mg PO twice daily[60]

Pembrolizumab[e,i]
(for MSI-H/dMMR tumors or TMB-high (≥10 mutations/megabase) tumors)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[44]

Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks[75]

Dostarlimab-gxly[e,i]
(for MSI-H/dMMR tumors)
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1,000 mg IV every 6 weeks[65]

[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[l] Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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Continued

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PRINCIPLES OF SYSTEMIC THERAPY
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PRINCIPLES OF RADIATION THERAPY

General Guidelines

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, and medical oncologists, radiologists, gastroenterologists, and pathologists.
- CT scans, barium swallow, EUS, endoscopy reports, and FDG-PET or FDG-PET/CT scans, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders prior to simulation.
- All available information from pre-treatment diagnostic studies should be used to determine the target volume.
- In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal and EGJ cancers. Siewert III tumors patients may receive perioperative chemotherapy or preoperative chemoradiation depending on institutional preference, and are generally more appropriately managed with radiation according to guidelines applicable to gastric cancers. These recommendations may be modified depending on the location of the bulk of the tumor.

Simulation and Treatment Planning

- CT simulation and conformal treatment planning should be used with either 3D conformal radiation or intensity-modulated radiation therapy (IMRT). Proton beam therapy[a] is appropriate in clinical settings where reduction in dose to organs at risk (eg, heart, lungs) is required that cannot be achieved by 3-D techniques, ideally within a clinical trial or registry study.[1,2]
- It is optimal to treat patients in the supine position as the setup is generally more stable and reproducible.
- The patient should be instructed to avoid intake of a heavy meal 3 hours before simulation and treatment for lesions requiring therapy of the proximal stomach.
- When clinically appropriate, IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily setup.
- Respiratory motion may be significant for distal esophageal and EGJ lesions. When 4D-CT planning or other motion management techniques are used, margins may be modified to account for observed motion and may also be reduced if justified. The 4D-CT data may also be used to create an internal target volume (ITV) from which subsequent clinical target volume (CTV) and planning target volume (PTV) expansions can be made.
- Target volumes need to be carefully defined and encompassed while designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion should be taken into account. For structures such as the lungs, attention should be given to the lung volume receiving low to moderate doses, as well as the volume receiving high doses. Attention should be paid to sparing the uninvolved stomach that may be used for future reconstruction (ie, anastomosis site).

[a] Data regarding proton beam therapy are early and evolving. Ideally, patients should be treated with proton beam therapy within a clinical trial.

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PRINCIPLES OF RADIATION THERAPY

Target Volume (General Guidelines):

- **Gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified on the planning scan and other pre-treatment diagnostic studies listed in the General Guidelines section above.**
- **CTV may include the areas at risk for microscopic disease. CTV is defined as the primary tumor plus a 3- to 4-cm expansion superiorly and inferiorly along the length of the esophagus and cardia and a 1-cm radial expansion.[3] The nodal CTV should be defined by a 0.5- to 1.5-cm expansion from the nodal GTV. CTV should also include coverage of elective nodal regions such as the celiac axis; however, this decision would depend on the location of the primary tumor within the esophagus and EGJ.**
- **PTV expansion should be 0.5 to 1 cm. The uncertainties arising from respiratory motion should also be taken into consideration.**
- **Elective treatment of node-bearing regions depends on the location of the primary tumor in the esophagus and EGJ.**
  - **Cervical esophagus: Consider treatment of the supraclavicular nodes and treatment of higher echelon cervical nodes, especially if the nodal stage is N1 or greater.**
  - **Proximal third of the esophagus: Consider treatment of para-esophageal lymph nodes and supraclavicular lymph nodes.**
  - **Middle third of the esophagus: Consider treatment of para-esophageal lymph nodes.**
  - **Distal third of esophagus and EGJ: Consider para-esophageal, lesser curvature, splenic nodes, and celiac axis nodal regions.**

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PRINCIPLES OF RADIATION THERAPY

Normal Tissue Tolerance Dose-Limits[4,5]

- **Treatment planning is essential to reduce unnecessary dose to organs at risk.**
- **Lung dose may require particular attention, especially in the preoperatively treated patient. It is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.**

Lungs[b]
- **V_{40Gy} ≤ 10%**
- **V_{30Gy} ≤ 15%**
- **V_{20Gy} ≤ 20%**
- **V_{10Gy} ≤ 40%**
- **V_{05Gy} ≤ 50%**
- **Mean < 20 Gy**

Spinal Cord
- **Max ≤ 45 Gy**

Bowel
- **Max dose < 54 Gy**
- **V_{45Gy} < 195 cc**

Heart
- **V_{30Gy} ≤ 30% (closer to 20% preferred)**
- **Mean < 30 Gy (closer to 26 Gy preferred)**

Left Kidney, Right Kidney (evaluate each one separately):
- **V_{20Gy} ≤ 33%**
- **Mean < 18 Gy**

Liver
- **V_{30Gy} ≤ 33%**
- **Mean < 25 Gy**

Stomach
- **Mean < 45 Gy**
- **Max dose < 54 Gy**

[b] Lung dose-volume histogram (DVH) parameters as predictors of pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy should be strongly considered, though consensus on optimal criteria has not yet emerged. Every effort should be made to keep the lung volume and doses to a minimum. Treating physicians should be aware that the DVH reduction algorithm is hardly the only risk factor for pulmonary complications. Important considerations may also include plans for post-treatment surgery, pretreatment pulmonary function, and relevant comorbidities. DVH parameters as predictors of pulmonary complications in esophageal cancer patients are an area of active development among the NCCN Member Institutions and others.

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References

PRINCIPLES OF RADIATION THERAPY

RT Dosing

- **Preoperative RT: 41.4–50.4 Gy (1.8–2.0 Gy/day) (total 23–28 fractions)[c]**
- **Postoperative RT: 45–50.4 Gy (1.8–2.0 Gy/day) (total 25–28 fractions)**
- **Definitive RT: 50–50.4 Gy (1.8–2.0 Gy/day)[6] (total 25–28 fractions)**

Supportive Care

- **Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment interruptions.**
- **During the radiation treatment course, patients should be seen for status check at least once a week with notation of vital signs, weight, and blood counts.**
- **Antiemetics should be given on a prophylactic basis when appropriate. Antacid, proton pump inhibitors, and antidiarrheal medications may be prescribed when needed.**
- **If estimated caloric intake is <1500 kcal/day, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomy tubes (J-tubes) or nasogastric feeding tubes may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.**
- **Adequate enteral and/or IV hydration is necessary throughout chemoradiation and recovery.**

[c] Patients who are at risk for not having surgery due to comorbidities or other risk factors should receive radiation doses of 50–50.4 Gy (1.8–2.0 Gy/day) because the lower preoperative therapy dose may not be adequate.

References

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PRINCIPLES OF RADIATION THERAPY
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PRINCIPLES OF PALLIATIVE/BEST SUPPORTIVE CARE[1-7]

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

Dysphagia

- **Assess the extent of disease and the functional degree of swallowing impairment, preferably through a standardized scoring scale and confirm the etiology of dysphagia**
- **Dysphagia grading scale[8]**
  - **Grade 0: Able to eat solid food without special attention to bite size or chewing**
  - **Grade 1: Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed**
  - **Grade 2: Able to swallow semisolid food (consistency of baby food)**
  - **Grade 3: Able to swallow liquids only**
  - **Grade 4: Unable to swallow liquids or saliva**
- **Dysphagia arising from esophageal cancer most often is due to obstruction, but on occasion may be primarily due to tumor-related dysmotility.**
- **Patients with dysphagia who are not candidates for curative surgery should be considered for palliation of their dysphagia symptoms, based on symptom severity. This can be achieved through multiple modalities, though placement of an esophageal stent is most commonly utilized. In contrast, stent placement is generally not advised in patients who may undergo curative surgery in the future due to concerns that stent-related adverse events may preclude curative surgery in the future.**

[a] For patients who have immune-mediated toxicity, See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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Continued
References

PRINCIPLES OF PALLIATIVE/BEST SUPPORTIVE CARE[1-7]

Obstruction

- Complete esophageal obstruction
  - Endoscopic lumen restoration, generally performed via simultaneous retrograde (via a gastrostomy tract) and antegrade endoscopy
  - Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful.
    - ◊ Surgical or radiologic placement of J-tube or gastrostomy tube
  - External beam radiation therapy (EBRT)
  - Brachytherapy may be considered in place of EBRT if a lumen can be restored that allows for the use of appropriate applicators. Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.
  - Photodynamic therapy (PDT) can effectively treat esophageal obstruction, but is less commonly performed due to associated photosensitivity and costs.[9]
  - Chemotherapy
  - Surgery may on occasion be useful in carefully selected patients.
- Severe esophageal obstruction (able to swallow liquids only)
  - Wire-guided dilation or balloon dilation (caution should be exercised when dilating malignant strictures as this may be associated with an increased risk of perforation)
  - Endoscopy or fluoroscopy-guided placement of partially or fully covered expandable metal stents.
    - ◊ There are data suggesting a lower migration and stent occlusion rates with the larger diameter covered expandable metal stents, but an increased risk of other complications such as bleeding and esophago-respiratory fistula.[10]
    - ◊ If possible, the distal end of the stent should remain above the EGJ to reduce symptoms of reflux and risk of aspiration.
  - EBRT[11] and brachytherapy both effectively treat malignant dysphagia.
    - ◊ The onset of symptom relief for EBRT or brachytherapy is slower compared to endoscopic palliation but is also likely to be more durable.[1,12]
  - Other measures as stated above
- Moderate esophageal obstruction (able to swallow semisolid food)
  - Measures stated above may be considered, but should be balanced with the associated risks.

Pain

- If patient is experiencing tumor-related pain, then the pain should be assessed and treated in accordance with the NCCN Guidelines for Adult Cancer Pain.
  - Severe uncontrolled pain following esophageal stent placement should be treated with endoscopic removal of the stent once the uncontrollable nature of the pain is established.

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References

PRINCIPLES OF PALLIATIVE/BEST SUPPORTIVE CARE[1-7]

Bleeding

- **Acute bleeding from esophageal cancer may represent a pre-terminal event secondary to tumor-related aorto-esophageal fistualization. Endoscopic assessment and intervention may lead to precipitous exsanguination, and therefore should be undertaken cautiously.**
  - **If bleeding appears to be primarily from the tumor surface, then endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation may be useful for control of bleeding; however, limited data suggest that while endoscopic therapies may initially be effective, the rate of recurrent bleeding is very high.[13]**
- **Chronic blood loss from esophageal cancer**
  - **EBRT**

Nausea/Vomiting

- **If the patient is experiencing nausea and vomiting, then he/she should be treated in accordance with the NCCN Guidelines for Antiemesis.**
- **Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if luminal enhancement is indicated.**

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PRINCIPLES OF SURVEILLANCE

- **The surveillance strategies after successful therapy for esophageal and EGJ cancers remain controversial, with no high-level evidence to guide development of algorithms that balance benefits and risks (including cost) within this cohort.**
- **The goal of this document is to provide guidance for stage-specific surveillance based on the currently available retrospectively analyzed literature[1-6] and the expertise of the panel members to individualize surveillance recommendations. It is hoped that prospective data will emerge and we will be able to propose surveillance recommendations based on the evidence.**
- **It should be noted that although the majority (~90%) of relapses occur within the first 2 years after completion of local therapy, potentially actionable relapses have been recognized sometimes more than 5 years after local therapy. Metachronous malignancy (a second cancer in the residual esophagus or in the case of SCC in a different organ) is also a consideration in long-term survivors.**
- **The recommendations outlined below are following completion of local therapy.**

p-Stage 0–I (Tis, T1a, and T1b)

Differences in follow-up for early-stage esophageal cancer reflect a heterogeneous potential for relapse and overall survival.[7-13] Whereas fully treated Tis and T1a, N0 disease have prognoses that approximate a non-cancer cohort, T1b disease does not perform as well. Thus, recommendations vary according to the depth of invasion and treatment modality. Evidence-based guidelines have not been established for all stages of completely treated early-stage esophageal cancer. The following suggestions are based on results from trials and current practice.

See Table 1 for specific surveillance recommendations.

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References

PRINCIPLES OF SURVEILLANCE

Table 1

Tumor Classification	Type of Therapy Rendered	Surveillance Recommendations
Tis or T1a with/ without BE	**Endoscopic resection (ER)/ablation**	• Once eradication of all neoplasia/high-risk preneoplasia has been achieved, endoscopic surveillance is recommended. • Upper GI endoscopy (EGD) should be performed every 3 months for the first year, then every 6 months for the second year, and then annually indefinitely.[b] • Imaging studies as a surveillance tool are not recommended.
Tis, T1a	**Esophagectomy**	Although the goal of the resection would be to resect all areas of Tis or T1a and Barrett esophagus (BE), patients with incompletely resected BE should undergo ablation and then endoscopic surveillance as above (Tis/T1a ER/ablation). Otherwise, EGD as needed based on symptoms. Imaging studies as a surveillance tool are not recommended.
pT1b[a] (N0 on EUS)	**ER/ablation**	• Once eradication of all cancer/HGD has been achieved, endoscopic surveillance is recommended. • EGD every 3 months for the first year, every 4–6 months for the second year, then annually indefinitely. EUS may be considered in conjunction with EGD. Further therapy will be determined if either BE, cancer, or malignant lymphadenopathy is diagnosed at surveillance. • Imaging (CT chest/abdomen with contrast unless contraindicated) may be considered every 12 months for up to 3 years and then as clinically indicated.
T1b, Any N[a]	**Esophagectomy**	• Imaging (CT chest/abdomen with contrast unless contraindicated) should be considered every 12 months for up to 3 years if the patient is likely to tolerate additional curative-intent therapy for recurrence. • EGD as needed based on symptoms and radiographic findings. • Although the goal of the resection would be to resect all areas of T1b and BE, patients with incompletely resected BE should undergo ablation and endoscopic surveillance every 3 months for the first year, every 4–6 months for the second year, then annually for 3 more years.
	Chemoradiation	• EGD every 3–6 months for the first 2 years then annually for 3 more years. Imaging (CT chest/abdomen with contrast unless contraindicated) should be considered every 6–9 months for the first 2 years, then annually up to 5 years. • Patients who are candidates for salvage esophagectomy may also undergo EUS/FNA as indicated based on imaging studies.

[a] ER/ablation for T1b can be considered for superficial disease or for non-surgical candidate.

[b] Shaheen NJ, Falk GW, Iyer PG, et al. ACG clinical guideline: Diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30-50.

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

Continued
References

PRINCIPLES OF SURVEILLANCE

Stage II or III (T2–T4,N0–N+,T4b) treated with bimodality therapy (definitive chemoradiation)
Literature suggests that locoregional relapses are common after bimodality therapy.[3] Therefore, EGD is a valuable surveillance tool in these patients. Most relapses (95%) occur within 24 months. Thus, surveillance for at least 24 months is recommended for these patients.[3]

Stage II or III (T2–T4,N0–N+,T4b) treated with trimodality therapy
Literature suggests that local/regional relapses are uncommon; therefore, EGD surveillance is not recommended.[1,2,4] The risk and rate of relapse have been correlated with surgical pathology (yp) stage. For example, yp stage III patients have a much higher rate of relapse (and relapses occurring early during surveillance) than patients with yp stage 0 (relapses are not frequent in these patients). Literature also suggests that 90% of relapses occur within 36 months of surgery; therefore, surveillance for at least 36 months is recommended.

See Table 2 for specific surveillance recommendations.

Table 2

Tumor Classification	Type of Therapy Rendered	Surveillance Recommendations
T2–T4,N0–N+,T4b	**Bimodality therapy (definitive chemoradiation)**	• Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence. • EGD every 3–6 months for the first 2 years, every 6 months for the third year, then as clinically indicated. • The value of carcinoembryonic antigen (CEA) and other tumor markers is unknown.
T2–T4,N0–N+,T4b	**Trimodality therapy**	• Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence. Unscheduled evaluation is recommended if a patient becomes symptomatic. • The value of CEA and other tumor markers is unknown. • EGD surveillance as clinically indicated.

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PRINCIPLES OF SURVIVORSHIP

Surveillance: See ESOPH-9, ESOPH-17, and Principles of Surveillance (ESOPH-I)

- **Surveillance should be performed in conjunction with good routine medical care, including routine health maintenance, preventive care, and cancer screening.**
- **In general, routine esophageal/EGJ cancer-specific surveillance is not recommended for more than 5 years following the end of treatment.**
- **Annual history and physical exam is reasonable as potential second primary cancers (second cancer in residual esophagus or second primary squamous cell cancer in a separate organ) are possible.**

Management of Long-Term Sequelae of Disease or Treatment

- **For common survivorship issues, see NCCN Guidelines for Survivorship**
- **Esophageal/EGJ cancer-specific issues:[1-6]**
  - **Gastrointestinal issues:[7-10]**
    - **Malnutrition/malabsorption:[11-13]**
      - **Monitor weight regularly after esophagectomy to ensure stability, recognizing that progressive weight loss is expected in the first 6 months**
      - **Monitor for malnutrition, especially during initial 6 months after surgery[14,15]**
        - **Consider monitoring vitamin B, folic acid, vitamin D, and calcium levels**
      - **Consider referral to dietician or nutrition services for individualized counseling**
      - **Assess for and address contributing medical and/or psychosocial factors**
    - **Delayed gastric emptying:[16]**
      - **Encourage small portions and more frequent eating (5 small meals/day)**
      - **Minimize high fat and fiber content in food**
      - **Consider referral to gastroenterology for refractory symptoms[a]**
    - **Dumping syndrome:**
      - **Encourage frequent meals scheduled throughout day (5 small meals/day)**
      - **Consume a diet high in protein and fiber, and low in simple carbohydrates or concentrated sweets**
      - **Avoid fluid consumption with meals**
    - **Reflux symptoms:**
      - **Avoid lying flat after eating**
      - **Use a foam wedge (triangular) pillow in bed and avoid full prone sleeping position at night**
      - **Consider proton pump inhibitors, although it is usually biliary reflux that exacerbates reflux symptoms**
    - **Dysphagia:**
      - **Evaluate for anastomotic stricture**

[a] Consider botulinum toxin injection of pylorus if emptying procedure was not performed at original surgery.

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Continued
References

PRINCIPLES OF SURVIVORSHIP

Management of Long-Term Sequelae of Disease or Treatment (continued)

- **Esophageal/EGJ cancer-specific issues:[1-6]**
  - **Other issues:**
    - ◊ **Monitor patients who are on anti-hypertensive therapy, as hypertension will improve in many patients with weight loss in the first 6 months after esophagectomy**
    - ◊ **Monitor patients with glucose intolerance, as hyperglycemia will improve in many patients with weight loss in the first 6 months after esophagectomy**
    - ◊ **Radiation-induced cardiotoxicity[17-20]**
      - **Encourage coordination with primary care physician (PCP) for age-appropriate cardiac risk factor (eg, hypertension, diabetes, lipids, obesity) management/modification**
      - **Encourage health behaviors as listed below**
      - **Consider referral to cardiologist for management as clinically indicated**
    - ◊ **Chemotherapy-induced neuropathy:**
      - **Consider duloxetine for painful neuropathy only (not effective for numbness or tingling)**
      - **See NCCN Guidelines for Survivorship (SPAIN-3) and NCCN Guidelines for Adult Cancer Pain (PAIN-3 through PAIN-5; PAIN-H)**
    - ◊ **Fatigue:**
      - **Encourage physical activity and energy conservation measures as tolerated**
      - **Assess and address contributing medical and/or psychosocial factors**
      - **See NCCN Guidelines for Survivorship (SFAT-1) and NCCN Guidelines for Cancer-Related Fatigue**

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Continued
References

PRINCIPLES OF SURVIVORSHIP

Counseling Regarding Health Behaviors:
- See NCCN Guidelines for Survivorship (HL-1)
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle and avoid inactivity. Goal: at least 30 minutes of moderate-intensity activity most days of the week. Modify physical activity recommendations based on treatment sequelae (ie, neuropathy).
- Consume a healthy diet with emphasis on plant sources, with modifications as needed based on treatment sequelae (ie, dumping syndrome, reflux, delayed gastric emptying).
- Limit alcohol consumption.
- Encourage smoking cessation as appropriate. See NCCN Guidelines for Smoking Cessation.
- Additional preventive health measures and immunizations should be performed as indicated under the care of or in conjunction with a PCP.

Cancer Screening Recommendations (for average-risk survivors):
- Breast Cancer: See NCCN Guidelines for Breast Cancer Screening and Diagnosis
- Colorectal Cancer: See NCCN Guidelines for Colorectal Cancer Screening
- Prostate Cancer: See NCCN Guidelines for Prostate Cancer Early Detection
- Lung Cancer: See NCCN Guidelines for Lung Cancer Screening

Survivorship Care Planning and Coordination of Care:
- See NCCN Guidelines for Survivorship (SURV-1 through SURV-B)
- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections
- Encourage maintenance of a therapeutic relationship with a PCP throughout life. The oncologist and PCP should have defined roles in survivorship care, with roles communicated to patient.
- Planning for ongoing survivorship care[b]
  - Information on treatment received including all surgeries, radiation therapy, and systemic therapies
  - Information regarding follow-up care, surveillance, and screening recommendations
  - Information on post-treatment needs, including information regarding acute, late and long-term treatment-related effects and health risks when possible (See NCCN Guidelines for Treatment by Cancer Type)
  - Delineation regarding roles of oncologists, PCPs, and subspecialty care physicians in long-term care and the timing of transfer of care if appropriate
  - Healthy behavior recommendations (See NCCN Guidelines for Survivorship [HL-1])
  - Periodic assessment of ongoing needs and identification of appropriate resources

[b] From Commission on Cancer. Optimal Resources for Cancer Care (2020 Standards): https://www.facs.org/-/media/files/quality-programs/cancer/coc/optimal_resources_for_cancer_care_2020_standards.ashx and NCCN Guidelines for Survivorship.

References

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

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

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

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

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

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

Squamous Cell Carcinoma

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

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

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

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

Clinical Staging (cTNM)

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

Pathological (pTNM)

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

Postneoadjuvant Therapy (ypTNM)

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

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

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

Clinical Staging (cTNM)

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

Pathological (pTNM)

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

Postneoadjuvant Therapy (ypTNM)

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

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Esophageal and Esophagogastric Junction Cancers

Discussion

This discussion corresponds to the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers. Last updated on February 11, 2022.

Table of Contents

Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus or esophagogastric junction (EGJ) constitute a major global health problem, especially in low and middle income countries.[1] The global incidence of esophageal cancer shows wide geographic variation, with a 60-fold difference between high- and low-incidence regions.[2] The highest-incidence area, often referred to as the "esophageal cancer belt," spans from northern Iran through the Central Asian republics and into northern China.[1,3] Other high-incidence areas include southern and eastern Africa and Northern France.[4] Globally, there were an estimated 604,000 cases and more than 544,000 deaths in 2020, making esophageal cancer the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related deaths in the world.[5,6] In contrast, esophageal cancer is one of the least commonly diagnosed cancers in North America. In the United States, an estimated 20,640 people are expected to be diagnosed and 16,410 people are expected to die of this disease in 2022, making esophageal cancer the 20th most commonly diagnosed cancer and the 11th leading cause of cancer-related deaths in the United States.[7-9] However, incidence rates of esophageal cancer have been increasing in the United States over the past several years and 5-year survival rates remain low {segal].

Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma, which differ in their pathology, tumor location, and prognosis.[10] In contrast to adenocarcinoma, SCC is more likely to localize at or higher than the tracheal bifurcation, has a proclivity for earlier lymphatic spread, and is associated with a poorer prognosis.[10,11] SCC is the most common histology in Eastern Europe and Asia, while adenocarcinoma is most common in North America and Western Europe. Tobacco and alcohol consumption are major risk factors for SCC, whereas tobacco use is a moderate risk factor for adenocarcinoma.[12-14] The risk for SCC decreases substantially after smoking cessation, whereas the risk for adenocarcinoma remains unchanged even several years after smoking cessation.[15,16] SCC has become less common in the West in recent decades due to reduced tobacco and alcohol use, and now accounts for less than 30% of all esophageal cancers in the United States and Western Europe.[1]

In contrast, the incidence of esophageal adenocarcinoma has increased in the West, likely reflecting rising rates of obesity.[1] High body mass index (BMI) has been established as the strongest risk factor for adenocarcinoma of the esophagus.[13,17,18] A meta-analysis found that individuals with a BMI ≥30 kg/m^2 had a higher relative risk of developing esophageal adenocarcinoma than individuals with a BMI of 25 to 30 kg/m^2.[17] Obesity contributes to the development of gastroesophageal reflux disease (GERD), a major underlying cause of esophageal adenocarcinoma.[19-21] GERD is associated with the development Barrett esophagus, a precancerous condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[22] Patients with Barrett esophagus have a 30 to 60 times greater risk of developing adenocarcinoma of the esophagus than the general population.[20] Older age, male gender assigned at birth, long-standing GERD, hiatal hernia size, and the length of Barrett esophagus are strongly associated with higher grades of dysplasia and increased risk of esophageal adenocarcinoma development.[23-25]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers, an electronic search of the PubMed database was performed to obtain key literature published since the last Guidelines update, using the following search terms: esophageal cancer, esophageal squamous cell carcinoma, esophageal

adenocarcinoma, EGJ cancer, and gastroesophageal junction cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[26]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Esophageal and EGJ Cancers

Although early age of onset and family history are associated with hereditary cancer, specific recommendations for esophageal and EGJ cancer risk assessment are not possible at this time due to limited data. Referral to a cancer genetics professional is recommended for individuals with a known high-risk syndrome associated with esophageal and EGJ cancers. The most common hereditary cancer predisposition syndromes are discussed in detail below.

Tylosis

Tylosis (also known as focal non-epidermolytic palmoplantar keratoderma [PPK] or Howel-Evans syndrome) is a very rare autosomal dominant syndrome caused by germline mutations in the *RHBDF2* gene.[27] PPK is a complex group of hereditary syndromes characterized by abnormal skin thickening on the palms of the hands and soles of the feet. PPK is classified as diffuse, punctate, or focal based on the patterns of skin thickening, and as epidermolytic or non-epidermolytic based on histology. The focal non-epidermolytic form of PPK (tylosis) is specifically associated with a higher lifetime risk of developing SCC of the middle and distal esophagus.[28,29] In individuals with tylosis, the average age at diagnosis of esophageal SCC is 45 years. The risk of developing SCC of the esophagus has been reported to be 40% to 90% by age 70 years.[30,31] Routine screening by upper GI endoscopy is recommended for patients with tylosis and their family members after 20 years of age.[28]

Familial Barrett Esophagus

Barrett esophagus is a condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to the development of adenocarcinoma (see *Barrett Esophagus* below).[22] The familial aggregation of Barrett esophagus and adenocarcinoma of the esophagus or EGJ is termed familial Barrett esophagus (FBE).[32-34] Reviews of hospital case series indicate that between 5% and 7% of Barrett esophagus and esophageal adenocarcinoma cases report a family history of either disease.[35] In one cohort study, family history was identified as an independent predictor for the presence of Barrett esophagus and adenocarcinoma of the esophagus or EGJ, after adjusting for age, sex, and the presence of obesity 10 or more years prior to study enrollment.[33] A study by Chak et al identified Barrett esophagus in 21% of first-degree relatives of patients with Barrett esophagus or esophageal adenocarcinoma.[36] Furthermore, Barrett

esophagus was identified significantly more often in siblings and offspring of FBE probands than in probands with isolated cases of Barrett esophagus.

FBE may be associated with one or more autosomally inherited dominant susceptibility alleles.[37] Reports have identified germline mutations in a variety of susceptibility genes that may be associated with the development of Barrett esophagus; however, none has been validated.[38,39] Since development of Barrett esophagus is strongly associated with GERD, it is possible that it is GERD that is inherited, with Barrett esophagus occurring as a consequence. However, since GERD is not always observed in patients with FBE, and there is an unusually high rate of progression to adenocarcinoma in families with FBE, additional genetic factors may be required for the development of FBE.[35] A recent study using whole exome sequencing (WES) on four distant relatives from a multiplex, multigenerational family with FBE identified the uncharacterized gene *VSIG10L* as a candidate FBE susceptibility gene, with a putative role in maintaining normal esophageal homeostasis.[40] However, future studies on the prevalence of *VSIG10L* mutations in this population are needed to allow for risk stratification of FBE susceptibility.

Potential family history of Barrett esophagus and adenocarcinoma of the esophagus or EGJ should be determined for patients presenting with GERD, especially Caucasian males greater than 40 years of age. Screening for Barrett esophagus by upper GI endoscopy is recommended in family members with FBE after 40 years of age, especially if the individual has a history of GERD.

Bloom Syndrome

Bloom syndrome (BS) is a rare autosomal recessive syndrome belonging to a group of chromosomal breakage syndromes. BS is characterized by mutations in the *BLM/RECQL3* gene at 15q26.1 and is associated with strikingly elevated sister chromatid exchange rates in all cells, resulting in an increased predisposition to a wide variety of malignancies.[41] Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphoid neoplasms, and Wilms tumor are the predominant cancers diagnosed before 20 years of age, whereas carcinomas of many different organ sites including SCC of the esophagus are diagnosed after 20 years of age.[28,42] Individuals with BS are often diagnosed with cancers at an earlier age than the general population. The presence of chromosomal quadraradials with breakage may be used for the diagnosis of BS.[28] Screening for GERD (with or without endoscopy to detect early esophageal cancer) after 20 years of age may be considered.

Fanconi Anemia

Fanconi anemia (FA) is an autosomal recessive disorder characterized by congenital malformations, progressive pancytopenia, and an increased predisposition to the development of hematologic malignancies and solid tumors.[28] FA is caused by mutations in one of 15 genes encoding the FA pathway, with *FANCA, FANCC, FANCG*, and *FANCD2* being the most common.[43] AML is the most common cancer occurring in patients with FA; however, patients with FA are also at an increased risk of developing SCC of the head, neck, and esophagus.[28,44,45] Individuals with FA are identified by pancytopenia, chromosomal breakage, and hematologic abnormalities, including anemia, bleeding, and easy bruising. Karyotyping does not identify individuals with FA, but enhanced chromosomal breakage with mitomycin C can identify homozygotes.[28,46] Endoscopy of the esophagus may be considered as a screening strategy in individuals with FA.

Staging

The tumor (T), node (N), and metastasis (M) staging system used by the American Joint Committee on Cancer (AJCC) is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. Staging recommendations for

esophageal and EGJ cancers presented in the Eighth Edition of the AJCC Cancer Staging Manual include clinical staging (cTNM; newly diagnosed, not-yet-treated patients), pathologic staging (pTNM; patients undergoing resection without prior treatment), and post neoadjuvant pathologic staging (ypTNM; patients receiving preoperative therapy).[11] The Eighth Edition also introduced modifications regarding tumors located at the EGJ. Using this system, tumors with an epicenter located greater than 2 cm into the proximal stomach are now staged as gastric carcinomas, even if the EGJ is involved. Tumors involving the EGJ with an epicenter less than or equal to 2 cm into the proximal stomach will still be staged as esophageal carcinomas.

The Eighth Edition of the AJCC Cancer Staging Manual provides additional resources for esophageal and EGJ cancers not available in the Seventh Edition, including the incorporation of newly constructed cTNM and ypTNM stage groupings, to fulfill unmet needs in staging patients under different circumstances. The stage groupings presented in the Eighth Edition are based on updated data with a significantly increased sample size and number of risk adjustment variables. The current stage groupings were determined using a risk-adjusted random survival forest analysis of collated data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for 22,654 patients spanning six continents who were treated with esophagectomy alone or esophagectomy with preoperative and/or postoperative therapy.[11] Use of these data reflects the current preference for treating locally advanced esophageal cancers with preoperative therapy and represents a major advancement over the seventh edition, which was entirely based on data from patients treated with esophagectomy alone. The availability of these data led to the ability to explicitly define cTNM and ypTNM cohorts and stages. The larger dataset also allowed for better separation of SCC and adenocarcinoma staging.[11] However, limitations of this data set still remain, including missing patient variables, heterogeneity of clinical staging among different centers, and poor representation of untreatable or inoperable patients, such as those with T4b and M1 cancers. Additionally, the exact modalities used to arrive at the initial clinical stages were not available for analysis. Nevertheless, the Eighth Edition of the AJCC Cancer Staging Manual represents the best worldwide clinical esophageal cancer staging data currently available. Survival analysis of this data set revealed that survival decreased with increasing anatomic tumor size and depth (pT), presence of regional lymph node metastases (pN), presence of distant metastases (pM), increasing histologic grade (G1–4), and advancing age.[47,48] Survival increased with a more distal location of cancer within the esophagus. In addition, survival was significantly affected by histopathologic type, with SCC having worse survival than adenocarcinoma.[48] Analysis of this larger dataset also illuminated significant differences in outcome when comparing the same stage groups between patients receiving preoperative therapy versus those treated with surgery alone, emphasizing the importance of having separate pTNM and ypTNM stage groupings to stage patients more accurately within each treatment algorithm.

In esophageal cancer, patient survival is best correlated with pTNM stage, regardless of whether the patient has received preoperative therapy (ypTNM).[11] Although surgical pathology yields the most accurate staging, advances in endoscopic techniques and imaging modalities such as endoscopic ultrasound (EUS), CT, and 18-fluorodeoxyglucose (FDG)-PET/CT have greatly improved the accuracy of clinical staging.[49] In general, initial staging of locoregional disease is usually best done with a combination of CT and EUS, while staging of distant metastatic disease is best assessed with FDG-PET/CT.[50] Locoregional staging with preoperative EUS provides excellent cT staging accuracy and is the only method capable of delineating the layers of the esophageal wall.[51] In a meta-analysis of 49 studies, EUS had excellent sensitivity and specificity

for accurately cT staging esophageal cancer, but performed better in advanced-stage disease (pooled sensitivity of 92% for cT4 tumors vs. 82% for cT1 tumors).[52] EUS has shown poor accuracy for distinguishing between early-stage tumors limited to the mucosa (cT1a) from those extending into the submucosa (cT1b).[52-55] Therefore, endoscopic resection (ER), which is essential for the accurate staging of early-stage cancers, should be performed for early-stage tumors (cT1a and cT1b ≤2 cm) as it provides more accurate information on the depth of tumor invasion than EUS.[56,57] Ultimately, a cancer that is completely removed by ER should be assigned pathologic staging.[11]

CT of the chest and abdomen with oral and IV contrast or FDG-PET/CT from skull base to mid-thigh can be used to determine the location of the primary tumor and its proximity to other structures. Although FDG-PET/CT has higher sensitivity for detecting esophageal cancer than CT alone, it has a limited role in cT staging other than for determining invasion of the mediastinum.[58] The diagnostic benefit of FDG-PET/CT is particularly limited in early-stage (cT1) tumors because of the low prevalence of distant metastases and the high rate of false-positive FDG-PET findings.[59,60] FDG-PET/CT also has limited ability to differentiate between cT1, cT2, and cT3 tumors.[11,50] Although the intensity of FDG uptake and cT category are positively related, this association is weak.[59,61,62] Therefore, chest/abdominal CT scan should be performed with oral and IV contrast in all patients as part of the initial workup (as well as pelvic CT scan with contrast if clinically indicated) while FDG-PET/CT should be reserved for patients with no evidence of M1 disease.

While CT and FDG-PET/CT may be used to describe the locoregional lymph nodes (cN), these techniques are suboptimal for detecting locoregional nodal metastasis because of their low sensitivity.[51,61,63-66] CT has a pooled sensitivity of 30% to 60% for detecting enlarged nodes greater than 1 cm.[49] FDG-PET/CT also has a low pooled sensitivity (~51%) in locoregional nodal assessment since these nodes are often obscured by the metabolic activity in the primary tumor.[67] In contrast, EUS has high sensitivity (~85%) for assessing the degree of nodal involvement.[52] Furthermore, the addition of fine-needle aspiration (FNA) to EUS (EUS-FNA) has shown greater sensitivity and accuracy than either EUS alone or CT scan in the evaluation of cN staging, especially in assessing locoregional and celiac lymph nodes.[52,68-70] In a study that compared the performance characteristics of EUS and EUS-FNA for preoperative cN staging in 74 patients with esophageal cancer, EUS-FNA was more sensitive (93% vs. 63%; $P = .01$) and accurate (93% vs. 70%; $P = .02$) when compared to EUS alone.[69] In another study that compared the performance characteristics of CT, EUS, and EUS-FNA for preoperative cN staging in 125 patients with esophageal cancer, EUS-FNA was more sensitive than CT (83% vs. 29%; $P < .001$) and more accurate than CT (87% vs. 51%; $P < .001$) or EUS alone (87% vs. 74%; $P = .012$).[70] Additionally, a retrospective review of 148 patients with esophageal cancer who underwent nodal staging with EUS-FNA and FDG-PET found that the addition of FDG-PET did not alter nodal staging in any patient with complete EUS-FNA, suggesting a limited role for FDG-PET alone in detecting locoregional metastatic nodes.[71]

While contrast-enhanced CT is the most widely used modality for detecting distant metastases in esophageal cancer, FDG-PET/CT is more sensitive than CT alone for staging cM disease.[11,50,61,63,72] The addition of FDG-PET improves the detection of distant metastases that may remain occult on CT scan of the chest and abdomen, thereby allowing proper patient selection for surgical resection.[11,50] In a prospective multicenter trial of 129 patients with esophageal cancer without definite distant metastases, PET identified metastatic sites in 41% of cases and altered management in 38% of cases.[73] However, potential pitfalls of FDG-PET/CT include the poor detection of hepatic metastases when the CT component is performed without IV contrast and the high rate of false-positive FDG-PET findings.[59,60,65,66]

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

Siewert Classification of EGJ Adenocarcinoma

In 1996, Siewert et al classified EGJ adenocarcinoma into three types based purely on the anatomic location of the epicenter of the tumor or the majority of the tumor mass.[74] In 2000, this classification was slightly changed.[75] Siewert Type I tumors are now defined as an adenocarcinoma of the lower esophagus with the tumor epicenter located within 1 to 5 cm above the anatomic EGJ. Siewert Type II tumors are defined as a true carcinoma of the cardia with the tumor epicenter located within 1 cm above and 2 cm below the EGJ. Siewert Type III tumors are defined as a subcardial carcinoma with the tumor epicenter located between 2 to 5 cm below the EGJ, which infiltrates the EGJ and the lower esophagus from below.

In the Eighth Edition of the AJCC Cancer Staging Manual, EGJ tumors with epicenters located within 2 cm of the proximal stomach (Siewert Types I and II) are staged as esophageal adenocarcinoma.[11] EGJ tumors with epicenters located greater than 2 cm into the stomach (Siewert Type III) are now staged using the gastric cancer staging system. In general, Siewert Types I and II tumors should be managed in accordance with guidelines for esophageal and EGJ cancers, while Siewert Type III tumors are more appropriately managed in accordance with guidelines for gastric cancer. Therapeutic decisions may be refined according to the location of the individual tumor, nodal distribution, and specific requirements for local control. However, the management approach for Siewert Type III tumors remains a subject of disagreement and debate. An individualized therapeutic approach may be preferred for specific patients and tumor locations, based on thorough pretreatment staging.

Barrett Esophagus

Barrett esophagus is a condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to the development of dysplasia.[22] Barrett esophagus can progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and in some cases to adenocarcinoma of the esophagus.[20] In a large case-controlled study, severe and frequent GERD symptoms, nocturnal GERD symptoms, and a family history of GERD were the factors most strongly associated with an increased risk of developing Barrett esophagus in the general population.[76] A recent systematic review and meta-analysis also identified obesity, family history of Barrett esophagus, and male gender as risk factors for the development of Barrett esophagus.[77] Patients with Barrett esophagus are at a greater risk of developing adenocarcinoma of the esophagus than the general population. Older age, male gender, long-standing GERD, hiatal hernia size, and the length of Barrett esophagus are strongly associated with the progression of Barrett esophagus to adenocarcinoma.[21,23-25,78-80] Additionally, biomarkers such as aneuploidy and loss of heterozygosity of *p53* have also been associated with an increased risk of progression of Barrett esophagus to HGD and/or adenocarcinoma.[78] However, these biomarkers require further prospective evaluation as predictors of risk for the development of

HGD and adenocarcinoma of the esophagus in patients with Barrett esophagus.

Diagnosis

Endoscopy should be performed on patients with severe symptoms of GERD, especially those with a family history of Barrett esophagus or esophageal cancer. Multiple biopsies (6–8) using larger size endoscopy forceps should be performed to provide sufficient material for histologic interpretation and for appropriate biomarkers.[81] The location, length, and circumferential extent of Barrett esophagus should be characterized in accordance with the Prague classification and mucosal nodules should be carefully documented.[82] For patients with metaplasia or LGD, GERD can be controlled with histamine receptor antagonists or proton pump inhibitors (PPIs). The use of wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS3D), a relatively new sampling technique combining an abrasive brush biopsy of the Barrett esophagus mucosa with computer-assisted pathology analysis to highlight abnormal cells, may help increase the detection of esophageal dysplasia in patients with Barrett esophagus. In a multicenter prospective trial, patients with Barrett esophagus (n = 160) were randomized to receive biopsy sampling in conjunction with WATS or biopsy sampling alone. Results showed that the addition of WATS to biopsy sampling was feasible and yielded an additional 23 cases of HGD/esophageal adenocarcinoma (absolute increase, 14.4%).[83] Two other studies have reported similar results.[84,85] However, the utility and accuracy of WATS for detecting HGD/adenocarcinoma in patients with Barrett esophagus needs to be evaluated in larger phase III randomized trials.

Treatment

ER, either by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), followed by radiofrequency ablation (RFA) has become the standard treatment for most patients with Barrett esophagus and HGD. Alternative strategies include cryoablation or photodynamic therapy (PDT).[86-88] Surgical resection is reserved for patients with HGD and characteristics that are unfavorable for non-surgical therapy, such as nodularity or long-segment involvement. Initial concerns regarding the use of ESD for Barrett esophagus involved the perceived increased risk of complications, including stricture formation, associated with deep submucosal dissection. However, a recent retrospective analysis found no increase in complication rates with the use of ESD compared to EMR followed by RFA.[89] Additionally, a meta-analysis by Yang et al found that ESD for the management of early Barrett esophagus was associated with a high en-bloc resection rate, acceptable safety profile, and low recurrence rate after curative resection. These data suggest that ESD is safe and highly effective for the management of Barrett esophagus neoplasia.[90]

Based on randomized trials, RFA alone may also be useful for Barrett esophagus patients with confirmed LGD or HGD.[91-94] In a multicenter randomized clinical trial that enrolled 136 patients with Barrett esophagus and LGD, RFA was found to be safe and effectively eradicated LGD and reduced the rate of progression from LGD to HGD and adenocarcinoma over 3 years of follow-up.[93] A study reporting the long-term outcome of this trial confirmed that RFA of Barrett esophagus with LGD significantly reduced the risk of malignant progression after a median follow-up of 73 months.[95] In a multicenter randomized trial involving patients with HGD, complete eradication occurred in 81% of those in the RFA group compared to 19% of those in the control group ($P < .001$).[91]

Surveillance

Some studies suggest that the rate of progression of Barrett esophagus to adenocarcinoma of the esophagus is much lower than previously

reported.[96,97] However, recent data have demonstrated an increased prevalence of HGD and adenocarcinoma on index endoscopy in Barrett esophagus patients over the past 25 years.[98] Endoscopic surveillance with multiple biopsies (6–8) should be performed to evaluate the progression of Barrett esophagus from metaplasia to LGD, HGD, or adenocarcinoma. Larger forceps are recommended during surveillance endoscopy of Barrett esophagus for the detection of dysplasia.[81]

The current clinical guidelines from the American College of Gastroenterology recommend endoscopic surveillance in patients with Barrett esophagus at intervals determined by the presence and grade of dysplasia.[92] Given the low risk of progression of Barrett esophagus to esophageal adenocarcinoma, endoscopic surveillance at 3- to 5-year intervals is reasonable for patients without dysplasia. The presence of dysplasia of any grade should be confirmed by a second pathologist with expertise in GI pathology. Patients with confirmed LGD should receive endoscopic therapy. If endoscopic therapy is not performed, annual surveillance is recommended until two examinations in a row are negative for dysplasia, after which time surveillance intervals for non-dysplastic Barrett esophagus can be followed (every 3–5 years). If HGD is confirmed, patients should be managed with endoscopic therapy unless they have life-limiting comorbidity. Typically, endoscopic surveillance should employ four-quadrant biopsies at 2-cm intervals in patients without dysplasia and 1-cm intervals in patients with prior dysplasia. For patients with results indefinite for dysplasia, endoscopy should be repeated after treatment for 3 to 6 months with acid-suppressive medications. If the “indefinite for dysplasia” reading is confirmed on this examination, a surveillance interval of 12 months is recommended. A retrospective study found that Barrett esophagus indefinite for dysplasia was associated with a similar risk of progression to adenocarcinoma as Barrett esophagus with LGD.[99] A recent systematic review and meta-analysis reached the same conclusion.[100] Therefore, surveillance for these patients should follow the recommendations for LGD.

Pathologic Review and Biomarker Testing

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

Principles of Pathologic Review

A specific diagnosis of esophageal SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise specified are staged using the TNM staging system for SCC.[11] In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade, which are required for staging. The pathology report of a surgical biopsy specimen should also document the presence or absence of Barrett esophagus. Biopsies showing Barrett esophagus with suspected dysplasia should be reviewed by a second expert GI pathologist for confirmation.[92] Barrett esophagus with HGD is reported as intraepithelial neoplasia (dysplasia) (Tis) for staging purposes.[11]

In the case of ER specimens, the depth of tumor invasion, presence of lymphovascular invasion (LVI), and status of mucosal and deep margins should also be reported. The pathology report for esophagectomy

specimens without prior chemoradiation should include all elements as for ER specimens plus the location of the tumor midpoint in relation to the EGJ, whether the tumor crosses the EGJ, the lymph node status, and the number of lymph nodes recovered. In the case of esophagectomy with prior chemoradiation and without grossly obvious residual tumor, the tumor site should be thoroughly sampled, with submission of the entire EGJ or ulcer/tumor bed for specimens. The pathology report should include all elements as for esophagectomy without prior chemoradiation, plus assessment of the treatment response.

Assessment of Treatment Response

Response of the primary tumor to previous chemotherapy and/or radiation therapy (RT) should be reported. The prognostic significance of pathologic complete response (pCR) and histologic tumor regression after induction therapy in patients with esophageal cancer has been demonstrated in several studies.[101-107] Residual primary tumor in the resection specimen following preoperative therapy is associated with shorter overall survival (OS) for both SCC and adenocarcinoma of the esophagus.[102,104,108,109] In a retrospective study of 235 patients, post-treatment pathologic stage was the best predictor of survival outcome for patients with locoregional carcinoma of the esophagus or EGJ who underwent preoperative chemoradiation followed by esophagectomy.[108]

Although scoring systems for tumor response in esophageal cancer have not been uniformly adopted, the panel recommends using the modified Ryan scheme in the College of American Pathologists (CAP) Cancer Protocol for Esophageal Carcinoma because it generally provides good reproducibility among pathologists.[110,111] The following scheme is suggested: 0 (complete response; no viable cancer cells, including lymph nodes); 1 (near complete response; single cells or rare small groups of cancer cells); 2 (partial response; residual cancer cells with evident tumor regression, but more than single cells or rare small groups of cancer cells); and 3 (poor or no response; extensive residual cancer with no evident tumor regression). Because of the impact of residual nodal metastases on survival, it is recommended that lymph nodes be included in the regression score.[112] Sizable pools of acellular mucin may be present after chemoradiation, but should not be interpreted as representing residual tumor.

Role of FDG-PET Scans in the Assessment of Treatment Response

The prognostic significance of metabolic response after preoperative therapy, as measured by a decrease in 18-FDG standardized uptake value (SUV) on post-treatment PET scan, has been evaluated in many studies in patients with locally advanced esophageal or EGJ cancer.[113-138] In many retrospective studies, a decrease in FDG SUV on post-treatment PET scan was a predictive factor that correlated with pathologic response and improved survival.[113-124] However, the cut-off values for the reduction in FDG SUV between pre- and post-treatment scans and the percent change in FDG SUV between pre- and post-treatment scans used to distinguish metabolic responders from non-responders varied widely between studies. In a study by Cerfolio et al, the median SUV of esophageal cancer decreased by 72% in patients who were complete pathologic responders, by 58% in patients who were partial responders, and by 37% in patients who had a minimal pathologic response.[117] In this study, patients were likely to be complete pathologic responders when the SUV decreased by more than 64% (P = .003) between pre- and post-treatment FDG-PET scans. In a similar study, Smith et al reported that patients who had a decrease in SUV greater than 50% had a 12-month disease-free survival (DFS) advantage over patients who had a decrease in SUV less than 50% (93% vs. 43%, P = .025).[118] Regardless of the cut-off values used, these studies all concluded that FDG-PET is predictive of pathologic response and survival in patients with esophageal cancer who undergo preoperative treatment.

The prognostic significance of FDG-PET has also been evaluated in prospective studies.[125-130] However, many of these prospective studies are limited by their small sample size, with the exception of the MUNICON II trial, which included 110 patients with locally advanced adenocarcinoma of the EGJ.[126] In this study, metabolic responders were defined as those with a decrease of greater than or equal to 35% in SUV following preoperative therapy. After a median follow-up of 2.3 years, median OS was not reached in metabolic responders, whereas the median OS was 25.8 months in non-responders (P = .015). Median event-free survival (EFS) was 29.7 months and 14 months, respectively, for metabolic responders and non-responders (P = .002). Major histologic remissions (<10% of residual cancer) were noted in 58% of metabolic responders but in 0% of non-responders. This study prospectively demonstrated that metabolic response as measured by FDG-PET is predictive of pathologic response and survival in patients with gastroesophageal carcinoma following preoperative therapy. Additional studies have reported similar outcomes.[139-141]

Although adding induction chemotherapy to chemoradiation and surgery has not been shown to improve survival over chemoradiation and surgery alone, response on FDG-PET scan to induction chemotherapy was shown in the MUNICON-1 trial to be a biomarker of benefit from chemotherapy.[126] FDG-PET non-responders in this trial had chemotherapy terminated and were referred for earlier surgery as they do not clearly benefit from therapy continuation. MUNICON-2 indicated that FDG-PET non-responders to induction chemotherapy did not benefit from the subsequent addition of RT to chemotherapy prior to surgery.[142] The CALGB 80803 trial used FDG-PET scan response to induction chemotherapy to direct either continuation of the same chemotherapy regimen during chemoradiation (infusional fluorouracil/oxaliplatin or carboplatin/paclitaxel) in FDG-PET responders, or to cross over to an alternative regimen during chemoradiation in FDG-PET non-responders.[143,144] The primary endpoint, to enhance pCR rate at surgery in FDG-PET non-responders who changed chemotherapy during radiation, was met, indicating the potential for FDG-PET scan to direct selection of chemotherapy during chemoradiation after induction chemotherapy. The most promising results of this trial were in patients who were FDG-PET responders receiving mFOLFOX followed by infusional fluorouracil/oxaliplatin/radiation and surgery, providing additional support for the use of fluorouracil/oxaliplatin combined with RT as preoperative treatment. This strategy needs to be further developed before adoption into clinical practice.

In contrast, other studies have reported that FDG-PET has a limited utility for assessing response to preoperative therapy in patients with esophageal cancer, except for the detection of distant metastases.[131-138,145,146] However, FDG-PET was performed either during preoperative therapy or soon after the completion of preoperative therapy in many of these studies, which may reflect an inflammatory effect of radiation that obscures tumor-specific metabolic changes.[136,147] RT and chemoradiation often cause local inflammatory reactions in the esophagus. Uptake of FDG in these inflammatory lesions occurs commonly resulting in false-positive results on PET scan. Therefore, increased FDG uptake due to radiation-induced inflammation limits the use of FDG-PET for early response assessment of esophageal carcinomas.[147] To reduce the incidence of false-positive results due to inflammation, the guidelines recommend that FDG-PET/CT (preferred) or FDG-PET should be performed at least 5 to 8 weeks after the completion of preoperative therapy. However, the guidelines caution that post-treatment FDG-PET results should not be used to select patients for surgery since FDG-PET cannot distinguish microscopic residual disease.[113,115,133]

Principles of Biomarker Testing

Presently, immunohistochemistry (IHC) and/or molecular testing for HER2/*ERBB2* status, microsatellite instability (MSI) or mismatch repair (MMR) status, PD-L1 expression, tumor mutational burden-high (TMB-H) status, and neurotrophic tropomyosin-related kinase *(NTRK)* gene fusions are utilized in the clinical management of advanced esophageal and EGJ cancers. When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated next-generation sequencing (NGS) assay performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved environment may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC, in situ hybridization (ISH), or targeted polymerase chain reaction (PCR) should be considered first, followed by NGS testing as appropriate.

Assessment of HER2 Overexpression

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of esophageal and EGJ cancers.[148] However, unlike in breast cancer, the prognostic significance of HER2 status in esophageal and EGJ cancer is unclear. Some studies have reported that HER2 positivity is correlated with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[149,150] HER2 positivity also seems to be associated with poorer survival in patients with SCC of the esophagus.[151] While further studies are needed to assess the prognostic significance of HER2 status in esophageal cancer, the addition of HER2 monoclonal antibodies to chemotherapy regimens is a promising treatment option for patients with HER2 overexpression positive disease.

The reported rates of HER2 positivity in esophageal and EGJ cancers vary widely (2%–45%)[149] and are more frequently seen in adenocarcinoma of the esophagus (15%–30%) than in SCC (5%–13%).[151-154] Additionally, HER2 positivity has been reported to be higher in patients with EGJ adenocarcinomas than in patients with gastric adenocarcinomas.[155-157] The HER-EAGLE study, which examined the HER2 positivity rate in a large multinational population of nearly 5000 patients with gastric or EGJ adenocarcinoma, reported that 14.2% of samples were HER2 overexpression positive.[158] HER2 positivity was significantly higher in males versus females, in EGJ tumors versus stomach tumors, and in intestinal subtypes versus diffuse subtypes. In the ToGA trial, HER2-positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[159] Therefore, classification of gastroesophageal cancers based on histologic subtype and primary tumor location may have implications for therapy.

HER2 testing is recommended for esophageal or EGJ adenocarcinoma patients at the time of diagnosis if metastatic adenocarcinoma is documented or suspected. In concordance with HER2 testing guidelines from CAP, the American Society for Clinical Pathology (ASCP), and the American Society for Clinical Oncology (ASCO),[160] the NCCN Guidelines recommend using IHC and, if needed, ISH techniques to assess HER2 status in esophageal and EGJ cancers. NGS offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, fusions, deletions, TMB, and MSI status. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression of metastatic adenocarcinoma.

IHC evaluates the membranous immunostaining of tumor cells, including the intensity and extent of staining and the percentage of immunoreactive tumor cells, with scores ranging from 0 (negative) to 3+ (positive). In 2008, Hofmann et al refined this 4-tiered scoring system to

assess HER2 status in gastric cancer by using a cut-off of greater than or equal to 10% immunoreactive tumor cells.[157,161] In a subsequent validation study (n = 447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[162] This modified HER2 scoring system is therefore recommended by the panel. A score of 0 (membranous reactivity in <10% of cancer cells) or 1+ (faint membranous reactivity in ≥10% of cancer cells) is considered to be HER2-negative. A score of 2+ (weak to moderate membranous reactivity in ≥10% of cancer cells) is considered equivocal and should be additionally examined by fluorescence in situ hybridization (FISH) or other ISH methods. FISH/ISH results are expressed as the ratio between the number of copies of the *ERBB2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (*ERBB2*:CEP17). Alternatively, FISH/ISH results may be given as the average *ERBB2* copy number per cell. Cases that have an IHC score of 3+ (strong membranous reactivity in ≥10% of cancer cells) or an IHC score of 2+ and are FISH/ISH positive (*ERBB2*:CEP17 ratio ≥2 or average *ERBB2* copy number ≥6 signals/cell) are considered HER2 positive. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. See *Principles of Pathologic Review and Biomarker Testing: Assessment of Overexpression or Amplification of HER2 in Esophageal and Esophagogastric Junction Cancers - Table 3* in the algorithm for more information.

MSI and MMR Testing

Testing for MSI by PCR/NGS or MMR by IHC should be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancers in patients who are candidates for treatment with PD-1 inhibitors.[163] MSI status is assessed by PCR or NGS to measure gene expression levels of microsatellite markers (ie, *BAT25*, *BAT26*, *MONO27*, *NR21*, *NR24*).[164] MMR deficiency is evaluated by IHC to assess nuclear expression of proteins involved in DNA mismatch repair (ie, MLH1, MSH2, MSH6, PMS2).[165] PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by deficient MMR function. Testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or MMR-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[166] Testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment in the appropriate clinical context.

PD-L1 Testing

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

Liquid Biopsy

The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of “liquid biopsy.”[150,167] Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of

mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. In a study that analyzed the genomic alterations of 55 patients with advanced gastroesophageal adenocarcinomas using NGS performed on plasma-derived ctDNA, 69% of patients had 1 or more characterized alterations theoretically targetable by an FDA-approved agent (on- or off-label).[150] Therefore, for patients who have advanced or metastatic esophageal/EGJ cancers and who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.

Surgery

Surgery is a major component of treatment for locoregional esophageal and EGJ cancers. Improvements in staging techniques, patient selection, post-surgical care, and surgical experience have led to a marked reduction in surgical morbidity and mortality in recent years. Additionally, randomized trials have shown that preoperative chemoradiation[168] and perioperative chemotherapy[169] have significantly improved survival in patients with resectable, locoregionally advanced esophageal and EGJ cancers.

Surgical Approaches

The type of esophageal resection is dictated by the tumor location as well as the available choices for conduit. Several operative techniques are acceptable for esophagectomy in patients with resectable esophageal or EGJ cancers.[170] The two most common surgical approaches, transthoracic and transhiatal esophagectomy, are described in detail below. The NCCN Guidelines emphasize that esophagectomy should always be performed in high-volume centers by experienced surgeons.[171]

Transthoracic Esophagectomy

Ivor Lewis esophagectomy (right thoracotomy and laparotomy)[172] and McKeown esophagectomy (right thoracotomy followed by laparotomy and cervical anastomosis)[173] are the two standard options for transthoracic esophagectomy. Ivor Lewis esophagectomy, the most frequently used procedure for transthoracic esophagectomy, uses laparotomy and right thoracotomy, with upper thoracic esophagogastric anastomosis at or above the azygos vein.[172] Mobilization of the stomach for use as the conduit is performed, with dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries. This approach may be used for distal thoracic lesions, but the proximal esophageal margin will be inadequate for tumors in the middle esophagus. McKeown esophagectomy, with an anastomosis in the cervical region, is similar in conduct, but with the advantage of being applicable for tumors in the upper, middle, and lower thoracic esophagus.

Transhiatal Esophagectomy

Transhiatal esophagectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[174] The mobilization of the stomach for use as the conduit is performed as in the Ivor Lewis esophagectomy. This procedure is completed through the abdominal incision, and the gastric conduit is drawn through the posterior mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be hazardous. In a prospective trial involving 220 patients with

adenocarcinoma of the mid-to-distal esophagus or gastric cardia, transhiatal esophagectomy was associated with lower post-surgical morbidity than transthoracic esophagectomy with extended en-bloc lymphadenectomy.[175] In a large population-based study that assessed outcomes after transthoracic and transhiatal esophagectomy, transhiatal esophagectomy offered an early survival advantage. However, long-term survival was similar for the two surgical approaches.[176] Though long-term survival differences have not been demonstrated, many experts believe that the lower lymph node retrieval associated with transhiatal esophagectomy represents a less effective oncologic approach. However, transhiatal esophagectomy may be associated with improved health-related quality of life. In a study of 111 patients with lower-third esophageal or EGJ cancer, patients who received transhiatal esophagectomy had better role functioning (functional ability in different roles such as physical activities and achievement beliefs) at 6 months after surgery (P = .046) and less nausea/vomiting (P = .045), dyspnea (P = .029), and constipation (P = .003) at 12 months after surgery than those in the transthoracic group.[177] However, this will need to be confirmed in larger studies.

Transthoracic or Thoracoabdominal Esophagectomy

Left transthoracic or thoracoabdominal esophagectomy uses a contiguous abdominal and left thoracic incision through the eighth intercostal space.[178] Mobilization of the stomach for use as the conduit is performed as previously described, and esophagectomy is accomplished through the left thoracotomy. Esophagogastric anastomosis is performed in the left chest, usually just superior to the inferior pulmonary vein, although it may be performed higher if the conduit is tunneled under the aortic arch. This approach may be used for lesions in the distal esophagus, particularly bulky tumors.[178]

Minimally Invasive Esophagectomy

Minimally invasive esophagectomy (MIE) strategies include minimally invasive Ivor Lewis esophagectomy (laparoscopy and limited right thoracotomy) and minimally invasive McKeown esophagectomy (right thoracoscopy, limited laparotomy/laparoscopy, and cervical anastomosis). MIE strategies may be associated with decreased postoperative mortality, shorter recovery times, and increased long-term survival. In a phase II multicenter prospective study involving 104 patients with HGD or esophageal cancer of the mid-to-distal esophagus, the Ivor Lewis MIE strategy was shown to be safe and feasible, as demonstrated by low perioperative mortality (2.1%) and good oncologic results.[179] Another study of MIE (mainly using thoracoscopic mobilization) involving 222 patients reported a mortality rate of only 1.4% and an average hospital stay of only 7 days, which is significantly less than most open procedures.[180] However, it is important to note that 62% of patients in this study had early-stage disease. In a systematic review and meta-analysis of studies reporting long-term outcomes, patients had 18% lower 5-year all-cause mortality following MIE compared with open esophagectomy.[181] In a multicenter randomized trial of 115 patients with esophageal or EGJ cancers, patients receiving MIE procedures had significantly lower rates of pulmonary infection than those receiving an open procedure.[182] A randomized controlled trial found that a hybrid MIE approach, in which surgeons combined a laparoscopic abdominal access route with an open thoracotomy, resulted in lower incidence of postoperative complications.[183] However, no statistically significant differences in either 3-year OS or DFS were observed. A retrospective analysis of 551 patients showed that patients who received MIE (n = 145) had significantly improved DFS and OS rates compared to patients who received open esophagectomy (n = 406; 3-year DFS rate, 81.7 vs. 69.3%, P = .021; 3-year OS rate, 89.9 vs. 79.2%, P = .007).[184] Open esophagectomy may be preferred over MIE for certain patients with

previous abdominal surgery, large and/or bulky tumors, possibly unusable gastric conduit, and difficulty with lymph node dissection. Although MIE is an evolving treatment option for patients with esophageal cancer, it is reasonable to replace invasive open procedures with MIE when possible, especially in older patients or those with significant comorbidities.[185-187]

Robotic-assisted MIE is an emerging technique that offers a realistic three-dimensional (3D) view that facilitates dissection in the narrow working environment; however, it is expensive and typically requires longer operation time.[188] The safety and feasibility of robotic-assisted MIE as compared to conventional MIE was analyzed in a systematic review and meta-analysis that reported similar rates of R0 resection, 30- and 90-day mortality, postoperative complications, and length of hospital stay between the two techniques.[188] In a randomized controlled trial involving 112 patients, robotic-assisted MIE was associated with a lower percentage of postoperative and cardiopulmonary complications, decreased pain, improved functional recovery, and better postoperative quality of life compared to open esophagectomy.[189] Oncologic outcomes were comparable at a medium follow-up of 40 months. Another prospective trial involving 106 patients also reported lower postoperative pain severity and decreased pulmonary and infectious complications in patients receiving robotic-assisted MIE versus open esophagectomy.[190] However, larger randomized controlled studies are needed to evaluate the benefits and risks of robotic-assisted MIE in patients with esophageal cancer.

Anastomosis and Choice of Conduit

The optimal location of the anastomosis has been debated. Potential advantages of a cervical anastomosis include more extensive resection of the esophagus, possibility of avoiding thoracotomy, less severe symptoms of reflux, and less severe complications related to anastomotic leakage. Advantages of a thoracic anastomosis may include lower incidence of anastomotic leakage, lower stricture rate, and lower rate of left recurrent nerve injury. In a prospective randomized trial, cervical and thoracic anastomoses after esophageal resection were equally safe when performed in a standardized way.[191] Gastric conduit is preferred for esophageal reconstruction by the majority of esophageal surgeons.[192] Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[193]

Principles of Surgery

All patients should be evaluated to determine whether they are medically fit enough to tolerate general anesthesia and major abdominal and/or thoracic surgery.[194] Prior to surgery, clinical staging should be performed to assess resectability with CT scan of the chest and abdomen, whole-body FDG-PET (integrated FDG-PET/CT scan is preferred), and EUS.[50] Esophagectomy should be considered for all medically fit patients with resectable esophageal cancer (>5 cm from cricopharyngeus). Cervical or cervicothoracic esophageal cancers less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Enteral nutritional support should be considered for patients with significant dysphagia and/or weight loss prior to or during induction therapy. A jejunostomy feeding tube is preferred over a gastrostomy feeding tube for preoperative nutritional support since placement of a gastrostomy tube may compromise the integrity of gastric conduit for reconstruction.

The Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJ. The surgical approaches for Siewert Type I and II tumors are similar to those described above. Siewert Type III tumors are considered gastric cancers and the surgical approach for these tumors is described in the NCCN Guidelines for Gastric Cancer.[74,195,196] 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 and III tumors.[197] Positive peritoneal cytology in the absence of visible peritoneal metastases is associated with poor prognosis in patients with EGJ adenocarcinoma.[198] Patients with advanced tumors or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

Lymph node dissection (lymphadenectomy) can be performed using the standard or extended (en-bloc) technique. The number of lymph nodes removed has been shown to be an independent predictor of survival after esophagectomy.[199,200] In a retrospective analysis of 4882 patients in the SEER database, patients diagnosed with invasive esophageal cancer who had 12 or more lymph nodes examined had significantly reduced mortality compared to those who had 0 to 11 lymph nodes examined; patients who had 30 or more lymph nodes examined had the lowest mortality of any group.[201] A report from the WECC database, which analyzed 4627 patients who had esophagectomy without preoperative therapy, suggested that a greater extent of lymphadenectomy was associated with increased survival for all patients with node-positive cancers.[200] Based on this study, optimum lymphadenectomy in node-positive cancers was 10 nodes for pT1, 15 nodes for pT2, and 29 to 50 nodes for pT3/T4. Therefore, the NCCN Guidelines recommend that a thorough dissection be performed to identify all lymph nodes with at least 15 lymph nodes submitted for pathologic evaluation and adequate nodal staging in patients undergoing esophagectomy without preoperative chemoradiation. The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown, although a recent study by Guo et al showed that resection of 13 to 29 nodes was associated with improved progression-free survival (PFS) and OS in patients with locally advanced esophageal SCC receiving preoperative chemoradiation.[202] However, it is important to note that extensive lymphadenectomy (>29 nodes) did not seem to be correlated with increased survival in these patients.[202,203] A recently published meta-analysis demonstrated a survival benefit for an increased lymph node yield from esophagectomy regardless of whether or not patients had received preoperative therapy.[204] Therefore, the NCCN Guidelines also recommended resection of at least 15 lymph nodes for patients with esophageal cancer who received preoperative therapy.

Patients with Tis or T1a tumors may be treated with endoscopic therapies (see below). Patients with positive deep margins after ER or with tumors invading into the submucosa (T1b) or deeper may be treated with esophagectomy. Patients with T1–T3 tumors are considered to be potentially resectable, even in the presence of regional nodal metastases, although patients with bulky tumors and/or multi-station nodal involvement have poor OS. T4a tumors with involvement of the pericardium, pleura, or diaphragm may be resectable; however, T4a tumors with distant metastases including non-regional lymph node involvement, EGJ tumors with supraclavicular lymph node involvement, and T4b tumors with involvement of the heart, great vessels, trachea, or adjacent organs including liver, pancreas, lung, and spleen are considered unresectable.

Surgery is usually performed with curative intent, but may be included as a component of palliative care for dysphagia or fistula. Palliative resections, however, should be avoided when possible in patients with clearly unresectable or advanced cancer with comorbidities, including severe cardiac or pulmonary disease. These patients may benefit from noninvasive palliative interventions. Palliative esophagectomy can also be considered for patients with cervical esophageal cancer who develop localized resectable recurrence or untreatable stricture after definitive chemoradiation if there is no distant recurrence.[205]

Endoscopic Therapies

Endoscopic therapies including ER (EMR or ESD) and endoscopic ablation (cryoablation or RFA) have been used as alternatives to surgery for the treatment of early-stage esophageal and EGJ cancers, with much

less treatment-related morbidity than surgical resection. Several retrospective studies have demonstrated that ER and endoscopic ablation procedures are effective treatment options for select patients with Barrett esophagus and early-stage esophageal or EGJ cancers.[206-209] In a SEER database analysis of 1458 patients with T1N0 esophageal cancer, the OS rates were similar after treatment with surgery or endoscopic therapy (EMR, RFA, cryoablation, or PDT). However, patients treated with endoscopic therapy had improved cancer-specific survival and decreased morbidity, supporting the use of endoscopic therapy as an effective treatment option for patients with early-stage disease.[208]

EMR is widely used for the treatment of early esophageal SCC in Japan and is gaining acceptance in Western countries for the treatment of Barrett esophagus and superficial adenocarcinomas.[210-213] Complete Barrett eradication EMR (CBE-EMR) has been shown to be a highly effective long-term treatment option for patients with Barrett esophagus and HGD.[214-218] ESD has also been established as a safe and effective procedure for patients with early-stage esophageal and EGJ cancers, resulting in high en-bloc resection rates and lower rates of major complications.[219-222] Retrospective studies have reported significantly better en-bloc resection and local recurrence rates for ESD than for EMR in patients with early-stage SCC of the esophagus.[223,224]

RFA alone or in combination with ER is an effective treatment option for the complete eradication of residual dysplasia or Barrett esophagus.[91,95,206,207,225-228] Endoscopic cryoablation has also been reported to be safe and well-tolerated in patients with Barrett esophagus and early-stage esophageal cancers.[229,230] PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett esophagus and HGD.[231-233] However, the use of PDT as an endoscopic therapy for esophageal cancers is losing popularity due to the potential for long-term complications.

Principles of Endoscopy

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

Diagnosis

Diagnostic endoscopies are performed to determine the presence and location of esophageal neoplasia and to biopsy suspicious lesions. The location of the tumor relative to the teeth and EGJ, the length of the tumor, the degree of obstruction, and the extent of circumferential involvement should be carefully recorded to assist with treatment planning. Tumor length has been identified as an independent predictor of long-term survival in patients with esophageal adenocarcinoma, with improved 5-year survival rates for patients with a tumor length less than or equal to 2 cm compared to those with a tumor length greater than 2 cm.[234] High-resolution endoscopic imaging and narrow-band imaging may be used to enhance visualization during endoscopy, with improved detection of lesions in the esophagus and stomach.[235-237] Multiple biopsies (6–8), using standard-size endoscopy forceps, should be performed to provide sufficient material for histologic interpretation and testing for appropriate biomarkers.[110] Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment.

ER of focal nodules should be performed in the setting of early-stage disease to provide accurate information on the depth of invasion, the degree of differentiation, and the presence of LVI.[238-240] The depth of tumor invasion, evidence of LVI, and the status of resection margins have been

identified as the strongest predictors of OS.[241-243] ER may be fully therapeutic when a lesion is fully removed and histopathologic assessment demonstrates extension no deeper than the superficial submucosa and negative deep margins. However, patients with poorly differentiated tumors, deep submucosal invasion, and/or LVI are at significantly higher risk of lymph node involvement.[241,244,245]

Staging

EUS should be performed prior to any treatment to provide evidence of the depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and signs of distant metastasis, such as lesions in surrounding organs (M).[52,53] Mediastinal and perigastric lymph nodes are readily identified by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well-circumscribed, and rounded structures in these areas indicates the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but can also be confirmed with the use of FNA biopsy for cytology assessment.[68-70] Review of CT and FDG-PET scans prior to EUS is recommended to become familiar with the nodal distribution for FNA biopsy. FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. Obstructing tumors may increase the risk of perforation while performing staging EUS. The use of wire-guided EUS probes, or mini probes, may permit EUS staging with a lower risk of perforation. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate, but there is increased risk of perforation after dilation.

ER is recommended for small nodular lesions (≤2 cm), as it provides more accurate depth of invasion information than EUS.[56,57] A decision to proceed with further treatment, such as ablation or surgical resection, or to consider the ER completely therapeutic would depend on the final pathologic assessment of the ER specimen.

Treatment

The goal of endoscopic therapy is the complete removal or eradication of early-stage disease and Barrett esophagus. Endoscopic therapy is preferred for patients with early-stage cancer because the risk of lymph node metastases, local or distant recurrence, and death from esophageal cancer following endoscopic therapy is relatively low.[246,247] However, a thorough and detailed discussion regarding the comparative risk of esophagectomy versus the potential for concurrent nodal disease should be undertaken between patient and surgeon, especially in cases with larger tumors or deeper invasion.

Early-stage disease (ie, pTis, pT1a, select superficial pT1b without LVI) and HGD can be effectively treated with ER and/or ablation.[242,246-250] Full characterization evaluating the presence of nodularity, lateral spread, multifocal disease, and lymph node metastasis is important to permit decisions on endoscopic therapies with ablative methods and/or ER.[91,230,233,251] Areas of nodularity or ulceration should be resected rather than ablated. Completely flat, small lesions (≤2 cm) of squamous cell Tis or HGD as well as Barrett esophagus associated with flat HGD should be treated with ER as it provides more accurate histologic assessment.[57] Ablative therapy of residual Barrett esophagus should be performed following ER.[209] Larger flat lesions (>2 cm) can also be treated effectively with ER, but this is associated with a greater risk of complications.[226,252] Such lesions can be treated effectively by ablation alone; however, there are limited data available on treating squamous cell HGD by ablation alone.[91,206,207,209,230,252]

Endoscopic therapies also play a role in palliative care. Esophageal dilation can be performed with the use of dilating balloons or bougies for temporary relief from tumor obstruction or strictures. However, caution must be exercised to avoid overdilation, as this may lead to perforation. Long-term relief from dysphagia can be achieved with endoscopic tumor ablation, PDT and cryoablation, or endoscopic placement of self-

expanding metal stents (SEMS).[253] Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic- or radiographic-assisted placement of a feeding gastrostomy or jejunostomy tube. However, the placement of a feeding gastrostomy tube should be avoided prior to esophagectomy since it may compromise the gastric vasculature and interfere with the use of the stomach as a conduit.

Surveillance

Endoscopic surveillance following treatment of esophageal and EGJ cancers requires careful attention to detail for mucosal surface changes and multiple biopsies of any visualized abnormalities. EUS has a high sensitivity for detecting recurrent disease.[254,255] EUS-FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging. It should be noted that following chemotherapy or RT, EUS exams have a reduced ability to accurately determine the present stage of the disease.[256] Similarly, biopsies may not accurately detect the presence of residual disease following chemotherapy or RT.[257] Consider deferring assessment endoscopy with biopsy to 6 or more weeks after completion of preoperative therapy in patients whom avoidance of surgery is being considered.

Endoscopic surveillance should include a search for the presence of Barrett esophagus and four-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent HGD and LGD using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett esophagus is not recommended. Endoscopic surveillance after completion of ER or ablation for early-stage disease should continue after completion of treatment. Biopsies of the neo-squamous mucosa are recommended, even in the absence of mucosal abnormalities, as dysplasia may occasionally be present beneath the squamous mucosa.

Radiation Therapy

Several historical series have reported results of using RT alone to treat patients with esophageal cancer with unfavorable features, such as patients with cT4 tumors or those who are not medically fit for surgery.[258-260] Overall, the 5-year survival rate for patients treated with conventional doses of RT alone is 0% to 10%.[258-260] Shi et al reported a 33% 5-year survival rate with the use of late-course accelerated fractionation to a total dose of 68.4 Gy.[261] However, in the RTOG 85-01 trial, all patients in the RT-alone arm who received 64 Gy at 2 Gy per day with conventional techniques died of cancer within 3 years.[262] In the adjuvant setting, randomized trials have not shown a survival advantage for preoperative or postoperative RT.[263-265] A meta-analysis from the Oesophageal Cancer Collaborative Group showed no clear evidence of a survival advantage with preoperative RT.[266] Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

Brachytherapy is also a palliative modality and results in a local control rate of 25% to 35% and a median survival time of approximately 5 months. In a randomized trial, Sur et al reported no significant difference in local control or survival with high-dose brachytherapy compared with external beam RT (EBRT).[267] In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 combined modality regimen (fluorouracil and cisplatin with 50 Gy of EBRT) followed by an intraluminal boost.[268] The local failure rate was 27%, and acute toxicity rates were 58% (grade 3), 26% (grade 4), and 8% (grade 5). The cumulative incidence of treatment-related esophageal fistula was 18% per year, and the crude incidence was 14%. Therefore, the additional benefit of adding intraluminal brachytherapy to RT or combined modality therapy, although reasonable, remains unclear. Alternative RT techniques, such as hypoxic cell sensitizers and hyperfractionation, have also not resulted in a clear survival advantage for

patients with esophageal or EGJ cancers. Experience with intraoperative RT as an alternative to EBRT in esophageal cancer is limited.[269]

Intensity-modulated RT (IMRT) has also been investigated in patients with esophageal cancer.[270-273] Retrospective studies comparing 3D conformal RT (3D-CRT) versus IMRT for patients with esophageal cancer have generally shown superior dose conformity and homogeneity as well as a reduction of RT dose delivered to the lungs and heart with IMRT.[270,271] Additionally, Roeder et al reported that IMRT with concurrent chemotherapy in the definitive treatment of esophageal cancer is feasible and yields good results with acceptable toxicity and low side effects to the skin, lungs, and heart.[273] A phase II trial of postoperative IMRT with concurrent chemotherapy for node-positive esophageal SCC also showed this regimen to be safe and effective with 1-year OS and PFS rates of 91.2% and 80.4%, respectively, and controllable toxicities.[274] Two recent phase III trials have safely employed IMRT with concurrent chemotherapy as definitive treatment of esophageal cancer.[275,276]

An emerging RT technique that may offer further sparing of normal tissues is proton beam therapy (PBT). Protons have a minimal exit dose beyond the target volume, which limits exposure of adjacent organs to radiation.[277,278] Therefore, the use of PBT may improve the therapeutic ratio by limiting cardiopulmonary toxicities while simultaneously delivering high radiation doses to the target area.[278-280] A direct comparison between IMRT, 3D-CRT, and PBT in 10 patients with esophageal cancer showed that PBT significantly reduced radiation doses to various volumes of the heart and lungs.[281] Furthermore, PBT was shown to be consistently superior to IMRT in lowering mean lung/heart radiation doses, especially when certain parameters such as beam arrangements and weighting were optimized to enhance normal tissue sparing.[277] A phase IIb trial that randomized 145 patients to receive IMRT or PBT reported that PBT reduced the risk and severity of adverse events while maintaining similar rates of 3-year PFS (50.8% for IMRT and 51.2% for PBT) and 3-year OS (44.5% for both).[282] PBT is also associated with lower rates of postoperative complications, including pulmonary, cardiac, GI, and wound complications, as well as reduced length of hospital stays.[283,284] However, data regarding PBT are early and evolving. Therefore, the NCCN Guidelines recommend that patients with esophageal cancer be treated with PBT within a clinical trial. An ongoing phase III study comparing PBT to photon therapy for patients with esophageal cancer is currently recruiting patients (Clinical Trial ID: NCT03801876).

Intensity-modulated PBT (IMPT), also referred to as pencil beam scanning, is a more recent technological advancement in which magnets are used to steer the proton beam toward the target volume.[284] A study from the Mayo Clinic showed significantly improved sparing of the lungs, heart, kidneys, liver, and small bowel using IMPT compared with IMRT in patients with distal esophageal cancer.[284] Additionally, a study comparing IMPT with ordinary PBT in patients with distal esophageal or EGJ cancer found that IMPT was associated with significant reductions in mean RT dose to the heart and liver.[285] However, the evidence supporting the use of IMPT is currently limited to dosimetric comparisons. Clinical outcomes of IMPT for esophageal cancer are needed, and prospective evaluation is ongoing.

Principles of Radiation Therapy

General Guidelines

RT (preoperative, postoperative, or palliative) can be an integral part of treatment for esophageal and EGJ cancers. In general, Siewert Type I and II tumors should be managed with RT guidelines applicable to esophageal and EGJ cancers. Siewert Type III tumors are generally more appropriately managed with RT guidelines applicable to gastric cancer (see the NCCN Guidelines for Gastric Cancer). These recommendations may be modified depending on the location of the bulk of the tumor. The panel recommends involvement of a multidisciplinary team, which should

include medical, radiation, and surgical oncologists; radiologists; gastroenterologists; and pathologists to determine optimal treatment recommendations. All available information from pretreatment diagnostic studies (EUS, endoscopy reports, and FDG-PET or FDG-PET/CT scans) should be reviewed by the multidisciplinary team and used to determine the target volume and field borders prior to simulation. Image guidance may be used appropriately to enhance clinical targeting.

A dose range of 41.4 to 50.4 Gy is recommended by the panel for preoperative RT. The recommended dose range for postoperative RT is 45 to 50.4 Gy. Non-surgical candidates should receive RT doses of 50 to 50.4 Gy because lower doses may not be adequate. There is no evidence from randomized trials to support the additional benefit of this higher dose range.[275,276,286] All RT doses should be delivered in fractions of 1.8 to 2 Gy per day. It is optimal to treat patients in the supine position as this setup is generally more stable and reproducible.

Simulation and Treatment Planning

CT simulation and conformal treatment planning should be used. When clinically appropriate, IV and/or oral contrast may be used for CT simulation to aid in target localization. The use of an immobilization device is strongly recommended for reproducibility. Respiratory motion may be particularly significant for distal esophageal and EGJ lesions. When 4D-CT planning or other motion management techniques are used, margins may be modified to account for observed respiratory motion and may also be reduced if justified. The 4D-CT data can also be used to create an internal target volume (ITV) from which subsequent clinical target volume (CTV) and planning target volume (PTV) expansions can be made. A small trial involving 15 patients with esophageal carcinoma evaluated the use of 4D-PET/CT in PTV delineation.[287] Overlap analysis demonstrated that approximately 20% of the PTV delineated by 4D-PET/CT is not included in the PTV delineated by 4D-CT. This may lead to under-coverage of target volume and a potential geometric miss with the use of 4D-CT. However, the potential value of 4D-PET/CT for PTV delineation needs to be confirmed in larger randomized trials in patients with esophageal and EGJ cancers.

IMRT or PBT may be used in clinical settings where dose reduction to organs at risk is required and cannot be achieved by 3D techniques.[270,271] IMRT is now standardly employed in the preoperative, definitive, and postoperative treatment of esophageal and esophagogastric cancer. Target volumes need to be carefully defined and encompassed when designing IMRT plans. In designing IMRT for organs at risk, such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses. In addition, the uninvolved stomach that may be used for future reconstruction should also be spared from high doses. Uncertainties from variations in stomach filling and respiratory motion should also be considered. Patients should be instructed to avoid intake of a heavy meal 3 hours before simulation and treatment.

Target Volume

The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified by pre-treatment diagnostic studies as described above. The CTV includes areas at risk for microscopic disease and is defined as the primary tumor plus a 3- to 4-cm superior and inferior expansion and a 1-cm radial expansion.[288] The nodal CTV includes a 0.5- to 1.5-cm expansion from the nodal GTV. The CTV should also include coverage of elective nodal regions such as the celiac axis; however, this decision depends on the location of the primary tumor. The PTV should include the CTV plus an expansion margin of 0.5 to 1 cm.

Normal Tissue Tolerance and Dose Limits

Treatment planning is essential to reduce unnecessary RT doses to organs at risk (liver, kidneys, spinal cord, heart, and lungs) and to limit the volume of organs at risk receiving high RT doses. Particular effort should be made to keep RT doses to the left ventricle of the heart to a minimum. Additionally, use of lung dose-volume histogram (DVH) parameters as predictors of pulmonary complications in patients treated with concurrent chemoradiation should be strongly considered, though consensus on optimal criteria has not yet emerged. Please see *Principles of Radiation Therapy* in the algorithm for recommended criteria for DVH parameters.[289,290] Although every effort should be made to minimize RT doses to organs at risk, it is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.

Supportive Care

Careful monitoring and management of acute toxicities with aggressive supportive care is essential to avoid treatment interruptions or dose reductions. During an RT treatment course, patients' vital signs, weight, and blood counts should be measured at least once per week. Prophylactic antiemetics should be given when appropriate. Additionally, antacids, PPIs, and antidiarrheal medications may be prescribed when needed. If the estimated caloric intake is inadequate (<1500 kcal/day), oral and/or enteral nutrition should be considered. Feeding jejunostomy tubes or nasogastric feeding tubes may be placed if clinically indicated. Adequate enteral and/or IV hydration is necessary throughout chemoradiation and recovery.

Combined Modality Therapy

Combined modality therapy has been shown to significantly increase survival in patients with esophageal and EGJ cancer with locoregional disease compared to resection alone.[291-293] Preoperative chemoradiation is the preferred approach for localized resectable adenocarcinoma.[168] Perioperative chemotherapy and preoperative chemotherapy are also options for adenocarcinoma of the thoracic esophagus or EGJ.[294-296] Other treatment options include postoperative chemoradiation[297,298] and postoperative chemotherapy.[299] Definitive chemoradiation should be reserved for patients with unresectable disease or those who decline surgery.[286,300-302]

Preoperative Chemoradiation Therapy

Preoperative chemoradiation is associated with improved OS, DFS, and pCR compared with preoperative chemotherapy or surgery alone in patients with locoregional esophageal cancer.[303-309] Results from the multicenter phase III randomized CROSS trial, the largest trial in its class, showed that preoperative chemoradiation with paclitaxel and carboplatin significantly improved OS and DFS compared to surgery alone in patients with resectable (T2–T3,N0–1,M0) esophageal or EGJ cancers (n = 366; 75% had adenocarcinoma and 23% had SCC).[168] Median OS was 49 months in the preoperative chemoradiation arm (n = 178) compared to 24 months in the surgery alone arm (n = 188; hazard ratio [HR], .657; 95% CI, 0.495–0.871; P = .003). The R0 resection rate was also higher in the preoperative chemoradiation arm compared to the surgery alone arm (92% vs. 69%; P < .001). The 1-, 2-, 3-, and 5-year OS rates were 82%, 67%, 58%, and 47%, respectively, in the preoperative chemoradiation arm compared to 70%, 50%, 44%, and 34%, respectively, in the surgery alone arm. Although the rate of pCR was higher in patients with SCC than those with adenocarcinoma (49% vs. 23%; P = .008), the histologic subtype was not a prognostic factor for survival.[168] After a minimum follow-up of 24 months, the overall rate of recurrence was 35% in the preoperative chemoradiation arm compared to 58% in the surgery alone arm.[310] Additionally, preoperative chemoradiation significantly reduced locoregional recurrence from 34% to 14% (P < .001) and peritoneal carcinomatosis from 14% to 4% (P < .001).[310] Importantly, preoperative

chemoradiation did not negatively impact postoperative health-related quality of life compared to surgery alone in patients participating in the CROSS trial.[311] A study reporting the long-term results of the CROSS trial verified that median OS was significantly improved in the preoperative chemoradiation group.[312] After a median follow-up of 84.1 months, median OS was 48.6 months in the preoperative chemoradiation group compared to 24 months in the surgery alone group (HR, 0.68; 95% CI, 0.53–0.88; *P* = .003). Median OS for patients with SCC was 81.6 months in the preoperative chemoradiation group and 21.1 months in the surgery alone group (*P* = .008); for patients with adenocarcinomas, median OS was 43.2 months and 27.1 months, respectively (*P* = .038). The results of these studies confirmed the survival benefit for preoperative chemoradiation therapy with paclitaxel and carboplatin in patients with resectable esophageal or EGJ cancers. Therefore, the panel recommends combined paclitaxel and carboplatin as a category 1 preferred regimen for preoperative chemoradiation.

The panel also recommends fluorouracil and oxaliplatin (FOLFOX) as a category 1 preferred option for preoperative chemoradiation. The efficacy and safety of preoperative FOLFOX combined with RT was evaluated in a single-arm phase II SWOG trial involving 93 patients with clinically staged II or III esophageal adenocarcinoma.[313] Twenty-six patients (28%) had confirmed pCR (95% CI, 19.1–38.2%) and 19.4% of patients experienced grade 4 treatment-related toxicities. At a median follow-up of 39.2 months, estimates of median and 3-year OS were 28.3 months and 45.1%, respectively. A small trial of 38 patients with stage II–IV esophageal adenocarcinoma also showed that FOLFOX combined with RT is safe and effective in the preoperative setting, with 38% of patients achieving pCR.[314] PROTECT is an ongoing randomized phase II trial that will compare preoperative chemoradiation with FOLFOX to paclitaxel and carboplatin, both with concurrent RT (41.4 Gy), in patients with resectable stage IIB–III esophageal and EGJ cancers of SCC or adenocarcinoma histology.[315] This trial will directly compare two standards of preoperative chemoradiation in the setting of resectable, locally advanced esophageal or EGJ cancers. Participation in this trial is highly encouraged (Clinical Trial ID: NCT02359968).

Other recommended regimens for preoperative chemoradiation include fluorouracil and cisplatin (category 1),[316,317] irinotecan and cisplatin (category 2B),[318] and paclitaxel and a fluoropyrimidine (fluorouracil or capecitabine [category 2B]).[319] CALGB 9781 was a prospective phase III trial that randomized patients (n = 56) with stage I–III esophageal cancers to receive preoperative chemoradiation with fluorouracil and cisplatin followed by surgery (n = 30) or surgery alone (n = 26).[316] After a median follow-up of 6 years, the median OS was 4.5 years in the preoperative chemoradiation group versus 1.8 years in the surgery alone group (*P* = .002). Patients receiving preoperative chemoradiation also had an improved 5-year OS rate (39% vs. 16%). The results from this trial reflect a long-term survival advantage with the use of preoperative chemoradiotherapy with fluorouracil and cisplatin in the treatment of esophageal cancer. Irinotecan and cisplatin showed modest activity in a single-institution retrospective trial involving patients (n = 44) with locally advanced esophageal carcinoma.[318] All patients underwent R0 resection and the pCR rate was 25%. The median DFS and OS were 24 months and 34 months, respectively, and the 3-year OS rate was 46%.

Studies have compared preoperative chemoradiation with chemoradiation alone in patients with esophageal SCC. A trial by Stahl et al randomized 172 esophageal SCC patients to receive either induction chemotherapy followed by preoperative chemoradiation plus surgery or induction chemotherapy followed by chemoradiation alone.[320] Although the 2-year PFS rate was better in the preoperative chemoradiation group (64.3%) than in the chemoradiation alone group (40.7%), there was no difference in OS. Additionally, the preoperative chemoradiation group had significantly higher treatment-related mortality than the chemoradiation

alone group (12.8% vs. 3.5%, respectively). Long-term results with a median follow-up time of 10 years also showed no clear difference in survival between the two groups.[321] The FFCD 9102 trial also showed that adding surgery to chemoradiation provides little benefit compared to treatment with additional chemoradiation alone in patients with locally advanced SCC of the esophagus who responded to initial chemoradiation therapy.[317] A meta-analysis of randomized controlled trials compared chemoradiation plus surgery with chemoradiation alone in patients with at least T3 and/or N+ thoracic esophageal cancer (93% had SCC).[322] The authors concluded that the addition of surgery to chemoradiation in locally advanced esophageal SCC has little impact on OS, and may be associated with higher treatment-related mortality. The addition of surgery may delay locoregional recurrence; however, this endpoint was not well-defined in the included studies. In contrast, a follow-up study that analyzed long-term outcomes in patients not eligible for randomization in the FFCD 9102 trial (ie, those with no clinical response to initial chemoradiation) found that median OS was longer in clinical non-responders who underwent surgery compared to non-surgical patients (17 vs. 5.5 months, respectively).[323]

A recent phase III trial (NEOCRTEC5010) compared safety and survival outcomes of preoperative chemoradiation plus surgery (n = 224) with surgery alone (n = 227) in patients with locally advanced esophageal SCC.[324] Compared with the surgery alone group, the preoperative chemoradiation group had a higher R0 resection rate (98.4% vs. 91.2%; *P* = .002), improved median OS (100.1 months vs. 66.5 months; HR, 0.71; 95% CI, 0.53–0.96; *P* = .025), and prolonged DFS (100.1 months vs. 41.7 months; HR, 0.58; 95% CI, 0.43–0.78; *P* < .001). Incidences of postoperative complications were similar between the two groups. This trial shows that preoperative chemoradiation improves survival over surgery alone among patients with locally advanced esophageal SCC, with acceptable toxicities.

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Preoperative induction chemotherapy followed by concurrent chemoradiation has also been evaluated in clinical trials for patients with locally advanced esophageal and EGJ cancers.[325-333] In a phase III study, Stahl et al compared preoperative chemotherapy (fluorouracil and cisplatin) with preoperative chemotherapy followed by concurrent chemoradiation therapy using the same regimen in 119 patients with locally advanced adenocarcinoma of the lower esophagus or EGJ.[329] Patients were randomized to receive chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiation and surgery (arm B). Patients in arm B had a higher probability of achieving pCR (15.6% vs. 2.0%, respectively) and tumor-free lymph nodes at resection (64.4% vs. 37.7%, respectively) than patients in arm A. Patients in arm B also had improved 3-year OS rates (47.4% vs. 27.7% in arm A). Although the study was closed prematurely due to low accrual and statistical significance was not achieved, there was a trend towards a survival advantage for preoperative sequential chemotherapy and chemoradiation compared to preoperative chemotherapy alone in patients with EGJ adenocarcinoma.

In a phase II study, preoperative chemotherapy with irinotecan and cisplatin followed by concurrent chemoradiation with the same regimen resulted in moderate response rates in patients with resectable, locally advanced gastric and EGJ adenocarcinoma.[330] R0 resection was achieved in 65% of patients and the median OS and actuarial 2-year survival rates were 14.5 months and 35%, respectively.[330] In another phase II trial that evaluated preoperative chemotherapy with irinotecan and cisplatin followed by concurrent chemoradiation, the rate of pCR (16%) was relatively low and the rates of R0 resection (69%), PFS (15.2 months), and OS (31.7 months) were either comparable or inferior to those observed for preoperative chemoradiation in phase II trials.[332]

In the phase II SAKK 75/02 trial, preoperative chemotherapy with docetaxel and cisplatin followed by chemoradiation with the same regimen was effective in patients with SCC or adenocarcinoma of the esophagus (n = 66). Of the 57 patients who underwent surgery, R0 resection was achieved in 52 of them. Median OS and EFS were 36.5 months and 22.8 months, respectively.[331] However, the results of another phase II trial showed that induction chemotherapy (oxaliplatin and fluorouracil) before preoperative chemoradiation with the same regimen resulted in a non-significant increase in the rate of pCR and did not prolong OS in patients with esophageal cancer.[333] Therefore, induction chemotherapy prior to preoperative chemoradiation therapy is feasible and may be appropriate for select patients. However, this approach needs to be further evaluated in phase III randomized clinical trials.

Perioperative Chemotherapy

The survival benefit of perioperative chemotherapy in gastroesophageal cancers was first demonstrated in the landmark phase III MAGIC trial.[334] This study, which compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improves PFS and OS in patients with non-metastatic stage II and higher gastric or EGJ adenocarcinoma. In the randomized controlled phase II/III FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen in patients with resectable non-metastatic gastric or EGJ adenocarcinoma (≥cT2 and/or N+).[169,295] In the phase II part of the study, 265 patients were randomized to receive either three preoperative and postoperative cycles of ECF (n = 137) or four preoperative and postoperative cycles of FLOT (n = 128). Results showed that FLOT was associated with significantly higher proportions of patients achieving pCR than was ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; *P* = .02).[295] Additionally, FLOT was associated with a reduction in the percentage of patients experiencing at least one grade 3–4 adverse event, including neutropenia, leucopenia, nausea, infection, fatigue, and vomiting (40% of patients in the ECF group vs. 25% of patients in the FLOT group). In the phase III part of the trial, 716 patients were randomized to receive FLOT (n = 356) or ECF (n = 360).[169] Results showed that median OS was increased in the FLOT group compared with the ECF group (50 months vs. 35 months; HR = 0.77; 95% CI, 0.63–0.94). The percentage of patients with serious chemotherapy-related adverse events was the same in the two groups (27% in the ECF group vs. 27% in the FLOT group). Therefore, ECF should no longer be recommended in this setting. However, because of considerable toxicity associated with the FLOT regimen, the panel recommends its use in select patients with good performance status. The preferred perioperative regimen for most patients who have good to moderate performance status is FOLFOX.

In the FNCLCC ACCORD 07 trial (n = 224 patients; 75% had adenocarcinoma of the lower esophagus or EGJ), Ychou et al reported that perioperative chemotherapy with fluorouracil and cisplatin significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[294] At a median follow-up of 5.7 years, the 5-year OS rate was 38% for patients in the perioperative chemotherapy group and 24% for patients in the surgery alone group (*P* = .02). The corresponding 5-year DFS rates were 34% and 19%, respectively. Although this trial was prematurely terminated due to low accrual, the panel feels that perioperative fluorouracil and cisplatin is a viable treatment option for patients with locally advanced resectable esophageal or EGJ cancers.

The recently published phase III NEO-AEGIS trial directly compared preoperative chemoradiation (CROSS regimen) to perioperative chemotherapy (modified MAGIC or FLOT regimen) in 377 patients with locoregional adenocarcinoma of the esophagus or EGJ.[335] At a median follow-up of 24.5 months, there were 143 deaths (70 in the CROSS arm and 73 in the MAGIC/FLOT arm), with 3-year estimated survival probabilities of 56% and 57%, respectively (HR, 1.02), indicating no

survival difference between the two modalities. However, all pathologic endpoints (pCR rate, N0 and R0 resection status) favored preoperative chemoradiation. These data strongly suggest non-inferiority of perioperative chemotherapy to preoperative chemoradiation, making perioperative chemotherapy a viable treatment option for patients with locoregional adenocarcinoma. The results of other prospective trials are awaited.

Preoperative Chemotherapy

Clinical trials have investigated chemotherapy alone in the preoperative setting for locally advanced esophageal cancer.[296,336-338] In the Medical Research Council OEO2 trial, 802 patients with potentially resectable esophageal cancer were randomly assigned to receive either two cycles of preoperative fluorouracil and cisplatin followed by surgery or surgery alone.[336] Median survival was 16.8 months in the preoperative chemotherapy group compared with 13.3 months in the surgery alone group, and 2-year survival rates were 43% and 34%, respectively. Long-term follow-up confirmed the survival benefit of preoperative chemotherapy with fluorouracil and cisplatin, with a 23% 5-year survival rate in the preoperative chemotherapy group compared to 17.1% in the surgery alone group (HR, 0.84; 95% CI, 0.72–0.98; P = .03).[336,337] The Medical Research Council OEO5 trial compared preoperative chemotherapy with two cycles of fluorouracil and cisplatin to four cycles of epirubicin, oxaliplatin, and capecitabine (ECX) followed by surgery in 897 patients with lower esophageal or EGJ adenocarcinoma. Although there was a trend towards prolonged PFS and DFS with ECX, this did not translate into an OS benefit.[296] Furthermore, ECX was associated with higher toxicity than fluorouracil and cisplatin (47% vs. 30% grade 3–4 toxicities; P < .001).

The OEO2 trial demonstrated an increase in the 2-year survival rate and median survival duration of patients who received preoperative chemotherapy with fluorouracil and cisplatin. However, another large randomized trial failed to demonstrate a survival advantage for this regimen. In the INT-113 trial, patients with resectable esophageal cancer (n = 440) randomized to receive preoperative fluorouracil and cisplatin or surgery alone showed no difference in median survival after a median follow-up of 55.4 months (14.9 vs. 16.1 months; P = .53).[339] Long-term results of this trial confirmed that there was no difference in 5-year OS in patients who had received preoperative fluorouracil and cisplatin compared to those treated with surgery alone.[340] The panel does not strongly endorse fluorouracil and cisplatin as an optimal preoperative strategy and therefore lists it as a category 2B recommendation in the guidelines.

Definitive Chemoradiation Therapy

Given the efficacy and safety of combined paclitaxel and carboplatin as a preoperative chemoradiation regimen as reported in the CROSS trial,[168] the NCCN Panel also recommends this regimen as a preferred option for definitive chemoradiation. In a retrospective comparison, definitive chemoradiation with paclitaxel and carboplatin resulted in superior OS, disease-specific survival, locoregional control, and palliation in patients with unresectable esophageal cancer compared to cisplatin and irinotecan.[341] The FOLFOX regimen as well as combined fluorouracil and cisplatin have also been proven as effective definitive chemoradiation regimens in clinical trials. The efficacy of chemoradiation therapy with fluorouracil and cisplatin versus RT alone, each without resection, was studied in an early randomized trial (RTOG 85-01) involving patients with esophageal SCC or adenocarcinoma (cT1–cT3, N0–1, M0).[262,342] Compared to patients who received RT alone, patients who received chemoradiation showed a significant improvement in both median survival (14 vs. 9 months) and 5-year OS (27% vs. 0%) 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 chemoradiation arm (47% vs. 65% in the RT alone arm). A follow-up trial (INT-0123) compared two different RT doses used with the same chemotherapy regimen (fluorouracil and cisplatin).[286] In this trial, 218 patients with esophageal cancer with either SCC (85%) or adenocarcinoma (15%) (cT1–cT4, N0–1, M0) were randomly assigned to receive the standard RT dose of 50.4 Gy or a higher dose of 64.8 Gy. No significant difference was observed in median survival (13 months vs. 18 months), 2-year OS (31% vs. 40%), or locoregional failure (56% vs. 52%) rates between the high-dose and standard-dose RT arms. Two more recent phase III trials (ARTDECO and CONCORDE [PRODIGE-26]) have similarly shown no benefit to radiation dose escalation beyond 50 Gy in improving local control or survival.[275,276] These results support the use of RT at a dose of 50 to 50.4 Gy for definitive chemoradiation.

In a randomized phase III trial (PRODIGE5/ACCORD17), 267 patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to receive definitive chemoradiation with either FOLFOX or fluorouracil and cisplatin.[300] The median PFS was 9.7 months in the FOLFOX group compared to 9.4 months in the fluorouracil and cisplatin group (P = .64).[300] Although definitive chemoradiation with FOLFOX was not associated with a PFS benefit compared to fluorouracil and cisplatin, the investigators suggest that FOLFOX might be a more convenient option for patients with localized esophageal cancer who may not be candidates for surgery. After a 6-month follow-up, an updated analysis revealed no significant differences in health-related quality of life between patients receiving definitive chemoradiation with FOLFOX versus those receiving fluorouracil and cisplatin.[343] Therefore, FOLFOX and fluorouracil plus cisplatin are both category 1 preferred recommendations for definitive chemoradiation, although FOLFOX is associated with fewer treatment-related adverse events.

Reports have also confirmed the efficacy of definitive chemoradiation using other chemotherapy regimens.[301,302,344] Definitive chemoradiation with docetaxel and cisplatin resulted in a high overall response rate (ORR) (98.3%; 71% complete response) and a median OS of 23 months in a small study of 59 patients with esophageal SCC.[301] The 3-year locoregional PFS, overall PFS, and OS rates were 60%, 29%, and 37%, respectively. In a phase II trial, chemoradiation with paclitaxel and cisplatin was well-tolerated and resulted in a complete histologic response in 19% of patients with locoregional esophageal cancer.[344] Median OS was 24 months and 1-, 2-, and 3-year survival probabilities were 75%, 50%, and 34%, respectively. Therefore, cisplatin with either docetaxel or paclitaxel are recommended regimens for definitive chemoradiation. Definitive chemoradiation with irinotecan and cisplatin[318] or paclitaxel and a fluoropyrimidine (fluorouracil or capecitabine)[319] are category 2B recommendations.

Postoperative Therapy

Nivolumab is a category 1, preferred recommendation for patients who have residual disease following preoperative chemoradiation and R0 resection.[345] See *Targeted Therapies* below for more information on nivolumab. The data for postoperative chemotherapy with capecitabine and oxaliplatin is derived from the phase III CLASSIC trial involving patients with stage II or IIIB gastric cancer. [299,346] In this study, patients who had not received preoperative therapy were randomized to receive either gastrectomy with D2 lymph node dissection alone (n = 515) or gastrectomy with D2 lymph node dissection followed by postoperative chemotherapy (n = 520). After a median follow-up of 34.2 months, postoperative chemotherapy with capecitabine and oxaliplatin significantly improved 3-year DFS (74%) compared to surgery alone (59%) for all disease stages (P < .0001).[346] After a median follow-up of 62.4 months, the estimated 5-year DFS rate was 68% for the postoperative chemotherapy group compared to 53% for the surgery alone group; the

corresponding estimated 5-year OS rates were 78% and 69%, respectively.[299] Based on these data, the panel recommends capecitabine and oxaliplatin as an option for postoperative chemotherapy in patients with resectable esophageal or EGJ cancers who had not received preoperative therapy. The panel also endorses the use of FOLFOX in this setting.

Postoperative Chemoradiation Therapy

The landmark INT-0116 trial investigated the effectiveness of surgery followed by postoperative chemotherapy plus chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[297,298] In this trial, 556 patients (stage IB–IV, M0) were randomized to receive surgery followed by postoperative chemotherapy plus chemoradiation (n = 281; bolus fluorouracil plus leucovorin before and after concurrent chemoradiation with the same regimen) or surgery alone (n = 275).[298] The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%). After a median follow-up of 5 years, median OS in the surgery-only group was 27 months compared to 36 months in the postoperative chemotherapy plus chemoradiation group (*P* = .005). The postoperative chemotherapy plus chemoradiation group also had better 3-year OS (50% vs. 41%) and relapse-free survival (RFS) rates (48% vs. 31%) than the surgery-only group. There was also a decrease in local failure as the first site of failure in the chemoradiation group (19% vs. 29%). After a median follow-up of greater than 10 years, survival remained improved in patients treated with postoperative chemoradiation.[297] Additionally, data from a retrospective analysis showed that postoperative chemoradiation according to the INT-0116 protocol resulted in improved 3-year DFS rates after curative resection in patients (n = 211) with EGJ adenocarcinoma and positive lymph nodes who did not receive neoadjuvant chemotherapy (37% vs. 24% after surgery alone).[347]

The results of the INT-0116 trial established the efficacy of postoperative chemoradiation in patients with resected gastric or EGJ adenocarcinoma who have not received preoperative therapy. However, the dosing and schedule of chemotherapy agents used in this trial was associated with high rates of grade 3–4 hematologic and GI toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group, 17% discontinued treatment and three patients died as a result of chemoradiation-related toxicities, including pulmonary fibrosis, cardiac events, and myelosuppression. Therefore, the doses and schedule of chemotherapy agents used in the INT-0116 trial are not recommended by the panel due to concerns regarding toxicity. See *Principles of Systemic Therapy–Regimens and Dosing Schedules* in the algorithm for recommended modifications to this regimen.

In another trial that evaluated postoperative chemoradiation with cisplatin and fluorouracil in patients with poor-prognosis esophageal and EGJ adenocarcinoma, the projected rates of 4-year OS, RFS, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively, for patients with node-positive T3 or T4 tumors, which were better than the historical outcomes observed with surgery alone in these patients.[348] A recent meta-analysis of 2165 patients with esophageal cancer showed that postoperative chemoradiation significantly improved OS and significantly reduced the locoregional recurrence rate compared to non-chemoradiation postoperative treatments (postoperative chemotherapy alone, postoperative RT alone, or observation).[349] However, no difference was seen in the rate of distant metastases between these groups. The authors concluded that postoperative chemoradiation yields significant survival benefits and improves locoregional control with tolerable toxicity. However, results of meta-analyses should be considered hypothesis-generating and cannot change the standard of care. While the addition of postoperative chemoradiation has been associated with survival benefits in patients

with node-positive locoregional esophageal cancer,[350,351] it is important to note that the efficacy of postoperative chemoradiation compared to surgery alone has not been demonstrated in a randomized trial in patients with esophageal cancer.

Systemic Therapy for Locally Advanced or Metastatic Disease

First-Line Therapy

Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic esophageal or EGJ cancers.[352-354] First-line systemic therapy regimens with two cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.[355] Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Trastuzumab should be added to first-line chemotherapy for patients with HER2 overexpression positive adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred [category 1 for cisplatin;[157] category 2A for oxaliplatin]). An FDA-approved biologic medical product that is similar to trastuzumab (a biosimilar) is an appropriate substitute. Pembrolizumab can also be added to this regimen for treatment of HER2 overexpression positive adenocarcinoma.[356] Preferred regimens for HER2 overexpression negative disease include nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin for adenocarcinoma tumors with PD-L1 expression levels by CPS of ≥5 (category 1) or CPS of <5 (category 2B), and pembrolizumab combined with fluoropyrimidine (fluorouracil or capecitabine) and either cisplatin (category 1) or oxaliplatin for adenocarcinoma or SCC tumors with PD-L1 expression levels by CPS of ≥10 or CPS of <10 (category 2B).[357,358] See *Targeted Therapies* below for more information on trastuzumab, nivolumab, and pembrolizumab.

The preferred regimens for HER2 negative disease also include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin[359-361] or cisplatin.[359,362-364] A phase III trial conducted by the German Study Group compared treatment with fluorouracil and cisplatin to FOLFOX in patients (n = 220) with previously untreated advanced adenocarcinoma of the stomach or EGJ.[359] Results showed that FOLFOX (referred to as FLO) was associated with significantly less toxicity and showed a trend towards improved median PFS (5.8 vs. 3.9 months; *P* = .77) compared to fluorouracil and cisplatin (FLP). However, there was no significant difference in median OS (10.7 vs. 8.8 months, respectively) between the two groups. FOLFOX resulted in significantly superior response rates (41.3% vs. 16.7%; *P* = .12), time to treatment failure (5.4 vs. 2.3 months; *P* < .001), PFS (6.0 vs. 3.1 months; *P* = .029), and improved OS (13.9 vs. 7.2 months) compared with FLP in patients greater than 65 years (n = 94). Therefore, FOLFOX offers reduced toxicity and similar efficacy compared to fluorouracil plus cisplatin and may also be associated with improved efficacy in older adult patients.

Recommendations for the use of regimens combining a platinum agent with capecitabine as first-line therapy have been extrapolated from trials involving patients with advanced gastric cancer.[361,364-366] Results of a meta-analysis suggest that OS was superior in patients with advanced gastroesophageal cancer treated with capecitabine-based combinations compared to patients treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.[367] Therefore, capecitabine and oxaliplatin is also a preferred regimen for first-line treatment of patients with advanced esophageal or EGJ cancers. The GO2 phase III trial demonstrated that a low-dose capecitabine and oxaliplatin regimen (60% of the standard dose) was non-inferior in terms of PFS and resulted in significantly lower toxicities and

better overall treatment utility in elderly and/or frail patients with advanced gastroesophageal cancers (n = 514).[368] Therefore, this low-dose regimen is recommended as an alternative to standard-dose capecitabine and oxaliplatin for elderly and/or frail patients with advanced or metastatic disease. See *Principles of Systemic Therapy - Regimens and Dosing Schedules* in the algorithm for recommended modifications to this regimen.

First-line treatment with irinotecan-based regimens has been explored extensively in clinical trials involving patients with advanced or metastatic gastroesophageal cancers.[369-375] The results of a randomized phase III study comparing fluorouracil and irinotecan (FOLFIRI) to cisplatin and fluorouracil (CF) in patients with advanced gastric or EGJ adenocarcinoma (n = 337) showed that FOLFIRI was non-inferior to CF in terms of PFS, but not in terms of OS or time to progression.[370] FOLFIRI was also associated with a more favorable safety profile. A more recent phase III trial (French Intergroup Study) compared FOLFIRI with ECF as first-line treatment in patients (n = 416) with advanced or metastatic gastric or EGJ adenocarcinoma.[375] After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECF (5.1 months vs. 4.2 months; *P* = .008).[375] However, there were no significant differences in median PFS (5.3 months vs. 5.8 months; *P* = .96), median OS (9.5 months vs. 9.7 months; *P* = .95), or response rate (39.2% vs. 37.8%). Importantly, FOLFIRI was less toxic and better tolerated than ECF. Therefore, FOLFIRI may be recommended as a first-line therapy option for patients with advanced or metastatic esophageal or EGJ adenocarcinoma.

Docetaxel, cisplatin, and fluorouracil (DCF) has also demonstrated activity in patients with locally advanced or metastatic gastroesophageal cancer.[376,377] An international phase III study (V325) that randomized 445 patients with untreated advanced gastric or EGJ cancer to receive either DCF or CF found that the addition of docetaxel to CF significantly improved time to progression, OS, and ORR.[377] However, DCF was associated with increased toxicities including myelosuppression and infectious complications.[377] Various modifications of the DCF regimen have demonstrated improved safety compared to the DCF regimen evaluated in the V325 study.[378-381] Therefore, due to concerns regarding toxicity, dose-modified DCF or other DCF modifications should be used as alternative options to the standard DCF regimen for first-line therapy. Other recommended regimens for first-line therapy include paclitaxel with either cisplatin or carboplatin,[382-384] docetaxel with cisplatin,[376,385] or single-agent fluoropyrimidine (fluorouracil or capecitabine),[363,386,387] docetaxel,[352,388] or paclitaxel.[389,390] Docetaxel, carboplatin, and fluorouracil[381] is a category 2B recommendation in this setting.

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Nivolumab is preferred for second-line or subsequent therapy for esophageal SCC (category 1).[391] Pembrolizumab is preferred for second-line therapy for esophageal SCC with PD-L1 expression levels by CPS of ≥10 (category 1).[392] Ramucirumab (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) in combination with paclitaxel (preferred) or as a single agent are also recommended treatment options for second-line or subsequent therapy.[393,394] Fam-trastuzumab deruxtecan-nxki is a second-line treatment option for HER2 overexpression positive adenocarcinoma patients who have received prior trastuzumab-based therapy.[395] See *Targeted Therapies* below for more information on ramucirumab, nivolumab, pembrolizumab and fam-trastuzumab deruxtecan-nxki.

Single-agent docetaxel,[352,388] paclitaxel,[389,390,396] and irinotecan[353,396-398] are also category 1 preferred options for second-line or subsequent therapy. In a randomized phase III trial (COUGAR-02) single-agent docetaxel was

shown to significantly increase 12-month OS compared to active symptom control alone (5.2 months vs. 3.6 months, respectively; HR, 0.67; *P* = .01).[352] A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the two groups (9.5 months in the paclitaxel group vs. 8.4 months in the irinotecan group; HR, 1.13; *P* = .38).[396]

FOLFIRI is a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy.[397,399,400] A phase II trial investigating the efficacy and toxicity of FOLFIRI in patients (n = 40) with refractory or relapsed esophageal or gastric cancer reported an ORR of 29% and median OS of 6.4 months. Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in patients with advanced gastric cancer (n = 59) treated with FOLFIRI in the second-line setting.[397] Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.[401] In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%).

The trifluridine and tipiracil regimen was approved by the FDA in 2019 for previously treated recurrent or metastatic gastric and EGJ adenocarcinoma[402] based on results of the global phase III TAGS trial, in which 507 patients with heavily pretreated metastatic gastric or EGJ cancer were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n = 337) or placebo plus best supportive care (n = 170).[403] This study reported an improvement in median OS by 2.1 months with the trifluridine and tipiracil regimen compared to placebo (HR, 0.69; 95% CI, 0.56–0.85; *P* = .0003). PFS was also significantly longer in the trifluridine and tipiracil group (2.0 vs. 1.7 months; HR, 0.57; 95% CI, 0.47–0.70; *P* < .0001). The most frequently reported grade 3–4 toxicities were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%). Patients aged 65 years or older had a higher incidence of moderate renal impairment compared to the overall study population (31% vs. 17%).[404] Improvements in median OS and PFS and a similar safety profile were observed in a subgroup analysis of patients with metastatic EGJ adenocarcinoma (n = 145).[405] Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic EGJ adenocarcinoma in the third-line or subsequent setting. However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume EGJ adenocarcinoma who have minimal or no symptoms and the ability to swallow pills.

Other recommended regimens for second-line or subsequent therapy include irinotecan and cisplatin,[360,369] ramucirumab combined with irinotecan[406] or FOLFIRI,[407] and irinotecan and docetaxel (category 2B).[372] Options that are useful in certain circumstances include pembrolizumab[163,165,408] or dostarlimab-gxly[409] for MSI-H/dMMR tumors, pembrolizumab for TMB-H (≥10 mutations/megabase) tumors,[410] and entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors.[411,412] See *Targeted Therapies* below for more information on pembrolizumab, dostarlimab-gxly, entrectinib, and larotrectinib.

Targeted Therapies

At present, several targeted therapeutic agents, trastuzumab, pembrolizumab/nivolumab, and entrectinib/larotrectinib, have been approved by the FDA for use in advanced esophageal and EGJ cancers. Treatment with trastuzumab is based on the presence of HER2 overexpression.[141] Treatment with pembrolizumab/nivolumab is based on testing for MSI by PCR/NGS or MMR by IHC, PD-L1 expression by IHC, or high TMB by NGS.[163,165,357,408,410,413,414] Treatment with the tropomyosin receptor kinase (TRK) inhibitors entrectinib and larotrectinib is based on

testing for *NTRK* gene fusions.[415,416] When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC/ISH/targeted PCR should be considered first, followed by NGS testing as appropriate.

Trastuzumab

The ToGA trial was the first randomized prospective phase III trial that evaluated the efficacy and safety of trastuzumab in HER2 overexpression positive advanced gastric and EGJ adenocarcinoma.[157] In this trial, 594 patients with HER2 overexpression positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.[157] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up time was 19 months and 17 months, respectively, in the two groups. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy in HER2 overexpression positive patients (13.8 vs.11 months, respectively; $P = .046$). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment for patients with HER2 overexpression positive advanced gastroesophageal adenocarcinoma. In a post-hoc subgroup analysis, the addition of trastuzumab to chemotherapy further improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR, 0.65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR, 1.07).

The phase II HERXO trial assessed the combination of trastuzumab with capecitabine and oxaliplatin in the first-line treatment of patients with HER2 overexpression positive advanced gastric or EGJ adenocarcinoma (n = 45).[417] At a median follow-up of 13.7 months, PFS and OS were 7.1 and 13.8 months, respectively, and 8.9%, 37.8%, and 31.1% of patients achieved a complete response, partial response, and stable disease. The most frequently reported grade 3 or higher adverse events were diarrhea (26.6%), fatigue (15.5%), nausea (20%), and vomiting (13.3%). In a retrospective study of 34 patients with HER2 overexpression positive metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2 overexpression positive tumors.[418] The ORR with this regimen was 41% and median PFS and OS were 9.0 months and 17.3 months, respectively. The most frequent grade 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combinations of trastuzumab with capecitabine and oxaliplatin or with modified FOLFOX are effective regimens with acceptable safety profiles in patients with HER2 overexpression positive gastroesophageal cancers. Therefore, trastuzumab should be added to first-line chemotherapy in combination with a fluoropyrimidine and a platinum agent (oxaliplatin is preferred over cisplatin due to lower toxicity) in patients with HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab may be combined with other chemotherapy agents for first-line therapy, but should not be continued in second-line therapy.[419]

Pembrolizumab can also be added to first-line fluoropyrimidine, platinum, and trastuzumab based on an interim analysis of the first 264 patients enrolled in the KEYNOTE-811 trial, which showed an improved ORR (74% vs. 52%; $P = .0001$) and median duration of response (10.6 vs. 9.5

months) with the addition of pembrolizumab to chemotherapy plus trastuzumab compared to the addition of placebo in patients with HER2 overexpression positive adenocarcinoma.[356]

Fam-trastuzumab deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of trastuzumab and a cytotoxic topoisomerase I inhibitor connected by a cleavable tetrapeptide-based linker. The efficacy and safety of fam-trastuzumab deruxtecan-nxki in advanced or metastatic gastric or EGJ adenocarcinoma was evaluated in the phase II DESTINY-Gastric01 trial, which included 188 patients with progressive disease following at least two prior lines of therapy, including trastuzumab.[395] Patients were randomized 2:1 to receive either fam-trastuzumab deruxtecan-nxki or physician's choice of chemotherapy (paclitaxel or irinotecan). The confirmed objective response rate for patients on fam-trastuzumab deruxtecan-nxki was 40.5% compared to 11% for those on chemotherapy. OS (12.5 vs. 8.4 months; *P* = .0097), median PFS (5.6 vs. 3.5 months) and duration of response (11.3 vs. 3.9 months) were also higher in the fam-trastuzumab deruxtecan-nxki group compared to the chemotherapy group. Fam-trastuzumab deruxtecan-nxki resulted in more toxicities than systemic chemotherapy in this trial. The most common adverse events (grade 3 or higher) were a decreased neutrophil count (51% of the fam-trastuzumab deruxtecan-nxki group and 24% of the chemotherapy group), anemia (38% and 23%, respectively), and decreased white blood cell count (21% and 11%). Fam-trastuzumab deruxtecan-nxki–related interstitial lung disease or pneumonitis occurred in 12 patients resulting in 1 drug-related death (due to pneumonia). No drug-related deaths occurred in the physician's choice group. The FDA has approved fam-trastuzumab derextecan-nxki to treat HER2 overexpression positive tumor patients in second-line or subsequent therapy. Therefore, fam-trastuzumab deruxtecan-nxki may be used as a second-line or subsequent treatment option for patients with HER2 overexpression positive adenocarcinoma following failure of prior trastuzumab-based regimen. However, careful patient selection and close monitoring of patients for excessive toxicity is recommended.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.[393,394] An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[393] In this study, 355 patients were randomized to receive ramucirumab (n = 238) or placebo (n = 117). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). Ramucirumab was associated with higher rates of hypertension than placebo (16% vs. 8%), whereas rates of other adverse events were similar.

The international phase III RAINBOW trial evaluated paclitaxel with or without ramucirumab in patients (n = 665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.[394] Patients randomized to receive ramucirumab plus paclitaxel (n = 330) had significantly longer median OS (9.63 months) compared to patients receiving paclitaxel alone (n = 335; 7.36 months; *P* < .0001). The median PFS was 4.4 months and 2.86 months, respectively, and the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone (*P* = .0001). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel. An exposure-response analysis revealed that ramucirumab was a significant predictor of OS and PFS in both studies.[420] Based on these results, ramucirumab (as a single agent or in combination with paclitaxel) was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or

progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy. The guidelines recommend ramucirumab as a single agent (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) or in combination with paclitaxel (preferred) as treatment options for second-line or subsequent therapy in patients with advanced or metastatic esophageal or EGJ adenocarcinoma.[393,394]

Ramucirumab combined with FOLFIRI can be an option for second-line or subsequent therapy for patients with advanced esophageal or EGJ adenocarcinoma. In a multi-institutional retrospective analysis of 29 patients with advanced gastric or EGJ adenocarcinoma who received FOLFIRI plus ramucirumab in the second-line setting, the ORR was 23% with a disease control rate of 79%.[407] Median PFS was 6 months and median OS was 13.4 months. Six- and 12-month OS were 90% and 41%, respectively. No new safety signals were observed with the combination treatment, making FOLFIRI plus ramucirumab a safe, non-neurotoxic alternative to ramucirumab plus paclitaxel. Ramucirumab combined with irinotecan is also an option for second-line or subsequent therapy for patients with advanced adenocarcinoma.[406]

Due to the results of the international phase III RAINFALL trial, in which treatment with ramucirumab did not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma, the addition of ramucirumab to first-line chemotherapy is not recommended at this time.[421]

Nivolumab

Nivolumab is a monoclonal PD-1 antibody that was approved by the FDA in April 2021, in combination with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with advanced or metastatic esophageal or EGJ adenocarcinoma.[422] This approval was based on results from the phase III Checkmate-649 trial, which randomized 1581 patients with previously untreated, HER2-negative, unresectable gastric, EGJ, or esophageal adenocarcinoma to receive chemotherapy alone or nivolumab plus chemotherapy (capecitabine and oxaliplatin or modified FOLFOX).[357] The addition of nivolumab to chemotherapy resulted in significant improvements in OS (14.4 vs. 11.1 months; HR, .71; $P < .0001$) and PFS (7.7 vs. 6 months; HR, .68; $P < .0001$) compared to chemotherapy alone in patients with a PD-L1 CPS of ≥5 (n = 955). Additional results also showed some improvement in OS and PFS in patients with a PD-L1 CPS of ≥1 (n = 1296; OS = 14 vs. 11.3 months, HR = .77; PFS = 7.5 vs. 6.9, HR = .74) and in all randomly assigned patients (OS = 13.8 vs. 11.6, HR = .8; PFS = 7.7 vs. 6.9, HR = .77). Among all patients, 59% of those in the nivolumab plus chemotherapy group and 44% of those in the chemotherapy alone group experienced grade 3–4 treatment-related adverse events. The most common any-grade treatment-related adverse events were nausea, diarrhea, and peripheral neuropathy across both groups. Sixteen treatment-related deaths occurred in the nivolumab plus chemotherapy group compared to 4 in the chemotherapy alone group. Therefore, nivolumab plus fluoropyrimidine- and oxaliplatin-based chemotherapy is a preferred first-line treatment option for patients with HER2-negative esophageal or EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥5 (category 1) or <5 (category 2B).

In May 2021, nivolumab was approved for patients with completely resected esophageal or EGJ tumors with residual pathologic disease who had received preoperative chemoradiation.[423] This approval was based on results from the phase III Checkmate-577 trial, which evaluated the safety and efficacy of nivolumab (N = 532) versus placebo (N = 262) in this setting.[345] After a median follow-up of 24.4 months, median DFS was significantly longer in the nivolumab group compared to the placebo group (22.4 vs. 11 months; HR, .69; $P < .001$). The DFS benefit with nivolumab was observed regardless of PD-L1 expression levels. Grade 3–4 adverse

events occurred in 13% of patients in the nivolumab group and 6% in the placebo group. The most common adverse events in the nivolumab group were fatigue, rash, musculoskeletal pain, and pruritus. Postoperative nivolumab is a new effective treatment option for patients at high risk for recurrence due to the presence of residual pathologic disease following preoperative chemoradiation and R0 resection.

Nivolumab was also approved by the FDA in June 2020 for the treatment of patients with unresectable advanced, recurrent, or metastatic esophageal SCC after prior fluoropyrimidine- and platinum-based chemotherapy.[424] This approval was based on results from the international phase III ATTRACTION-3 trial, which compared nivolumab to chemotherapy in patients with advanced esophageal SCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen.[391] Patients (n = 419) were randomized 1:1 to receive nivolumab or investigator's choice of chemotherapy (either docetaxel or paclitaxel). Median OS was significantly improved in patients receiving nivolumab compared to those receiving chemotherapy (10.9 vs. 8.4 months; *P* = .019). Importantly, the OS benefit was observed regardless of tumor PD-L1 expression levels. The ORR was 19.3% in the nivolumab arm versus 21.5% in the chemotherapy arm, with a median response duration of 6.9 and 3.9 months, respectively. Grade 3–4 treatment-related adverse events occurred in 18% of patients in the nivolumab group, the most common being anemia, and in 63% of patients in the chemotherapy group, the most common being decreased neutrophil count. Since nivolumab was associated with a significant improvement in OS and a favorable safety profile compared to chemotherapy, it is a category 1 recommendation in this setting and represents a new and effective second-line treatment option for patients with previously treated advanced esophageal SCC.

Pembrolizumab

Pembrolizumab is a PD-1 antibody that was FDA approved in 2017 for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[425] This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across five multicenter single-arm clinical trials.[163,165,408] The ORR was 39.6% and responses lasted 6 or more months for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses and the ORR was similar irrespective of cancer type. Therefore, pembrolizumab is a second-line or subsequent therapy option for patients with MSI-H/dMMR gastroesophageal tumors.

In 2019, the FDA approved pembrolizumab for the second-line treatment of esophageal SCC with PD-L1 expression levels by CPS of ≥10 based on the results of the KEYNOTE-180 and KEYNOTE-181 trials.[426] In the phase II single-arm KEYNOTE-180 trial, which evaluated pembrolizumab monotherapy in 121 patients with progressive disease following 2 or more prior lines of therapy, the ORR was 9.9% among all patients.[427] The ORR was 14.3% among patients with esophageal SCC (n = 63), 5.2% among patients with adenocarcinoma (n = 58), 13.8% among patients with PD-L1–positive tumors (n = 58), and 6.3% among patients with PD-L1–negative tumors (n = 63). Overall, 12.4% of patients had grade 3–5 treatment-related adverse events and five patients discontinued treatment because of toxicity. Long-term results demonstrated a durable clinical benefit for pembrolizumab in this treatment population.[428] These results demonstrated the efficacy and tolerability of pembrolizumab in heavily pretreated esophageal SCC with high PD-L1 expression. The phase III KEYNOTE-181 trial evaluated pembrolizumab versus investigator's choice of chemotherapy (docetaxel, paclitaxel, or irinotecan) as second-line therapy in 628 patients with

advanced SCC or adenocarcinoma of the esophagus or EGJ.[392] Patients (401 with SCC and 222 with PD-L1 CPS ≥10) were randomized to pembrolizumab or chemotherapy and randomization was stratified by histology (SCC vs. adenocarcinoma) and region (Asia vs. rest of world). Pembrolizumab significantly improved median OS (9.3 vs. 6.7 months; *P* = .007) and 12-month OS rates (43% vs. 20%) compared to chemotherapy in patients with esophageal SCC tumors with PD-L1 CPS ≥10. Fewer patients had grade 3–5 treatment-related adverse events with pembrolizumab compared to chemotherapy (18% vs. 41%). Based on these data, pembrolizumab is a category 1, preferred second-line therapy option for patients with advanced esophageal SCC with PD-L1 expression levels by CPS of ≥10.

In June 2020, the FDA approved pembrolizumab for the treatment of patients with metastatic TMB-H solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[429] This approval was based on a retrospective analysis of 102 patients enrolled in the KEYNOTE-158 trial who had tumors identified as TMB-H.[410] The ORR for these patients was 29%, with a 4% complete response rate. The median duration of response was not reached, with 50% of patients having response durations for 24 months or longer. Based on these data, pembrolizumab may be used for the second-line or subsequent treatment of patients with TMB-H gastroesophageal tumors. However, it should be noted that no patients with gastroesophageal cancer were included in the KEYNOTE-158 trial.

First-line treatment with pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy was approved by the FDA in March 2021 for patients with locally advanced or metastatic esophageal or EGJ tumors.[430] This approval was based on data from the phase III KEYNOTE-590 trial, which randomized 749 patients with previously untreated, locally advanced, or metastatic esophageal SCC, esophageal adenocarcinoma, or EGJ adenocarcinoma to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy.[358] At a median follow-up of 22.6 months, statistically significant improvements in OS and PFS were observed in patients randomized to pembrolizumab plus chemotherapy. Median OS was 13.9 months for the pembrolizumab arm versus 8.8 months for the chemotherapy arm in patients with SCC and PD-L1 CPS ≥10 (HR, 0.57; *P* < .0001), 12.6 months versus 9.8 months in patients with SCC (HR, 0.72; *P* = .0006), 13.5 versus 9.4 months in patients with PD-L1 expression ≥10 (HR = 0.62; *P* < .0001), and 12.4 versus 9.8 months in all patients (HR, 0.73; *P* < .0001). Pembrolizumab plus chemotherapy was also superior to placebo plus chemotherapy for PFS in patients with SCC (6.3 vs. 5.8 months; HR, 0.65; *P* < .0001), PD-L1 CPS ≥10 (7.5 vs. 5.5 months; HR, 0.51; *P* < .0001), and in all patients (6.3 vs. 5.8 months; HR, 0.65; *P* < .0001). The most common adverse events in patients who received pembrolizumab were nausea, constipation, diarrhea, vomiting, stomatitis, fatigue, decreased appetite, and weight loss. Grade 3 or higher treatment-related adverse events occurred in 72% of patients receiving pembrolizumab and 68% of those receiving placebo. Based on these results, pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy may be used for the first-line treatment of patients with SCC or adenocarcinoma with PD-L1 expression levels by CPS of ≥10 (category 1 in combination with cisplatin) or <10 (category 2B).

Additional trials of pembrolizumab in gastroesophageal cancers are ongoing. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing KEYNOTE trials of pembrolizumab in patients with gastric, esophageal, or EGJ cancers.

Dostarlimab-gxly

Dostarlimab-gxly, an anti-PD-1 antibody, was approved by the FDA in August 2021 for the treatment of patients with dMMR recurrent or

advanced solid tumors that have progressed on or following prior treatment, who have no satisfactory alternative treatment options, and who had not previously received a PD-1 or PD-L1 inhibitor.[431] This approval was based on data from the nonrandomized phase 1 multi-cohort GARNET trial, which evaluated the safety and antitumor activity of dostarlimab-gxly in 209 patients with dMMR solid tumors who had not received prior PD-1, PDL-1, or CTLA4 inhibitors.[409,432] The majority of patients had endometrial or GI cancers. The ORR was 42%, with a 9% complete response rate and 33% partial response rate, and the median duration of response was 35 months. The most common treatment-related adverse events were fatigue, anemia, diarrhea, and nausea. Immune-mediated adverse events also occurred, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities. Based on these data, dostarlimab-gxly may be used for second-line or subsequent therapy for patients with MSI-H/dMMR gastroesophageal tumors.

Entrectinib and Larotrectinib

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode TRK fusion proteins (TRKA, TRKB, TRKC), which have increased kinase function and are implicated in the oncogenesis of many solid tumors including head and neck, thyroid, soft tissue, lung, and colon.[412,433] Although believed to be extremely rare in gastroesophageal cancers, one case report provides evidence that *NTRK* gene fusions do occur in gastric adenocarcinoma and may be associated with an aggressive phenotype.[434-436] No such case report for *NTRK* gene fusions in esophageal or EGJ cancers has yet been published.

In 2018, the FDA granted accelerated approval to the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged ≥12 years) with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[416] This FDA approval was based on data from three multicenter single-arm clinical trials. Patients with prospectively identified *NTRK* gene fusion-positive cancers were enrolled into one of three protocols: a phase I trial involving adults (LOXO-TRK-14001), a phase I–II trial involving children (SCOUT), and a phase II trial involving adolescents and adults (NAVIGATE).[412] A total of 55 patients with unresectable or metastatic solid tumors harboring an *NTRK* gene fusion who experienced disease progression following systemic therapy were enrolled across the three protocols and treated with larotrectinib. The most common cancer types represented were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR across the three trials was 75%, with a complete response rate of 22%. At a median follow-up of 9.4 months, 86% of the patients with a response were either continuing treatment with larotrectinib or had undergone curative-intent surgery. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Response duration was ≥6 months for 73%, ≥9 months for 63%, and ≥12 months for 39% of patients. At the time of data analysis, the median duration of response and PFS had not been reached. Adverse events were predominantly grade 1, the most common being increased aspartate aminotransferase (AST) levels, vomiting, constipation, and dizziness. The SCOUT (Clinical Trial ID: NCT02637687) and NAVIGATE (Clinical Trial ID: NCT02576431) trials are still actively recruiting patients with *NTRK* gene fusion-positive tumors.

In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.[415] The approval of entrectinib for the treatment of *NTRK* gene

fusion-positive tumors was based on data from three multicenter, single-arm, phase I and phase II clinical trials. A total of 54 patients aged 18 years or older with metastatic or locally advanced *NTRK* gene fusion-positive solid tumors were enrolled into one of the three protocols (ALKA-372-001, STARTRK-1, or STARTRK-2).[411] The most common cancer types represented were sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal. The ORR across the three trials was 57%, with a complete response rate of 7%. Response duration was ≥6 months for 68% of patients and ≥12 months for 45% of patients. The median duration of response was 10 months. The most common grade 3–4 treatment-related adverse events were increased weight and anemia while the most common serious treatment-related adverse events were nervous system disorders. STARTRK-2 (Clinical Trial ID: NCT02568267) is still actively recruiting patients with *NTRK* gene fusion-positive tumors. Based on these data, entrectinib and larotrectinib are recommended as second-line or subsequent treatment options for patients with *NTRK* gene fusion-positive gastroesophageal tumors.

Treatment Guidelines

The management of patients with esophageal and EGJ cancers requires the expertise of several disciplines, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines are also desirable. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of patients with esophagogastric cancers. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the patient. See *Principles of Multidisciplinary Team Approach for Esophagogastric Cancers* in the algorithm for more information.

Workup

Newly diagnosed patients should undergo a complete history and physical examination, complete blood count (CBC), comprehensive chemistry profile, and upper GI endoscopy with biopsy of the primary tumor. Histologic evaluation is required for correct diagnosis of SCC or adenocarcinoma; the extent of tumor involvement into the EGJ and cardia should be clearly documented, where applicable. CT scan (with oral and IV contrast) of the chest and abdomen should also be performed. Pelvic CT with contrast should be obtained when clinically indicated. EUS and FDG-PET/CT evaluation from skull base to mid-thigh are recommended if metastatic disease is not evident. ER is essential for the accurate staging of early-stage cancers (T1a or T1b); early-stage cancers can best be diagnosed by ER. ER may also be therapeutic for early-stage disease. Biopsy of metastatic disease should be performed as clinically indicated. Assessment of Siewert tumor type should also be included as part of the initial workup in all patients with EGJ adenocarcinoma.[74,75] If the tumor is located at or above the carina and there is no evidence of metastatic disease, bronchoscopy (including biopsy of any abnormalities and cytology of the washings) should be performed. For patients in whom the upper GI tract cannot be visualized, a double contrast barium study of the upper GI tract is an alternative option. Nutritional assessment and counseling as well as smoking cessation advice, counseling, and pharmacotherapy (as indicated) are recommended for all patients.

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

with esophageal and EGJ cancers. See *Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers* in the algorithm for more information.

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

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

Additional Evaluation

Additional evaluations are warranted to assess a patient's medical condition, their ability to tolerate major surgery, and the feasibility of resection. These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. Laparoscopy is optional for EGJ adenocarcinoma if there is no evidence of metastatic disease. 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 select patients when colon interposition is planned.

Additional evaluation enables patients with locoregional cancer to be further classified into the following groups:

- Medically fit for surgery
- Non-surgical candidates (medically unable to tolerate major surgery or medically fit patients who decline surgery)

An enteric feeding tube should be considered in surgical candidates for preoperative nutritional support. A percutaneous gastrostomy tube may be considered for patients with cervical esophageal tumors receiving definitive chemoradiation or for patients with marginally resectable disease. Multidisciplinary expertise is recommended prior to placement of a percutaneous gastrostomy tube. The approach, timing, and location of the feeding tube should be discussed with the surgeon prior to its placement.

Primary Treatment

Medically Fit Patients: Squamous Cell Carcinoma

Endoscopic therapies (ER with or without ablation) are the preferred primary treatment option for patients with pTis or pT1a tumors. Ablation alone may be appropriate for certain patients with pTis tumors. Available evidence indicates that ablation following ER may be effective for the complete removal of early-stage SCC of the esophagus.[206,437] Esophagectomy is also indicated for patients with extensive pTis or pT1a tumors, especially those with nodular disease that is not adequately controlled by ER with ablation.[241] Esophagectomy is the recommended primary treatment option for patients with pT1b, N0 tumors and cT1b–cT2, N0 low-risk lesions (<3 cm in diameter and well-differentiated). Preoperative chemoradiation (for non-cervical esophagus) and definitive chemoradiation (for cervical esophagus) are recommended for patients with cT2, N0 high-risk lesions (LVI, ≥3 cm, poorly differentiated) and cT1b–cT2, N+ or cT3-cT4a, any N tumors.[317,320] Histologic confirmation of suspected positive nodes is desirable. Definitive chemoradiation is an appropriate option for patients who decline surgery.[286,342,438] Definitive chemoradiation is also recommended for patients with cT4b (unresectable) tumors and occasionally can facilitate surgical resection in select patients.[439] Chemotherapy alone can be considered in the setting of invasion of the trachea, great vessels, vertebral body, or heart.

Medically Fit Patients: Adenocarcinoma

Primary treatment options for patients with pTis, pT1a or pT1b, N0 adenocarcinoma are similar to those described above for SCC. Some superficial pT1b tumors may be controlled by ER followed by ablation, while more invasive pT1b tumors, especially nodular disease that is not

adequately controlled by ER with ablation, may require esophagectomy.[241] Esophagectomy is also indicated for patients with cT1b–cT2, N0 low-risk lesions (<3 cm in diameter and well-differentiated). Primary treatment options for patients with cT2, N0 high-risk lesions (LVI, ≥3 cm, poorly differentiated), and cT1b–cT2, N+ or cT3-cT4a, any N tumors include preoperative chemoradiation (category 1; preferred),[168] definitive chemoradiation (only for patients who decline surgery),[286,300,342] perioperative chemotherapy,[169,294] or preoperative chemotherapy.[296] Histologic confirmation of suspected positive nodes is desirable. Repeat multidisciplinary consultation is recommended before proceeding to surgery for post-neoadjuvant T4a and bulky multiple nodal station N3. Definitive chemoradiation is the primary treatment option for patients with cT4b (unresectable) tumors and occasionally can facilitate surgical resection in select patients.[439] Chemotherapy alone can be considered in the setting of invasion of the trachea, great vessels, vertebral body, or heart.

Non-Surgical Candidates

Endoscopic therapies (ER with or without ablation) are the recommended primary treatment option for patients with pTis, pT1a or pT1b, N0 SCC or adenocarcinoma tumors. Ablation may not be needed if all lesions are completely excised by ER. Ablation alone may be an appropriate option for certain patients with pTis tumors. Definitive chemoradiation is recommended for non-surgical candidates with cT1b–cT4b, any N tumors who are able to tolerate chemoradiation. Palliative RT or palliative/best supportive care are the appropriate options for non-surgical candidates who are unable to tolerate chemoradiation.

Response Assessment and Additional Management

Additional management options are based on the assessment of response to primary treatment. FDG-PET/CT scans are useful for the evaluation of patients after chemoradiation for the detection of distant lymphatic and hematogenous metastases.[58,67] Therefore, assessment with FDG-PET/CT (preferred) or FDG-PET scan should be done ≥5 to 8 weeks after the completion of preoperative therapy and prior to surgery. Chest/abdominal CT scan with contrast is recommended, but is not required if FDG-PET/CT was done. Pelvic CT with contrast can be considered for distal lesions, if clinically indicated. Upper GI endoscopy and biopsy is recommended following definitive chemoradiation, but is optional after preoperative chemoradiation if surgery is planned.

Esophagectomy (preferred for adenocarcinoma) or surveillance (category 2B) is recommended for patients with no evidence of disease following preoperative chemoradiation. Esophagectomy is preferred for those with persistent local disease following preoperative chemoradiation. Patients with no evidence of disease following definitive chemoradiation should be managed with surveillance, while esophagectomy is preferred for those with persistent local disease following definitive chemoradiation. Alternatively, patients with persistent local disease or unresectable/metastatic disease following either preoperative or definitive chemoradiation can be managed with palliative/best supportive care.

Postoperative Management

Postoperative management is based on surgical margins, pathologic tumor stage, nodal status, histology, and previous treatment. The components of postoperative management have not been established in randomized trials for patients with esophageal cancer. Available evidence for the use of postoperative chemoradiation and postoperative chemotherapy comes from prospective randomized trials involving patients with gastric cancer.[297-299]

Patients with SCC Who Have Not Received Preoperative Chemoradiation

Surveillance is recommended for patients with R0 resection (no cancer at resection margins), irrespective of their nodal status. Patients with R1 (microscopic residual cancer) or R2 (macroscopic residual cancer or M1) resection should be treated with fluoropyrimidine-based chemoradiation. Alternatively, patients with R2 resection can receive palliative management.

Patients with SCC Who Have Received Preoperative Chemoradiation

Surveillance is recommended for patients with completely resected T0, N0 tumors. Nivolumab is recommended for patients with completely resected T+ and/or N+ tumors following preoperative chemoradiation (category 1).[345] Patients with R1 or R2 resection should be observed until disease progression or receive palliative management.

Patients with Adenocarcinoma Who Have Not Received Preoperative Chemoradiation or Chemotherapy

Surveillance is recommended for patients with R0 resection and negative nodal status. Chemoradiation is an alternative option for patients with pT3–pT4a tumors or select patients with pT2 tumors in the lower esophagus or EGJ and high-risk features (category 2B).[297,298] High-risk features include poorly differentiated or higher-grade cancer, LVI, perineural invasion, or age less than 50 years. Patients with node-negative pT3–pT4a tumors can also receive chemotherapy. For patients with R0 resection and N+, any T tumors, surveillance, chemoradiation,[297,298] or chemotherapy is recommended. Patients with R1 resection should receive chemoradiation while those with R2 resection can receive either chemoradiation or palliative management.

Patients with Adenocarcinoma Who Have Received Preoperative Chemoradiation or Chemotherapy

Chemotherapy, if received perioperatively, is a category 1 recommendation for patients following complete resection. Nivolumab is a category 1 recommendation for patients with completely resected T+ and/or N+ tumors following preoperative chemoradiation.[345] Observation until disease progression is an alternative option for these patients. Based on current data, adjuvant chemoradiation is not recommended for node-positive patients following R0 resection.

Patients with R1 or R2 resection should be treated with chemoradiation, if not received preoperatively. Alternatively, patients with R1 resection can be observed until disease progression or considered for re-resection. Palliative management is an alternative option for patients with R2 resection.

Follow-up/Surveillance

All patients should be followed systematically. However, surveillance strategies after successful therapy of esophageal and EGJ cancers remain controversial, with no high-level evidence to guide development of algorithms that balance benefits and risks (including cost) within this cohort. The stage-specific surveillance strategies provided in this guideline are based on currently available evidence from retrospective studies[310,440-444] and expert consensus. Although ~90% of recurrences occur within the first 2 years after the completion of local therapy, potentially actionable recurrences have sometimes been recognized more than 5 years after local therapy. Therefore, while routine esophageal/EGJ cancer-specific surveillance is generally not recommended for more than 5 years following the end of treatment, additional follow-up after 5 years may be considered based on risk factors and comorbidities. Differences in follow-up for early-stage disease reflect a heterogeneous potential for relapse and OS.[209,445-450] For example, whereas fully treated Tis and T1a, N0 disease have

prognoses that approximate a non-cancer cohort, T1b disease does not perform as well. Thus, surveillance recommendations vary according to the depth of invasion as well as the treatment modality received by the patient.

In general, follow-up for asymptomatic patients should include a complete history and physical examination every 3 to 6 months for the first 2 years, every 6 to 12 months for years 3 to 5, and then annually thereafter. CBC, chemistry profile, upper GI endoscopy with biopsy, and imaging studies should be performed as clinically indicated. In addition, some patients may require dilatation of an anastomotic or a chemoradiation-induced stricture. Nutritional assessment and counseling are also recommended.

Stage 0–I (Tis, T1a, and T1b)

Evidence-based guidelines have not been established for all stages of completely treated, early-stage esophageal cancer. The surveillance recommendations outlined in the guidelines are based on available evidence from trials and current practice. Endoscopic surveillance with EGD is recommended for patients with early-stage (Tis, T1a, and T1b) tumors treated with ER/ablation or chemoradiation. EUS in conjunction with EGD may be considered for patients with T1b tumors treated with ER/ablation. In patients with Tis, T1a, and T1b tumors treated with esophagectomy, EGD should be performed as clinically indicated based on symptoms. Additionally, imaging studies (chest/abdominal CT with contrast, unless contraindicated) should be considered during the surveillance of patients with T1b tumors. However, imaging studies as surveillance tools are not recommended for patients with Tis and T1a tumors.

See *Principles of Surveillance - Table 1* in the algorithm for specific recommendations.

Stage II–III (T2–T4a, N0–N+, T4b)

Locoregional recurrence is common after bimodality therapy (definitive chemoradiation),[443] making EGD a valuable surveillance tool in these patients. Since the majority of recurrences (95%) occur within 2 years of completing local therapy, routine surveillance for at least 24 months is recommended for patients with T2–T4b, any N tumors following bimodality therapy. Imaging studies (chest/abdominal CT with contrast, unless contraindicated) should be considered every 6 months for up to 2 years, if the patient is likely to tolerate additional curative-intent therapy for recurrence.[443] EGD should be performed every 3 to 6 months for the first 2 years, every 6 months for the third year, and then as clinically indicated.

Since the majority of recurrences (90%) occur within 3 years of surgery, routine surveillance for at least 36 months is recommended for patients with T2–T4b, any N tumors following trimodality therapy. However, since locoregional recurrence is relatively uncommon after trimodality therapy and most luminal recurrences can be detected by routine imaging studies, EGD surveillance is not recommended.[310,441,442] Imaging studies (chest/abdominal CT with contrast, unless contraindicated) should be considered every 6 months for at least 2 years, if the patient is likely to tolerate additional curative-intent therapy for recurrence. Unscheduled evaluation is recommended if a patient becomes symptomatic.

See *Principles of Surveillance - Table 2* in the algorithm for specific recommendations.

Unresectable, Locally Advanced, Recurrent, or Metastatic Disease

When locoregional recurrence develops after prior chemoradiation therapy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option. Concurrent chemoradiation (preferred), surgery, chemotherapy, and palliative management/best

supportive care are recommended options for patients who develop a locoregional recurrence following prior esophagectomy and had not previously received chemoradiation. Those who are medically unable to tolerate major surgery and those who develop an unresectable or metastatic recurrence should receive palliative management. If not done previously, MSI or MMR, PD-L1, and HER2 (only for adenocarcinoma) testing should be performed in patients with documented or suspected metastatic disease. NGS may be considered via a validated assay.

Palliative management and best supportive care are always indicated for patients with unresectable locally advanced, recurrent, or metastatic disease. The decision to offer palliative/best supportive care alone or with systemic therapy is dependent upon the patient's performance status. The Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[451-453] Patients with higher ECOG PS scores are considered to have worse performance status while lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score less than 60% or an ECOG PS score greater than or equal to 3 should be offered palliative/best supportive care only. Systemic therapy can be offered in addition to palliative/best supportive care for patients with better performance status (KPS score ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared to palliative/best supportive care alone has been demonstrated in small cohorts of patients with esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma trials.[352,353] In a phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n = 33), EGJ (n = 59), or stomach (n = 76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine-based combination chemotherapy.[352] After a median follow-up of 12 months, the median OS was 5.2 months for patients in the docetaxel and best supportive care group compared to 3.6 months for those in the best supportive care alone group (P = .01). In another randomized phase III study, the addition of second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n = 40).[353] Median survival was 4 months in the irinotecan and best supportive care group compared to 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual.

A Cochrane database systematic review of five randomized controlled trials involving 750 patients with advanced esophageal or EGJ cancer demonstrated a benefit in OS for patients receiving chemotherapy and/or targeted therapy and best supportive care compared to those receiving best supportive care alone.[354] The only individual agent found by more than one study to improve both OS and PFS was ramucirumab. Although the addition of palliative chemotherapy or targeted therapy increased the frequency of grade ≥3 adverse events, treatment-related deaths did not increase. Importantly, patient-reported quality of life often improved with the addition of systemic therapy to best supportive care. Therefore, the addition of systemic therapy to best supportive care can improve the quality of life and may prolong survival in patients with advanced esophageal or EGJ cancers.

See *Principles of Systemic Therapy* in the algorithm for a full list of specific regimens for unresectable locally advanced, recurrent, or metastatic disease. Some of the regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

Leucovorin Shortage

Leucovorin is indicated with certain fluorouracil-based regimens. However, there is currently a shortage of leucovorin in the United States.[454] There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. One is the use of levoleucovorin, which is commonly used in Europe. A levoleucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin in all patients, since lower doses are likely to be as efficacious as higher doses based on several studies in patients with colorectal cancer.[455-457] However, the panel recommends use of these regimens without leucovorin in situations where leucovorin is not available.

Palliative/Best Supportive Care

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

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Dysphagia most often arises due to obstruction, but can also be associated with tumor-related dysmotility. Assessing the extent of disease and severity of swallowing impairment, preferably through a standardized scoring scale,[458] is essential to initiate appropriate interventions for long-term palliation of dysphagia in patients with esophageal cancer. Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Individualized management of esophageal cancer-related dysphagia is strongly encouraged. Patients with dysphagia who are not candidates for curative surgery should be considered for palliation of their symptoms. Palliative management of dysphagia can be achieved through multiple modalities, though placement of permanent or temporary SEMS is the most common and can achieve long-term results.[253] However, the guidelines emphasize that stent placement is generally not advised in patients who are surgical candidates due to concerns that stent-related adverse events may preclude future curative surgery.

A clinical trial involving 45 patients with esophageal carcinoma found that temporary placement of SEMS with concurrent RT significantly reduced the total number of patients with 1 or more complications (P = .042) and increased resultant PFS and OS rates (P = .005 and P = .001, respectively) compared with permanent stent placement.[459] Additionally, membrane-covered stents have been shown to have significantly better palliation than conventional bare metal stents because of the decreased rate of tumor in-growth, which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[253] However, the optimal extent of the covering to prevent recurrent obstruction is unknown. In a recent trial of 98 patients with malignant dysphagia randomized to receive either a fully covered or partially covered SEMS, there was no significant difference in recurrent obstruction between the two stent types (19% for fully covered SEMS vs. 22% for partially covered SEMS; P = .65).[460] The times to recurrent obstruction and the rates of adverse events were also similar. Another recent trial investigating stent migration found no significant differences in either migration distance or migration frequency between the two stent types.[461] However, there was a trend towards better dysphagia relief with the fully covered stents as measured by the Watson and Ogilvie dysphagia scores (P = .081 and P = .067, respectively). These

results suggest that fully covered SEMS may not lower the recurrent obstruction or stent migration rates compared to partially covered SEMS, but may be more effective in the palliation of dysphagia.

The optimal stent diameter needed to effectively palliate dysphagia in patients with esophageal cancer is also unknown. While there are data suggesting lower migration and re-obstruction rates with larger-diameter covered expandable metal stents, there may be a higher risk of stent-related complications.[462] In a prospective trial, 100 patients with unresectable esophageal cancer were randomized to receive a SEMS with either an 18- or 23-mm shaft diameter, but identical design, and followed until death.[463] Dysphagia was resolved after stent placement in 95% of patients in both groups. The incidence of adverse events was similar in both groups, but there was a trend toward longer survival in the small-diameter group (median survival, 5.9 vs. 3 months; $P = .10$). After 6 months, the cumulative incidence of recurrent dysphagia was 38% versus 47% in the small-diameter versus large-diameter group, respectively ($P = .23$). These data suggest that small-diameter and large-diameter esophageal SEMS provide similar palliation of dysphagia, with a trend toward increased survival with the use of small-diameter stents.

A recent phase III randomized controlled trial compared the efficacy of chemoradiation versus RT alone for the palliation of malignant dysphagia in 220 patients with esophageal cancer.[464] Palliative chemoradiation showed a slight, but statistically insignificant, increase in the percentage of patients experiencing dysphagia relief compared with RT alone (45% vs. 35%; $P = .13$), with minimal improvements in PFS (4.1 vs. 3.4 months; $P = .58$) and OS (6.9 vs. 6.7 months; $P = .88$). However, patients receiving chemoradiation experienced significantly higher rates of grade 3–4 toxicities than patients receiving RT alone (36% vs. 16%; $P = .0017$). Therefore, a short course of RT alone may be used for palliation of dysphagia symptoms in patients with esophageal cancer who are not candidates for SEMS placement, including those who will undergo surgical intervention.

Obstruction

For patients with severe esophageal obstruction (those able to swallow liquids only), treatment options include endoscopy- or fluoroscopy-guided placement of fully or partially covered SEMS, as described above, as well as endoscopic lumen enhancement (wire-guided dilation or balloon dilation). Caution should be exercised when dilating malignant strictures, as this may be associated with an increased risk of perforation.[465] For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, generally performed via simultaneous retrograde (via a gastrostomy tract) and antegrade endoscopy. Surgical or radiologic placement of a jejunostomy or gastrostomy tube may be necessary to provide adequate hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful. Other options for palliation of esophageal obstruction include EBRT, chemotherapy, or surgery (in select patients). Brachytherapy may be considered instead of EBRT, if a lumen can be restored that allows for the use of appropriate applicators to decrease excessive RT dose to mucosal surfaces. Single-dose brachytherapy was associated with fewer complications and better long-term relief of obstruction compared with the use of metal stents.[466] However, brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy. PDT can effectively treat esophageal obstruction, but is less commonly performed due to associated photosensitivity and costs.

Pain

Patients experiencing cancer-related pain should be assessed and treated according to the NCCN Guidelines for Adult Cancer Pain. Severe,

uncontrolled pain following stent placement should be treated with immediate endoscopic removal of the stent.

Bleeding

Acute bleeding from esophageal cancer may represent a pre-terminal event secondary to tumor-related aorto-esophageal fistulization. Bleeding that occurs primarily from the tumor surface may be controlled with endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation. However, limited data suggest that while endoscopic therapies may initially be effective, endoscopic intervention may lead to precipitous exsanguination and is associated with a high rate of recurrent bleeding.[467] Chronic blood loss from esophageal cancer can be managed with EBRT.

Nausea and Vomiting

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

Survivorship

In addition to survivorship care relevant to all cancer survivors (see NCCN Guidelines for Survivorship), esophageal and EGJ cancer survivors have special long-term care needs due to the nature of their illness and treatments. Therefore, screening and management of long-term sequelae are important for all esophageal and EGJ cancer survivors. However, due to a lack of large randomized trials, the survivorship management recommendations provided by the panel are based on smaller studies and clinical experience. Survivorship care planning should include appropriate timing of transfer of care to a primary care physician and maintenance of a therapeutic relationship with the primary care physician throughout life. The oncology team and primary care physician should have clearly delineated roles in survivorship care, with these roles communicated to the patient. In general, routine esophageal/EGJ cancer-specific surveillance is not recommended for more than 5 years following the end of treatment. Surveillance should be performed in conjunction with good routine medical care, including routine health maintenance, preventive care, and cancer screening. Annual history and physical examination is reasonable as potential second primary cancers (second cancer in residual esophagus or second primary SCC in a separate organ) are possible. Esophageal and EGJ cancer survivors should be counseled to maintain a healthy body weight, adopt a physically active lifestyle, consume a healthy diet with an emphasis on plant-based sources, and limit alcohol intake. Smoking cessation should also be encouraged, as appropriate. Additional preventive health measures and immunizations should be performed as indicated under the care of or in conjunction with a primary care physician.

Common issues facing esophageal and EGJ cancer survivors include GI issues, chemotherapy-induced neuropathy, RT-induced cardiotoxicity, and fatigue. Survivors of esophageal and EGJ cancers who underwent esophagectomy are at particular risk for clinically relevant long-term health issues, especially GI-related issues, which have been shown to negatively impact survivors' quality of life.[468-471] Several studies have indicated that survivors frequently experience GI dysfunctions such as malnutrition/malabsorption, dysphagia, dumping syndrome, delayed gastric emptying, and reflux symptoms following esophagectomy, which often persist many years after surgery.[468-476] As a result of GI dysfunctions, survivors who underwent esophagectomy have unique nutritional needs due to frequent vitamin and mineral deficiencies.[474,477] Studies have shown that substantial weight loss and long-term deficiencies in vitamin B_{12}, folic acid, vitamin D, and calcium are common

following esophagectomy.[474,477-480] Therefore, the weight and nutritional status of esophageal cancer survivors should be carefully monitored, recognizing that progressive weight loss in the first 6 months is expected. Delayed gastric emptying after esophageal substitution with gastric conduit is another common GI-related long-term sequelae following esophagectomy, which affects as many as 37% of patients.[473,475] Eating smaller portions more frequently (5 small meals a day), as well as minimization of fat and fiber content in the diet, should be encouraged. Referral to gastroenterology should be considered for refractory symptoms.

Treatment with chemoradiation puts survivors at risk for RT-induced cardiotoxicity due to the close proximity of the esophagus to the heart.[481-483] Studies utilizing the SEER database to investigate the late cardiotoxic effects of RT in survivors of esophageal cancer revealed an increased risk for cardiac-related death in those who had received RT as part of their initial therapy compared to those who had not.[482,483] Receipt of RT was a predictive factor for cardiac-related death on univariate (HR, 1.53; $P < .0001$) and multivariate (HR, 1.62; $P < .0001$) analyses.[482] The risk for cardiac-related death became significant 8 months after diagnosis ($P < .05$) and the median time to cardiac-related death was 289 months.[482,483] Therefore, the cardiac health of esophageal cancer survivors should be carefully monitored following RT. The panel suggests coordination between the oncology care team, primary care physicians, and cardiologists for management of cardiac toxicities, as clinically indicated. Additionally, painful chemotherapy-induced neuropathy can be effectively treated with duloxetine. However, it should be noted that duloxetine is ineffective for numbness or tingling.

The panel recommends the development of a survivorship care plan that includes information on treatments received (surgeries, RT, and systemic therapies), follow-up care, surveillance, screening recommendations, and post-treatment needs regarding acute, late, and long-term treatment-related effects and health risks. Roles of oncologists, primary care physicians, and subspecialty care physicians in the survivorship care plan should be clearly delineated. Long-term survivorship care plans should also include a periodic assessment of ongoing needs and identification of appropriate resources, including timing of transfer of care, if appropriate.

Summary

Cancers of the esophagus and EGJ are common in many parts of the world. SCC is the most common histology in Eastern Europe and Asia, while adenocarcinoma has become increasingly more common in North America and Western Europe. Tobacco and alcohol use are major risk factors for developing SCC of the esophagus. Obesity, GERD, and Barrett esophagus are the major risk factors for developing adenocarcinoma of the esophagus or EGJ. In addition, some hereditary cancer predisposition syndromes are associated with an increased risk of developing esophageal and EGJ cancers. Referral to a cancer genetics professional is recommended for an individual with a genetic predisposition. The NCCN Panel strongly recommends multidisciplinary team management as essential for all patients with localized esophageal or EGJ cancer. Best supportive care is an integral part of treatment, especially in patients with unresectable locally advanced, recurrent, or metastatic disease.

ER (with or without ablation) is recommended for patients with early-stage (Tis, T1a, or superficial T1b) tumors. Esophagectomy is the preferred primary treatment option for medically fit patients with T1b–T2, N0 low-risk lesions. For medically fit patients with locally advanced resectable tumors (T2, N0 high-risk lesions, T1b–T2, N+ and T3–T4a, any N tumors), primary treatment options include preoperative chemoradiation (category 1, preferred for adenocarcinoma), definitive chemoradiation (only in non-surgical candidates or patients who decline surgery), or preoperative/perioperative chemotherapy (only for adenocarcinoma).

Definitive chemoradiation is the recommended treatment option for patients with T4b (unresectable) tumors, with chemotherapy alone reserved for the setting of invasion into the heart, vertebral body, trachea, or great vessels. Patients with unresectable or metastatic disease should be offered best supportive care and palliative management with or without systemic therapy, depending on performance status.

Patients with SCC who have not received preoperative therapy should receive surveillance following R0 resection or postoperative chemoradiation following R1 or R2 resection. For patients with SCC who have received preoperative chemoradiation therapy, nivolumab is recommended (category 1) following R0 resection in patients with T + and/or N + tumors, while observation is recommended for patients following R1 or R2 resections. For patients with adenocarcinoma who have not received preoperative therapy, the panel has included postoperative chemoradiation as an option following R0 resection for patients with N + any T tumors, node-negative T3–T4a tumors, and select patients with T2 tumors and high-risk features (category 2B). Postoperative chemoradiation is also recommended for all patients with R1 or R2 resections in this setting. Postoperative chemotherapy is recommended following R0 resection for all patients with adenocarcinoma who received chemotherapy preoperatively, irrespective of nodal status (category 1). For patients with adenocarcinoma who have received preoperative chemoradiation, nivolumab is recommended (category 1) following R0 resection in patients with T + and/or N + tumors. Patients with R1 resection can be considered for re-resection while patients with R2 resection should receive palliative management.

Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal and EGJ cancers. Trastuzumab plus chemotherapy is recommended as first-line therapy for patients with HER2 overexpression positive adenocarcinoma. Preferred regimens for HER2 overexpression negative disease include nivolumab combined with chemotherapy for adenocarcinoma tumors with PD-L1 expression levels by CPS of ≥5 (category 1) or CPS of <5 (category 2B), and pembrolizumab combined chemotherapy for adenocarcinoma or SCC tumors with PD-L1 CPS of ≥10 or CPS of <10 (category 2B). Ramucirumab, as a single agent or in combination with paclitaxel (preferred), and pembrolizumab (for MSI-H/dMMR or TMB-H tumors) are included as options for second-line or subsequent therapy for patients with metastatic disease. Pembrolizumab has also been included as a second-line therapy option for esophageal SCC with PD-L1 expression levels by CPS of ≥10. Dostarlimab-gxly is an alternative option to pembrolizumab for MSI-H/dMMR tumors. Nivolumab is included as a preferred second-line therapy option for esophageal SCC and entrectinib and larotrectinib for second-line or subsequent therapy for *NTRK* gene fusion-positive tumors.

The NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers are based on evidence- and consensus-based treatment approaches for the management of patients with esophageal and EGJ cancers. The panel encourages patients with esophageal and EGJ cancers to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

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