National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Esophageal and Esophagogastric Junction Cancers

Version 2.2018 — May 22, 2018

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Esophageal and Esophagogastric Junction Cancers

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Δ Genetics
§ Radiotherapy/Radiation oncology
‡ Hematology/Hematology oncology
≠ Pathology
¥ Patient advocacy
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NCCN Guidelines Version 2.2018 Sub-Committees
Esophageal and Esophagogastric Junction Cancers

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≠ Pathology
Δ Genetics

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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.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

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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NCCN Guidelines Version 2.2018 Updates Esophageal and Esophagogastric Junction Cancers

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Updates in Version 2.2018 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 1.2018 include:

ESOPH-F Principles of Systemic Therapy

- **The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.**
- **The regimen and dosing schedule pages were updated to reflect the changes noted above.**

ESOPH-J Principles of Survivorship

- **This is a new section that provides recommendations for survivorship including Management of long-term sequelae of disease or treatment, Counseling regarding health behaviors, Cancer screening recommendations (for average risk survivors), and Survivorship care planning and coordination.**

MS-1

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

Updates in Version 1.2018 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 4.2017 include:

ESOPH-1

- **Workup; Fifth bullet revised: "PET/CT evaluation *(skull base to mid-thigh)* if no evidence of M1 disease."**

Adenocarcinomas

ESOPH-13

- **Primary Treatment Options for Medically Fit Patients: For cT4b the following option was added, "*Consider chemotherapy alone in the setting of invasion of trachea, great vessels, or heart See Palliative Management (ESOPH-18)*"**

ESOPH-16

- **R0 resection; Postoperative Management: For Node negative and Node positive pathways, revised, "Observation until progression ~~(if received preoperative chemotherapy or chemoradiation)~~"**
- **R1 resection:**
  - **"*Observation until progression*" added as an option.**
  - **"Chemotherapy if received preoperatively" removed as an option.**

Continued

Squamous Cell Carcinoma and Adenocarcinoma

ESOPH-8 and ESOPH-17

- **Management of Non-Surgical Candidates:**
  - **cT1b-T4a N0-N+ or cT4b (unresectable); Non-surgical candidate able to tolerate chemoradiation: Revised "Definitive chemoradiation (50–50.4 Gy of RT + concurrent chemotherapy) ~~(Fluoropyrimidine- or taxane-based)~~"**

ESOPH-9 and ESOPH-18

- **Follow-up/Surveillance**
  - **Third bullet: "Imaging studies *as clinically indicated*"**
  - **Fourth bullet: "Upper GI endoscopy and biopsy *as clinically indicated*"**
- **Palliative Management**
  - **"Locoregional recurrence: Prior esophagectomy, no prior chemoradiation" pathway: Revised, "Concurrent chemoradiation ~~(Fluoropyrimidine- or taxane-based)~~ preferred"**

ESOPH-B Principles of Pathologic Review and Biomarker Testing

- **Title revised, "Principles of Pathologic Review and ~~HER2~~ *Biomarker* Testing"**
- **This section was extensively revised and includes new recommendations for "Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing" and "PD-L1 Testing."**

ESOPH-F Principles of Systemic Therapy

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- **Perioperative Chemotherapy revisions**
  - **"Fluoropyrimidine and oxaliplatin" changed to a preferred option.**
  - **"Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)" added as an option with corresponding footnote, "*Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit*."**
  - **The following regimens were removed:**
    - ◊ **ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)**
    - ◊ **ECF modifications (category 2B for all modifications)**
      - **– Epirubicin, oxaliplatin, and fluorouracil**
      - **– Epirubicin, cisplatin, and capecitabine**
      - **– Epirubicin, oxaliplatin, and capecitabine**

4 of 12 Principles of Systemic Therapy--Regimens and Dosing Schedules

- **The regimen and dosing schedule pages were updated to reflect the changes on ESOPH-F 2 of 12**

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- **The reference pages were updated to reflect the changes in the algorithm.**

Continued

NCCN Guidelines Version 2.2018 Updates
Esophageal and Esophagogastric Junction Cancers

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ESOPH-I Principles of Surveillance

1 of 4

- **First bullet revised: "The surveillance strategies after successful local therapy for esophageal and EGJ cancers remain controversial, with ~~little prospective data to construct appropriate algorithms that balance the benefits and risks (including cost) within a population~~ *no high-level evidence to guide development of algorithms that balance benefits and risks (including cost) within this cohort*."**

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- **T1b, Any N; Esophagectomy: Revised recommendation, "Imaging (CT chest/abdomen with contrast unless contraindicated) ~~can~~ should be considered ~~starting at 6–12 months~~ *every 12 months* for up to 3 years ~~then as clinically indicated~~ *if the patient is likely to tolerate additional curative-intent therapy for recurrence*. EGD as needed...."**

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- **T2-T4, N0-N+, T4b; Bimodality therapy (definitive chemoradiation): Revised recommendation, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) ~~are recommended~~ *should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence*. ~~Frequency may be every 4–6 months in the first 12 months and then less frequently in the next 24 months~~. EGD every...."**
- **T2-T4, N0-N+, T4b; Trimodality therapy: Recommendation revised, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) ~~are recommended~~ *should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence*. ~~Frequency of surveillance may be every 4–6 months in the first 12 months and every 6–9 months in the next 24 months~~. Unscheduled..."**

ST-1 Staging

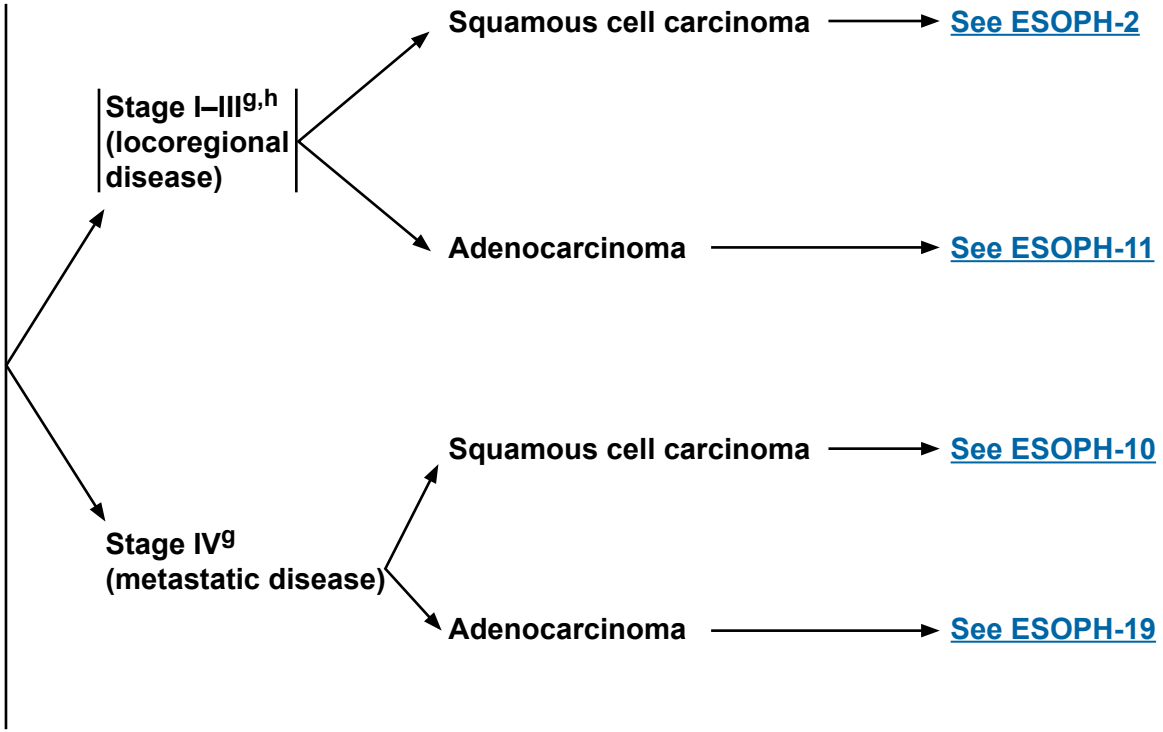
- **The AJCC 7th Edition Cancer Staging Tables were updated to the 8th edition.**

WORKUP

- **H&P**
- **Upper GI endoscopy and biopsy[a]**
- **Chest/abdominal CT with oral and IV contrast**
- **Pelvic CT with contrast as clinically indicated**
- **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]**
- **Biopsy of metastatic disease as clinically indicated**
- **MSI-H/dMMR testing if metastatic disease is documented/suspected**
- **HER2[c] and PD-L1 testing if metastatic adenocarcinoma is documented/suspected**
- **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]**

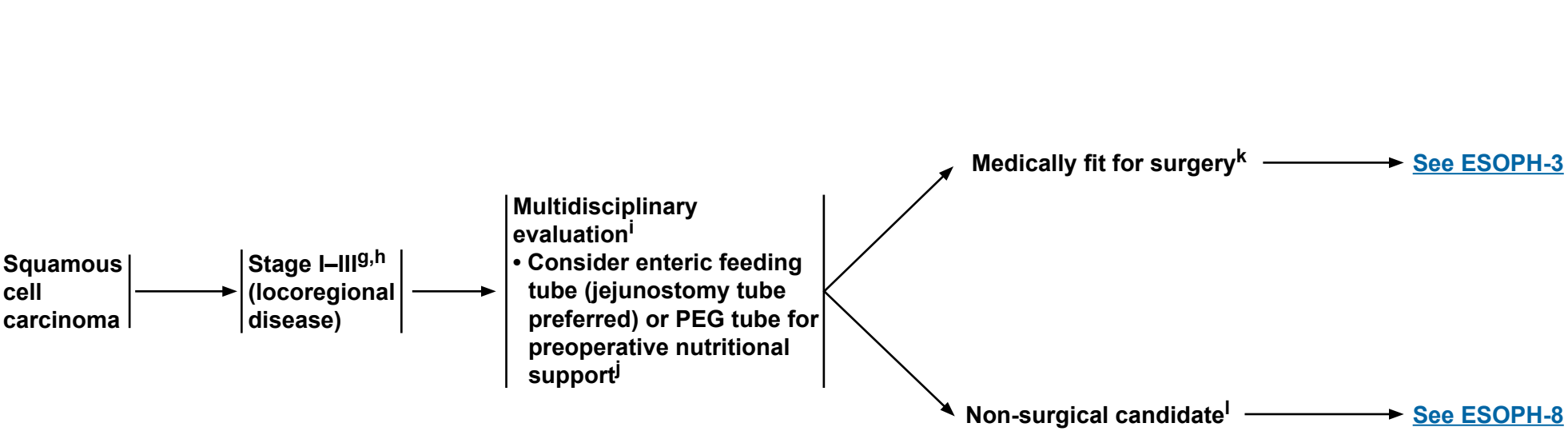
CLINICAL STAGE[g]

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 and Ovarian.
[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the esophagogastric junction/distal esophagus may still 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 cancer patient 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 esophagogastric junction/distal esophagus may still be considered for combined modality therapy.
[i] See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[j] Percutaneous endoscopic gastrostomy (PEG) tube may be considered for patients with cervical esophagus receiving definitive chemoradiation or for patients with marginally resectable disease. Multidisciplinary expertise is recommended prior to placement of PEG tube.
[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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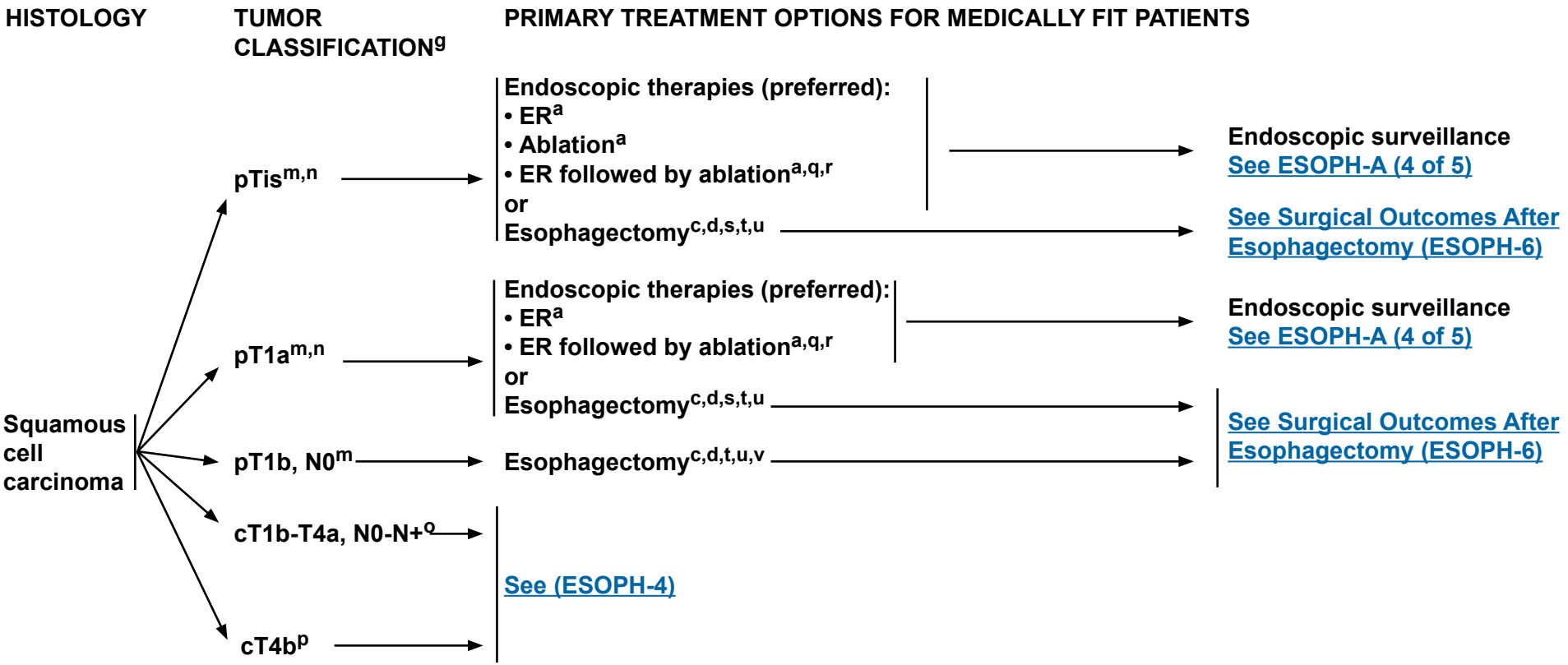

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[m] pTis, pT1a, and pT1b tumor classifications are defined by pathology of 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/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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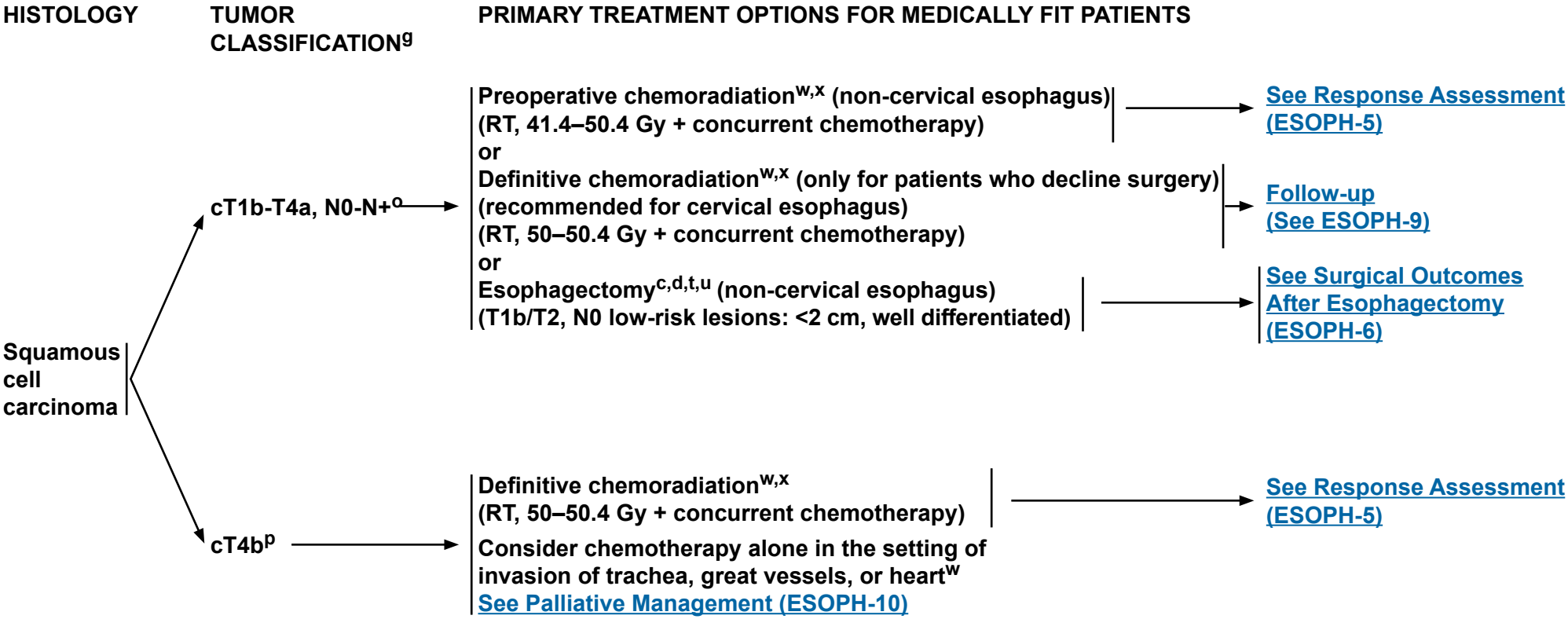

[c]See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d]See Principles of Surgery (ESOPH-C).
[g]See Staging (ST-1) for tumor classification.
[o]Preclinical staging cannot establish the number of positive nodes.
[p]For select patients, consider endoluminal stenting when appropriate. 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]See Principles of Systemic Therapy (ESOPH-F).
[x]See Principles of Radiation Therapy (ESOPH-G).

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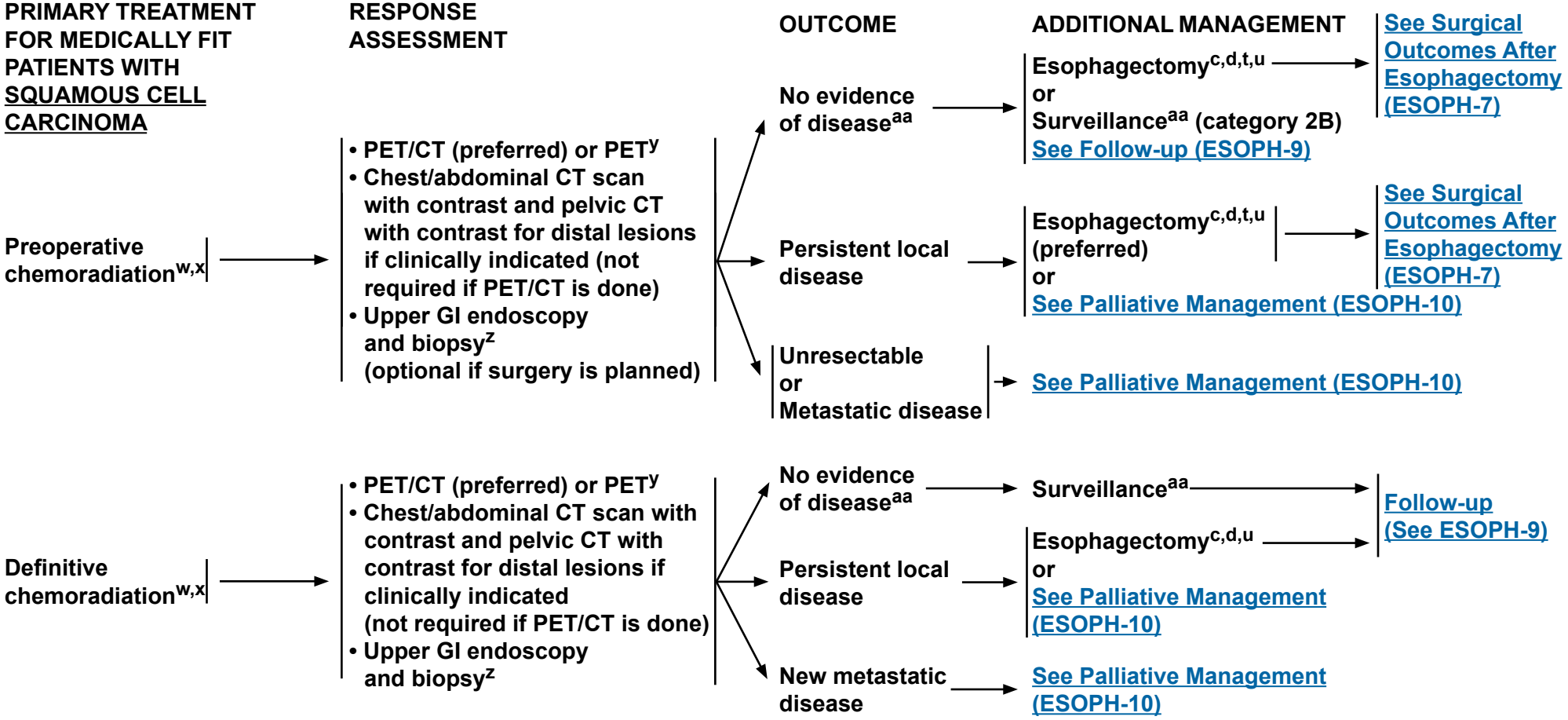

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[y] Assessment ≥ 5–8 weeks after completion of preoperative therapy.
[z] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[aa] If surveillance is being considered for potentially operable patients, upper GI endoscopy and biopsy should be done.

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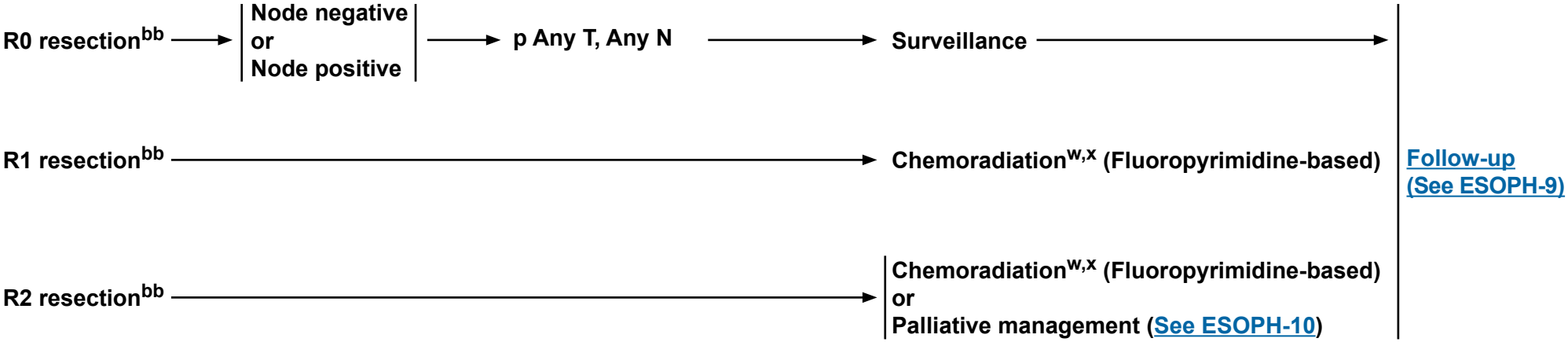
SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Not Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g]

POSTOPERATIVE MANAGEMENT



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

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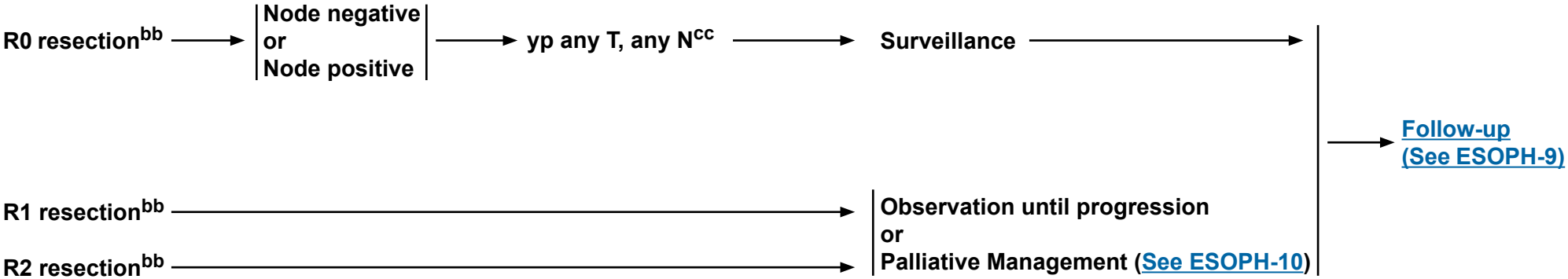
SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g,cc]

POSTOPERATIVE MANAGEMENT



[g]See Staging (ST-1) for tumor classification.
[bb]R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[cc]The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.

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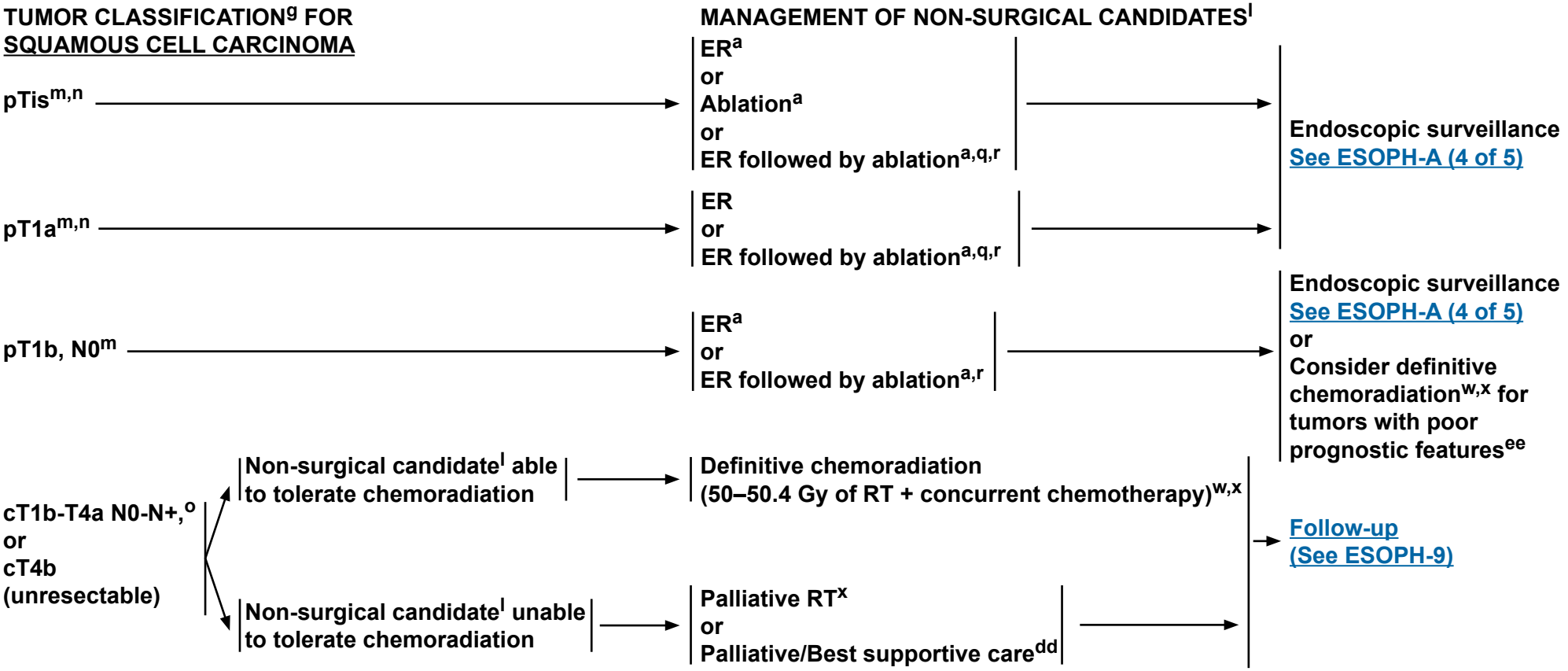

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[g] See Staging (ST-1) for tumor classification.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[m] pTis, pT1a, and pT1b tumor classification are defined by pathology of the diagnostic ER specimen. 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 high-grade dysplasia/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.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[ee] Poor prognostic features include lymphovacular 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[ff,gg]

- H&P
  - If asymptomatic: H&P every 3–6 mo for 1–2 y, every 6–12 mo for 3–5 y, then annually
- Chemistry profile and CBC, as clinically indicated
- Imaging studies as clinically indicated[ff]
- Upper GI endoscopy and biopsy as clinically indicated[z,ff]
- Dilatation for anastomotic stenosis
- Nutritional assessment and counseling

RECURRENCE

- Locoregional recurrence: Prior esophagectomy, no prior chemoradiation
- Locoregional recurrence (Prior chemoradiation, no prior esophagectomy)
  - Resectable and medically operable
  - Unresectable or medically inoperable
- Metastatic disease

PALLIATIVE MANAGEMENT

- Concurrent chemoradiation[w,x] (preferred) or Surgery[c,d] or Chemotherapy[w] or Palliative/ Best supportive care[dd]
- Esophagectomy[c,d,t,u]

Chest/ abdominal CT with contrast[ff] → Recurrence → See Palliative Management (ESOPH-10)

Chest/ abdominal CT with contrast[ff] → Recurrence → See Palliative Management (ESOPH-10)

See Palliative Management (ESOPH-10)

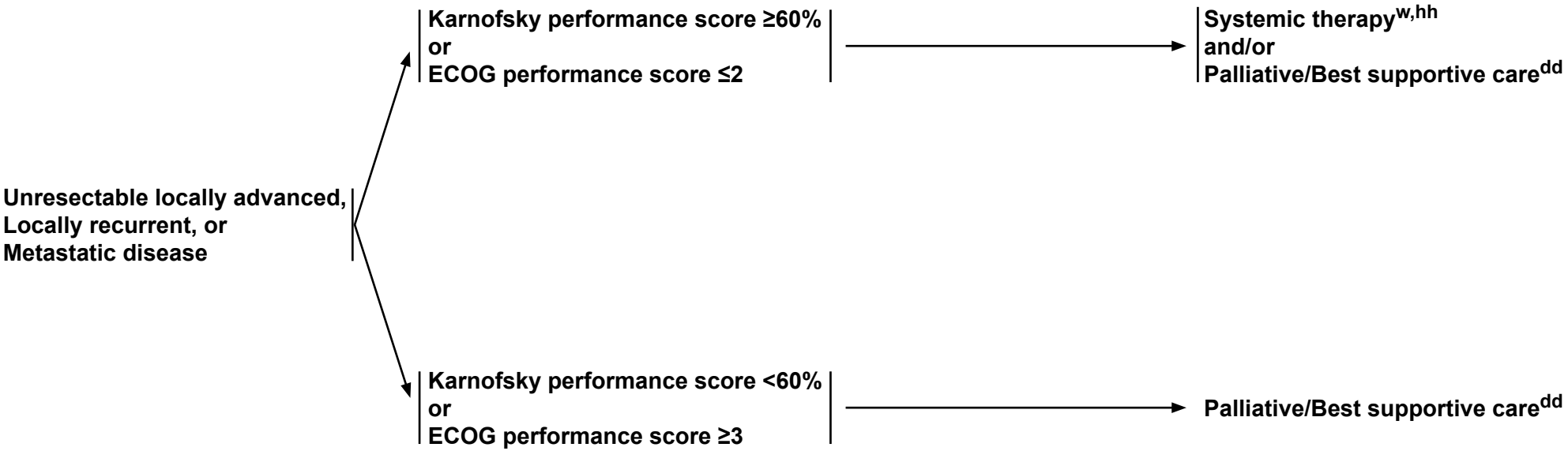
[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[z] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[ff] See Principles of Surveillance (ESOPH-I).
[gg] 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FOR SQUAMOUS CELL CARCINOMA

PERFORMANCE STATUS

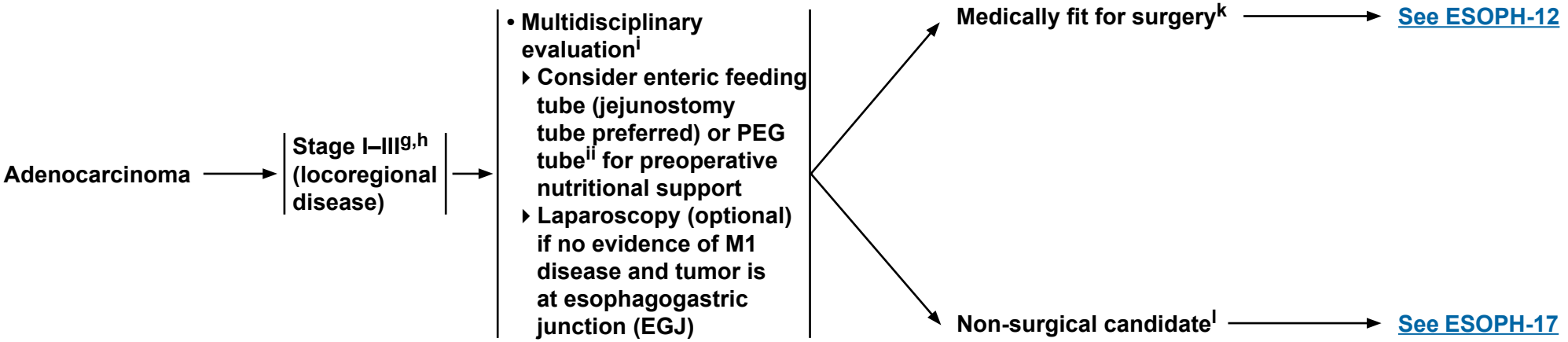
PALLIATIVE MANAGEMENT



[w] See Principles of Systemic Therapy (ESOPH-F).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[hh] Further treatment after two sequential regimens should be dependent on performance status and availability of clinical trials.

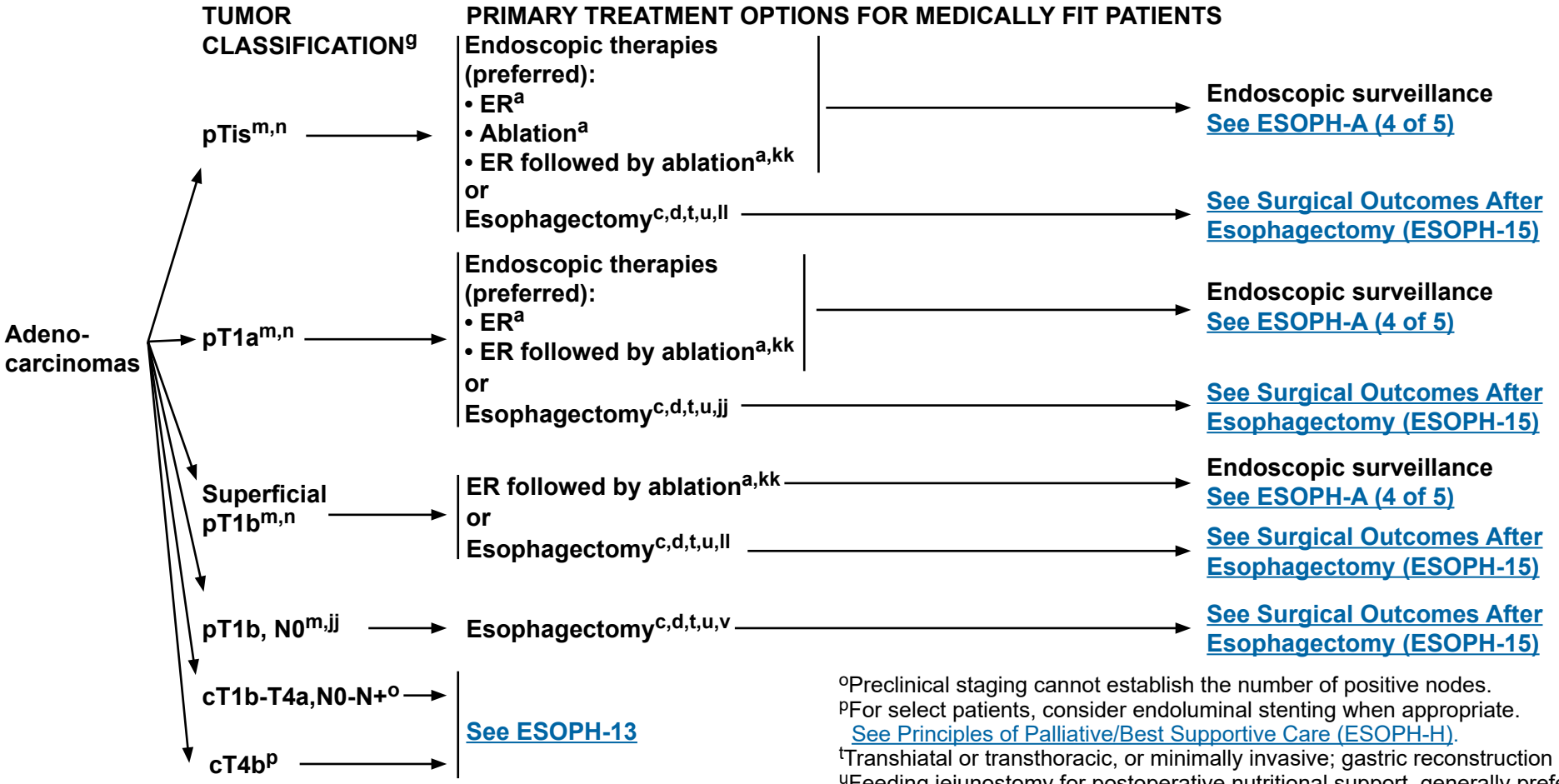
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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



[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the esophagogastric junction/distal esophagus may still be considered for combined modality therapy.
[i] See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[k] Medically able to tolerate major surgery.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[ii] Multidisciplinary expertise is recommended prior to placement of PEG tube.

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



[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.
[v] Definitive chemoradiation may be an appropriate option for patients who decline surgery, see (ESOPH-17).
[jj] Diagnostic ER can be considered to confirm the pathologic staging and for treatment in select patients.
[kk] ER followed by ablation to completely eliminate residual dysplasia or Barrett's epithelium.
[ll] 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.

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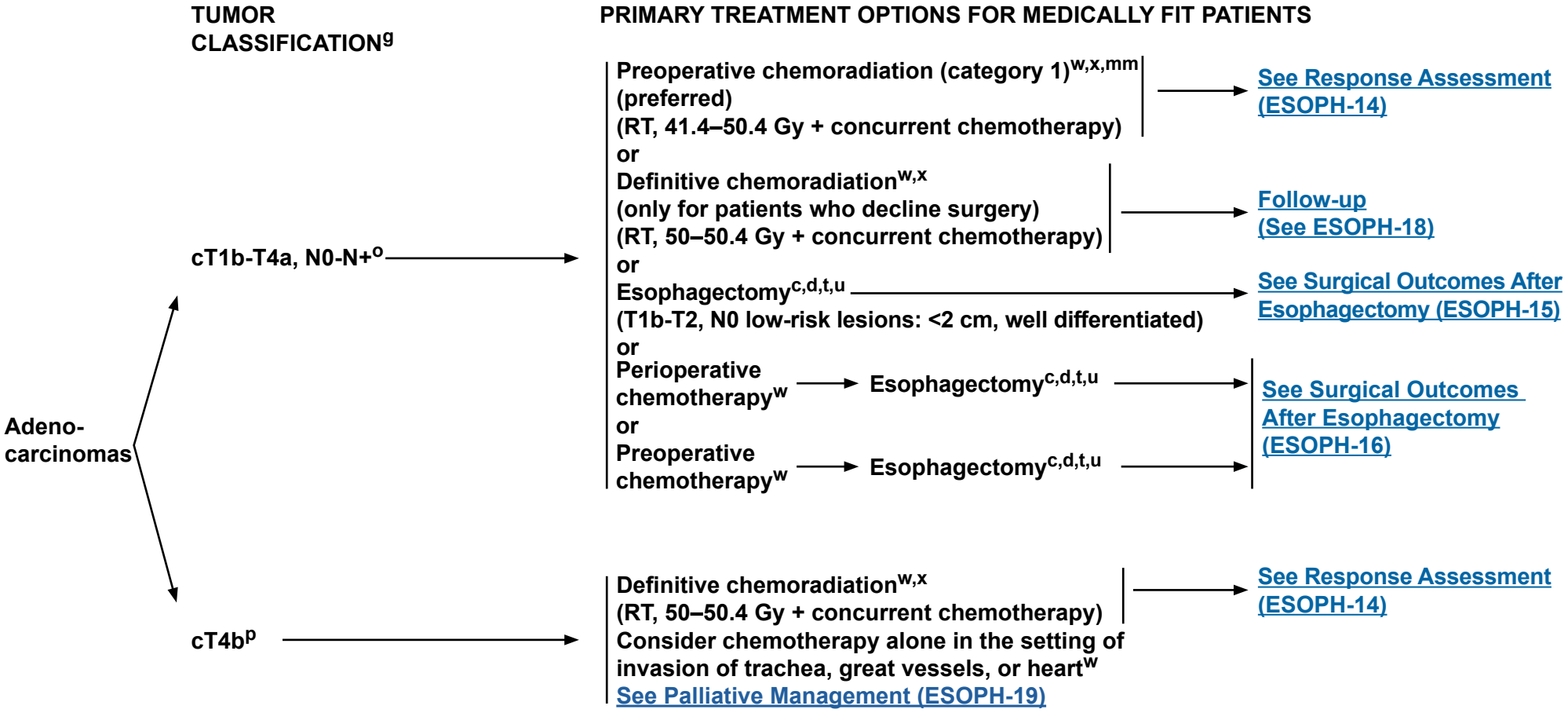
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[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]See Principles of Systemic Therapy (ESOPH-F).
[x]See Principles of Radiation Therapy (ESOPH-G).
[mm]Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (van Hagen P, Hulshof MC, van Lanschot JJ, et al, CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084)

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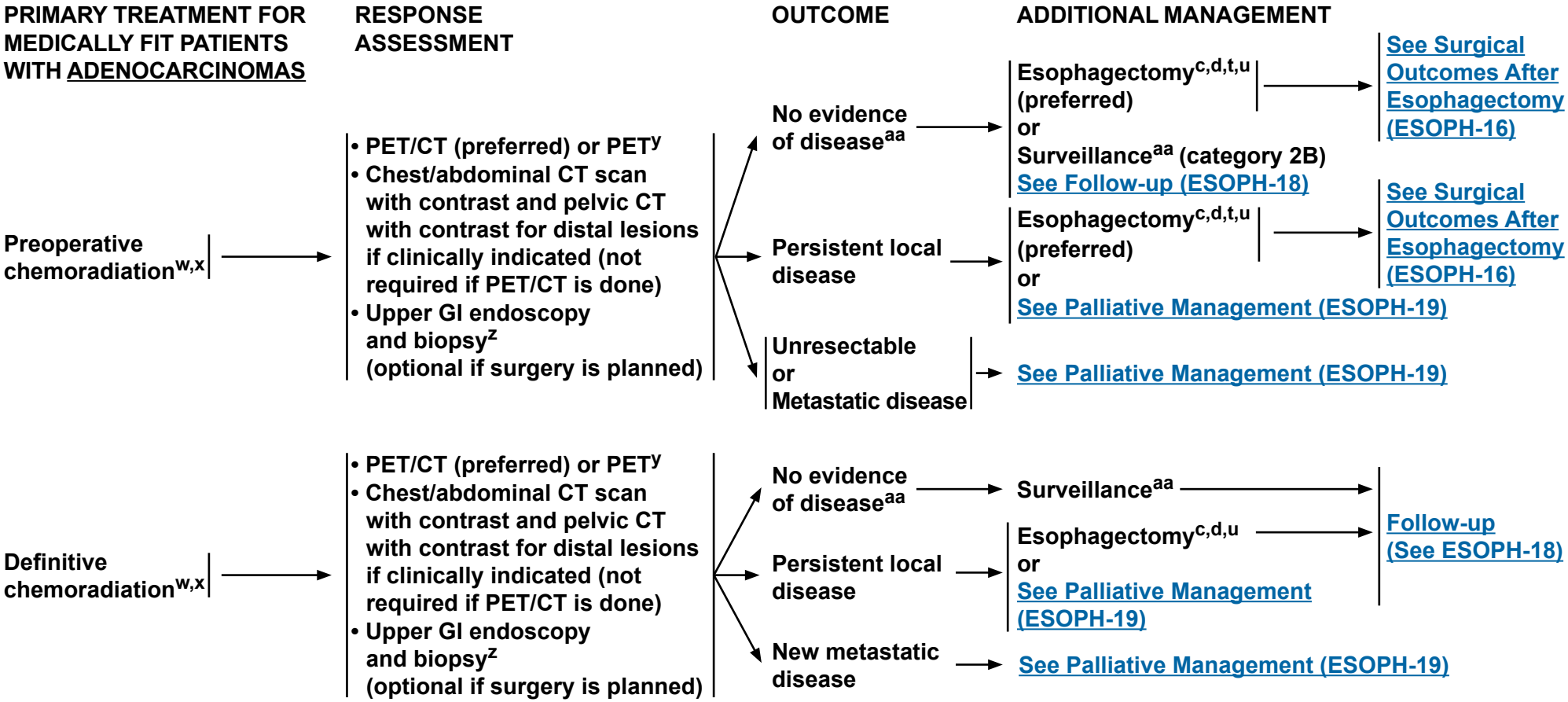

[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[y] Assessment ≥5–8 weeks after completion of preoperative therapy.
[z] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[aa] If surveillance is being considered for potentially operable patients, upper GI endoscopy and biopsy should be done.

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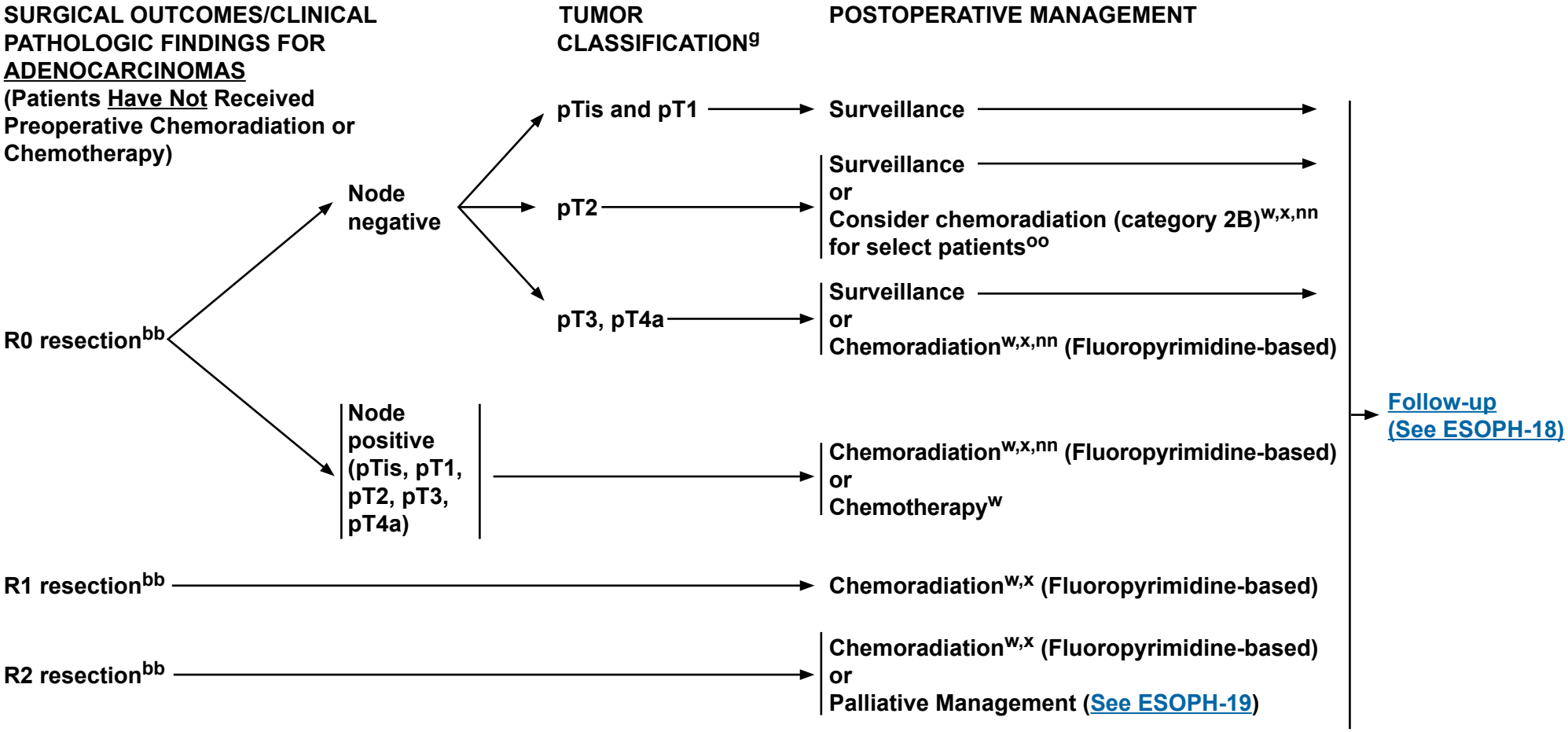
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] See Staging (ST-1) for tumor classification.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[bb] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[nn] Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333. See Principles of Systemic Therapy (ESOPH-F).
[oo] Consider chemoradiation for patients with high-risk lower esophagus or EGJ adenocarcinoma. High-risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, perineural invasion, or <50 years of age.

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR ADENOCARCINOMAS (Patients Have Received Preoperative Chemoradiation or Chemotherapy)

TUMOR CLASSIFICATION[g]

POSTOPERATIVE MANAGEMENT

R0 resection[bb]

- **Node negative (yp Any T)[cc]** → **Observation until progression or Chemotherapy[w,pp] if received perioperatively (category 1)**
- **Node positive (yp Any T)[cc]** → **Observation until progression or Chemoradiation[w,x] (fluoropyrimidine-based), only if not received preoperatively (category 2B) or Chemotherapy[w,pp] if received perioperatively (category 1)**

R1 resection[bb] → **Chemoradiation[w,x] (fluoropyrimidine-based), only if not received preoperatively or Observation until progression or Consider re-resection**

R2 resection[bb] → **Chemoradiation[w,x] (fluoropyrimidine-based), only if not received preoperatively or Palliative Management (See ESOPH-19)**

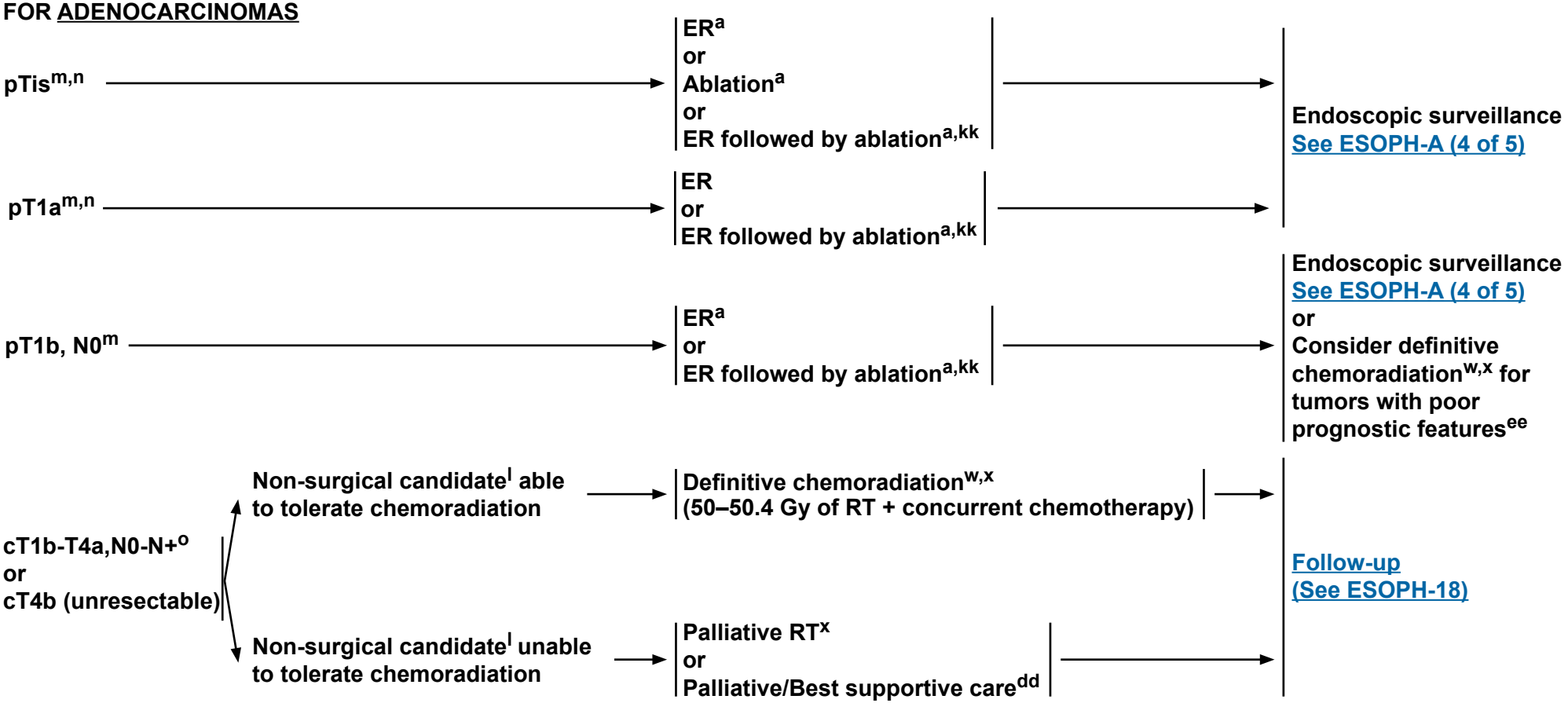
→ **Follow-up (See ESOPH-18)**

[g] See Staging (ST-1) for tumor classification.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[bb] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[cc] The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.
[pp] 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.

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

TUMOR CLASSIFICATION[g] FOR ADENOCARCINOMAS

MANAGEMENT OF NON-SURGICAL CANDIDATES[l]



[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.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[ee] Poor prognostic features include lymphovacular invasion (LVI), poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2 cm or more.
[kk] ER followed by ablation may be used to completely eliminate residual dysplasia or Barrett's epithelium.

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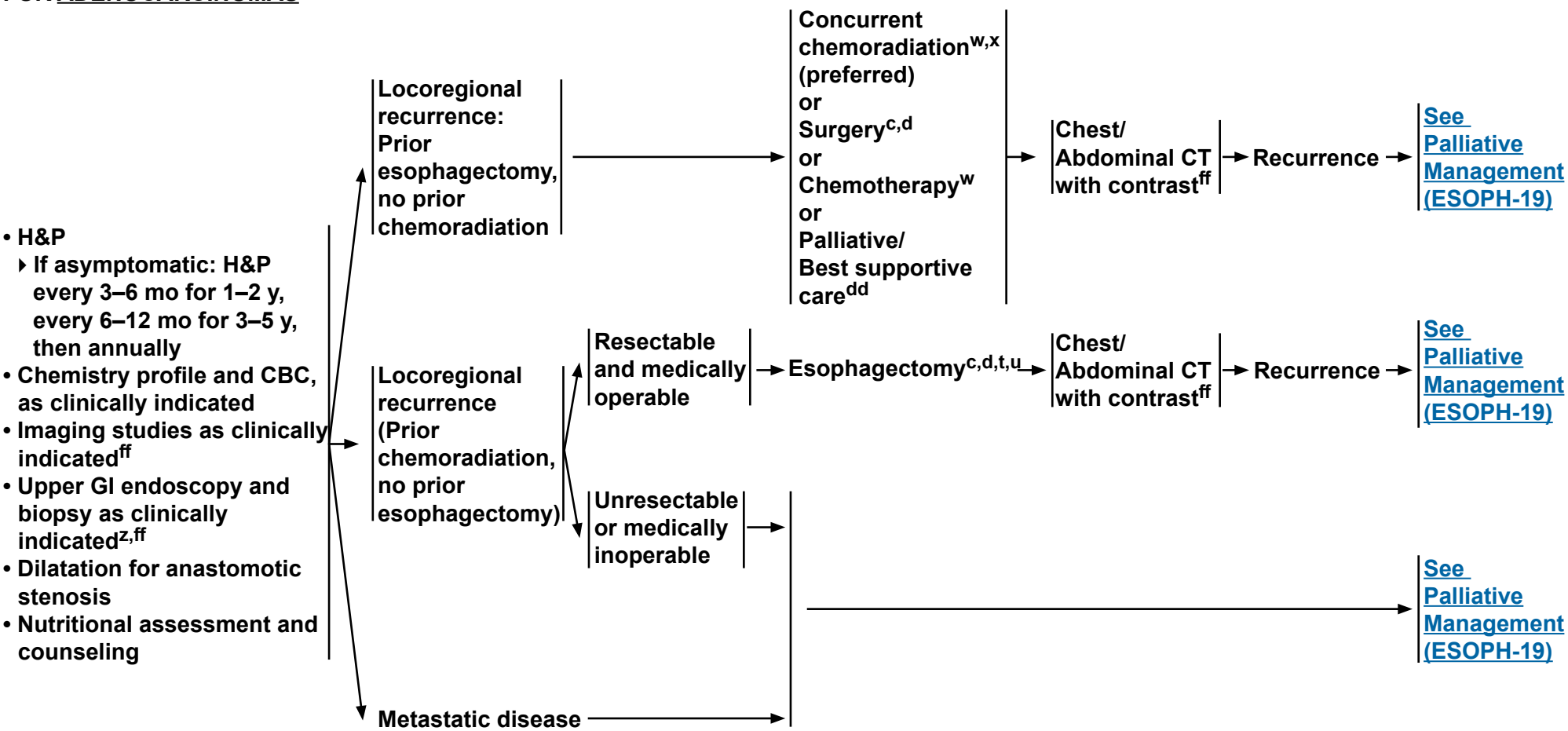
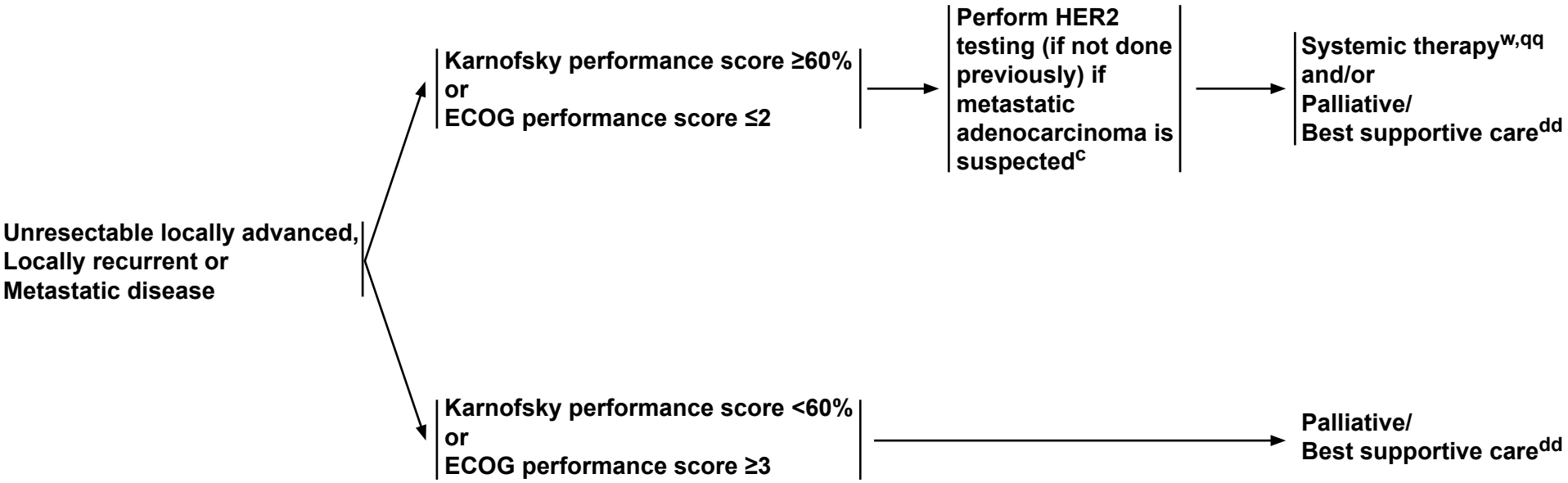
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[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.
[w] See Principles of Systemic Therapy (ESOPH-F).
[x] See Principles of Radiation Therapy (ESOPH-G).
[z] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H)
[ff] See Principles of Surveillance (ESOPH-I).
[gg] 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FOR ADENOCARCINOMAS | **PERFORMANCE STATUS** | **PALLIATIVE MANAGEMENT**



[c] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[w] See Principles of Systemic Therapy (ESOPH-F).
[dd] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[qq] 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 esophagogastric junction 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's esophagus should be characterized in accordance with the Prague criteria,[1] and mucosal nodules should be carefully documented.**
- **High-resolution endoscopic imaging and narrow-band imaging are presently available and may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[2]**
- **Multiple biopsies, 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's 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's 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 less than or equal to 2 cm in diameter is fully removed and histopathologic assessment demonstrates well or moderate differentiation, invasion no deeper than the superficial submucosa, no lymphovascular invasion (LVI), and clear lateral and deep margins.[6,7,8]**
- **Cytologic brushings or washings are rarely adequate in the initial diagnosis.**

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

STAGING

- Endoscopic ultrasound (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 correspond 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 less than or equal to 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 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.

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

Continued

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's 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's 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's esophagus should be performed following ER.[17] Complete eradication of Barrett's 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 less than or equal to 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, less than or equal to 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

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY (REFERENCES)

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[9]Barbour AP, Rizk NP, Gerdes H, et al. Endoscopic ultrasound predicts outcomes for patients with adenocarcinoma of the gastroesophageal junction. J Am Coll Surg 2007;205:593-601.

[10]Thosani N, Singh H, Kapadia A, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc 2012;75:242-253.

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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's esophagus is reported for staging purposes as 'carcinoma in situ (Tis)[b,c,d] • Histologic type[e] • Grade[f] • Presence or absence of Barrett's esophagus
Endoscopic 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 endoscopic mucosal resection plus: • Location of tumor midpoint in relationship to EGJ[g] • Whether tumor crosses EGJ • Lymph node status and number of lymph nodes recovered
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's esophagus with high-grade dysplasia in an esophageal resection specimen is reported as "carcinoma in situ (Tis)." The term "carcinoma in situ" is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states.[1]
[c]Biopsies showing Barrett's esophagus with suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.[2]
[d]Invasion of a thickened and duplicated muscularis mucosae should not be misinterpreted as invasion of the muscularis propria in Barrett's esophagus.[3]
[e]A specific diagnosis of squamous cell carcinoma or adenocarcinoma should be established when possible for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the TNM system for squamous cell carcinoma.[1]
[f]Pathologic grade is needed for stage grouping in the AJCC TNM 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 squamous cell carcinoma (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

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

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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Continued

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 therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization methods is recommended.[11]

TABLE 3 Immunohistochemical Criteria for Scoring HER2 Expression in Esophageal and Esophagogastric Junction Cancers*,**

	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

***The NCCN Guidelines Panel recommends that HER2 immunohistochemistry be ordered/performed first, followed by in situ hybridization (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.**

**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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Continued

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Microsatellite Instability (MSI)* or Mismatch Repair (MMR)* Testing

- **MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma or EGJ,[12] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed paraffin-embedded tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.**

PD-L1 Testing

- **PD-L1 testing may be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on formalin-fixed paraffin-embedded tissue is available as an aid in identifying gastroesophageal junction adenocarcinoma 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 Esophagogastric Junction Cancers**
  - **This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissues from esophageal or EGJ adenocarcinoma. 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.**

*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

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Continued

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING (REFERENCES)

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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 PET (integrated PET/CT is preferred), and endoscopic ultrasound (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 center located within 1 cm to 5 cm above the anatomic EGJ.
    - ◊ Siewert Type II: true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ.
    - ◊ Siewert Type III: subcardial carcinoma with the tumor center between 2 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 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 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]

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Continued

PRINCIPLES OF SURGERY

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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.

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

- Esophageal Cancer, Tylosis with Non-epidermolytic Palmoplantar Keratosis (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's Esophagus[3]
  - Familial Barrett's esophagus (FBE) includes adenocarcinoma of the esophagus (EAC) and adenocarcinoma of the EGJ. Development of Barrett's esophagus (BE) 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 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 FA-A (FANCA) and FA-C (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 the mitomycin C can identify homozygotes but not heterozygotes.

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

Surveillance Recommendations

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

Syndrome	Gene(s)	Inheritance Pattern	Surveillance Recommendations
Esophageal cancer, tylosis with non-epidermolytic palmoplantar keratosis (PPK) and Howel-Evans syndrome[1,2]	*RHBDF2*	Autosomal dominant	Surveillance by upper gastrointestinal endoscopy is recommended in family members with tylosis after 20 years of age.
Familial Barrett's esophagus (FBE)[3]	Candidate genes have not been validated	Autosomal dominant	Potential family history of BE, EAC, or EGJ adenocarcinoma should be determined for patients presenting with GERD, especially Caucasian males older than 40 years of age.
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 surveillance strategy in individuals identified with FA.

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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

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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 should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 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.**

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[4]Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-1708.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

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

Other Recomended 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
- Fluorouracil and cisplatin (category 1)[11]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]
- Paclitaxel and carboplatin[1]

Other Recomended 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)
(3 cycles preoperative and 3 cycle postoperative)

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

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

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

Postoperative Chemotherapy
- Capecitabine and oxaliplatin[d,16]

Preoperative Chemotherapy (2 cycles)
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

[a]Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion.
[b]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[d]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.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

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

- **Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma**
  (See Principles of Pathologic Review and Biomarker Testing [ESOPH-B])
  - **Combination with fluoropyrimidine and cisplatin (category 1)[17]**
  - **Combination with other chemotherapy agents (category 2B)**
  - **Trastuzumab is not recommended for use with anthracyclines**

First-Line Therapy

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

Preferred Regimens

- **Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[18-21] (category 1)**
- **Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[19,22,23]**

Other Recommended Regimens

- **Paclitaxel with cisplatin or carboplatin[24-26]**
- **Docetaxel with cisplatin[27,28]**
- **Fluoropyrimidine[20,29,30] (fluorouracil[a] or capecitabine)**
- **Docetaxel[31,32]**
- **Paclitaxel[33,347]**
- **Fluorouracil[a,e] and irinotecan[35]**
- **DCF modifications**
  - **Docetaxel, cisplatin, and fluorouracil[a,36]**
  - **Docetaxel, oxaliplatin, and fluorouracil[37]**
  - **Docetaxel, carboplatin, and fluorouracil (category 2B)[38]**
- **ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[39]**
- **ECF modifications (category 2B)[40,41]**
  - **Epirubicin, oxaliplatin, and fluorouracil**
  - **Epirubicin, cisplatin, and capecitabine**
  - **Epirubicin, oxaliplatin, and capecitabine**

[a]Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion.
[e]Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.

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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
- **Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]**
- **Docetaxel (category 1)[31,32]**
- **Paclitaxel (category 1)[33,34,43]**
- **Irinotecan (category 1)[43-46]**
- **Fluorouracil[a,e] and irinotecan[44,47,48]**
- **Pembrolizumab**
  - **For second-line or subsequent therapy for MSI-H or dMMR tumors[49,50]**

Other Recommended Regimens
- **Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[51]**
- **Irinotecan and cisplatin[22,52]**
- **Pembrolizumab**
  - **For third-line or subsequent therapy for PD-L1 positive esophageal and EGJ adenocarcinoma[f,53]**
- **Docetaxel and irinotecan (category 2B)[54]**

[a]Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion.
[e]Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[f]Pembrolizumab is approved for patients with EGJ adenocarcinoma with PD-L1 expression levels ≥1 as determined by an FDA-approved test. The NCCN Panel recommends that the pembrolizumab treatment option be extended to patients with esophageal cancer, in addition to EGJ, adenocarcinomas with PD-L1 expression levels ≥1.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

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 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 and 3 cycles after 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 for 5 weeks[55]

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[56]

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]

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]

[g]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

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

PERIOPERATIVE CHEMOTHERAPY (INCLUDING EGJ)

PREFERRED REGIMENS

Fluoropyrimidine and oxaliplatin

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[19]

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

Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)

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 for 4 cycles preoperatively and 4 cycles postoperatively for a total of 8 cycles[8]

OTHER RECOMMENDED REGIMENS

Fluorouracil and cisplatin

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 for 4–6 cycles preoperatively and 4–6 cycles postoperatively for a total of 12 cycles

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]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

DEFINITIVE CHEMORADIATION (NON-SURGICAL)

PREFERRED REGIMENS

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 2–4 cycles for 2 cycles with radiation followed by 2 cycles without radiation[11]

Fluorouracil and oxaliplatin
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 cisplatin
Cisplatin 30 mg/m² IV on Day 1
Capecitabine 800 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[50]

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[55]

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

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[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]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

POSTOPERATIVE CHEMORADIATION (INCLUDING EGJ)

Fluorouracil (bolus) and leucovorin (category 1)[15,57]
Cycles 1, 3, and 4 (before and after radiation)
Leucovorin 20 mg/m² IV Push on Days 1– 5
Fluorouracil 425 mg/m² IV Push daily on Days 1–5
Cycled every 28 days

Cycle 2 (with radiation)
Leucovorin 20 mg/m² IV Push on Days 1–4 and 31–33
Fluorouracil 400 mg/m² IV Push daily on Days 1–4 and 31–33
35-day cycle

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[15,57] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE ABOVE SPECIFIED DOSES OR SCHEDULE OF CYTOTOXIC AGENTS BECAUSE OF CONCERNS REGARDING TOXICITY.
THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

- **1 cycle before and 2 cycles after chemoradiation**
  Capecitabine 750–1000 mg/m² PO BID on Days 1–14
  Cycled every 28 days[58]

- **2 cycles before and 4 cycles after chemoradiation**
  Leucovorin 400 mg/m² IV on Day 1
  Fluorouracil 400 mg/m² IV Push on Day 1
  Fluorouracil 2400 mg/m² IV continuous infusion over 46 hours daily on Day 1
  Cycled every 14 days

With radiation
Fluorouracil 200–250 mg/m² IV continuous infusion over 24 hours daily on Days 1–5 or 1–7
Weekly for 5 weeks[59]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5 or 1–7
Weekly for 5 weeks[60]

POSTOPERATIVE CHEMOTHERAPY

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]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

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

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then
Trastuzumab 6 mg/kg IV every 21 days[17]
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 cisplatin

Cisplatin 75–100 mg/m^2 IV on Day 1
Fluorouracil 750–1000 mg/m^2 IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days[18]

Cisplatin 50 mg/m^2 IV daily on Day 1
Leucovorin 200 mg/m^2 IV on Day 1
Fluorouracil 2000 mg/m^2 IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days[19,20]

Cisplatin 80 mg/m^2 IV daily on Day 1
Capecitabine 1000 mg/m^2 PO BID on Days 1–14
Cycled every 21 days[21]

PREFERRED REGIMENS--continued

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 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 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[22]

Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 200 mg/m^2 IV on Day 1
Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[19]

Capecitabine 1000 mg/m^2 PO BID on Days 1–14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days[23]

OTHER RECOMMENDED REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135–200 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 2
Cycled every 21 days[24]

Paclitaxel 90 mg/m^2 IV on Day 1
Cisplatin 50 mg/m^2 IV on Day 1
Cycled every 14 days[25]

Paclitaxel 200 mg/m^2 IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[26]

Docetaxel and cisplatin

Docetaxel 70–85 mg/m^2 IV on Day 1
Cisplatin 70–75 mg/m^2 IV on Day 1
Cycled every 21 days[27,28]

Fluoropyrimidine

Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IV Push on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[20]

Fluorouracil 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[29]

Capecitabine 1000–1250 mg/m^2 PO BID on Days 1–14
Cycled every 21 days[30]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

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

FIRST-LINE THERAPY--continued
OTHER RECOMMENDED REGIMENS--continued
Taxane

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[31,32]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[33]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[34]

Fluorouracil and irinotecan

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 (only for adenocarcinoma)[35]

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[61]

OTHER RECOMMENDED REGIMENS--continued
DCF modifications

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[36]

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[37]

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[38]

OTHER RECOMMENDED REGIMENS--continued
ECF

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[39]

ECF modifications

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[40,41]

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[40,41]

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[40,41]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES[g]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)
SECOND-LINE AND SUBSEQUENT THERAPY

PREFERRED REGIMENS

Ramucirumab and paclitaxel (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m^2 on Days 1, 8, and 15
Cycled every 28 days[42]

Taxane
Docetaxel 75–100 mg/m^2 IV on Day 1
Cycled every 21 days[31,32]

Paclitaxel 135–250 mg/m^2 IV on Day 1
Cycled every 21 days[33]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[34]

Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15
Cycled every 28 days[43]

PREFERRED REGIMENS--continued

Irinotecan
Irinotecan 250–350 mg/m^2 IV on Day 1
Cycled every 21 days[45]

Irinotecan 150–180 mg/m^2 IV on Day 1
Cycled every 14 days[43,44]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[46]

Fluorouracil and irinotecan
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 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days
(only for adenocarcinoma)[44]

Pembrolizumab (for second-line or subseqent therapy for MSI-H/dMMR tumors)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[53]

OTHER RECOMMENDED REGIMENS

Ramucirumab (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[51]

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[22,52]

Pembrolizumab (for third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[53]

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[54]

[g]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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

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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, endoscopic ultrasound (EUS), endoscopy reports, and PET or PET/CT scans, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders 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. Intensity-modulated radiation therapy (IMRT) or 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.
- 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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Continued

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.[1] 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

- **Treatment planning is essential to reduce unnecessary dose to organs at risk, including liver.**
- **Lung dose may require particular attention, especially in the preoperatively treated patient. Normal lung (more than 2 cm outside the target volume) should not receive more than 40 Gy. It is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.**

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

Cord
- **Max ≤ 45 Gy**

Bowel
- **Max bowel dose < Max PTV dose**
- **D_{05} ≤ 45 Gy**

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

Left Kidney, Right Kidney (evaluate each one separately):
- **No more than 33% of the volume can receive 18 Gy**
- **Mean dose < 18 Gy**

Liver
- **V_{20Gy} ≤ 30%**
- **V_{30Gy} ≤ 20%**
- **Mean < 25 Gy**

Stomach
- **Mean < 30 Gy (if not within PTV)**
- **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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PRINCIPLES OF RADIATION THERAPY

Dose

- **Preoperative RT: 41.4–50.4 Gy (1.8–2.0 Gy/d)[c]**
- **Postoperative RT: 45–50.4 Gy (1.8–2.0 Gy/d)**
- **Definitive RT: 50–50.4 Gy (1.8–2.0 Gy/d)[2]**
  - **Higher doses may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned.[d]**

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 and antidiarrheal medications may be prescribed when needed.**
- **If estimated caloric intake is <1500 kcal/d, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomies (J-tube) 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 early 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 (1.8–2.0 Gy/d) because the lower preoperative therapy dose may not be adequate.

[d]Published studies have reported radiation doses from 60–66 Gy (1.8–2.0 Gy/d). 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/d).

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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.

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.**

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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 jejunal or gastrostomy tube
  - External beam radiation therapy
  - Brachytherapy may be considered in place of external beam radiation 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 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.
  - External beam radiation therapy[11] and brachytherapy both effectively treat malignant dysphagia
    - ◊ The onset of symptom relief for external beam radiation therapy or brachytherapy is slower compared to endoscopic palliation but is also likely to be more durable.[12,13]
  - 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 uncontrollable nature of pain is established.

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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 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.[14]**
- **Chronic blood loss from esophageal cancer**
  - **External beam radiation therapy**

Nausea/Vomiting

- **If patient is experiencing nausea and vomiting, then the patient 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 local 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.**

pStage 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.

Note: All recommendations are category 2A unless otherwise indicated.
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Continued

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.** 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's 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* (N0 on EUS)	**ER/ablation**	Once eradication of all neoplasia/high-risk preneoplasia 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*	**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 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.

*ER/ablation for T1b can be considered for superficial disease or for non-surgical candidate.
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Continued

PRINCIPLES OF SURVEILLANCE

Stage II or III (T2-T4, N0-N+, T4b) treated with bimodality therapy (definitive chemoradiation)

Literature suggests that local/regional 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 after trimodality therapy and most luminal recurrences are detected by other imaging modalities.[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) rather 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 as a surveillance tool is not recommended.

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Continued

PRINCIPLES OF SURVEILLANCE

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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, surveillance may not be necessary for more than 5 years following the end of treatment.**
- **Routine esophageal/EGJ cancer-specific surveillance is not recommended beyond 5 years.**
- **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

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

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 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
- Colorectal Cancer: See NCCN Guidelines for Colorectal Cancer Screening
- Prostate Cancer: See NCCN Guidelines for Prostate 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)
- 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.
- Recommend provision of survivorship care plan that includes:
  - Summary of treatment, including all surgeries, radiation treatment, and chemotherapy received
  - Description of acute and long-term effects of treatment, and possible late sequelae of treatment, with anticipated time to development and/or resolution
  - Surveillance recommendations
  - Health behavior recommendations
  - Delineation of roles of oncologists and PCPs, with timing of transfer of care as appropriate

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Continued

PRINCIPLES OF SURVIVORSHIP
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Table 1
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

Definition of Primary Tumor (T)

T Category	T Criteria
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

Definition of Regional Lymph Node (N)

N Category	N Criteria
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

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

Definition of Histologic Grade (G)

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

Squamous Cell Carcinoma

Definition of Location (L)

Location Category	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.	

Continued

Table 1 **(continued)**

AJCC PROGNOSTIC STAGE GROUPS (Squamous Cell Carcinoma)

Clinical Staging (cTNM)

	cT	c N	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	Any	Lower
	T3	N0	M0	G1	Upper/middle
Stage IIB	T3	N0	M0	G2-3	Upper/middle
	T3	N0	M0	GX	Any
	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)

	yp T	yp N	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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***Table 1* (continued)**

AJCC PROGNOSTIC STAGE GROUPS (Adenocarcinoma)

Clinical Staging (cTNM)

	T	N	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)

	yp T	yp N	M
Stage I	T0	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

Discussion

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.

NCCN Guidelines Version 2.2018
Esophageal and Esophagogastric Junction Cancers

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Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach constitute a major global health problem. A dramatic shift in the location of upper GI tract tumors has occurred in the United States.[1,2] Changes in the histology and location of upper GI tract tumors have also been observed in some parts of Europe.[3] In Western countries, the most common site of esophageal cancer is in the lower third of the esophagus, which often involves the EGJ.

Esophageal cancer is the sixth most common cause of cancer-related deaths worldwide and is 3 to 4 times more common in men than in women.[4,5] It is endemic in many parts of the world, particularly in developing nations, where it is the fifth most common cause of cancer-related deaths.[4] In 2018, an estimated 17,290 people will be diagnosed with esophageal cancer and 15,850 people will die of this disease in the United States.[6] The incidence of esophageal cancer represents one of the widest variations, with a 60-fold difference between high- and low-incidence regions.[7] The highest-risk area, often referred to as the "esophageal cancer belt," spans from northern Iran through the Central Asian republics and into northern China.[5] Other high-prevalence areas include southern and eastern Africa and Northern France.[8]

Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma.[9] 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.[10-12] The risk of SCC decreases substantially after smoking cessation, whereas the risk for adenocarcinoma remains unchanged even after several years of smoking cessation.[13] SCC has become increasingly less common in the West over recent decades, due to reductions in tobacco and alcohol use, and now accounts for <30% of all esophageal cancers in the United States and Western Europe.[5]

In contrast, the incidence of adenocarcinomas has increased in the West, likely due to rising obesity rates.[5] Obesity and high body mass index (BMI) have been established as strong risk factors for adenocarcinoma of the esophagus.[11,14,15] A meta-analysis of case-control and cohort studies on BMI and esophageal cancer found that individuals with a BMI ≥30 kg/m^2 had a higher relative risk (2.34, 95% CI, 1.95–2.81) for developing esophageal adenocarcinoma than individuals with a BMI of 25 to 30 kg/m^2 (1.71; 95% CI, 1.50–1.96).[14] Obesity contributes to the development of gastroesophageal reflux disease (GERD) and Barrett's esophagus, the two major underlying causes of esophageal adenocarcinoma.[16-18] GERD is associated with a high BMI and is also a risk factor for Barrett's esophagus, a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[19] Patients with Barrett's esophagus have a 30 to 60 times greater risk of developing adenocarcinoma of the esophagus than the general population.[17] Age, male gender, long-standing GERD, hiatal hernia size, and the length of Barrett's esophagus are strongly associated with higher grades of dysplasia.[20,21] These preliminary findings warrant further prospective evaluation of predictors of risk for the development of high-grade dysplasia (HGD) and adenocarcinoma of the esophagus in patients with Barrett's esophagus. Additionally, patients with adenocarcinoma or SCC of the esophagus are also at increased risk of developing second primary cancers, such as head and neck and lung cancers.[22]

In general, SCC seems to be more sensitive to chemotherapy, radiation therapy (RT), and chemoradiation than adenocarcinoma, but long-term outcomes appear to be the same. Adenocarcinoma may be associated with a better long-term prognosis after resection than SCC;[23] however, more concrete data are required for such an assertion.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Esophageal and EGJ Cancers, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: esophageal cancer, esophageal squamous cell carcinoma, esophageal adenocarcinoma, esophagogastric junction, gastroesophageal junction, endoscopic treatment, endoscopic resection, ablation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[24]

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. 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

Referral to a cancer genetics professional is recommended for individuals with a known high-risk syndrome associated with esophageal and EGJ cancers. Although early age of onset and multiple family members with esophageal or EGJ cancers are associated with hereditary disease, specific recommendations for esophageal and EGJ cancer risk assessment are not possible at this time due to limited data. See *Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers* in the algorithm.

Tylosis

Tylosis (also known as non-epidermolytic palmoplantar keratosis [PPK] or Howel-Evans syndrome) is a very rare autosomal dominant syndrome caused by germline mutations in the *RHBDF2* gene.[25] Individuals with germline *RHBDF2* mutations have an increased risk for SCC of the esophagus.[25] Tylosis is classified into diffuse, punctate, or focal forms according to the patterns of skin thickening on palms and soles. Diffuse tylosis is further divided into epidermolytic and non-epidermolytic forms. Non-epidermolytic tylosis is associated with a high risk of developing SCC of the middle and distal esophagus.[26] In individuals with tylosis, the average age at diagnosis of SCC of the esophagus is 45 years. The risk of developing SCC of the esophagus has been reported to be 40% to 90% by the age of 70 years.[27,28] Surveillance by upper GI endoscopy is recommended for patients with tylosis after 20 years of age.[26]

Familial Barrett's Esophagus

Barrett's 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.[19] The familial aggregation of Barrett's esophagus and adenocarcinoma of the esophagus or EGJ is termed familial Barrett's esophagus (FBE).[29-31] Reviews of hospital case series indicate that between 5% and 7% of Barrett's esophagus and esophageal adenocarcinoma cases report a family history of either disease.[32] In one cohort study, family history was identified as an independent predictor for the presence of Barrett's 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.[30]

FBE may be associated with one or more rare autosomally inherited dominant susceptibility alleles.[33] Reports have identified germline mutations in a variety of susceptibility genes that may be associated with the development of Barrett's esophagus.[34,35] Since development of Barrett's esophagus is strongly associated with GERD, it is possible that it is GERD that is inherited, with Barrett's 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 from GERD to adenocarcinoma in FBE families, additional genetic factors may be required for the development of FBE.[32] A recent study using whole exome sequencing (WES) on 4 distant relatives from a multiplex, multigenerational FBE family identified the uncharacterized gene *VSIG10L* as a candidate FBE susceptibility gene, with a putative role in maintaining normal esophageal homeostasis.[36] However, future studies on the prevalence of *VSIG10L* mutations in the population are needed to allow for risk stratification of FBE susceptibility.

A study by Chak et al showed that screening upper endoscopies identified Barrett's esophagus in 21% of first-degree relatives of patients with Barrett's esophagus or esophageal adenocarcinoma, and was identified significantly more often in siblings and offspring of FBE probands than in probands with isolated cases of Barrett's esophagus.[37] However, routine surveillance with upper endoscopy in FBE patients is controversial and is not recommended at this time. Potential family history of Barrett's esophagus and adenocarcinoma of the esophagus or EGJ should be determined for patients presenting with GERD, especially Caucasian males >40 years of age.

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 strikingly elevated sister chromatid exchange rates that are associated with an increased predisposition to a wide variety of malignancies.[38] Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphoid neoplasms, and Wilms tumor are the predominant cancers diagnosed before 25 years of age, whereas carcinomas of different anatomic sites including SCC of the esophagus are diagnosed after 20 years of age.[26,39] Individuals with BS are often diagnosed with cancers at an earlier age than those of the general population. Chromosomal quadraradials with breakage may be used for the diagnosis of BS.[26] Screening for GERD with or without endoscopy to detect early 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.[26] FA is caused by mutations in one of

15 genes encoding the FA pathway, with *FANCA, FANCC, FANCG*, and *FANCD2* being the most common.[40] 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.[26,41,42] 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 mitomycin C-induced chromosomal breakage analysis can identify homozygotes.[26,43] Endoscopy of the esophagus may be considered as a surveillance strategy in individuals with FA.

Staging

The tumor (T), node (N), and metastasis (M) staging system used by the AJCC is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. The eighth edition of the AJCC staging system for esophageal cancer is based on the risk-adjusted random survival forest analysis of collated data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for 22654 patients who were treated with esophagectomy alone or esophagectomy with preoperative and/or postoperative therapy.[44] In the data reported by the WECC, 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.[45,46] Survival increased with a more distal location of cancer within the esophagus. In addition, survival was significantly affected by histopathologic cell type, with SCC having worse survival than adenocarcinoma.[46]

The larger dataset used for this edition allowed for better separation of SCC and adenocarcinoma staging.[44] However, the data sets used for this new classification had several limitations, 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. Nonetheless, the eighth edition of the AJCC Cancer Staging Manual represents the best worldwide clinical esophageal cancer staging data currently available.

Patient outcomes may correlate with the clinical stage of the cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage (whether or not patient has received preoperative therapy). Although surgical pathology yields the most accurate staging, the advent of better imaging techniques has improved presurgical staging.[47] In North America and many western European countries, where screening programs for early detection of esophageal and EGJ cancers are not in use or practical because of low incidence, the diagnosis is often made late in the disease course. At diagnosis, nearly 50% of patients have cancer that extends beyond the locoregional confines of the primary 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, clinicians are often dealing with an advanced-stage, incurable cancer in newly diagnosed patients.

Esophagogastric Junction

Siewert et al classified EGJ adenocarcinoma into 3 types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass.[48] If the epicenter of the tumor or >66% of the tumor

mass is located <1 cm above the anatomic EGJ, then the tumor is classified as an adenocarcinoma of the distal esophagus, Type I. If the epicenter of the tumor or >66% of the tumor mass is located within 1 cm proximal and 2 cm distal to the anatomic EGJ, the adenocarcinoma is classified as Type II. If the epicenter of the tumor or >66% of the tumor mass is located >2 cm below the anatomic EGJ, the tumor is classified as Type III.[48]

In 2000, this classification was slightly changed.[49] Siewert Type I tumors are now defined as an adenocarcinoma of the distal esophagus with the tumor center 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 center located within 1 cm above and 2 cm below the EGJ. Siewert Type III tumors are defined as a subcardial carcinoma with the tumor center located between 2 to 5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below.

In the eighth edition of the AJCC staging system, tumors with midpoints in the lower thoracic esophagus, EGJ, or within the proximal 2 cm of the stomach that extends into the EGJ or esophagus (Siewert Types I and II) are classified as adenocarcinoma of the esophagus for the purposes of staging.[44] All cancers with a midpoint located >2 cm into the stomach (Siewert Type III), even those extending into the EGJ, are staged using the gastric cancer staging system. In general, Siewert Types I and II tumors should be managed with guidelines applicable to esophageal and EGJ cancers. Siewert Type III tumors are more appropriately managed with guidelines applicable to gastric cancer. Therapeutic decisions may be refined according to the location of the individual tumor, nodal distribution, and specific requirements for local control. 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's Esophagus

Barrett's 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.[19] Barrett's esophagus can progress to low-grade dysplasia (LGD) or HGD and in some cases to adenocarcinoma of the esophagus.[17] Patients with Barrett's esophagus are at a greater risk of developing adenocarcinoma of the esophagus than the general population. Age, male gender, long-standing GERD, hiatal hernia size, and the length of Barrett's esophagus are strongly associated with the progression of Barrett's esophagus to adenocarcinoma.[20,21,50] Biomarkers such as aneuploidy and loss of heterozygosity of *p53* have also been associated with an increased risk of progression to HGD and/or adenocarcinoma of the esophagus.[50] These preliminary results warrant further prospective evaluation as predictors of risk for the development of HGD and adenocarcinoma of the esophagus in patients with Barrett's esophagus. Endoscopy should be performed on patients with severe symptoms of GERD, especially those with a family history of Barrett's esophagus or esophageal cancer. The location, length, and circumferential involvement should be characterized in accordance with the Prague classification and mucosal nodules should be carefully documented.[51]

The use of wide-area transepithelial sampling (WATS), a relatively new technique combining abrasive brushing of the Barrett's esophagus mucosa with neural network analysis to highlight abnormal cells, may increase the detection of HGD and esophageal adenocarcinoma in Barrett's esophagus patients. In a multicenter

prospective trial, Barrett's esophagus patients (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%). [52]

Endoscopic resection (ER) with radiofrequency ablation (RFA) has become the preferred treatment for most patients with Barrett's esophagus and HGD. Alternative strategies include cryoablation or photodynamic therapy (PDT).[53-55] Surgical resection is reserved for patients with HGD and characteristics that are unfavorable for non-surgical therapy, such as nodularity or long-segment involvement. A meta-analysis by Yang et al found that endoscopic submucosal dissection (ESD) for the management of early Barrett's esophagus neoplasia was associated with a high en-bloc resection rate, acceptable safety profile, and low recurrence rate after curative resection, suggesting that ESD should be considered as a preferred option for the management of Barrett's esophagus neoplasia.[56] For patients with metaplasia or LGD, gastroesophageal reflux can be controlled with histamine receptor antagonists or proton pump inhibitors.

Endoscopic surveillance is performed to evaluate the progression from metaplasia to LGD, HGD, or adenocarcinoma. Larger forceps are recommended during surveillance endoscopy of Barrett's esophagus for the detection of dysplasia.[57] However, controversy exists when recommending a surveillance schedule for patients with Barrett's esophagus. Studies suggest that the rate of progression of Barrett's esophagus to adenocarcinoma of the esophagus is much lower than previously reported.[58,59] Dysplasia of any grade discovered during surveillance should be confirmed by an expert pathologist.

The updated guidelines from the American College of Gastroenterology recommend endoscopic surveillance every 3 years for patients without dysplasia on 2 consecutive endoscopies with biopsies within a year.[60] If the finding is LGD, endoscopy within 6 months is warranted to ensure that no HGD is present in the esophagus. Follow-up endoscopy is recommended annually until no dysplasia is detected on 2 consecutive endoscopies with biopsies. If HGD is discovered during surveillance, a subsequent endoscopy within 3 months is recommended to rule out adenocarcinoma of the esophagus. Follow-up endoscopy every 3 months is recommended thereafter.[60] For patients who are at high risk for cancer or refuse ER, continued surveillance every 3 months is an option if definitive therapy would be offered for those who develop adenocarcinoma. Based on randomized trials, endoscopic therapy is recommended for patients with confirmed HGD and may also be useful for patients with confirmed LGD.[61,62]

Principles of Pathology

Pathologic Review

A specific diagnosis of SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas are staged using the TNM system for SCC.[44] In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade (required for stage grouping). The pathology report of a surgical biopsy specimen should also document the presence or absence of Barrett's esophagus. Biopsies showing Barrett's esophagus with suspected dysplasia should be reviewed by a second expert GI pathologist for confirmation.[60] Barrett's esophagus with HGD is reported as carcinoma *in situ* (Tis) for staging purposes.[44]

In the case of ER specimens, the depth of tumor invasion, presence of lymphovascular invasion (LVI), and the status of mucosal and deep margins should also be reported. The pathology report for esophagogastrectomy 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 esophagogastrectomy 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 esophagogastrectomy without prior chemoradiation, plus assessment of the treatment response.

Assessment of Treatment Response

The prognostic significance of pathologic complete response (pCR) and histologic tumor regression after induction therapy in patients with adenocarcinoma and SCC of the esophagus has been demonstrated in several studies.[63-69] Posttreatment pathologic stage was the best predictor of survival outcome for patients with locoregional carcinoma of the esophagus or EGJ who underwent preoperative chemoradiation followed by esophagectomy.[70]

Although tumor regression grading systems for 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.[71,72] This scheme is based on a 4-tiered classification system: 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.[73] Sizable pools of acellular mucin may be present after chemoradiation, but should not be interpreted as representing residual tumor. See the *Principles of Pathologic Review and Biomarker Testing: Assessment of Treatment Response -Table 2* in the algorithm for more information.

Role of PET Scans in the Assessment of Treatment Response

The prognostic significance of metabolic response after preoperative therapy as defined by PET scans has been evaluated in retrospective[74-84] and prospective studies[85-100] in patients with locally advanced esophageal cancer. However, the timing of posttreatment PET before surgery (2–6 weeks)[85,89,93,95] and the cut-off values for the reduction in the 18-fluorodeoxyglucose (FDG) standardized uptake value (SUV) between pre- and posttreatment PET scans (35%–80%)[85-87,95] have varied widely across the studies. In addition, the prospective studies are limited by their small sample size, with the exception of the MUNICON II study that included 110 patients with locally advanced adenocarcinoma of the EGJ.[95] In this study, metabolic responders were defined as those with a decrease of ≥35% in SUV after 2 weeks of induction chemotherapy. 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 metabolic non-responders.

In some retrospective studies, FDG uptake on a single posttreatment PET scan was the only predictive factor that correlated with pathologic response and survival. However, the specific uptake value used as a cutoff in these series also varied from 2.5 to 4.[74,78] Swisher et al showed that the 2-year survival rate was 60% for patients with a post chemoradiation FDG uptake <4 and 34% for those with a FDG uptake ≥4; PET scans, however, could not distinguish patients with microscopic residual disease.[74] In a more recent retrospective study using the same cut-off value (FDG uptake <4), Bruzzi et al reported that PET scan has a limited utility for assessing therapeutic response, although it was useful in the detection of distant metastases in patients with locally advanced, potentially resectable esophageal cancer.[76] Other studies have also reported that the accuracy of PET for detecting non-responders is too low to justify the use of PET to determine early discontinuation of preoperative therapy in patients with potentially resectable esophageal cancer.[97,99]

In patients who are treated with preoperative chemoradiation, RT-induced ulceration has been associated with false-positive results on PET/CT scans, precluding accurate detection of residual esophageal tumor.[101] However, PET/CT when used in combination with endoscopy was found to be useful in identifying patients with a high risk of residual tumor following preoperative chemoradiation.[101] A population-based study by Healy et al used the SEER database and Medicare claims data to evaluate the feasibility and efficacy of PET scans to detect tumor recurrence in asymptomatic esophageal cancer patients. Findings suggested there was no association between the use of PET scans for routine surveillance and improved 2-year survival, indicating that the use of PET is not ideal for the detection of recurrent esophageal cancer.[102] Therefore, the guidelines recommend consideration of PET/CT (preferred) or PET only for the assessment of response to preoperative or definitive chemoradiation therapy before surgery or initiation of postoperative treatment. The guidelines emphasize that PET scans should not be used for the selection of patients for surgery following preoperative chemoradiation or for routine surveillance following completion of treatment.

Assessment of HER2 Overexpression or Amplification

Overexpression or amplification of the human epidermal growth factor receptor 2 (*HER2*) gene and protein have been implicated in the development of esophageal and EGJ adenocarcinomas.[103] HER2 positivity in esophagogastric cancers varies widely (2%–45%)[104] and is more frequently seen in adenocarcinoma of the esophagus (15%–30%) than in SCC (5%–13%).[105-107] Additionally, HER2 positivity has been reported to be higher in patients with EGJ adenocarcinomas than in patients with gastric adenocarcinomas.[108,109] In the ToGA trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2-positive advanced EGJ or gastric cancers, HER2-positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[110]

Unlike in breast cancer, the prognostic significance of HER2 status in patients with esophageal cancer is unclear. Some studies have reported that HER2 overexpression is correlated with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[104] HER2 overexpression also seems to be associated with poorer survival in patients with SCC of the esophagus.[105] 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-positive advanced or metastatic disease.

Immunohistochemistry (IHC) is the most widely used primary test for the assessment of HER2 overexpression. IHC evaluates the

membranous immunostaining of the tumor cells, including the intensity and extent of staining and the percentage of immunoreactive tumor cells, with scores ranging from 0 to 3+. The NCCN Guidelines recommend that cases showing 2+ (equivocal) expression of HER2 by IHC should be additionally examined by fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) methods. FISH/ISH results are expressed as the ratio between the number of copies of the *HER2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (HER2:CEP17). Alternatively, FISH/ISH results may be given as the average *HER2* copy number per cell.

According to the HER2 scoring system for breast cancer proposed by ASCO/CAP, uniform intense membrane staining in >30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to two major differences in HER2 staining patterns between breast and gastroesophageal cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastroesophageal cancer), it has been reported that application of this scoring system would not identify many gastroesophageal cancer patients who could otherwise be candidates for anti-HER2 therapy.[111,112] Results from two separate series also demonstrated that the HER2 scoring system for breast cancer identified a significantly lower percentage of patients with gastroesophageal cancer meeting the criteria for HER2 positivity by IHC (5.4% vs. 11% in the ToGA trial).[113,114] In 2008, Hofmann et al developed a modified 4-tiered HER2 scoring system specifically for gastric cancer by using the assessment area cut-off of at least 10% stained tumor cells for resection specimens and omitting this area cut-off for biopsy specimens.[111] In a subsequent validation study (n = 447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[112] This modified HER2 scoring system is recommended by the panel.

HER2 testing at the time of diagnosis is recommended for all esophageal or EGJ adenocarcinoma patients if metastatic disease is documented or suspected. The NCCN Guidelines recommend that assessment of HER2 status should be performed first using IHC following the Hoffmann-modified scoring system.[111,113] A score of 0 or 1+ is considered to be negative for HER2 overexpression. A score of 2+ is considered equivocal and should be confirmed with FISH/ISH techniques. Cases that have an IHC score of 3+ or an IHC score of 2+ and are FISH/ISH positive (HER2:CEP17 ratio ≥2 or average *HER2* copy number ≥6 signals/cell) are considered positive for HER2 overexpression. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further testing. These guidelines are in agreement with the recommendations for HER2 testing in gastroesophageal adenocarcinoma that were recently published by ASCO, CAP, and the American Society for Clinical Pathology (ASCP).[115] See the *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.

New and Emerging Biomarkers

In its first-ever site-agnostic approval, the FDA approved pembrolizumab for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) solid tumors in the second-line or subsequent setting.[116] Therefore, dMMR/MSI-H testing should be performed in all esophageal and EGJ adenocarcinoma patients if metastatic disease is documented or suspected. Results are interpreted as MSI-H or dMMR in accordance with guidelines for colorectal cancer specimens (see NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal).

In addition, pembrolizumab has been granted accelerated FDA approval as a third- or subsequent-line treatment option for patients with recurrent, locally advanced, or metastatic EGJ adenocarcinoma whose tumors express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥1 as determined by an FDA-approved companion diagnostic test.[117] CPS is determined by the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells evaluated, multiplied by 100. Therefore, PD-L1 testing is also recommended for all patients with advanced esophageal or EGJ adenocarcinomas if metastatic disease is documented or suspected. The panel recommends that the pembrolizumab treatment option be extended to patients with esophageal, in addition to EGJ, adenocarcinomas with a CPS ≥1.

Surgery

Surgery is a major component of treatment for early-stage esophageal and EGJ cancers. Improvements in staging techniques, patient selection, support systems, 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[118] and perioperative chemotherapy[119,120] have significantly improved survival in patients with resectable esophageal and EGJ cancers. With the incidence of esophageal cancer (particularly adenocarcinoma of the distal esophagus) increasing dramatically, the hope is that surveillance programs will continue to detect earlier stages of cancer, thus increasing the number of patients who can benefit from therapy.

Currently, endoscopic ultrasound (EUS) and integrated PET/CT scans are utilized to select patients for surgery, to exclude metastatic disease, and to identify and quantify lymph node involvement. For patients with locally advanced cancer, lymph node involvement has been shown to be a strong independent predictor of poor survival with surgery alone. These patients should therefore be considered for preoperative therapy. In the future, molecular techniques may result in improved prognostic stratification, improved patient selection for surgical therapy, and improved OS.[121-123]

Surgical Approaches

Several operative techniques are acceptable for esophagogastrectomy in patients with resectable esophageal or EGJ cancers.[124] Transthoracic and transhiatal esophagogastrectomy are the two most common surgical approaches. The type of esophageal resection is dictated by the tumor location as well as the available choices for conduit. Acceptable operative techniques and the choice of conduit are described below. Esophagectomy should always be performed in high-volume esophageal cancer centers by experienced surgeons.[125]

Transthoracic Esophagogastrectomy

Ivor Lewis esophagogastrectomy (right thoracotomy and laparotomy),[126] and McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis)[127] are the two standard options for transthoracic esophagogastrectomy. Ivor Lewis esophagogastrectomy, the most frequently used procedure for transthoracic esophagogastrectomy, uses laparotomy and right thoracotomy, with upper thoracic esophagogastric anastomosis at or above the azygos vein.[126] 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 lesions in the distal thoracic location, 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 Esophagogastrectomy

Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[128] The mobilization of the stomach for use as the conduit is performed as in the Ivor-Lewis esophagogastrectomy. This procedure is completed through the abdominal incision, and the gastric conduit is drawn through the posterior mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be hazardous. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en-bloc lymphadenectomy.[129] In the largest population-based study, which 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.[130] Though 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.

Transthoracic or Thoracoabdominal Esophagogastrectomy

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision through the eighth intercostal space.[131] 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.[131]

Minimally Invasive Esophagectomy

Minimally invasive esophagectomy (MIE) strategies include minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy and limited thoracotomy or thoracoscopy) and minimally invasive McKeown esophagogastrectomy (thoracoscopy, limited laparotomy or laparoscopy, and cervical incision). MIE strategies may be associated with decreased morbidity and shorter recovery times. In a phase II multicenter prospective study involving 104 patients with HGD or esophageal cancer of the mid- or 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.[132] 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.[133] However, it is important to note that 62% of patients in this study had early-stage disease. 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 open esophagectomy, providing evidence for the short-term benefits of MIE over invasive procedures.[134] Another report involving 56 patients showed that MIE was comparable to open esophagectomy, but the use of neoadjuvant treatment slightly increased the surgical mortality from 1.5% to 1.8%.[135] Open esophagectomy may still be preferred over MIE for certain patients with previous abdominal surgery, large and bulky tumors, possibly unusable gastric conduit, and difficulty with lymph node dissection.

MIE is an evolving treatment option for patients with esophageal cancer, although it is reasonable to replace thoracotomy with thoracoscopy when possible, especially in older patients and those with significant comorbidities.[136-138]

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.[139] Gastric conduit is preferred for esophageal reconstruction by the majority of esophageal surgeons.[140] Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[141]

Principles of Surgery

All patients should be assessed for the physiologic ability to undergo esophageal resection,[142] which involves assessing whether they are medically fit to tolerate general anesthesia and major abdominal and/or thoracic surgery. Prior to surgery, clinical staging should be performed to assess resectability with CT scan of the chest and abdomen, whole-body PET (integrated PET/CT scan is preferred), and EUS.[143] Pretreatment nutritional support should be considered as supportive care for patients with significant dysphagia and/or weight loss during induction chemoradiation. Enteral nutrition is the best option and a jejunostomy feeding tube is preferred over a gastrostomy feeding tube or percutaneous endoscopic gastrostomy (PEG) feeding tube for preoperative nutrition support.

Surgery is usually performed with a 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.

Esophagectomy should be considered for all medically fit patients with localized resectable esophageal cancer (>5 cm from cricopharyngeus). Cervical or cervicothoracic esophageal cancers <5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Palliative esophagectomy can be considered for patients with cervical esophageal cancer who develop localized resectable recurrence or untreatable stricture after definitive chemoradiation if there is no distant recurrence.[144]

The Siewert tumor type should be assessed in all patients with adenocarcinomas involving the EGJ. The surgical approaches for Siewert Type I and II EGJ 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.[48,145,146] 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.[147] Positive peritoneal cytology in the absence of visible peritoneal metastases is associated with poor prognosis in patients with EGJ adenocarcinoma.[148] Patients with advanced tumors, clinical stage T3 tumors, or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

Lymph node dissections (lymphadenectomy) can be performed using the standard or extended (en-bloc) technique. In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the SEER database, patients who had >12 lymph nodes examined had significantly reduced mortality compared to those who had no lymph nodes evaluated; patients who had ≥30 lymph nodes examined had the lowest mortality of any group.[149] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[150,151] A report from the WECC database, which analyzed 4627 patients who had esophagectomy alone, also suggested that greater extent of lymphadenectomy was associated with increased survival for all patients with pN0M0 moderately and poorly differentiated cancers and all node-positive (pN+) cancers.[151] In patients undergoing esophagectomy without preoperative chemoradiation, the NCCN Guidelines recommend that at least 15 lymph nodes be removed for adequate nodal staging. The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown; however, it is important to note that extended lymphadenectomy does not seem to be correlated with increased survival in these patients.[152]

Patients with Tis or T1a tumors may be considered for endoscopic therapies (see below). Patients with positive deep margins after ER or with tumors in the submucosa (T1b) or deeper may be treated with esophagectomy. Patients with T1 to T3 tumors (stage I or II disease) are considered to be potentially resectable, even in the presence of regional nodal metastases, although patients with bulky, multi-station nodal involvement have poor OS. Selected patients with stage III disease may have resectable tumors as well. T4a tumors with involvement of the pericardium, pleura, or diaphragm may be resectable; however, EGJ tumors with supraclavicular lymph node involvement, stage IV tumors with distant metastases including non-regional 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.

Endoscopic Therapies

ER (endoscopic mucosal resection [EMR] or ESD) and endoscopic ablation (cryoablation or RFA) have been used as alternatives to surgery for the treatment of patients with early-stage esophageal and EGJ cancers, with much less treatment-related morbidity than surgical resection.

Retrospective studies have demonstrated that ER and endoscopic ablation procedures are effective treatment options for select patients with Barrett's esophagus and early-stage esophageal and EGJ cancers.[153-156] 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, supporting the use of endoscopic therapy as an effective treatment option for patients with early-stage disease.[155]

EMR is widely used for the treatment of early SCC of the esophagus in Japan and is gaining acceptance in Western countries for the treatment of Barrett's esophagus and superficial adenocarcinomas.[157-160] Complete Barrett's eradication EMR (CBE-EMR) has been shown to be a highly effective long-term treatment option for patients with Barrett's esophagus and HGD.[161-165] 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.[166-169] 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.[170,171]

RFA alone or in combination with ER is an effective treatment option for the complete eradication of residual dysplasia or Barrett's esophagus.[61,153,154,172-175] Endoscopic cryoablation has also been reported to be safe and well-tolerated in patients with Barrett's esophagus and early-stage esophageal cancers.[176,177] PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett's esophagus and HGD.[178-180] However, more recently, 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 degree of obstruction, and the length and extent of circumferential tumor involvement should be carefully recorded to assist with treatment planning. Esophageal tumor length has been identified as an independent predictor of long-term survival in patients with adenocarcinoma of the esophagus.[181] The 5-year survival rate was significantly higher for patients with a tumor length ≤2 cm (78%) compared to those with a tumor length >2 cm (29%).

Multiple biopsies (6–8), using standard-size endoscopy forceps, should be performed to provide sufficient material for histologic interpretation.[71] High-resolution endoscopy and narrow-band imaging may enhance visualization during endoscopy, with improved detection of lesions in the esophagus and stomach.[182,183] 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 (≤2 cm) 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.[184-186] The depth of tumor invasion, evidence of LVI, and the status of resection margins have been identified as the strongest predictors of OS.[187-189] ER may be potentially therapeutic when a lesion ≤2 cm in diameter is fully removed with clear lateral and deep margins and histopathologic assessment demonstrates well or moderate differentiation, invasion no deeper than the superficial submucosa, and no LVI.[187,190,191]

ER should also be considered in the treatment of Barrett's esophagus associated with HGD and patches of squamous cell dysplasia, specifically focusing on areas of nodularity or ulceration. Pathologists should provide an assessment of the depth of tumor invasion 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.

Staging

EUS performed prior to any treatment provides evidence of the depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes

likely to harbor cancer (N), and signs of metastasis, such as lesions in surrounding organs (M).[185,192,193] ER should be performed for small nodular lesions (≤2 cm), as it provides more accurate depth of invasion information than EUS.[194,195] A decision to proceed with further treatment, such as ablation or surgical resection, would depend on the final pathologic assessment of the ER specimen.

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.[196] The combined use of EUS and FNA (EUS-FNA) has a greater accuracy than EUS alone in the evaluation of lymph node metastasis, especially in celiac lymph nodes.[197,198] In a study that compared the performance characteristics of CT, EUS, and EUS-FNA for preoperative nodal staging in 125 patients with esophageal cancer, EUS-FNA was more sensitive than CT (83% vs. 29%) and more accurate than CT (87% vs. 51%) or EUS (87% vs. 74%) for nodal staging.[199] FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. Review of CT and PET scans prior to EUS is recommended to become familiar with the nodal distribution for FNA biopsy.

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.

Treatment

Tis, HGD, and well to moderately differentiated lesions (pT1a or pT1b) without evidence of LVI or lymph node metastases can be effectively treated with ER and/or ablation.[188,200-204] Small flat lesions (≤2 cm) of Tis, HGD, or Barrett's esophagus associated with HGD should be treated by ER as it provides more accurate histologic assessment.[194] Larger flat lesions (>2 cm) can also be treated effectively with ER, but this is associated with a greater risk of complications.[173,205] Therefore, such lesions may be treated by ablation alone.[61,153,154,173]

The goal of ER and/or ablation is the complete removal or eradication of early-stage disease and Barrett's esophagus. Endoscopic therapy is preferred for patients with early-stage cancer (well or moderately differentiated Tis or T1a ≤2 cm), because the risk of lymph node metastases, local or distant recurrence, and death from esophageal cancer following endoscopic therapy is low.[201,202] 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.

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 for dysphagia can be achieved with endoscopic tumor ablation, PDT and cryoablation, or endoscopic placement of self-expanding metal stents (SEMS).[206] 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 esophagogastrectomy since it may compromise the gastric vasculature and interfere with the use of the stomach as a conduit.

Surveillance

Endoscopic surveillance following definitive treatment of esophageal and EGJ cancers requires careful attention to detail for mucosal surface changes and multiple biopsies of any visualized abnormalities. EUS performed in conjunction with endoscopy has a high sensitivity for detecting recurrent disease.[207] EUS-FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging. Endoscopic surveillance after completion of ER or ablation for early-stage disease should also include a search for the presence of Barrett's esophagus and four-quadrant biopsies to detect residual or recurrent dysplasia. 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. The ablation of residual or recurrent HGD and LGD using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett's esophagus is not recommended. See *Principles of Surveillance* in the algorithm for more information.

Radiation Therapy

Several historical series have reported results of using RT alone to treat esophageal cancer patients with unfavorable features, such as clinical T4 cancer, and/or patients who are not medically fit for surgery.[208-210] Overall, the 5-year survival rate for patients treated with conventional doses of RT alone is 0% to 10%.[208-210] 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.[211] 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.[212] In the adjuvant setting, randomized trials have not shown a survival advantage for preoperative or postoperative RT.[213-215] A meta-analysis from the Oesophageal Cancer Collaborative Group showed no clear evidence of a survival advantage with preoperative RT.[216] Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

Brachytherapy alone 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).[217] 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.[218] 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 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. Experience with intraoperative RT as an alternative to EBRT in esophageal cancer is limited.[219]

Intensity-modulated RT (IMRT) has also been investigated in patients with esophageal cancer.[220-223] Retrospective studies comparing three-dimensional (3D) conformal RT (3D-CRT) vs. 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.[220,221] Additionally, Roeder et al reported that IMRT with concurrent systemic therapy in the definitive treatment of

esophageal cancer is feasible and yields good results with acceptable toxicity and low side effects to skin, lungs, and heart.[223]

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.[224,225] Therefore, the use of PBT may improve the therapeutic ratio by limiting cardiopulmonary toxicities while simultaneously delivering high radiation doses to the target area.[225-227] 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.[228] However, the number of patients in this study was very small. 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.[224] 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.[229,230]

Intensity-modulated proton beam therapy (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.[230] 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.[230] 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.[231] 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 diagnostic, staging, and treatment modalities. All available information from pretreatment diagnostic studies should be used to determine the target volume. Image guidance may be used appropriately to enhance clinical targeting.

A dose range of 41.4 to 50.4 Gy (delivered in fractions of 1.8–2 Gy per day) is recommended by the panel for preoperative RT. Nonsurgical candidates should receive RT doses of 50 to 50.4 Gy because lower doses may not be adequate. The recommended dose ranges for postoperative and definitive RT are 45 to 50.4 Gy and 50 to 50.4 Gy, respectively. For definitive therapy, higher doses (60–66 Gy) may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned.[232] However, there is no evidence from randomized trials to support the additional benefit of this higher dose range.[233]

Simulation and Treatment Planning

It is optimal to treat patients in the supine position as this setup is generally more stable and reproducible. CT simulation and conformal treatment planning should be used. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid in target localization. The use of an immobilization device is strongly recommended for reproducibility. 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 be used to create an internal target volume (ITV) from which subsequent clinical target volume (CTV) and planning target volume (PTV) can be made.

IMRT may be used in clinical settings where dose reduction to organs at risk is required and cannot be achieved by 3D techniques.[220,221] Target volumes need to be carefully defined and encompassed when designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion should be taken into account. 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. Since data regarding PBT techniques are early and emerging, the panel recommends that patients be treated with PBT within a clinical trial.

Target Volume

The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified by pre-treatment diagnostic studies such as CT scan, barium swallow, EUS, and/or PET/CT scans. The CTV is defined as the primary tumor plus a 3- to 4-cm superior and inferior expansion and a 1-cm radial expansion. The nodal CTV includes a 0.5- to 1.5-cm expansion from the nodal GTV. The CTV should also include areas at risk for microscopic disease and elective nodal regions such as the celiac axis. The PTV should include the CTV plus an expansion margin of 0.5 to 1 cm. See *Principles of Radiation Therapy* in the algorithm for more information.

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. Additionally, effort should be made to keep RT doses to the left ventricle of the heart to a minimum.

Lung dose may require particular attention, especially in the preoperatively treated patient. Normal lung (>2 cm outside the target volume) should not receive >40 Gy. Lung dose-volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients treated with concurrent chemoradiation. To reduce the incidence of postoperative pulmonary complications, the proportion of total lung receiving 5 Gy should be limited to 50% and the proportion of total lung receiving 20 Gy should be limited to 20%. However, it is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances. Optimal criteria for DVH parameters are actively being developed by NCCN Member Institutions.

Supportive Care

Careful monitoring and management of acute toxicities with aggressive supportive care is essential to avoid treatment interruptions or dose reductions. Prophylactic antiemetics should be given when appropriate. Additionally, antacid and antidiarrheal medications may be prescribed

when needed. If the caloric intake is inadequate (<1500 kcal/d), oral and/or enteral nutrition should be considered. Feeding jejunostomies or nasogastric feeding tubes may be placed if clinically indicated. Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery.

Combined Modality Therapy

Combined modality therapy has been employed for the treatment of esophageal and EGJ cancers because of the poor OS rates in patients who have been treated with resection alone.[234] Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ. Perioperative chemotherapy is an alternative option for adenocarcinomas of the distal esophagus and EGJ (see *Perioperative Chemotherapy* below).

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgical resection is the most common treatment approach for patients with resectable esophageal cancer.[235] The results of two meta-analyses have shown that preoperative chemoradiation significantly reduced 3-year mortality and locoregional recurrence rates when compared with surgery alone.[236,237] Another meta-analysis involving 1854 patients across 12 randomized trials showed a significant survival benefit for preoperative chemoradiation versus surgery alone in patients with resectable adenocarcinoma of the esophagus.[238] Additionally, Swisher et al reported that preoperative chemoradiation was associated with increased pCR (28% vs. 4%) and 3-year OS (48% vs. 29%) when compared with preoperative chemotherapy in patients with locally advanced esophageal cancer.[239]

Results from the multicenter phase III randomized CROSS trial, the largest trial in its class, showed that preoperative chemoradiation with carboplatin and paclitaxel significantly improved OS and disease-free survival (DFS) compared to surgery alone in patients with resectable (T2-3,N0-1,M0) esophageal or EGJ cancers (368 patients; 75% had adenocarcinoma and 23% had SCC).[118] Median survival time was 49 months in the preoperative chemoradiation arm compared to 24 months in the surgery alone arm. The R0 resection rate was also higher in the preoperative chemoradiation arm compared to the surgery alone arm (92% vs. 69%, respectively). The 1-, 2-, 3-, and 5-year survival 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% and 23%, respectively; $P = .008$), the histologic type was not a prognostic factor for survival. 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. Additionally, preoperative chemoradiation significantly reduced locoregional recurrence from 34% to 14% ($P < .001$) and peritoneal carcinomatosis from 14% to 4% ($P < .001$).[240] A study reporting the long-term results of the CROSS trial verified that median overall survival (OS) was significantly improved in the preoperative chemoradiation group after a median follow-up time of 84.1 months, confirming the OS benefits for chemoradiation therapy when added to surgery in patients with resectable esophageal or EGJ cancers.[241]

CALGB 9781 was a prospective Intergroup trial that randomized patients with stage I-III esophageal cancers to receive preoperative chemoradiation with cisplatin and fluorouracil or surgery alone.[242] After a median follow-up time of 6 years, an intent-to-treat analysis showed a median survival of 4.5 years versus 1.8 years in favor of preoperative

chemoradiation. Patients receiving preoperative chemoradiation also had a significantly better 5-year OS rate (39% vs. 16%). In contrast, the results of another randomized controlled trial (FFCD 9901) showed that preoperative chemoradiation with cisplatin and fluorouracil did not improve the rates of OS, or R0 resection, compared with surgery alone in patients with localized stage I or II esophageal cancer.[243] After a median follow-up of 93.6 months, the rate of R0 resection was 93.8% for preoperative chemoradiation versus 92.1% for surgery alone (*P* = .749), while the 3-year OS rates were 47.5% and 53.0%, respectively (*P* = .94). Furthermore, preoperative chemoradiation was associated with an enhanced postoperative mortality rate (11.1% vs. 3.4% for surgery alone; *P* = .049). Preoperative chemoradiation with cisplatin and fluorouracil also did not show any survival benefit when compared to preoperative chemotherapy in a phase II randomized study involving patients (n = 75) with resectable adenocarcinoma of the esophagus and EGJ.[244] The median PFS was 26 months and 14 months for preoperative chemotherapy and preoperative chemoradiation, respectively (*P* = .37). The corresponding median OS was 32 months and 30 months, respectively (*P* = .83). However, the pathologic response rate (31% vs. 8%; *P* = .01) and R1 resection rate (0% vs. 11%; *P* = .04) favored preoperative chemoradiation therapy.

The effectiveness of preoperative chemoradiation therapy in patients with locally advanced SCC of the esophagus has also been evaluated in randomized trials.[245,246] Stahl et al randomized 172 esophageal SCC patients to receive either induction chemotherapy followed by preoperative chemoradiation or induction chemotherapy followed by chemoradiation alone.[245] 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.[247] The FFCD 9102 trial also showed that adding surgery to chemoradiation provides no benefit compared to treatment with additional chemoradiation alone, especially in patients with locally advanced SCC of the esophagus who respond to initial chemoradiation therapy.[246] However, this trial suffered from suboptimal design and low number of patients. A meta-analysis by Vellayappan et al analyzed randomized controlled trials comparing chemoradiation plus surgery with chemoradiation alone in patients with at least T3 and/or N+ thoracic esophageal cancer (93% had SCC).[248] 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).[249] However, meta-analyses should be regarded as hypothesis-generating and cannot change the standard of care.

PROTECT is an ongoing prospective, randomized, multicenter phase II trial comparing two preoperative chemotherapy regimens (carboplatin plus paclitaxel vs. FOLFOX) in resectable stage IIB and stage III esophageal and EGJ cancers of SCC or adenocarcinoma histology.[250] Patients will be randomized to receive either 3 cycles of FOLFOX or combined carboplatin and paclitaxel with concurrent RT (41.4 Gy) followed by surgery. This trial will directly compare two standards of preoperative chemotherapy delivered with a common regimen of preoperative RT, in the setting of resectable, locally advanced

esophageal or EGJ cancers. Participation in this trial is highly encouraged (Clinical Trial ID: NCT02359968).

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Preoperative sequential chemotherapy followed by chemoradiation has also been evaluated in clinical trials for patients with locally advanced esophageal and EGJ cancers.[251-259] In a phase III study, Stahl et al compared preoperative chemotherapy (cisplatin, fluorouracil, and leucovorin) with preoperative chemoradiation therapy using the same regimen in 119 patients with locally advanced adenocarcinoma of the lower esophagus or EGJ.[255] 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 significantly 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 survival 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.[256] R0 resection was achieved in 65% of patients and the median survival and actuarial 2-year survival rates were 14.5 months and 35%, respectively.[256] In another phase II trial that evaluated preoperative chemotherapy with irinotecan and cisplatin followed by chemoradiation for esophageal and EGJ cancers, 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.[258]

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.[257] 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.[259] Therefore, induction chemotherapy prior to preoperative chemoradiation therapy is feasible and may be appropriate for select patients. However, this approach needs to further evaluated in phase III randomized clinical trials.

Postoperative Chemoradiation Therapy

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effectiveness of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[260] In this trial, 556 patients (stage IB to IV, M0) were randomized to receive surgery plus postoperative chemoradiation (n = 281; bolus fluorouracil plus leucovorin before and after concurrent chemoradiation with the same regimen) or surgery alone (n = 275). The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%). Median OS in the surgery-only group was 27 months compared to 36 months in the postoperative chemoradiation group (P = .005). The chemoradiation group also had better 3-year OS (50% vs. 41%) and recurrence-free survival (RFS) rates (48% vs. 31%) than the

surgery-only group. There was also a significant decrease in local failure as the first site of failure (19% vs. 29%) in the chemoradiation group. With a median follow-up time of over 10 years, survival remained improved in patients treated with postoperative chemoradiation. No increases in late toxic effects were noted.[261] 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).[262]

The results of the INT-0116 trial have established postoperative chemoradiation as a standard of care in patients with completely resected gastric or EGJ adenocarcinoma who have not received preoperative therapy. However, the dosing schedule of chemotherapy agents used in this trial was associated with high rates of grade 3 or 4 hematologic and GI toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group, 17% discontinued treatment and 3 patients died as a result of chemoradiation-related toxicities, including pulmonary fibrosis, cardiac event, and myelosuppression. Therefore, the doses and schedule of chemotherapy agents used in the INT-0116 trial are no longer recommended due to concerns regarding toxicity. See *Principles of Systemic Therapy- Regimens and Dosing Schedules* in the algorithm for modifications to this regimen recommended by the panel.

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, freedom from recurrence, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively, for patients with node-positive tumors (T3 or T4), which were better than the historical outcomes observed with surgery alone.[263] While the addition of postoperative chemoradiation has been associated with survival benefits in patients with lymph node-positive locoregional esophageal cancer,[264,265] 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.

Definitive Chemoradiation Therapy

Chemoradiation therapy vs. RT alone, each without resection, was studied in a randomized trial (RTOG 85-01) involving patients with esophageal SCC or adenocarcinoma (clinical stage T1-3, N0-1, M0).[212,266] Patients in the chemoradiation arm received 4 cycles of fluorouracil and cisplatin with RT (50 Gy at 2 Gy per day) given concurrently with day 1 of chemotherapy, while patients in the control arm received RT alone (64 Gy).[212,266] Patients who received combined modality therapy 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 combined modality arm (47% vs. 65%).

In a follow-up trial, INT-0123 compared two different RT doses used with the same chemotherapy regimen (fluorouracil and cisplatin).[233] In this trial, 218 esophageal cancer patients with either SCC (85%) or adenocarcinoma (15%) (clinical stage T1-4,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 survival (31% vs. 40%), or locoregional failure (56% vs. 52%) rates between the high-dose and standard-dose RT arms. The results of these two studies established

definitive chemoradiation with fluorouracil and cisplatin using the RT dose of 50.4 Gy as the standard of care for patients with SCC or adenocarcinoma of the esophagus.

Reports have also confirmed the efficacy of definitive chemoradiation using other chemotherapy regimens.[267-269] Definitive chemoradiation with docetaxel and cisplatin resulted in a high overall response rate (ORR) (98%; 71% complete response) and a median OS of 23 months in patients with esophageal SCC.[267] The rates of locoregional progression-free survival (PFS), PFS, and 3-year OS were 60%, 29%, and 37%, respectively. Definitive chemoradiation with carboplatin and paclitaxel resulted in superior OS, disease-specific survival, durable locoregional control, and palliation in about 50% of patients with unresectable esophageal cancer.[268] Definitive chemoradiation using the FOLFOX regimen (fluorouracil, leucovorin, and oxaliplatin) has also been proven effective. In a randomized phase III trial, 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.[269] The median PFS was 9.7 months in the FOLFOX group compared to 9.4 months in the fluorouracil and cisplatin group (P = .64).[269] Although definitive chemoradiation with FOLFOX was not associated with a PFS benefit compared to chemoradiation with 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.

Chemotherapy

Preoperative Chemotherapy

Clinical trials have investigated chemotherapy alone in the preoperative setting.[270-273] In the Medical Research Council OEO2 trial, 802 patients with potentially resectable esophageal cancer were randomly assigned to receive either 2 cycles of preoperative fluorouracil and cisplatin followed by surgery or surgery alone.[270] Median survival was 16.8 months in the preoperative chemotherapy group compared with 13.3 months in the surgery alone group (95% CI, 30–196), and 2-year survival rates were 43% and 34%, respectively (95% CI, 3–14). At a median follow-up of 6 years, DFS and OS were also significantly longer for the preoperative chemotherapy group, and these differences were consistent across SCC and adenocarcinoma patients.[270,271] Long-term follow-up confirmed the survival benefit of preoperative chemotherapy in patients with resectable esophageal cancer, with a 23.0% 5-year survival rate in the preoperative chemotherapy group compared to 17.1% in the surgery alone group (hazard ratio [HR] = 0.84; 95% CI, 0.72–0.98; P = .03).[271] However, this trial had several limitations, including the exclusion of patients accrued in China and the fact that nearly 10% of patients received off-protocol preoperative RT.

The Medical Research Council OEO5 trial compared preoperative chemotherapy with 4 cycles of epirubicin, oxaliplatin and capecitabine (ECX) to 2 cycles of cisplatin and fluorouracil followed by surgery in 897 patients with lower esophageal and EGJ adenocarcinoma. Although there was a trend towards prolonged PFS and DFS with ECX, this did not translate into an OS benefit.[273] Furthermore, ECX was associated with a higher toxicity than cisplatin and fluorouracil (47% vs. 30% grade 3/4 toxicities; P < .001). Therefore, the panel recommends preoperative chemotherapy with fluorouracil and cisplatin for adenocarcinoma of the thoracic esophagus or EGJ (category 2B).

Perioperative Chemotherapy

The survival benefit of perioperative chemotherapy in gastroesophageal cancers was first demonstrated in the landmark phase III MAGIC trial.[274] This study, which compared perioperative chemotherapy with

epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improved OS and PFS in patients with non-metastatic stage II and higher gastric and EGJ adenocarcinoma. In the phase II/III AIO-FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen with a primary endpoint of pathologic complete regression of the primary tumor.[120] Patients with resectable non-metastatic gastric or EGJ adenocarcinoma (≥cT2 and/or N+) were randomized to receive either 3 preoperative and 3 postoperative cycles of ECF (n = 137) or 4 preoperative and 4 postoperative cycles of FLOT (n = 128). In a report of the findings from the phase II part of the trial, FLOT was associated with significantly higher proportions of patients achieving pathologic complete regression than as for ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; *P* = .02).[120] 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). Therefore, perioperative chemotherapy with FLOT has largely replaced ECF due to its increased efficacy and similar safety profile. The phase III part of this trial is ongoing (Clinical Trials ID: NCT01216644). 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 patients with poor 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 (2 or 3 preoperative cycles and 3 or 4 postoperative cycles) significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[119] At the median follow-up time 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 fluorouracil and cisplatin is a viable treatment option for patients with locally advanced resectable gastroesophageal cancers.

Chemotherapy for Locally Advanced or Metastatic Disease

In randomized clinical trials, no consistent benefit has been seen for any specific chemotherapy regimen and chemotherapy has shown no survival benefit compared to best supportive care for patients with advanced or metastatic esophageal cancer.[275] Palliative chemotherapy is not known to provide any survival advantage, but it may improve quality of life in patients with metastatic or unresectable disease.[276] Cisplatin is one of the most active agents in the treatment of esophageal cancer, with a single-agent response rate consistently in the range of ≥20%.[277] Several other agents including irinotecan,[278-280] docetaxel,[281,282] and paclitaxel[283,284] have also shown single-agent activity in patients with advanced or metastatic esophageal cancer. Cisplatin plus fluorouracil is the most investigated combination regimen for patients with esophageal cancer, with response rates of 20% to 50%.

Cisplatin in combination with fluorouracil, with or without docetaxel, has also demonstrated activity in patients with locally advanced or metastatic esophagogastric cancers.[285-289] In a randomized multinational phase III study (V325), 445 previously untreated patients were randomized to receive either docetaxel, cisplatin, and fluorouracil (DCF) or cisplatin and fluorouracil (CF) every 3 weeks.[286] The majority of patients had advanced gastric adenocarcinoma and 19%–25% of patients had EGJ adenocarcinoma. At a median follow-up time of 13.6

months, time to progression and OS were significantly longer in the DCF group compared to the CF group (5.6 months vs. 3.7 months and 9.2 months vs. 8.6 months, respectively). At a median follow-up time of 23.4 months, the overall confirmed response rate was also significantly higher with DCF than CF (37% vs. 25%).[286] The 2-year survival rates for DCF and CF were 18% and 9%, respectively. However, DCF was associated with increased myelosuppression and infectious complications. Additionally, grade 3 or 4 toxicities occurred in 69% of patients in the DCF arm versus 59% of patients in the CF arm. The most frequent grade 3 or 4 toxicities in both treatment arms (DCF vs. CF) were neutropenia (82% vs. 57%), stomatitis (21% vs. 27%), diarrhea (19% vs. 8%), lethargy (19% vs. 14%), and complicated neutropenia (29% vs. 12%).

Various modifications of the DCF regimen have demonstrated efficacy and improved safety in clinical trials of patients with advanced esophagogastric cancers compared to the DCF regimen evaluated in the V325 study.[289-291] In a randomized phase II trial that evaluated the efficacy and tolerability of docetaxel plus oxaliplatin with or without infusional fluorouracil or capecitabine in patients with metastatic or locally recurrent gastric adenocarcinoma (including adenocarcinoma of the EGJ), docetaxel, oxaliplatin, and fluorouracil had a better safety profile and was associated with a higher response rate, and longer median PFS and OS (47%, 7.7 months and 14.6 months, respectively) compared to docetaxel and oxaliplatin (23%, 4.5 months and 9 months, respectively) or docetaxel, oxaliplatin, and capecitabine (26%, 5.6 months and 11.3 months, respectively).[290] The frequency of grade 3 or 4 toxicities was lower among patients treated with docetaxel, oxaliplatin, and fluorouracil (25%) compared to those treated with docetaxel and oxaliplatin (37%) or docetaxel, oxaliplatin, and capecitabine (38%). Febrile neutropenia was reported in only 2% of patients treated with docetaxel, oxaliplatin, and fluorouracil (compared to 14% and 9% for docetaxel/oxaliplatin and docetaxel/oxaliplatin/capecitabine, respectively), which is much lower than the 16.4% reported with DCF in the V325 trial.

In another randomized multicenter phase II study, a dose-modified DCF regimen was less toxic than standard DCF (even when given with growth factors) and was also associated with improved efficacy in previously untreated patients with metastatic gastric or EGJ adenocarcinoma.[291] In this study, 85 patients were randomized to receive dose-modified DCF (docetaxel 40 mg/m^2, cisplatin 40 mg/m^2, and fluorouracil 2000 mg/m^2; n = 54) or the standard DCF regimen (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and fluorouracil 750 mg/m^2 with growth factor support; n = 31). The standard DCF arm closed early due to toxicity (71% grade 3 to 4 toxicity within 3 months and 90% grade 3 to 4 toxicity over the course of treatment). In the dose-modified DCF arm, the grade 3 or 4 toxicity rates were 54% within the first 3 months and 76% over the course of treatment. The 6-month PFS rate was 63% for dose-modified DCF and 53% for standard DCF. Dose-modified DCF was also associated with improved median OS (18.8 months vs. 12.6 months; *P* = .007). Due to concerns regarding toxicity, the NCCN Panel does not recommend the standard DCF regimen as used in the V325 trial.[286] Therefore, dose-modified DCF or other DCF modifications should be used as alternative options for first-line therapy.[290,291]

The combination of fluorouracil, oxaliplatin, and leucovorin (FOLFOX) has been evaluated as an alternative to cisplatin-based regimens in patients with advanced or metastatic gastroesophageal cancers.[289,292] A phase III trial conducted by the German Study Group 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) compared to fluorouracil, leucovorin, and cisplatin (FLP) in

patients with metastatic esophagogastric cancer.[289] However, no significant difference was seen in median OS (10.7 vs. 8.8 months) between the two arms. In patients >65 years, FOLFOX resulted in significantly superior response rates (41.3% vs. 16.7%), time to treatment failure (5.4 vs. 2.3 months), PFS (6.0 vs. 3.1 months), and OS (13.9 vs. 7.2 months) compared with FLP.

Recommendations for the use of capecitabine-based regimens as first-line therapy for advanced or metastatic esophageal or EGJ cancers have been extrapolated from trials involving patients with advanced gastric cancer.[293-296] A phase III randomized trial (ML 17032) evaluated the efficacy of combined capecitabine and cisplatin (XP) compared to fluorouracil and cisplatin (FP) as first-line therapy in patients with previously untreated advanced gastric cancer.[295] ORR (41% vs. 29%) and OS (10.5 months vs. 9.3 months) were superior for patients who received the XP regimen. However, no difference in median PFS was observed (5.6 months for XP and 5.0 months for FP). A meta-analysis of the REAL-2 and ML17032 trials suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared to the 664 patients treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.[297] These results suggest that capecitabine may be as effective as fluorouracil in the treatment of patients with advanced gastroesophageal cancers.

Irinotecan-based combination regimens have been evaluated in prospective studies involving patients with advanced or metastatic esophageal and EGJ cancers.[298-304] The results of a randomized phase III study in patients with advanced gastric or EGJ adenocarcinoma (n = 337) showed that irinotecan in combination with fluorouracil and leucovorin (FOLFIRI) was non-inferior to CF in terms of PFS (PFS at 6 and 9 months was 38% and 20%, respectively, for IF compared to 31% and 12%, respectively, for CF), but not in terms of OS (9 months vs. 8.7 months) or time to treatment progression (5 months vs. 4.2 months).[299] FOLFIRI was also associated with a more favorable toxicity profile. A more recent phase III trial (French Intergroup Study) compared FOLFIRI with ECF as first-line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[304] In this study, 416 patients (65% had gastric adenocarcinoma and 33% had EGJ adenocarcinoma) were randomized to receive either FOLFIRI or ECF. After a median follow-up time 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).[304] 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. A phase II trial by Wolff et al showed that FOLFIRI is also active in patients with locally advanced or metastatic SCC or adenocarcinoma of the esophagus (n = 25).[300] Partial response was achieved in 33% of patients; 38% had stable disease and 8% had progressive disease. Median survival was 20 months and 10 months, respectively, for patients with adenocarcinoma and SCC. Therefore, the NCCN Panel feels that FOLFIRI is an acceptable first-line therapy option for patients with advanced or metastatic EGJ adenocarcinoma. Second-line therapy with irinotecan in combination with fluorouracil, docetaxel, or capecitabine has also demonstrated activity in patients with advanced or metastatic esophagogastric cancer that had progressed on platinum-based chemotherapy.[301,305,306]

Targeted Therapies

The targeted therapies trastuzumab, ramucirumab, and pembrolizumab have been approved for the treatment of advanced or metastatic gastroesophageal cancers.[113,117,307,308] A variety of investigational

agents targeting EGFR and c-MET have also shown encouraging results in patients with advanced or metastatic esophageal and EGJ cancers.[309-315] However, definite results of these ongoing studies are not yet available.

Trastuzumab

The ToGA trial was the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[113] In this trial, 594 patients with HER2-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.[113] 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 compared to chemotherapy alone in patients with HER2 overexpression or amplification (13.8 vs.11 months, respectively; *P* = .046). This study established trastuzumab in combination with chemotherapy as the standard of care for patients with HER2-positive advanced or metastatic gastric or EGJ adenocarcinoma. However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3+ or IHC 2+ and FISH positivity. In a post-hoc subgroup analysis, the addition of trastuzumab to chemotherapy substantially improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR = .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).

In a retrospective study of 34 patients with metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen improved tolerability compared with cisplatin plus fluorouracil in untreated patients with HER2-positive tumors.[316] 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 to 4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combination of mFOLFOX6 and trastuzumab is an effective regimen with an acceptable safety profile and warrants further study in patients with HER-2+ gastroesophageal cancers.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown promising results in patients with previously treated advanced or metastatic gastroesophageal cancers in phase III clinical trials.[307,308] 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.[307] In this study, 355 patients were randomized to receive ramucirumab (n = 238; 178 had gastric cancer and 60 had EGJ adenocarcinoma) or placebo (n = 117; 87 had gastric cancer and 30 had EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). The ramucirumab group was associated with higher rates of hypertension than the placebo group (16% vs. 8%), whereas rates of other adverse events were similar between the two groups.

In a more recent international phase III randomized trial (RAINBOW) that evaluated paclitaxel with or without ramucirumab in patients (n = 665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy, the combination of paclitaxel with ramucirumab

resulted in significantly higher OS, PFS, and ORR than paclitaxel alone.[308] 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, for the two treatment groups. Additionally, the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone (*P* = .0001). However, neutropenia and hypertension were more common with ramucirumab plus paclitaxel. Based on the results of these two studies, 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.

Pembrolizumab

Pembrolizumab is a PD-1 antibody that was approved by the FDA 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.[116] This first-ever tissue- and site-agnostic approval was based on several clinical trials that demonstrated the efficacy of pembrolizumab in MSI-H/dMMR solid tumors, including the KEYNOTE-016 trial.[317-319]

KEYNOTE-016 is a multicenter, open-label, phase II trial that evaluated the activity of pembrolizumab in patients with metastatic treatment-refractory dMMR colorectal cancers, MMR-proficient colorectal cancers, or dMMR non-colorectal cancers who had received at least two previous lines of chemotherapy. The immune-related ORR for patients with dMMR non-colorectal cancers was 71%, with an immune-related PFS rate of 67% at 20 weeks.[317] Median PFS was 5.4 months. Adverse events of clinical interest included rash or pruritus (24%, any grade); thyroiditis, hypothyroidism, or hypophysitis (10%, any grade); and asymptomatic pancreatitis (15%, any grade), which were similar to those reported in other trials involving pembrolizumab. In a recently reported expansion of this study, data from 86 patients with dMMR tumors representing 12 different cancer types achieved an ORR of 53% with 21% of patients achieving a complete response.[318] While median PFS and OS have not yet been reached, estimates of these outcomes at 1 and 2 years are 64% and 53% for PFS and 76% and 64% for OS, respectively. The KEYNOTE-016 trial is still recruiting patients at several institutions (Clinical Trial ID: NCT01876511).

Another 2017 pembrolizumab approval was for the treatment of patients with recurrent, locally advanced, or metastatic PD-L1-positive gastric or EGJ adenocarcinoma, who have progressed following two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2-targeted therapy.[117] This approval was based on the results of two KEYNOTE studies (KEYNOTE-012 and KEYNOTE-059). KEYNOTE-012 was a multicenter, open-label, phase Ib study that evaluated the safety and activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic gastric or EGJ adenocarcinoma.[320] The ORR was 22% and 13% of patients had grade 3 or 4 treatment-related adverse events including fatigue, pemphigoid, hypothyroidism, peripheral sensory neuropathy, and pneumonitis. The results of this trial justified the study of pembrolizumab monotherapy in cohort 1 of the phase II KEYNOTE-059 trial, which included 259 patients with gastric or EGJ adenocarcinoma who had progressed on two or more prior lines of therapy.[321] Of those with PD-L1–positive tumors (57.1%; n = 143), the ORR was 15.5% (95% CI, 10.1–22.4), with 2% (95% CI, 0.4–5.8) of patients achieving a complete response. Median duration of response

was 16.3 months. Analysis of cohorts 2 and 3 of the KEYNOTE-059 trial, which examine the efficacy of first-line pembrolizumab as a monotherapy or in combination with chemotherapy, is ongoing (Clinical Trial ID: NCT02335411).[322-324]

Recently, Doi et al analyzed preliminary data from the advanced esophageal cancer cohort (n = 23) of the KEYNOTE-028 trial, a multi-cohort phase Ib trial of pembrolizumab in patients with PD-L1–positive advanced solid tumors that have failed to respond to first-line therapy.[325] In patients with SCC or adenocarcinoma of the esophagus or EGJ, the ORR was 30% and the median duration of response was 15 months. By histologic subtype, the ORR was 28% for patients with SCC and 40% for patients with adenocarcinoma. Median PFS was 1.8 months (95% CI, 1.7–2.9) and the 6- and 12-month PFS rates were 30% and 22%, respectively. Median OS was 7 months (95% CI, 4.3–17.7) and the 6- and 12-month OS rates were 60% and 40%, respectively. Grade 3 immune-mediated adverse events, including decreased appetite (4%) and decreased lymphocyte count (9%), occurred in 17% of patients, but no grade 4 adverse events have been reported. A phase II trial involving patients with PD-L1–positive advanced solid tumors that failed to respond to first-line therapy is currently recruiting patients (KEYNOTE-158; Clinical Trial ID: NCT02628067).

Based on the KEYNOTE trials, pembrolizumab shows manageable toxicity and promising antitumor activity in patients with heavily pretreated PD-L1–positive or MSI-H/dMMR advanced esophageal or EGJ adenocarcinoma. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing clinical trials of pembrolizumab in patients with esophageal or EGJ cancers.

Other Immunotherapies

Preliminary studies have demonstrated the activity of nivolumab (a PD-1 antibody) and ipilimumab (a CTLA-4 antibody) for the treatment of advanced, recurrent, or metastatic gastric, esophageal, and EGJ cancers.[326-330] While these data are encouraging, the panel considers these studies too preliminary for inclusion in the guidelines and will reevaluate once more mature data become available.

The safety and activity of nivolumab in patients with treatment-refractory esophageal SCC was investigated in an open-label, single-arm, phase II trial.[326] Patients (n = 64) were given nivolumab intravenously every 2 weeks in 6-week cycles. At a median follow-up time of 10.8 months, the ORR was 17%. The most common grade 3 or 4 adverse events were dyspnea and hyponatremia (2% each), lung infection (8%), decreased appetite (3%), increased blood creatinine phosphokinase (3%), and dehydration (3%).

CheckMate-032 is an ongoing phase I/II open-label study to evaluate the safety and activity of nivolumab alone or in combination with ipilimumab for advanced or metastatic gastric, esophageal, and EGJ cancers.[327] Patients, irrespective of PD-L1 status, were treated with nivolumab 3 mg/kg (N3, n = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1 + I3, n = 49), or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3 + I1, n = 52). The ORR for each treatment group was 12%, 24%, and 8% for N3, N1+I3, and N3+I1, respectively. Among PD-L1–positive patients, the ORR was 19%, 40%, and 23%, respectively, in each treatment group. OS among PD-L1–positive patients was 6.2 and 5.6 months, respectively, for N3 and N3+I1, while OS was not reached in the N1+I3 treatment group. Treatment-related adverse events were consistent with previous reports, with serious events occurring in 10%, 43%, and 23% of patients treated with N3, N1+I3, and N3+I1, respectively. Although encouraging in combination with

nivolumab, ipilimumab monotherapy has not shown any benefit in the treatment of esophageal or EGJ cancers. A phase II trial comparing ipilimumab to best supportive care for treatment of gastric or EGJ cancers following first-line chemotherapy showed no significant improvement in OS or PFS for patients treated with ipilimumab.[329,330]

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. 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. If the cancer 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. EUS and PET/CT evaluation from skull base to mid-thigh is recommended if metastatic disease is not evident. PET/CT scans are also useful for the evaluation of patients after chemoradiation prior to surgery for the detection of distant lymphatic and hematogenous metastases.[331-333] HER2, MSI-H/dMMR, and PD-L1 testing are recommended if metastatic disease is documented or suspected. Assessment of Siewert tumor type should also be included as part of the initial workup in all patients with EGJ adenocarcinoma.[48,49] 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–III)
- Metastatic cancer (stage IV)

Additional Evaluation

Additional evaluations are warranted to assess a patient's medical condition, his/her ability to tolerate major surgery, and the feasibility of resection (especially for patients with celiac-positive disease). These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. An enteric feeding tube should be considered for preoperative nutritional support. Jejunostomy tube is preferred, but PEG tube may be considered for patients with cervical esophageal cancer receiving definitive chemoradiation or for patients

with marginally resectable disease. Multidisciplinary expertise is recommended prior to placement of a PEG tube. Histologic evaluation is required for correct diagnosis of SCC or adenocarcinoma. Laparoscopy is optional for EGJ adenocarcinoma if there is no evidence of metastatic disease. Evaluation of the colon using barium radiograph or colonoscopy may be warranted if colon interposition is planned as part of the surgical procedure. A superior mesenteric artery angiogram should be considered only in 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)

Primary Treatment

Medically Fit Patients: Squamous Cell Carcinoma

ER with or without ablation is the preferred primary treatment option for patients with Tis or T1a tumors (well- or moderately differentiated lesions ≤2 cm in diameter). Ablation alone may be appropriate for patients with Tis tumors. Available evidence (although very limited) indicates that ablation following ER may be effective for the complete removal of early-stage SCC of the esophagus.[153,334] Esophagectomy is indicated for patients with extensive Tis or superficial T1a tumors, especially nodular disease that is not adequately controlled by ER with ablation.[187] Esophagectomy is the recommended primary treatment option for patients with T1b, N0 tumors.[187]

Primary treatment options for patients with T1b–T4a, N+ tumors include preoperative chemoradiation (for non-cervical esophagus),[245,246] definitive chemoradiation (only for patients who decline surgery; recommended for cervical esophagus),[233,266,335] or esophagectomy (for non-cervical esophagus in patients with low-risk [T1b–T2,N0] and well-differentiated lesions <2 cm in diameter). Definitive chemoradiation is also the primary treatment option for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in select patients.[336] Chemotherapy alone can be considered in the setting of invasion of the trachea, great vessels, or heart. See *Principles of Systemic Therapy* in the algorithm for a list of specific regimens.

Medically Fit Patients: Adenocarcinoma

Primary treatment options for patients with Tis, T1a or T1b, N0 adenocarcinoma are similar to those described above for SCC. Superficial T1b tumors may be controlled by ER followed by ablation, while more invasive T1b tumors may require esophagectomy. Esophagectomy is also indicated for any nodular disease that is not adequately controlled by ER with ablation.[187]

Primary treatment options for patients with T1b–T4a, N+ tumors include preoperative chemoradiation (category 1; preferred),[118] definitive chemoradiation (only for patients who decline surgery),[233,266,269] esophagectomy (for patients with low-risk [T1b–T2,N0] and well-differentiated lesions <2 cm in diameter), perioperative chemotherapy,[119,120] or preoperative chemotherapy. [273] Definitive chemoradiation is the primary treatment option for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in select patients.[336] Chemotherapy alone can be considered in the setting of invasion of the trachea, great vessels, or heart. See *Principles of Systemic Therapy* in the algorithm for a list of specific regimens.

Non-Surgical Candidates

ER with or without ablation is recommended for patients with Tis, T1a or T1b, N0 tumors. Ablation may not be needed if all lesions are completely excised by ER. Ablation alone may be an appropriate option for patients with Tis tumors.

Definitive chemoradiation is recommended for non-surgical candidates with T1b–T4b, 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. Assessment with PET/CT (preferred) or PET scan should be done ≥5 to 8 weeks after the completion of preoperative therapy. Chest/abdominal CT scan with contrast is recommended, but is not required if 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) or surveillance (category 2B) is recommended for patients with no evidence of disease following preoperative chemoradiation. Esophagectomy is recommended 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 recommended for those with persistent local disease. Alternatively, patients with persistent local disease or unresectable/metastatic disease following either preoperative or definitive chemoradiation should be managed with palliative care.

Postoperative Management

Postoperative management is based on surgical margins, 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 (for patients who have not received preoperative chemoradiation) and perioperative chemotherapy (for patients with adenocarcinoma of the distal esophagus or EGJ) comes from prospective randomized trials involving patients with gastric cancer that have included patients with adenocarcinoma of the distal esophagus or EGJ.[120,260]

Patients with SCC Who Have Not Received Preoperative Chemoradiation

Surveillance is recommended for patients with R0 resection, irrespective of their nodal status. Patients with R1 or R2 resection should be treated with chemoradiation. Alternatively, patients with R2 resection can receive palliative management.

Patients with SCC Who Have Received Preoperative Chemoradiation

Surveillance is recommended for patients with R0 resection, irrespective of their nodal status. Patients with R1 or R2 resection should be observed until disease progression or be placed under palliative management.

Patients with Adenocarcinoma Who Have Not Received Preoperative Chemoradiation or Chemotherapy

For patients with R0 resection and negative nodal status, surveillance is recommended. Alternatively, patients with T3–T4a tumors or select patients with T2 tumors (category 2B) can receive chemoradiation. For patients with R0 resection and positive nodal status, chemoradiation 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

Postoperative chemotherapy is recommended (category 1) for all patients with R0 resection who had received preoperative chemotherapy, irrespective of their nodal status.[119] Observation until progression is an alternative option for completely resected, node-negative patients. Chemoradiation, if not received preoperatively, is an alternative option for completely resected, node-positive patients (category 2B). However, this approach has not been evaluated in prospective studies.

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 local 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 the available evidence from retrospective studies[240,337-341] and expert consensus. Although ~90% of relapses occur within the first 2 years after the completion of local therapy, potentially actionable recurrences have sometimes been recognized >5 years after local therapy. Therefore, additional follow-up after 5 years may be considered based on risk factors and comorbidities. Differences in follow-up for early-stage esophageal cancer reflect a heterogeneous potential for relapse and OS.[156,342-347] For example, whereas fully treated Tis and T1a, N0 disease have a prognosis that approximates a non-cancer cohort, T1b disease does not perform as well. Thus, surveillance recommendations vary according to the depth of invasion and treatment modality.

In general, for asymptomatic patients, follow-up 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 clinical 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. In patients with early-stage tumors treated with esophagectomy, endoscopic surveillance with EGD should be performed as clinically indicated based on symptoms. Additionally, imaging (chest/abdominal CT with contrast unless contraindicated) should be routinely performed 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–T4,N0–N+,T4b)

Locoregional recurrence is common after bimodality therapy (definitive chemoradiation),[340] 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 tumors following bimodality therapy. Imaging studies (chest/abdominal CT with contrast unless contraindicated) should be considered every 6 months for 2 years, if the patient is likely to tolerate additional curative-intent therapy for recurrence.[340] 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.

However, EGD for surveillance is not recommended after trimodality therapy since locoregional recurrence is uncommon and most luminal recurrences can be detected by routine imaging studies.[240,338,339] 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 tumors following trimodality therapy. 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. When patients experience another recurrence after surgery, palliative management should be provided. Palliative management, which includes concurrent chemoradiation (preferred), chemotherapy, and best supportive care, is recommended for patients who develop a locoregional recurrence following prior esophagectomy, those who are medically unable to tolerate major surgery, and those who develop an unresectable or metastatic recurrence.

Best supportive care is always indicated for patients with unresectable, locally advanced, recurrent or metastatic disease. The decision to offer best supportive care alone or with chemotherapy is dependent upon the patient's performance status. The ECOG Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[348-350] ECOG PS is a 5-point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher ECOG PS scores are considered to have poorer performance status. KPS is an ordered scale with 11 levels (0%–100%) in which patients are classified based on their degree of functional impairment (activity, work, and self-care). Lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score <60% or an ECOG

PS score ≥3 should be offered best supportive care only. Chemotherapy can be offered in addition to best supportive care for patients with better performance status (KPS score ≥60% or ECOG PS score ≤2). Additionally, HER2 testing should be performed in esophageal and EGJ adenocarcinoma patients with better performance status (KPS score ≥60 or ECOG PS score ≤2), if not done previously and if metastatic disease is suspected. See *Best Supportive Care* below for more information.

First-line palliative chemotherapy with two-drug regimens is preferred for patients with advanced disease because of lower toxicity. Three-drug regimens should be reserved for medically fit patients with good performance status and access to frequent toxicity evaluation. Based on the results of the ToGA trial, the guidelines recommend the addition of trastuzumab to first-line chemotherapy for patients with HER2-positive metastatic adenocarcinoma (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents).[113] The use of trastuzumab in combination with anthracyclines is not recommended.

The selection of regimens for second-line or subsequent therapy for patients with advanced or metastatic disease is dependent upon prior therapy and performance status. Based on the available data and FDA approvals, the guidelines have included ramucirumab as a single agent or in combination with paclitaxel (both category 1 for EGJ adenocarcinoma; both category 2A for esophageal adenocarcinoma) as preferred options for second-line or subsequent therapy.[307,308] Docetaxel,[282,351] paclitaxel,[283,284,352] and irinotecan[352-355] as single agents are also included as category 1 preferred options for second-line or subsequent therapy. Fluorouracil in combination with irinotecan may be considered as a preferred second-line option if not previously used in first-line therapy.[305,353,356] Other regimens for second-line or subsequent therapy include irinotecan in combination with either cisplatin[298,357] or docetaxel[301] (category 2B). Pembrolizumab is an option for second-line and subsequent therapy for MSI-H/dMMR tumors.[318,320] Third-line and subsequent therapy options include pembrolizumab for PD-L1–positive adenocarcinoma[321] as well as regimens recommended for second-line therapy that were not previously used.

The survival benefit of palliative chemotherapy compared to best supportive care alone has been demonstrated in small cohorts of patients with lower esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma trials.[351,354] In a randomized phase III study, 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).[354] The study was closed prematurely due to poor accrual. Median survival was 4 months in the irinotecan arm compared to 2.4 months in the best supportive care arm. In an open-label, multicenter, phase III randomized trial, the addition of docetaxel to active symptom control was associated with a survival benefit for patients with advanced, histologically confirmed adenocarcinoma of the esophagus, EGJ, or stomach that had progressed on or within 6 months of treatment with combination chemotherapy (platinum and fluoropyrimidine).[351] In this study, patients (n = 168) with an ECOG PS score of 0 to 2 were randomized to receive docetaxel plus active symptom control or active symptom control alone. After a median follow-up time of 12 months, the median OS was 5.2 months for patients in the docetaxel group compared to 3.6 months for those in the active symptom control only group (P = .01). Docetaxel was associated with higher incidence of grade 3–4 neutropenia, infection, and febrile neutropenia; however, disease-specific, health-related quality-of-life measures showed benefits for docetaxel in reducing dysphagia and abdominal pain.

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 chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States.[358] There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of 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.[359-361] Finally, if none of the above options is available, treatment without leucovorin would be reasonable. Under this circumstance, a modest increase in fluorouracil dose (in the range of 10%) may be considered for patients who can tolerate this without grade 2 or higher toxicity.

Best Supportive Care

The goal of best supportive care is to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of disease stage. In patients with unresectable or locally advanced cancer, best supportive care provides symptom relief and may result in prolongation of life, improvement in nutritional status, and improvement in overall quality of life.

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Assessing the extent of disease and severity of swallowing impairment 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. Treatment options for the management of dysphagia should be individualized and a multimodality interdisciplinary approach is strongly encouraged.

Patients with dysphagia who are not candidates for surgery should be considered for palliation of their symptoms. Palliative management of dysphagia can be achieved through multiple modalities, though the placement of permanent or temporary SEMS is the most common and can achieve long-term results.[362] Temporary placement of SEMS with concurrent RT was found to improve survival rates when compared with permanent stent placement.[363] Membrane-covered stents have significantly better palliation than conventional bare metal stents because of decreased rate of tumor in-growth, which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[362]

SEMS effectively palliate dysphagia in esophageal cancer patients, but the best stent diameter is 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.[364] In a prospective randomized 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.[365] 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.

Obstruction

For patients with severe esophageal obstruction (those able to swallow liquids only), treatment options include endoscopic lumen enhancement (wire-guided or balloon dilation), endoscopy, or fluoroscopy-guided placement of covered expandable metal stents, as described above. Caution should be exercised when dilating malignant strictures, as this may be associated with an increased risk of perforation.[366] For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, EBRT, chemotherapy, or surgery (in select patients). Surgical or radiologic placement of jejunostomy or gastronomy tubes may be necessary to provide adequate hydration and nutrition, if endoscopic lumen restoration is not undertaken or is unsuccessful. Brachytherapy may be considered instead of EBRT, if the lumen can be restored to allow for the use of appropriate applicators to decrease excessive dose on mucosal surfaces. Single-dose brachytherapy was associated with fewer complications and better long-term relief of obstruction compared with the use of metal stents.[367] However, brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.

Pain

Patients experiencing tumor-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 in patients with 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 bipolar electrocoagulation or argon plasma coagulation. Chronic blood loss from esophageal cancer can be managed with EBRT. Endoscopic therapies are generally not recommended for esophageal cancer-related bleeding, since endoscopic intervention may lead to precipitous exsanguination and is associated with a high rate of recurrent bleeding.

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. Survivors 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.[368-370] Several meta-analyses and prospective studies have indicated that esophageal cancer survivors frequently experience symptoms such as malnutrition, dysphagia, dumping syndrome, delayed gastric emptying, reflux, and fatigue following esophagectomy, which greatly diminish their health-related quality of life and often persist many years after surgery.[368-375] Therefore, screening and management of these long-term sequelae are needed for all esophageal and EGJ cancer survivors.

Due to the lack of large randomized trials on long-term sequelae in esophageal cancer survivors, the screening and management recommendations provided by the NCCN Panel are based on smaller studies and clinical experience. Survivors of esophageal and EGJ cancers, especially those who underwent esophagectomy, have unique nutritional needs due to frequent vitamin and mineral deficiencies and other GI dysfunctions.[373,376] 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.[373,376-379] Therefore, the weight and nutritional status of esophageal cancer survivors should be monitored, especially in the first 6 months following surgery. 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.[372,374] 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. These and other dietary changes are recommended by the panel to help manage GI-related dysfunctions. See the *Principles of Survivorship* section of the algorithm for more information.

RT for esophageal cancer puts survivors at risk for radiation-induced cardiotoxicity due to the close proximity of the esophagus to the heart.[380-382] Studies utilizing the SEER database to investigate the late cardiotoxic effects of RT in esophageal cancer survivors revealed an increased risk for cardiac-related death in those who had received RT as part of their initial therapy compared to those who did not.[381,382] 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.[381] 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 (95% CI, 255–367).[381,382] 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.

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. Barrett's esophagus, obesity, and GERD 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 esophageal and EGJ cancers. Best supportive care is an integral part of treatment, especially in patients with locally advanced or metastatic disease.

ER (with or without ablation) is recommended for patients with Tis, T1a, or superficial T1b tumors. Esophagectomy is the preferred primary treatment option for medically fit patients with T1b, N0 tumors. For medically fit patients with locally advanced resectable tumors (T1b, N+; T2–T4a, any N), primary treatment options include preoperative chemoradiation, definitive chemoradiation (only in non-surgical candidates or patients who decline surgery), preoperative chemotherapy (only for adenocarcinoma), or esophagectomy. Definitive chemoradiation is the recommended treatment option for patients with T4b tumors, with chemotherapy alone reserved for the setting of invasion into the heart, trachea, or great vessels.

Postoperative treatment is based on histology, surgical margins, nodal status, and prior treatment. Surveillance is recommended for patients with SCC (irrespective of their nodal status), if there is no residual disease at surgical margins (R0 resection). Following an R1 or R2 resection, patients with SCC who have received preoperative therapy should be observed until disease progression or referred to palliative management, while patients who have not had preoperative therapy can receive postoperative chemoradiation in this setting. 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 node-positive Tis-T4a tumors, node-negative T3-T4 tumors, and select patients with T2, N0 tumors and high-risk features (category 2B). Postoperative chemoradiation is also recommended for all patients with R1 or R2 resections in this setting. Perioperative chemotherapy is recommended following R0 resection for all patients with adenocarcinoma who received chemotherapy preoperatively, irrespective of nodal status (category 1). Concurrent chemoradiation is recommended for patients with unresectable disease, those who decline surgery, and for non-surgical candidates able to tolerate chemotherapy and RT.

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-positive advanced or metastatic adenocarcinoma. Ramucirumab, as a single agent or in combination with paclitaxel, is an option for second-line and subsequent therapy in patients with advanced or metastatic esophageal (category 2A) or EGJ (category 1) adenocarcinomas. Pembrolizumab is included as an option for second-line and subsequent therapy of MSI-H/dMMR tumors, and for third-line and subsequent therapy of PD-L1–positive adenocarcinomas.

The NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers provide an evidence- and consensus-based treatment approach. 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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