National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Esophageal and Esophagogastric Junction Cancers

(Excluding the proximal 5cm of the stomach)

Version 2.2013

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NCCN Guidelines Version 2.2013 Panel Members
Esophageal and Esophagogastric Junction Cancers

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Esophageal and Esophagogastric Junction Cancers

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§ Radiotherapy/Radiation oncology
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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

The NCCN Guidelines® for Esophageal and Esophagogastric Junction Cancers do not include the proximal 5cm of the stomach.

NCCN Guidelines Version 2.2013 Updates Esophageal and Esophagogastric Junction Cancers

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Discussion

The 2.2013 version of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers Guidelines represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

Updates in version 1.2013 of the Esophageal and Esophagogastric Junction Cancers Guidelines from version 2.2012 include:

Global Changes:

- **The Esophageal and Esophagogastric Junction Cancers Guidelines have been extensively revised to include separate treatment algorithms for the histologic classifications of Squamous Cell Carcinoma (ESOPH-1 through ESOPH-9) and Adenocarcinoma (ESOPH-10 through ESOPH-16).**

ESOPH-1

- **Workup**
  - **Fifth bullet: The recommendation was revised as follows, "PET-CT evaluation ~~preferred~~ if no evidence of M1 disease ~~(PET/CT preferred over PET scan)~~".**
  - **Seventh bullet: The recommendation was revised as follows, "Endoscopic ultrasound (EUS) if no evidence of M1 disease~~, with FNA as indicated~~".**
  - **"Nutritional assessment and counseling" was added.**
  - **The recommendation "Laparoscopy (optional) if no evidence of M1 disease and tumor is at esophagogastric junction (EGJ)," was removed.**
- **Footnote "b" is new to the algorithm: "EMR may also be therapeutic for early stage disease/lesions.**
- **Footnote "e" is new the algorithm: "Smoking cessation guidelines are available from the Public Health Service at www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf or http://guideline.gov/content.aspx?id=12520**
- **Footnote "h" was revised to include the definition of T4b tumors.**

ESOPH-2

- **Footnote "j" is new to the algorithm: "For patients receiving definitive RT, such as cervical esophagus, PEG may be considered".**

ESOPH-3

- **Footnote "q" is new to the algorithm: "Consider endoluminal stenting when appropriate".**

ESOPH- A: Principles of Endoscopic Staging and Therapy
1 of 4

- **Diagnosis**
  - **The fifth bullet was revised: "~~Endoscopic mucosal resection (EMR) can be therapeutic/diagnostic.~~ Endoscopic mucosal resection (EMR) of focal nodules can be performed in the setting of early stage disease to provide accurate T-staging including degree of differentiation and vascular and or lymphatic invasion~~, with the potential of being therapeutic.~~ This should be considered in the evaluation of areas of Barrett's esophagus associated with high grade dysplasia and also patches of squamous dysplasia. EMR can be fully therapeutic when a lesion less than 2 cm in diameter is removed and histopathologic assessment demonstrates well or moderate differentiation, no invasion beyond the muscularis mucosa, and no lymphovascular invasion".**
  - **The sixth bullet was revised: "Cytologic brushings or washings are rarely adequate in the initial diagnosis~~, but can be useful in confirming persistent disease following treatment~~."**

2 of 4

- **Staging**
  - **Second bullet: The last sentence was revised: "Loss of a bright tissue plane between the area of tumor and surrounding structures such as the ~~trachea, aorta, liver correlates with infiltration of tumor into surrounding organs (T4 disease)~~ 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".**
  - **The following bullet was added, "Endoscopic Mucosal Resection (EMR) of small lesions ≤ 3 cm can provide accurate T staging, complementing the results of EUS".**

NCCN Guidelines Version 2.2013 Updates Esophageal and Esophagogastric Junction Cancers

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ESOPH- A: Principles of Endoscopic Staging and Therapy---continued

3 of 4

- **Treatment; Third bullet: The following statement was added "Complete eradication of Barrett's epithelium can also be performed with more aggressive application of EMR at the initial interventions, and has been shown to be safe and effective".**
- **Post-Treatment Surveillance: The first bullet was revised: "Assessment with endoscopy with biopsy ~~and brushings~~ should be done ≥ 5-6 weeks after completion of preoperative therapy".**

ESOPH- B (3 of 4): Principles of Pathologic Review and HER2-neu Testing

- **The following statement was revised: "The NCCN Guidelines panel recommends that cases showing ~~less than 3+ overexpression~~ 2+ expression of HER2-neu by immunohistochemistry should be additionally examined by FISH or other in situ hybridization methods".**

ESOPH-D: Principles of Surgery

- **For clarity, "distal esophagus" changed to "lower esophagus".**

ESOPH-E: Principles of Systemic Therapy

- **The systemic therapies were divided into "Preferred Regimens" and "Other Regimens".**
- **The "Regimens and Dosing Schedules" were revised extensively including adding/removing schedules and changing doses.**

1 of 14:

- **Third bullet was revised: "Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation."**
- **The following statements are new to the algorithm:**
  - **Perioperative chemotherapy is an alternative, but less preferred option.**
  - **Induction chemotherapy may be appropriate as clinically indicated.**

2 of 14:

- **Preoperative Chemoradiation:**
  - **"Oxaliplatin and fluorouracil" changed from a category 2A to a category 1 recommendation.**
  - **The following combinations were removed:**
    - **Paclitaxel and cisplatin**
    - **Carboplatin and 5-FU (category 2B)**
    - **Oxaliplatin, docetaxel, and capecitabine (category 2B)**
- **Perioperative Chemotherapy: "Fluorouracil and cisplatin (category 1)" was added.**
- **Definitive Chemoradiation: Oxaliplatin, docetaxel, and capecitebine (category 2B) was removed.**
- **Postoperative Chemoradiation: "LV5FU2 before and after infusion 5-FU or capecitabine with radiation (preferred)" changed to "Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation".**
- **Postoperative Chemotherapy: "Capecitabine and cisplatin" was added.**
- **Sequential Chemotherapy and Chemoradiation: This section was removed from the guidelines.**

3 of 14:

- **The page title changed to "~~Definitive~~ Chemotherapy for Metastatic or Locally Advanced Cancer [where ~~chemoradiation~~ local therapy is not indicated]."**
- **First Line Therapy: The following recommendation was revised, "Two-drug cytotoxic regimens are preferred because of lower toxicity."**
- **Second Line Therapy: "Irinotecan and mitomycin (category 2B)" was removed.**
- **Alternative regimens for consideration:**
  - **The following combinations were removed:**
    - **Gemcitabine, fluorouracil, and leucovorin**
    - **Mitomycin, cisplatin, and 5-FU**
    - **Pegylated liposomal doxorubicin, cisplatin and 5-FU**
  - **Elontinb was clarified as "squamous cell carcinoma only".**

ESOPH-E: Principles of Systemic Therapy---continued
4 of 14:

- **The following footnote is new to the algorithm: "Chemotherapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice".**

7 of 14:

- **Postoperative chemoradiation (including EG junction):**
  - **The regimen for the Intergroup 0116 trial was added, with corresponding statement: "The panel acknowledges that the intergroup 0116 trial 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/m^2 PO BID on Days 1-14
      Cycled every 28 days
    - **1 cycle before and 2 cycles after chemoradiation**
      Leucovorin 400 mg/m^2 IV on Days 1 and 15 or Days 1, 2, 15, and 16
      Fluorouracil 400 mg/m^2 IVP on Days 1 and 15 or Days 1, 2, 15, and 16
      Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1, 2, 15, and 16
      Cycled every 28 days"

ESOPH-F: Principles of Radiation Therapy
1 of 4:

This section was revised extensively including the following:

- **General Guidelines:**
  - **The following bullet was added: "In general, Siewert I and II tumors should be managed with radiation guidelines applicable to esophageal cancers. Depending on the clinical situation, Siewert III tumors, may be more appropriately managed with radiation guidelines applicable to either esophageal or gastric cancers. These recommendations may be modified depending on where the bulk of the tumor is located."**

2 of 4:

- **Simulation and Treatment planning**
  - **Second bullet: The following sentence was added, "Attention should be paid to sparing the uninvolved stomach that may be used for future reconstruction (ie, anastomosis site)."**
- **Dose:**
  - **The following recommendation "Preoperative or Postoperative Therapy: 45-50.4 Gy (1.8-2 Gy/day)" changed to:**
    - **Preoperative Therapy 41.4-50.4 Gy (1.8-2 Gy/day)**
    - **Postoperative Therapy: 45-50.4 Gy (1.8-2 Gy/day)**
    - **Definitive Therapy: 50-50.4 Gy (1.8-2 Gy/day)**
      - **Higher doses may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned. (A corresponding footnote was added that states, Published studies have reported radiation doses from 60-66 Gy (1.8-2 Gy/day). However there is no randomized evidence to support any benefit or detriment of this dose range over 50-50.4 Gy (1.8-2 Gy/day)."**
- **Footnote b is new to the algorithm: "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 Gy/day) because the lower preoperative therapy dose may not be adequate."**

NCCN Guidelines Version 2.2013 Updates Esophageal and Esophagogastric Junction Cancers

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ESOPH-G: Principles of Best Supportive Care

- **Obstruction; Under "Endoscopic lumen enhancement":**
  - **The recommendation changed as follows, "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)".**
  - **Under "Endoscopy or fluoroscopy-guided placement of covered expandable metal stents": The recommendation changed as follows, "While there are data suggesting a lower migration and re-obstruction rate with the larger diameter covered expandable metal stents, they may be associated with a higher risk of other complications. If possible, the distal end of the stent should remain above the GEJ to reduce symptoms of reflux and risk of aspiration".**

WORKUP

- H&P
- Upper GI endoscopy and biopsy[a]
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT as clinically indicated
- PET-CT evaluation if no evidence of M1 disease
- CBC and chemistry profile
- Endoscopic ultrasound (EUS), if no evidence of M1 disease
- Endoscopic mucosal resection (EMR) may contribute to accurate staging of early stage cancers[b]
- Nutritional assessment and counseling
- Biopsy of metastatic disease as clinically indicated
- HER2-neu testing if metastatic adenocarcinoma is documented/suspected[c]
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category[d]
- Smoking cessation advice, counseling, and pharmacotherapy[e]

CLINICAL STAGE[f]

HISTOLOGIC CLASSIFICATION[c]

Stage I–III[f,g,h] (locoregional disease)

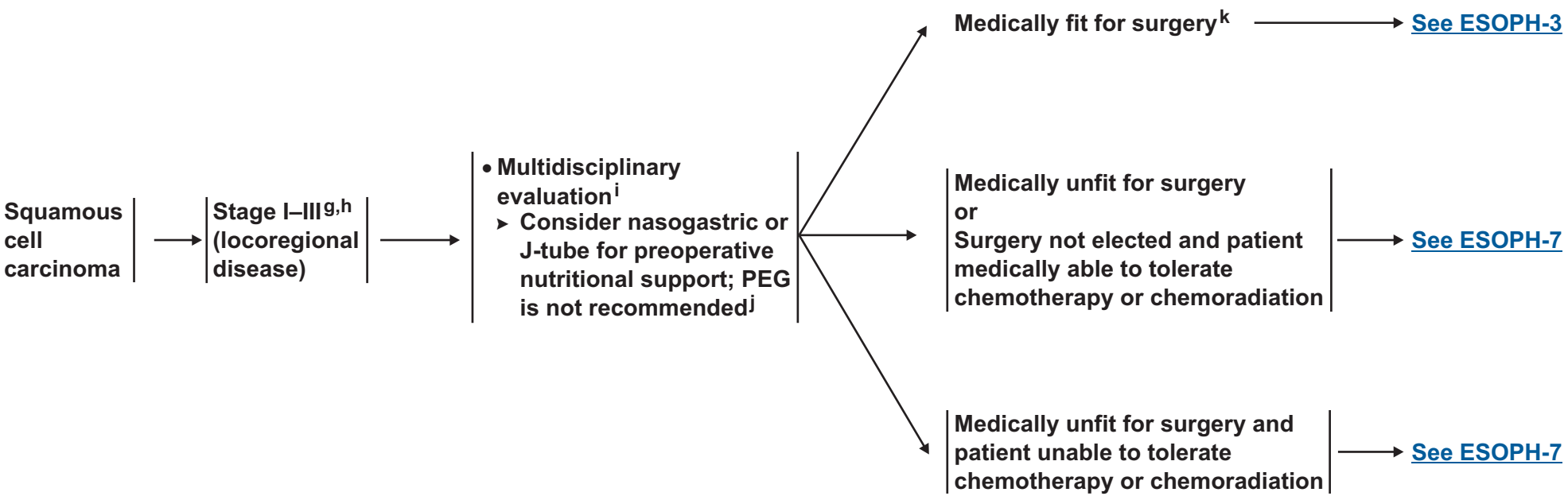
- Squamous cell carcinoma → See ESOPH-2
- Adenocarcinoma → See ESOPH-10

Stage IV[f] (metastatic disease)

- Squamous cell carcinoma → See ESOPH-9
- Adenocarcinoma → See ESOPH-17

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[b] EMR may also be therapeutic for early stage disease/lesions.
[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery ESOPH-D
[e] Smoking cessation guidelines are available from the Public Health Service at: www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf or http://guideline.gov/content.aspx?id=12520
[f] See Staging (ST-1).
[g] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
[h] T1-T3 tumors are resectable even with regional nodal metastases (N+). T4a (resectable): involvement of pericardium, pleura or diaphragm. T4b tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.

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.



[f] See Staging (ST-1).
[g] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
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[i] See Principles of Multidisciplinary Team Approach (ESOPH-C).
[j] Percutaneous endoscopic gastrostomy (PEG) may be considered for patients with cervical esophagus receiving definitive chemoradiation.
[k] Medically able to tolerate major abdominal and/or thoracic surgery.

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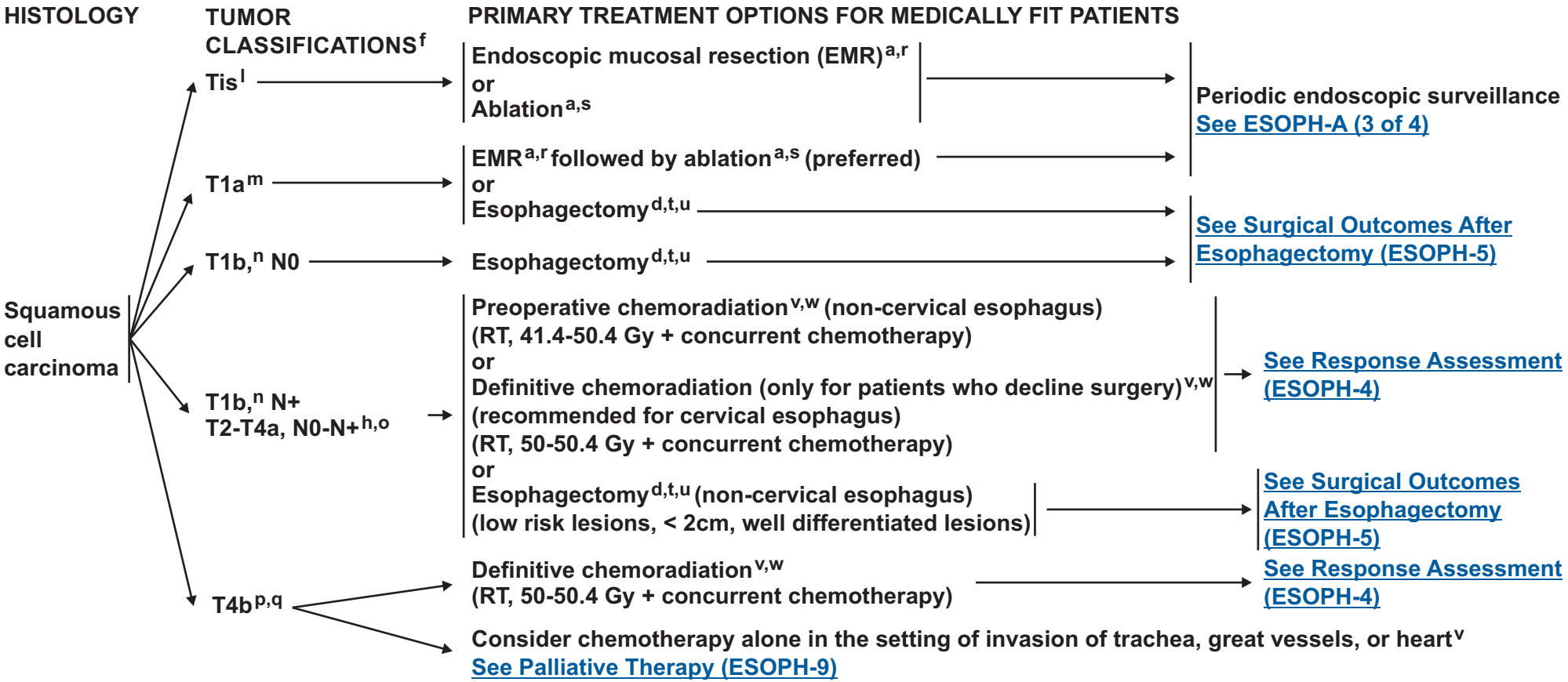

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
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[l] Tis: Defined as high-grade dysplasia or carcinoma in situ.
[m] T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[n] T1b: Tumors invading the submucosa.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[q] Consider endoluminal stenting when appropriate.
[r] May be applied to Tis or T1a, defined as tumor involving the mucosa, but not invading the submucosa.
[s] Ablation may not be needed for lesions that are completely excised.
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).

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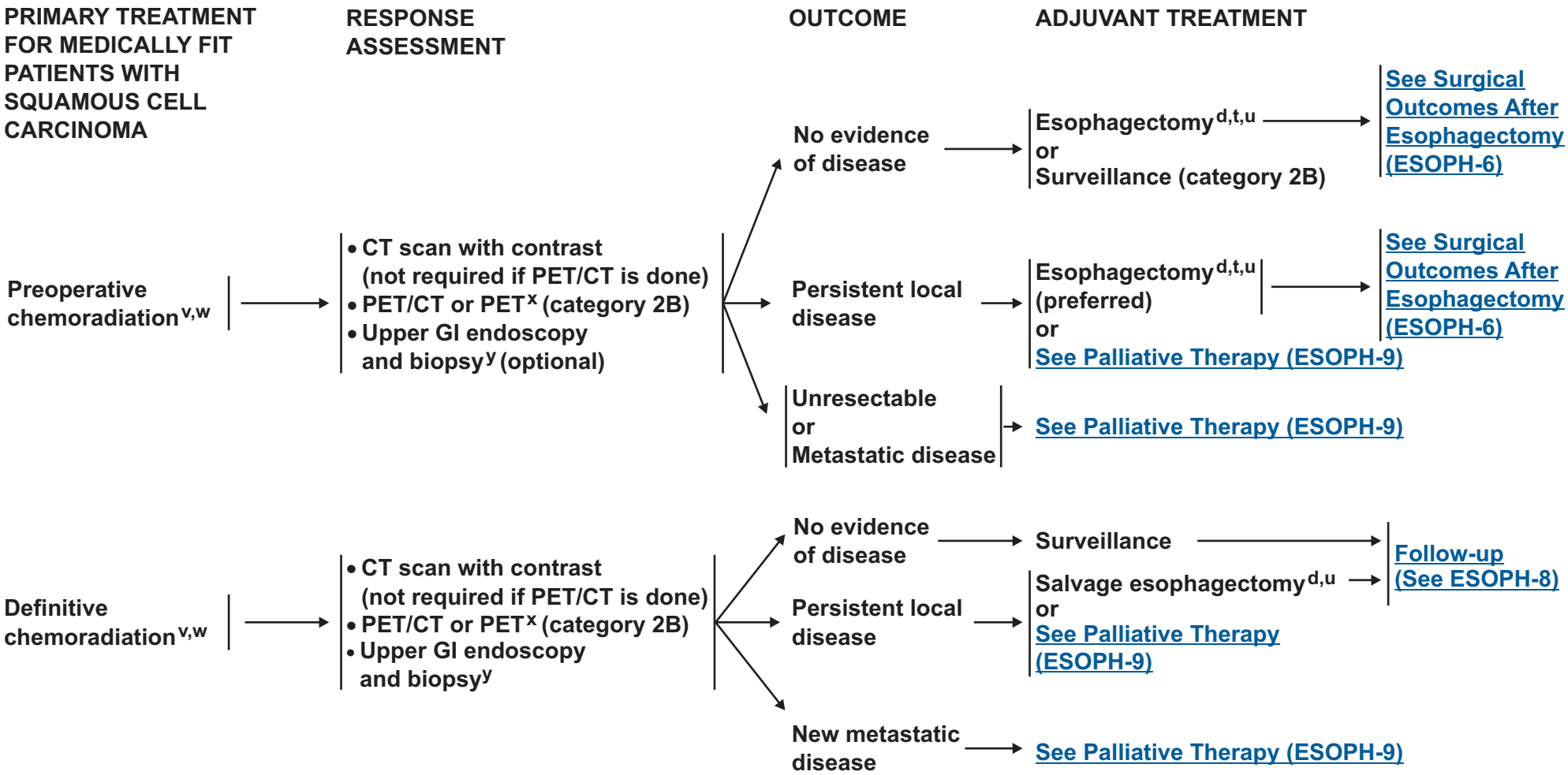

[d] See Principles of Surgery (ESOPH-D).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[x] Assessment ≥ 5-6 weeks after completion of preoperative therapy.
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 3 of 4).

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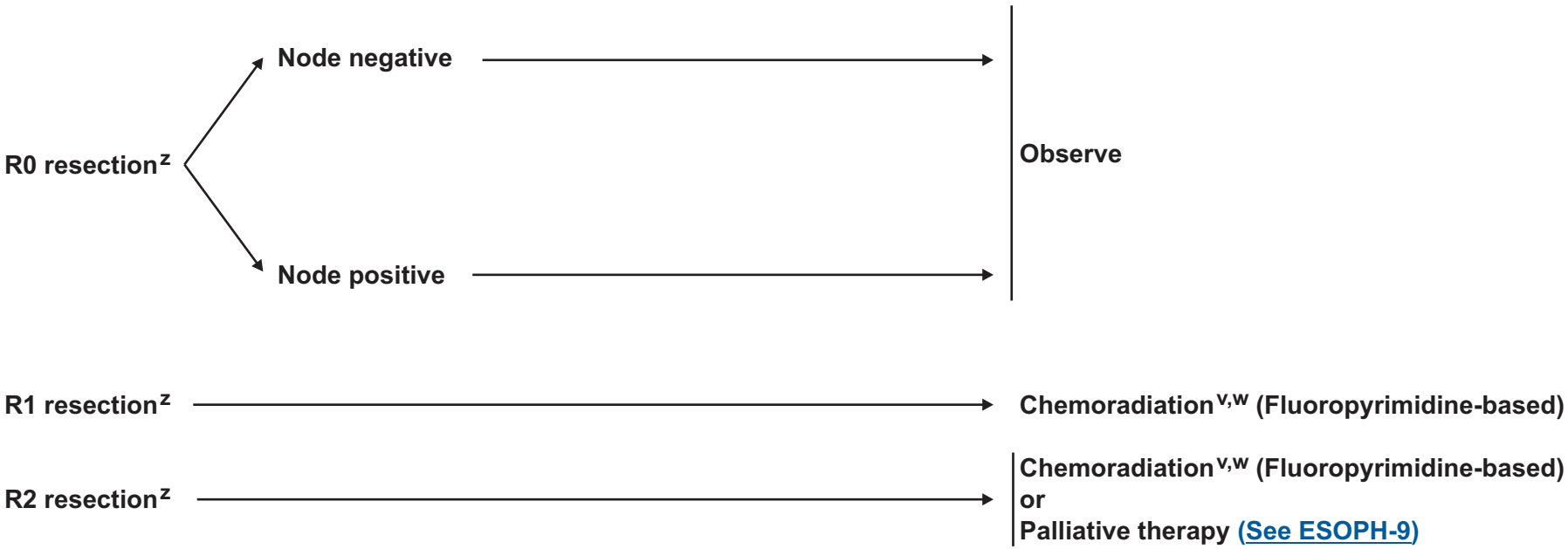
Follow-up (See ESOPH-8)

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

POSTOPERATIVE TREATMENT



[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[z] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1.

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(See ESOPH-8)

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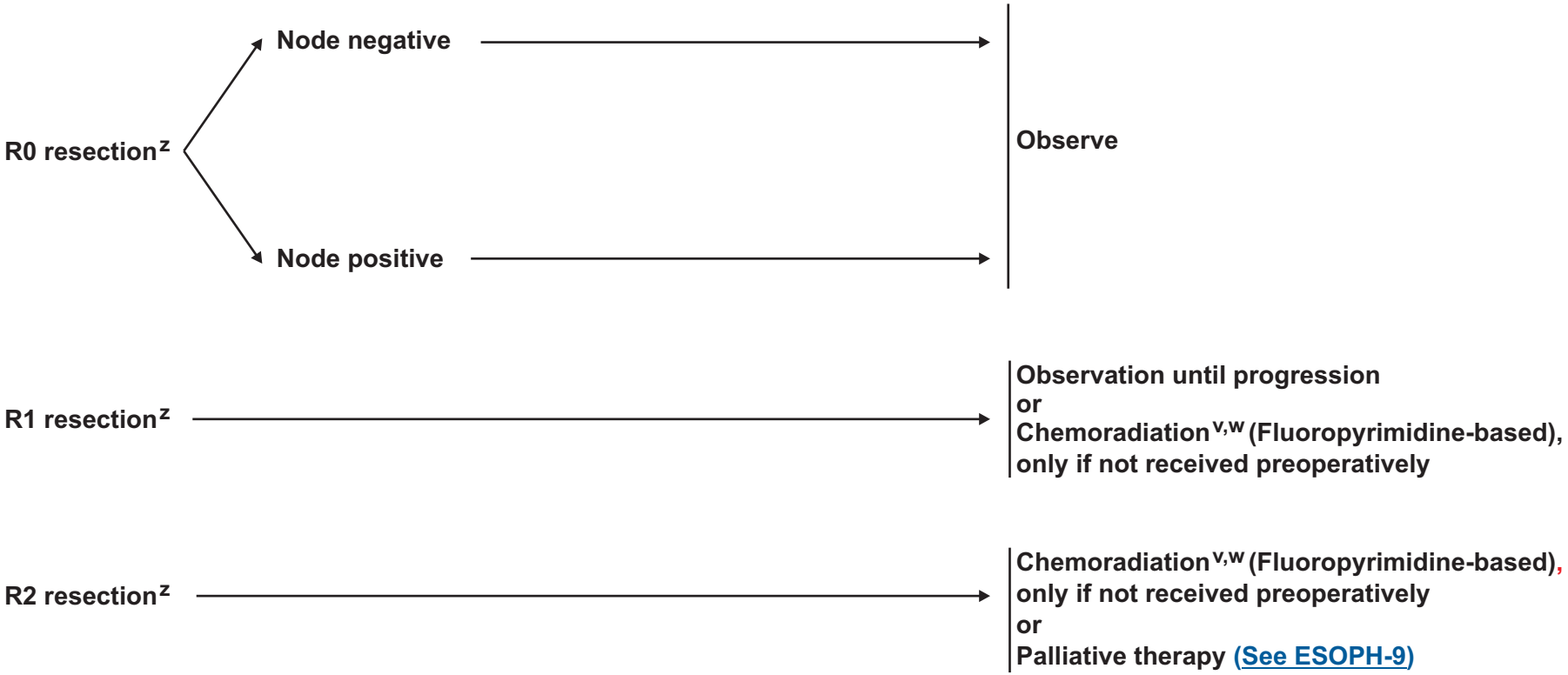

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(See ESOPH-8)

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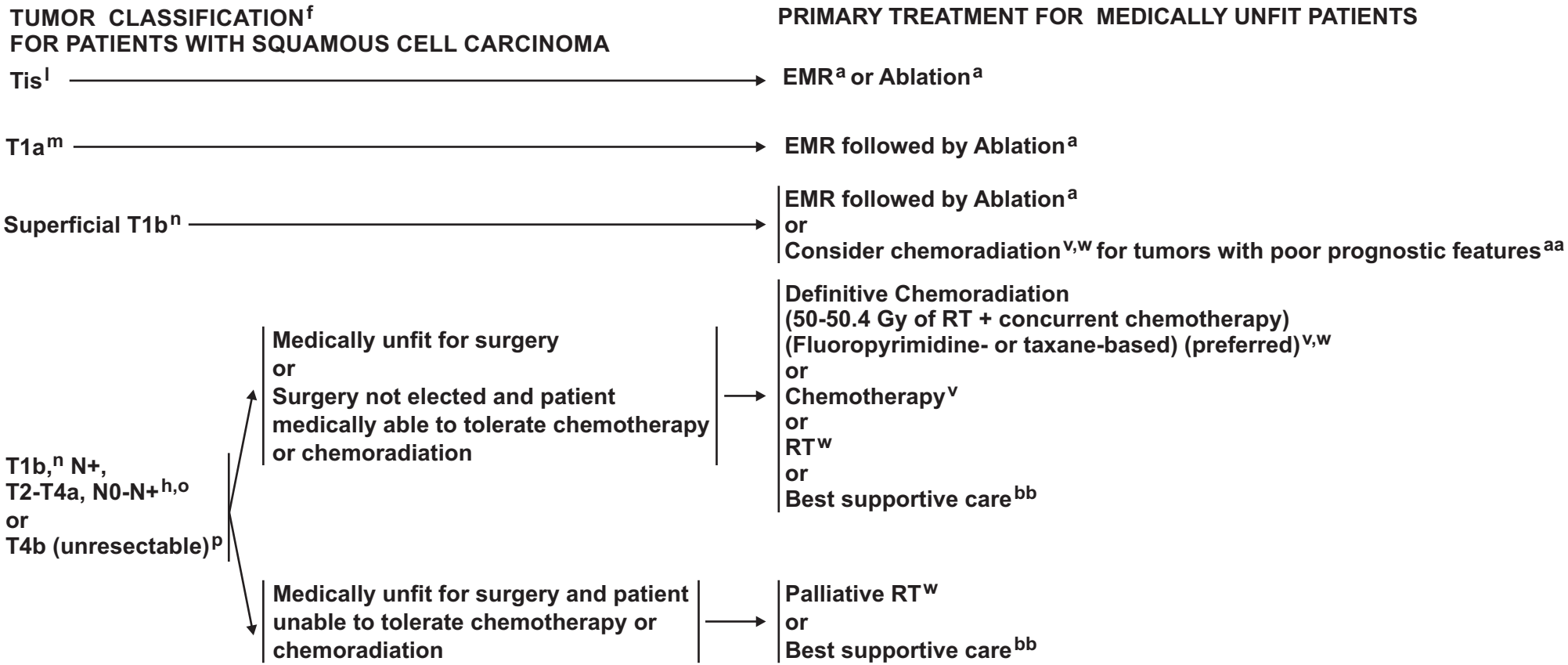

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
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[o] Preclinical staging cannot establish the number of positive nodes.
[p] T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[aa] Poor prognostic features include lymphovacular invasion (LVI), poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2 cm or more.
[bb] See Principles of Best Supportive Care (ESOPH-G).

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Follow-up (See ESOPH-8)

FOLLOW-UP FOR SQUAMOUS CELL CARCINOMA

- 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 as clinically indicated
- Upper GI endoscopy and biopsy as clinically indicated[y]
- Dilatation for anastomotic stenosis
- Nutritional assessment and counseling

RECURRENCE

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

PALLIATIVE/SALVAGE THERAPY

- Concurrent chemoradiation[v,w] (Fluoropyrimidine- or taxane-based) preferred
  or
  Surgery[d]
  or
  Chemotherapy[v]
  or
  Best supportive care[bb]
  → Recurrence → See Palliative Therapy (ESOPH-9)
- Resectable[d] and medically operable → Esophagectomy[d,t,u] → Recurrence → See Palliative Therapy (ESOPH-9)
- Unresectable or Medically inoperable → See Palliative Therapy (ESOPH-9)
- Metastatic disease → See Palliative Therapy (ESOPH-9)

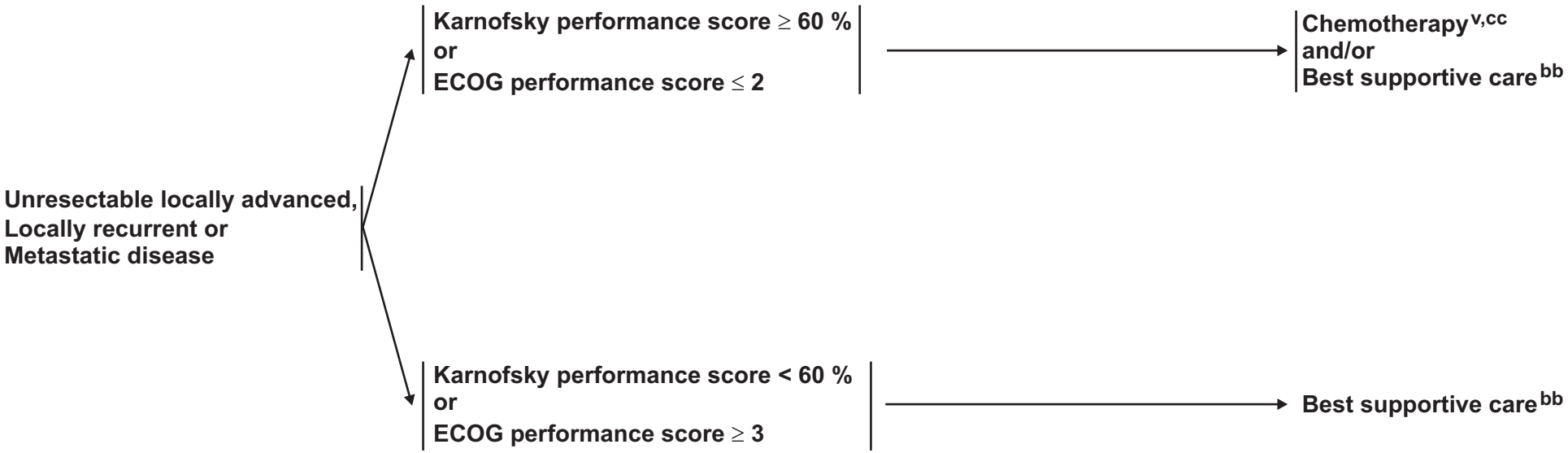
[d] See Principles of Surgery (ESOPH-D).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 3 of 4).
[bb] See Principles of Best Supportive Care (ESOPH-G).

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

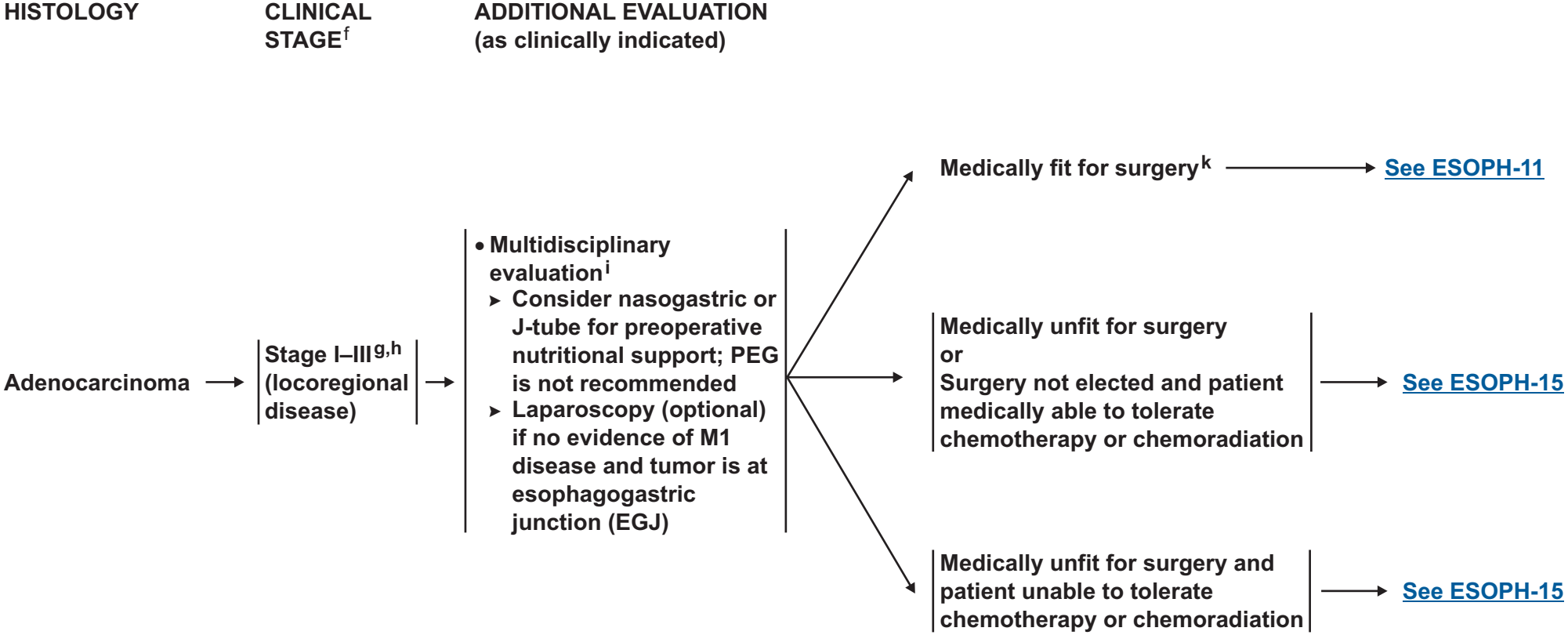
PALLIATIVE THERAPY



[v] See Principles of Systemic Therapy (ESOPH-E).
[bb] See Principles of Best Supportive Care (ESOPH-G).
[cc] Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

Back to Follow-up and Recurrence (ESOPH-8)

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.



[f] See Staging (ST-1).
[g] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
[h] T1-T3 tumors are resectable even with regional nodal metastases (N+). T4a (resectable): involvement of pericardium, pleura or diaphragm. T4b tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[i] See Principles of Multidisciplinary Team Approach (ESOPH-C).
[k] Medically able to tolerate major abdominal and/or thoracic surgery.

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Esophageal and Esophagogastric Junction Cancers

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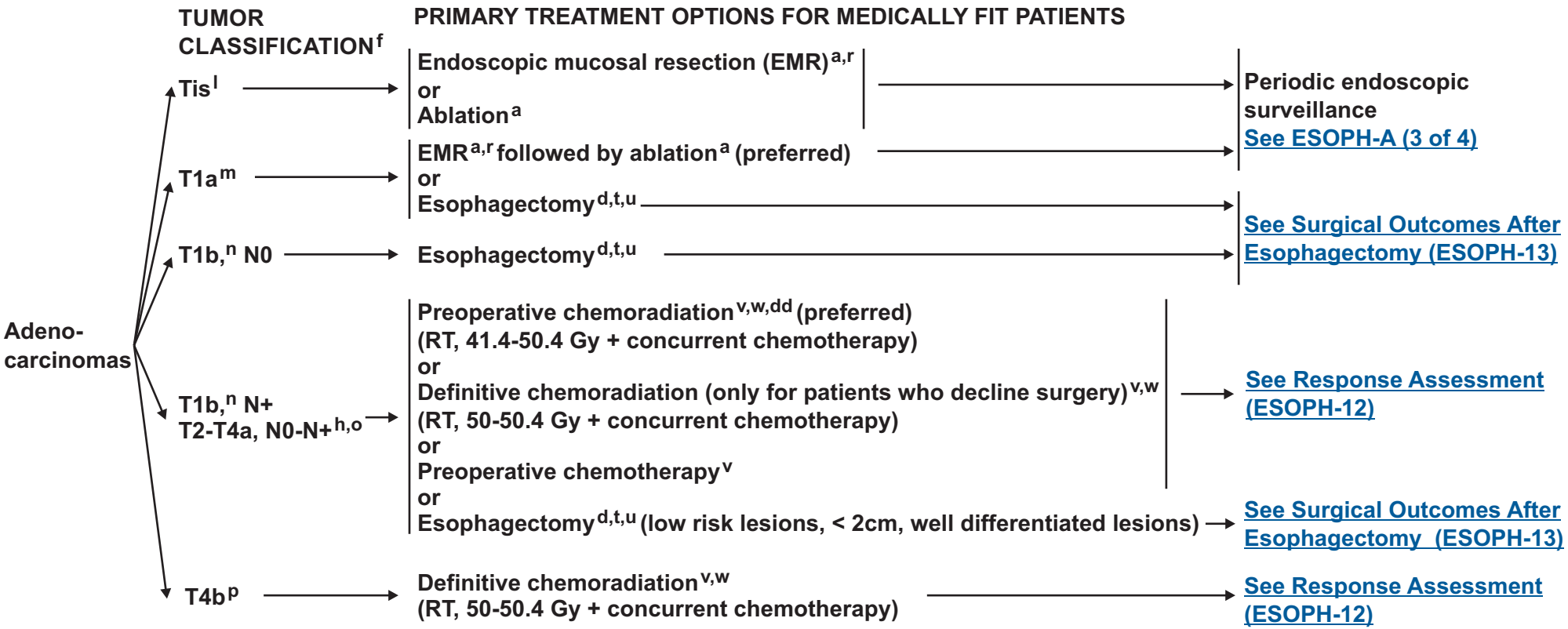

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[f] See Staging (ST-1).
[h] T1-T3 tumors are resectable even with regional nodal metastases (N+). T4a (resectable): involvement of pericardium, pleura or diaphragm. T4b tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[d] See Principles of Surgery (ESOPH-D).
[l] Tis: Defined as high-grade dysplasia or carcinoma in situ.
[m] T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[n] T1b: Tumors invading the submucosa.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[r] May be applied to Tis or T1a, defined as tumor involving the mucosa, but not invading the submucosa.
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[dd] 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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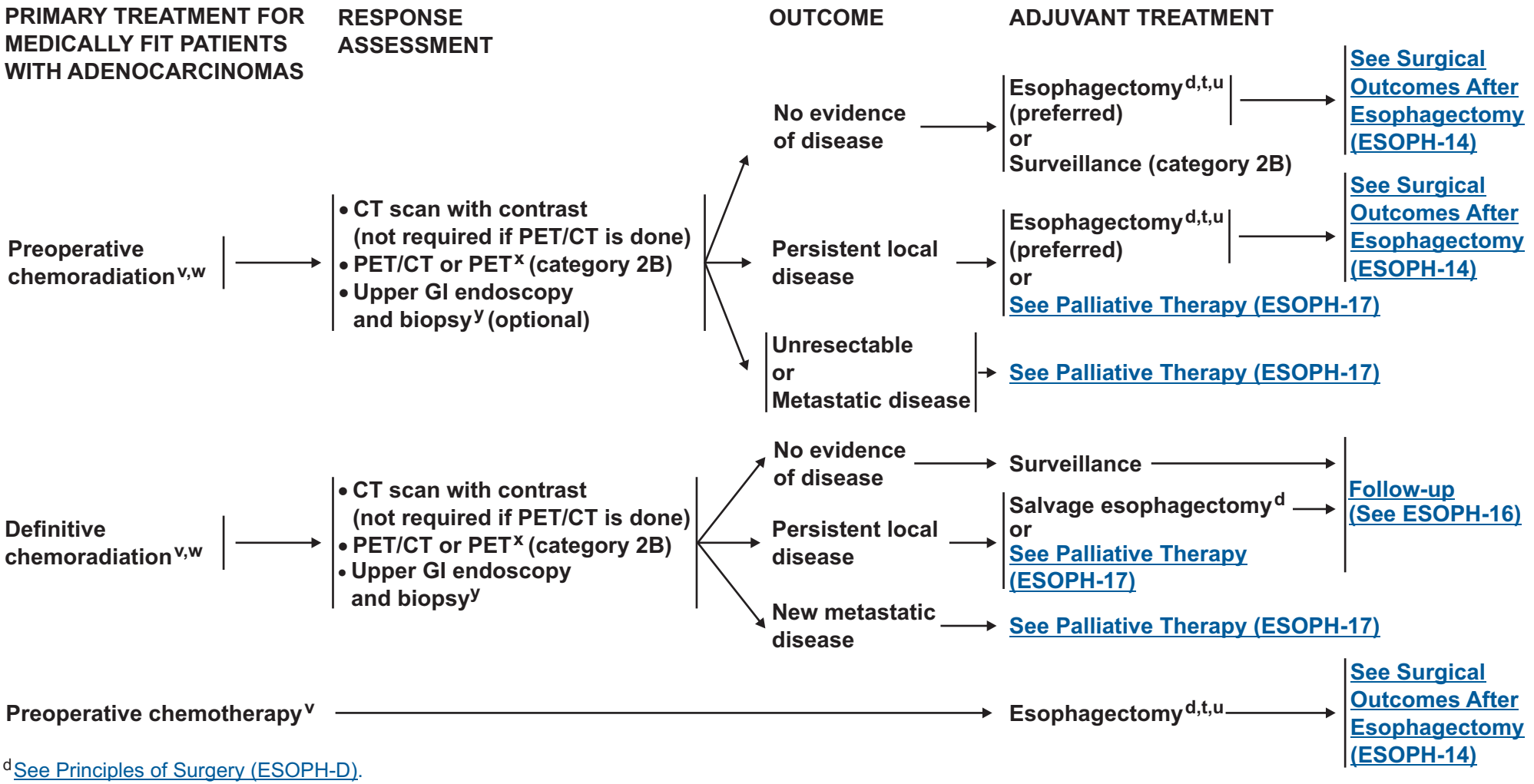

[d] See Principles of Surgery (ESOPH-D).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[x] Assessment ≥ 5-6 weeks after completion of preoperative therapy.
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 3 of 4).

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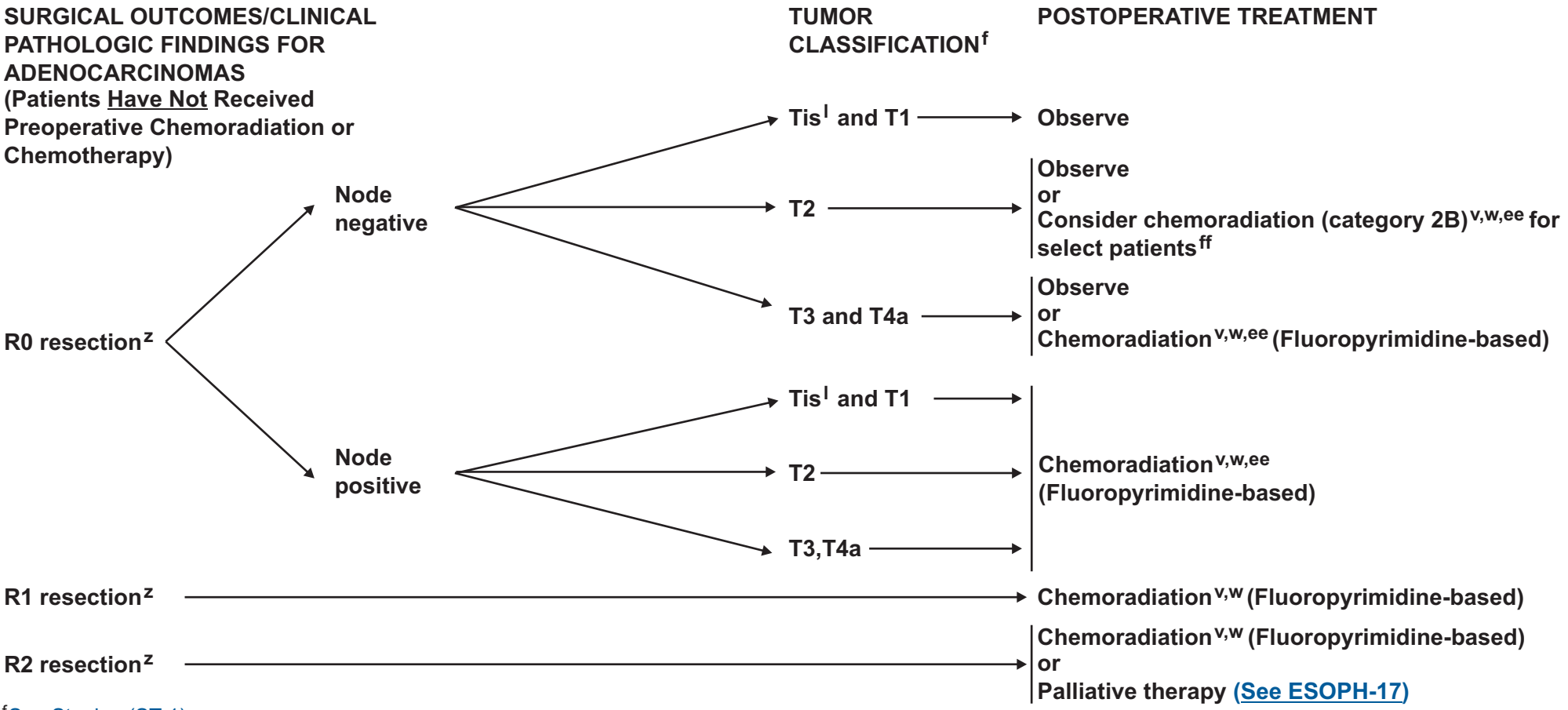

[f] See Staging (ST-1).

[l] Tis: Defined as high-grade dysplasia or carcinoma in situ.

[v] See Principles of Systemic Therapy (ESOPH-E).

[w] See Principles of Radiation Therapy (ESOPH-F).

[z] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1.

[ee] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730. 5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy (ESOPH-E).

[ff] 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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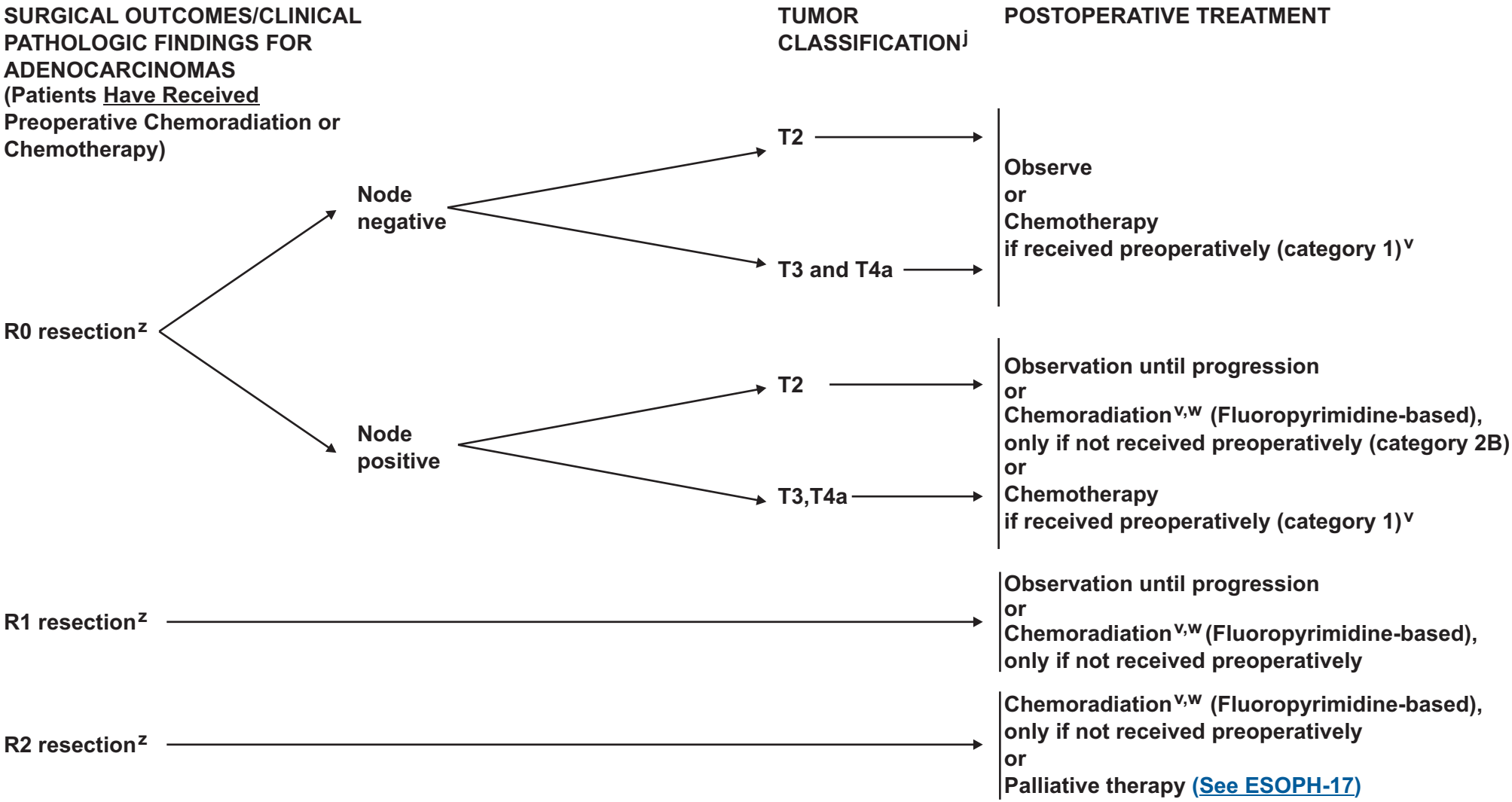
Follow-up (See ESOPH-16)



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

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Follow-up (See ESOPH-16)

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TUMOR CLASSIFICATION[f] FOR PATIENTS WITH ADENOCARCINOMAS

PRIMARY TREATMENT FOR MEDICALLY UNFIT PATIENTS

Tis[l] → **EMR or Ablation[a]**

T1a[m] → **EMR followed by Ablation[a]**

Superficial T1b[n] → **EMR followed by Ablation[a]**
or
Consider chemoradiation[v,w] for tumors with poor prognostic features[aa]

T1b,[n] N+,
T2-T4a, N0-N+[h,o]
or
T4b (unresectable)[p]

- **Medically unfit for surgery**
  or
  Surgery not elected and patient medically able to tolerate chemotherapy or chemoradiation
  → **Definitive Chemoradiation (50-50.4 Gy of RT + concurrent chemotherapy) (Fluoropyrimidine- or taxane-based) (preferred)[v,w]**
  or
  Chemotherapy[v]
  or
  RT[w]
  or
  Best supportive care[bb]
- **Medically unfit for surgery and patient unable to tolerate chemotherapy or chemoradiation**
  → **Palliative RT[w]**
  or
  Best supportive care[bb]

[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[f] See Staging (ST-1).
[h] T1-T3 tumors are resectable even with regional nodal metastases (N+). T4a (resectable): involvement of pericardium, pleura or diaphragm. T4b tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[l] Tis: Defined as high-grade dysplasia or carcinoma in situ.
[m] T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[n] T1b: Tumors invading the submucosa.
[o] Preclinical staging cannot establish the number of positive nodes.
[p] T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[aa] Poor prognostic features include lymphovacular invasion (LVI), poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2cm or more.
[dd] See Principles of Best Supportive Care (ESOPH-G).

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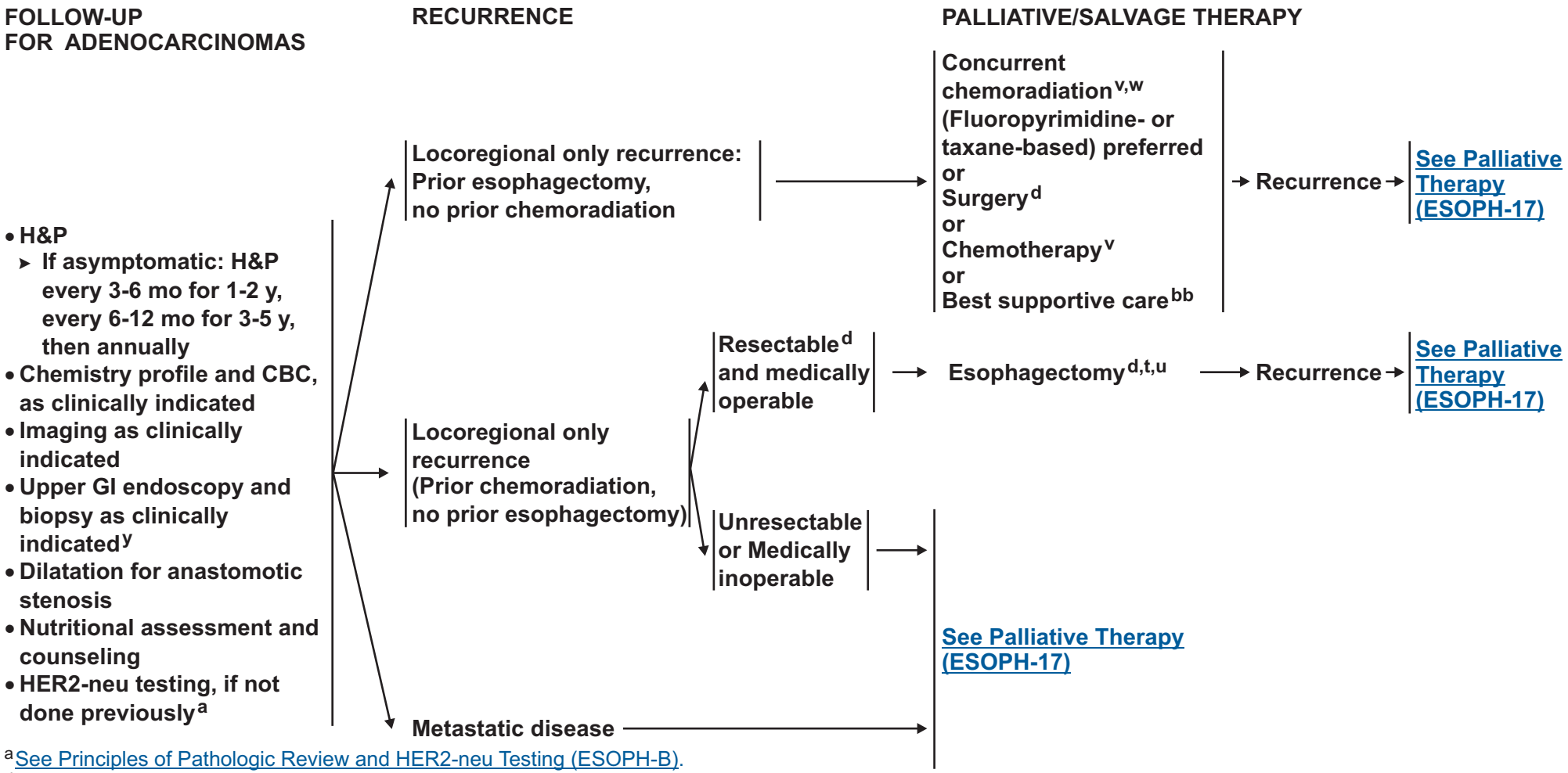
Follow-up (See ESOPH-16)



[a] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-D).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-E).
[w] See Principles of Radiation Therapy (ESOPH-F).
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 3 of 4).
[bb] See Principles of Best Supportive Care (ESOPH-G).

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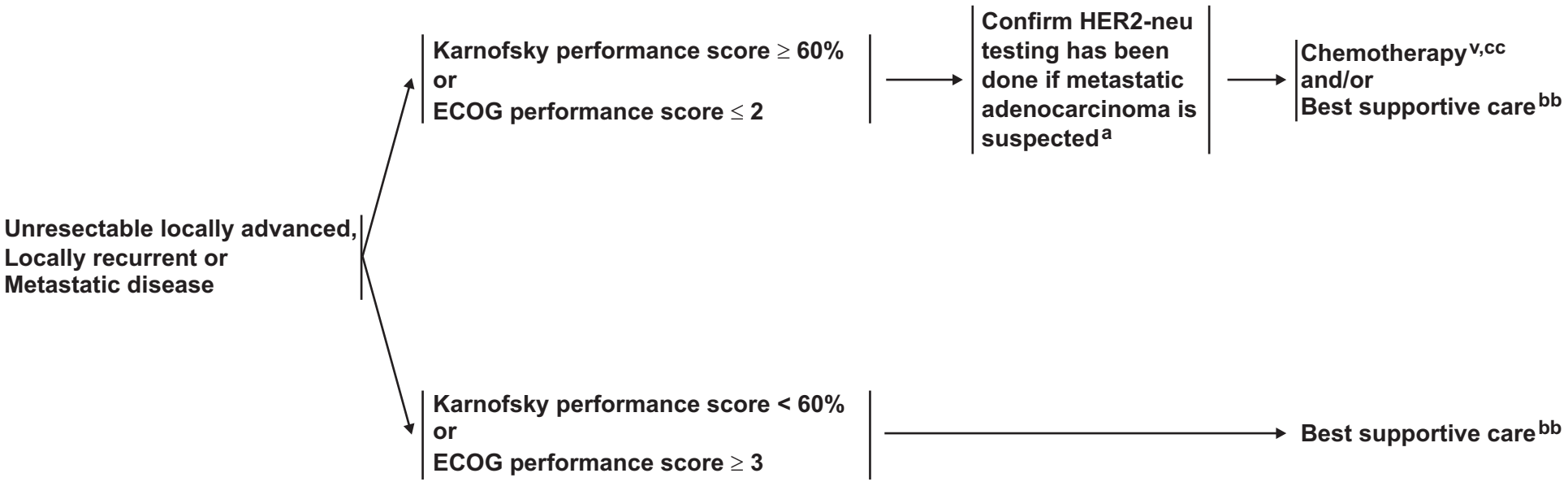
FOR ADENOCARCINOMAS

PERFORMANCE STATUS

PALLIATIVE THERAPY



[a] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[v] See Principles of Systemic Therapy (ESOPH-E).
[bb] See Principles of Best Supportive Care (ESOPH-G).
[cc] Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

Back to Follow-up and Recurrence (ESOPH-16)

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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

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

DIAGNOSIS

- **Diagnostic and surveillance endoscopies are performed with the goal of determining the presence and location of esophageal cancer and to biopsy any suspicious lesions. Thus, an adequate endoscopic exam addresses both of these components.**
- **The location of the tumor relative to the teeth and the esophagogastric junction (EGJ), the length of the tumor, the extent of circumferential involvement, and degree of obstruction should be carefully recorded to assist with treatment planning. If present, the location, length and circumferential extent of Barrett's esophagus should be characterized in accordance with the Prague criteria,[1] and mucosal nodules should be carefully documented.**
- **High-resolution endoscopic imaging and narrow-band imaging are presently available and may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[2]**
- **Multiple biopsies, 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 mucosal resection (EMR) of focal nodules can be performed in the setting of early stage disease to provide accurate T-staging including degree of differentiation and vascular and or lymphatic invasion.[5] This should be considered in the evaluation of areas of Barrett's esophagus associated with high grade dysplasia and also patches of squamous dysplasia. EMR can be fully therapeutic when a lesion less than 2 cm in diameter is removed and histopathologic assessment demonstrates well or moderate differentiation, no invasion beyond the muscularis mucosa, and no lymphovascular invasion.**
- **Cytologic brushings or washings are rarely adequate in the initial diagnosis.**

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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-stage), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N-stage), and occasionally signs of distant spread, such as lesions in surrounding organs (M-stage).[6]
- Hypoechoic (dark) expansion of the esophageal wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal esophageal wall corresponding with greater depths of tumor penetration, correlating with higher T-stages. A dark expansion of layers 1-3 correspond with infiltration of the superficial and deep mucosa plus the submucosal, T1 disease. A dark expansion of layers 1-4, correlates with penetration into the muscularis propria, T2 disease, and expansion beyond the smooth outer border of the muscularis propria correlates with invasion of the adventitia, T3 disease. Loss of a bright tissue plane between the area of tumor and surrounding structures such as the 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.
- Endoscopic Mucosal Resection (EMR) of small lesions $\leq$ 3 cm can provide accurate T staging, complementing the results of EUS.[7]
- 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 also confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[8] 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 on treatment decisions. The pre-procedure review of CT and PET scans, when available, prior to EGD/EUS, to become fully familiar with the nodal distribution for possible FNA is recommended.
- 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. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate but there is increased risk of perforation after dilation.

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Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

TREATMENT:

- The goal of EMR and/or ablation is the complete removal of all Barrett's metaplasia in addition to eradication of early malignancy.
- Early stage disease, Tis, also known as high grade dysplasia, needs to be fully characterized, including evaluating presence of nodularity, lateral spread and ruling out multifocal disease. This is important to permit decisions on endoscopic treatment with ablative methods such as radiofrequency ablation (RFA), cryoablation, photodynamic therapy (PDT) or EMR.[9-12] All focal nodules should be resected rather than ablated.
- T1a disease, carcinoma limited to the lamina propria or muscularis mucosae, in the absence of evidence of lymph node metastases, lymphovascular invasion or poor differentiation grade can be treated with full EMR. EUS staging prior to proceeding with mucosal resection in the setting of carcinoma is recommended. Ablative therapy of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed following mucosal resection. Complete eradication of Barrett's epithelium can also be performed with more aggressive application of EMR at the initial interventions, and has been shown to be safe and effective.[13]
- 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 cryotherapy, or endoscopic and radiographic assisted insertion of expandable metal or plastic stents.[14,15]
- 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:

- Assessment with endoscopy with biopsy should be done ≥ 5-6 weeks after completion of preoperative therapy.
- EUS exams performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the present stage of disease.[16] Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.[17]
- 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 performed in conjunction with endoscopy exams has a high sensitivity for recurrent disease.[18] EUS guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.
- Endoscopic surveillance after ablative therapy or EMR of early esophageal malignancy should continue after completion of treatment. Biopsies should be taken of the neo-squamous 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. Ablation of non-dysplastic Barrett's esophagus is not recommended.
- For follow-up, patients with Tis or T1a who undergo EMR should have endoscopic surveillance every 3 months for one year, then annually.

Continued

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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY (REFERENCES)

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[16]Ribeiro A, Franceschi D, Parra J, et al. Endoscopic ultrasound restaging after neoadjuvant chemotherapy in esophageal cancer. Am J Gastroenterol 2006;101:1216-1221.
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[18]Lightdale CJ, Botet JF, Kelsen DP, et al. Diagnosis of recurrent upper gastrointestinal cancer at the surgical anastomosis by endoscopic ultrasound. Gastrointest Endosc 1989;35:407-412.

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

TABLE 1 Pathologic Review

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

[a] Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at http://www.cap.org) for reporting pathologic findings is recommended.
[b] For purposes of data reporting, Barrett's esophagus with high-grade dysplasia in an esophageal resection specimen is reported as "carcinoma in situ (Tis) ." The term "carcinoma in situ" is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states.[1]
[c] Biopsies showing Barrett's esophagus with suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.[2]
[d] Invasion of a thickened and duplicated muscularis mucosae should not be misinterpreted as invasion of the muscularis propria in Barrett's esophagus.[3]
[e] A specific diagnosis of squamous cell carcinoma or adenocarcinoma should be established when possible for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the TNM system for squamous cell carcinoma.[1]
[f] Pathologic grade is needed for stage grouping in the AJCC TNM 7th edition.[1]
[g] Tumors arising in the proximal stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[1]

Continued

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of treatment response

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

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

TABLE 2

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

Reproduced and adapted with permission from Tang LH, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with carcinoma of the stomach. In: Washington K, ed. Reporting on Cancer Specimens: Case Summaries and Background Documentation. Northfield, IL: College of American Pathologists; 2012. (available at http://www.cap.org).

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

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

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

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

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

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

*Reprinted and adapted from The Lancet, 376(9742), Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. pages 687-697, 2010, with permission from Elsevier.

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

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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

[1] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
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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.
- 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 tumor type should be assessed in all patients with adenocarcinomas involving the esophagogastric junction (EGJ).[2, 3]
  - Siewert Type I: adenocarcinoma of the lower esophagus with the center located within 1 cm above and 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 EGJ, which infiltrates the EGJ and lower esophagus from below.
- The treatment of Siewert types I and II is as described in the manuscript, and a variety of surgical approaches may be employed.
- Siewert type III lesions are considered gastric cancers, and thus 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. 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 esophagogastric junction cancer:
  - T1a tumors, defined as tumors involving the mucosa but not invading the submucosa, may be considered for EMR + ablation or esophagectomy in experienced centers.[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:
  - T4b 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 and 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 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 esophagogastric junction cancer:
  - Ivor Lewis esophagogastrectomy (laparotomy + right thoracotomy)
  - McKeown esophagogastrectomy (right thoracotomy + laparotomy + cervical anastomosis)
  - Minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy + limited right thoracotomy)[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 salvage esophagectomy if they do not have distant recurrence.[15]

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

Continued

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PRINCIPLES OF SURGERY

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PRINCIPLES OF SYSTEMIC THERAPY

- **Chemotherapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status, medical comorbidities, toxicity profile, and HER2-neu expression (for adenocarcinoma only).**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without a compromise of efficacy.**
- **Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.**
- **Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.**
- **Infusional fluorouracil and capecitabine may be used interchangeably (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.[1]**
- **Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.**
- **Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.[2]**
- **Perioperative chemotherapy[3,4] is an alternative but less preferred option.**
- **Induction chemotherapy may be appropriate as clinically indicated.**
- **Upon completion of chemotherapy, patients should be assessed for response and monitored for any long-term complications.**
- **Please refer to the Principles of Radiation Therapy for the radiation therapy administration details. (ESOPH-F)**

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation:

- **Preferred Regimens:**
  - **Paclitaxel and carboplatin (category 1)[1]**
  - **Cisplatin and fluorouracil (category 1)[2,3]**
  - **Oxaliplatin and fluorouracil (category 1)[4,5]**
  - **Cisplatin and capecitabine[6]**
  - **Oxaliplatin and capecitabine[7]**
- **Other Regimens:**
  - **Irinotecan and cisplatin (category 2B)[8]**
  - **Docetaxel or paclitaxel and fluoropyrimidine (Fluorouracil or capecitabine) (category 2B)[9,10]**

Perioperative Chemotherapy

(3 cycles preoperative and 3 cycles postoperative)
(Only for adenocarcinoma of the thoracic esophagus or EGJ):

- **ECF (epirubicin, cisplatin and fluorouracil) (category 1)[11]**
- **ECF modifications (category 1)[12]**
  - **Epirubicin, oxaliplatin and fluorouracil**
  - **Epirubicin, cisplatin and capecitabine**
  - **Epirubicin, oxaliplatin and capecitabine**
- **Fluorouracil and cisplatin (category 1)[13]**

Definitive Chemoradiation:

- **Preferred Regimens:**
  - **Cisplatin and fluorouracil (category 1)[14]**
  - **Oxaliplatin and fluorouracil (category 1)[4,5]**
  - **Cisplatin and capecitabine[6]**
  - **Oxaliplatin and capecitabine[7]**
  - **Paclitaxel and carboplatin[1] (category 2A)**
- **Other Regimens:**
  - **Paclitaxel or docetaxel and cisplatin[15-17]**
  - **Irinotecan and cisplatin (category 2B)[8]**
  - **Docetaxel or paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[9,10]**

Postoperative Chemoradiation:

- **Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation[18-23]**

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

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

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

- **Trastuzumab can be added to chemotherapy for HER2-neu overexpressing adenocarcinoma**
  [See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B)]
  - **Combination with cisplatin and fluoropyrimidine (category 1 for first-line therapy)[24]**
  - **Combination with other chemotherapy agents (category 2B)**
  - **Trastuzumab is not recommended for use with anthracyclines**

First-Line Therapy

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

- **Preferred Regimens:**
  - **DCF (docetaxel, cisplatin and fluorouracil†) (category 1)[25-28]**
  - **DCF modifications**
    - **Docetaxel, oxaliplatin and fluorouracil†[,29,30]**
    - **Docetaxel, carboplatin and fluorouracil (category 2B)[31]**
  - **ECF (epirubicin, cisplatin and fluorouracil) (category 1)[32,33]**
  - **ECF modifications (category 1)[33]**
    - **Epirubicin, oxaliplatin and fluorouracil**
    - **Epirubicin, cisplatin and capecitabine**
    - **Epirubicin, oxaliplatin and capecitabine**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin (category 1)[34-37]**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[35,38,39]**
  - **Fluorouracil† and irinotecan[40-42]**
- **Other Regimens:**
  - **Paclitaxel with cisplatin or carboplatin[43-45]**
  - **Docetaxel with cisplatin[26,46,47]**
  - **Docetaxel and irinotecan (category 2B)[48]**
  - **Fluoropyrimidine (fluorouracil† or capecitabine)[41,49,50]**
  - **Docetaxel[51]**
  - **Paclitaxel[52,53]**

Second-Line Therapy

Dependent on prior therapy and performance status (PS):

- **Preferred Regimens:**
  - **Docetaxel (category 2B)[51]**
  - **Paclitaxel (category 2B)[52-54]**
  - **Irinotecan (category 2B)[54-57]**
- **Other Regimens:**
  - **Irinotecan and cisplatin[38,58]**
  - **Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine) (category 2B)[41,59,60]**
  - **Docetaxel and irinotecan (category 2B)[48]**

Alternative regimens for consideration (these may be combined with other regimens when appropriate) (category 2B):

- **Mitomycin and irinotecan[61-63]**
- **Mitomycin and fluorouracil†[,64]**
- **Etoposide[65,66]**
- **Erlotinib (for squamous cell carcinoma only)[67]**

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.

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

PREOPERATIVE CHEMORADIATION

PREFERRED REGIMENS

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

Cisplatin and fluorouracil
Cisplatin 75-100 mg/m^2 IV on Days 1 and 29
Fluorouracil 750-1000 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-4 and 29-32
35-day cycle[2]

Cisplatin 15 mg/m^2 IV daily on Days 1-5
Fluorouracil 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5
Cycled every 21 days for 2 cycles[3]

Oxaliplatin and fluorouracil
Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 800 mg/m^2 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[4]

Oxaliplatin 85 mg/m^2 IV on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m^2 IV daily on Days 1-33[5]

PREFERRED REGIMENS

Cisplatin and capecitabine
Cisplatin 30 mg/m^2 IV on Day 1
Capecitabine 800 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[6]

Oxaliplatin and capecitabine
Oxaliplatin 85 mg/m^2 IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m^2 PO BID on Days 1-5 for 5 weeks[7]

OTHER REGIMENS

Irinotecan and cisplatin
Irinotecan 65 mg/m^2 IV on Days 1, 8, 22, and 29
Cisplatin 30 mg/m^2 IV on Days 1, 8, 22, and 29[8]

Taxane and fluoropyrimidine
Paclitaxel 45 mg/m^2 IV on Day 1 weekly
Fluorouracil 300 mg/m^2 IV continuous infusion daily on Days 1-5
Weekly for 5 weeks[9]

Paclitaxel 45-50 mg/m^2 IV on Day 1
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[9]

Docetaxel 7.5 mg/m^2 IV on Day 1
Fluorouracil 200-300 mg/m^2 IV daily on Days 1-5
Weekly for 5 weeks[10]

Docetaxel 7.5 mg/m^2 IV on Day 1
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[10]

†† Chemotherapy 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††

PERIOPERATIVE CHEMOTHERAPY (INCLUDING EG JUNCTION)

ECF (epirubicin, cisplatin, and fluorouracil)

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[11]

ECF modifications

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m2 IV continuous infusion over 24 hours daily on Days 1-21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[12]

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Capecitabine 625 mg/m^2 PO BID on Days 1-21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[12]

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Capecitabine 625 mg/m^2 PO BID on Days 1-21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[12]

Fluorouracil and cisplatin

Fluorouracil 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5
Cisplatin 100 mg/m^2 IV on Day 1
Cycled every 28 days for 2-3 cycles preoperatively and 3-4 cycles postoperatively for a total of 6 cycles[13]

††Chemotherapy 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††

DEFINITIVE CHEMORADIATION (NON-SURGICAL)

PREFERRED REGIMENS

Cisplatin and fluorouracil

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 for 2-4 cycles for 2 cycles with radiation followed by 2 cycles without radiation[14]

Oxaliplatin and fluorouracil

Oxaliplatin 85 mg/m^2 IV on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m^2 IV daily on Days 1-33[5]

Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 800 mg/m^2 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[4]

Cisplatin and capecitabine

Cisplatin 30 mg/m^2 IV on Day 1
Capecitabine 800 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[6]

Oxaliplatin and capecitabine

Oxaliplatin 85 mg/m^2 IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m^2 PO BID on Days 1-5 for 5 weeks[7]

Paclitaxel and carboplatin

Paclitaxel 50 mg/m^2 IV on Day 1
Carboplatin AUC 2 IV on Day 1
Weekly for 5 weeks[1]

OTHER REGIMENS

Taxane and cisplatin

Paclitaxel 60 mg/m^2 IV on Days 1, 8, 15, and 22
Cisplatin 75 mg/m^2 IV on Day 1
Given for 1 cycle[15]

Docetaxel 60 mg/m^2 IV on Days 1 and 22
Cisplatin 60-80 mg/m^2 IV on Days 1 and 22
Given for 1 cycle[16]

Docetaxel 20-30 mg/m^2 IV on Day 1
Cisplatin 20-30 mg/m^2 IV on Day 1
Weekly for 5 weeks[17]

Irinotecan and cisplatin

Irinotecan 65 mg/m^2 IV on Days 1, 8, 22, 29
Cisplatin 30 mg/m^2 IV on Days 1, 8, 22, 29[8]

OTHER REGIMENS--continued

Taxane and fluoropyrimidine

Paclitaxel 45 mg/m^2 IV on Day 1 weekly
Fluorouracil 300 mg/m^2 IV continuous infusion daily on Days 1-5
Weekly for 5 weeks[9]

Paclitaxel 45-50 mg/m^2 IV on Day 1
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[9]

Docetaxel 7.5 mg/m^2 IV on Day 1
Fluorouracil 200-300 mg/m^2 IV daily on Days 1-5
Weekly for 5 weeks[10]

Docetaxel 7.5 mg/m^2 IV on Day 1
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5
Weekly for 5 weeks[10]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

POSTOPERATIVE CHEMORADIATION (INCLUDING EG JUNCTION)

5-FU (bolus) and leucovorin (category 1)[18]
Cycles 1, 3, and 4 (before and after radiation)
Leucovorin 20 mg/m^2 IVP on Days 1-5
5-FU 425 mg/m^2 IVP daily on Days 1-5
Cycled every 28 days

Cycle 2 (with radiation)
Leucovorin 20 mg/m^2 IVP on Days 1-4 and 31-33
5-FU 400 mg/m^2 IVP daily on Days 1-4
Cycled every 35-day cycle

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[18] 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/m^2 PO BID on Days 1-14
  Cycled every 28 days[19,20]

- **1 cycle before and 2 cycles after chemoradiation**
  Leucovorin 400 mg/m^2 IV on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 400 mg/m^2 IVP on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1, 2, 15, and 16
  Cycled every 28 days[21]

With radiation
Fluorouracil 200-250 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 or 1-7
Weekly for 5 weeks[22]

With radiation
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5 or 1-7
Weekly for 5 weeks[23]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

CHEMOTHERAPY 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[24]
or
Trastuzumab 6 mg/kg IV loading dose on
Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

DCF (docetaxel, cisplatin, and fluorouracil)

Docetaxel 75 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 1
Fluorouracil 1000 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-5
Cycled every 28 days[25]

Docetaxel 40 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IV on Day 1
Fluorouracil 1000 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1 and 2
Cisplatin 40 mg/m^2 IV on Day 3
Cycled every 14 days[26]

Docetaxel 60 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Fluorouracil 750 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-4
Cycled every 21 days[27]

Docetaxel 75-85 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 1
Fluorouracil 300 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-14
Cycled every 21 days[28]

PREFERRED REGIMENS--continued

DCF modifications

Docetaxel 50 mg/m^2 IV on Day 1
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 daily on Day 1
Cycled every 14 days[29]

Docetaxel 50 mg/m^2 IV on Day 1
Oxaliplatin 85 mg/m^2 IV on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[30]

Docetaxel 75 mg/m^2 IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-3
Cycled every 21 days[31]

ECF

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-21
Cycled every 21 days[32,33]

ECF modifications

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-21
Cycled every 21 days[33]

PREFERRED REGIMENS--continued

ECF modifications--continued

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Capecitabine 625 mg/m2 PO BID on Days 1-21
Cycled every 21 days[33]

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Capecitabine 625 mg/m^2 PO BID on Days 1-21
Cycled every 21 days[33]

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[34]

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 days5[3,36]

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[37]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

CHEMOTHERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE IS NOT INDICATED)

FIRST-LINE THERAPY---continued

PREFERRED REGIMENS

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 IVP on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[38]

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[35]

Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days[39]

Fluorouracil and irinotecan

Irinotecan 80 mg/m^2 IV on Day 1
Leucovorin 500 mg/m^2 IV on Day 1
Fluorouracil 2000 mg/m^2 IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 1 week off treatment[40]

Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[41]

Irinotecan 80 mg/m^2 IV on Day 1
Leucovorin 500 mg/m^2 IV combined with
Fluorouracil 2000 mg/m^2 IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[42]

OTHER 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[43]

Paclitaxel 90 mg/m^2 IV on Day 1
Cisplatin 50 mg/m^2 IV on Day 1
Cycled every 14 days[44]

Paclitaxel 200 mg/m^2 IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[45]

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[28,46,47]

Docetaxel and irinotecan

Docetaxel 35 mg/m^2 IV on Days 1 and 8
Irinotecan 50 mg/m^2 IV8on Days 1 and 8
Cycled every 21 days[48]

OTHER REGIMENS--continued

Fluoropyrimidine

Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[41]

Fluorouracil 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5
Cycled every 28 days [49]

Capecitabine 1000-1250 mg/m^2 PO BID on Days 1-14
Cycled every 21 days[50]

Taxane

Docetaxel 75-100 mg/m^2 IV on Day 1
Cycled every 21 days[51]

Paclitaxel 135-250 mg/m^2 IV on Day 1
Cycled every 21 days[52]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[53]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

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

SECOND-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[24]
or
Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Taxane

Docetaxel 75-100 mg/m^2 IV on Day 1
Cycled every 21 days[51]

Paclitaxel 135-250 mg/m^2 IV on Day 1
Cycled every 21 days[52]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[53]

Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15
Cycled every 28 days[54]

Irinotecan

Irinotecan 250-350 mg/m^2 IV on Day 1
Cycled every 21 days[55]

Irinotecan 150-180 mg/m^2 IV on Day 1
Cycled every 14 days[54,56,55]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[56]

OTHER REGIMENS

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[38,58]

Irinotecan and fluoropyrimidine

Irinotecan 250 mg/m^2 IV on Day 1
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Cycled every 21 days[59]

Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 600-1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[41,60]

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[48]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

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

ALTERNATIVE REGIMENS FOR CONSIDERATION

Mitomycin and irinotecan
Mitomycin 6 mg/m^2 IV on Day 1
Irinotecan 125 mg/m^2 IV on Days 2 and 9
Cycled every 28 days[61]

Irinotecan 150 mg/m^2 IV on Days 1 and 15
Mitomycin 8 mg/m^2 IV on Day 1
Cycled every 28 days[62]

Irinotecan 125 mg/m^2 Day 1
Mitomycin 5 mg/m^2 IV on Day 1
Cycled every 14 days[63]

Mitomycin, leucovorin, and fluorouracil
Mitomycin 10 mg/m^2 IV on Days 1 and 22
Leucovorin 500 mg/m^2 IV on Day 1
Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[64]

Etoposide
Etoposide 90-120 mg/m^2 IV on Days 1-3
Cycled every 28 days[65,66]

Erlotinib (for squamous cell carcinoma only)
Erlotinib 150 mg PO daily[67]

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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.

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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, 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.
- In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal cancers. Depending on the clinical situation, Siewert III tumors, may be more appropriately managed with radiation therapy guidelines applicable to either esophageal or gastric cancers. These recommendations may be modified depending on where the bulk of the tumor is located.

Simulation and Treatment Planning

- Use of CT simulation and 3D treatment planning is strongly encouraged.
- When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily set-up.
- The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified on the planning scan and other exams listed in the General section above. The clinical target volume (CTV) should include the areas at risk for microscopic disease. CTV is defined as the primary tumor plus a 3-4 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. The planning target volume (PTV) expansion should be 0.5 to 1 cm. The uncertainties arising from respiratory motion should also be taken into consideration. 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 4DCT data may also be used to create an internal target volume (ITV) from which subsequent CTV and PTV expansions can be made.
- Recommended elective treatment of node bearing regions depends upon the location of the primary tumor in the esophagus.
  - Cervical esophagus: Treat the supraclavicular nodes and consider treatment of higher echelon cervical nodes, especially if the nodal stage is N1 or greater.
  - Proximal third of the esophagus: Treat para-esophageal lymph nodes and supraclavicur lymph nodes.
  - Middle third of the esophagus: Treat para-esophageal lymph nodes.
  - Distal third of esophagus and the gastro-esophageal junction: para-esophageal lymph nodes, lesser curvature lymph nodes in the situation of distal lesions, and the celiac axis.

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Continued

PRINCIPLES OF RADIATION THERAPY

Simulation and Treatment Planning---continued

- **Lung dose guidelines: Normal lung (more than 2 cm outside the target volume) should not receive more than 40 Gy. To reduce the incidence of postoperative pulmonary complications (as well as symptomatic pneumonitis) a guideline is to limit the proportion of total lung receiving 20 Gy or more to 20% and 10 Gy or more to 40%, although it is recognized that these guidelines may be exceeded as needed to achieve other important planning goals, and as further information becomes available.**
- **Intensity modulated radiation therapy (IMRT) may be appropriate in selected cases to reduce dose to normal structures such as heart and lungs. In designing IMRT plans, for structures such as the lungs, attention should be given to the lung volume receiving low to moderate doses, 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).**

Blocking

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

Dose

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

[a]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 co-morbidities. DVH parameters as predictors of pulmonary complications in esophageal cancer patients are an area of active development among the NCCN institutions and others.

[b]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 Gy/day) because the lower preoperative therapy dose may not be adequate.

[c]Published studies have reported radiation doses from 60-66 Gy (1.8-2 Gy/day). However there is no randomized evidence to support any benefit or detriment of this dose range over 50-50.4 Gy (1.8-2 Gy/day).

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PRINCIPLES OF RADIATION THERAPY

Supportive Therapy

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

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PRINCIPLES OF RADIATION THERAPY
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PRINCIPLES OF 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, the functional degree of swallowing impairment and confirm the etiology of dysphagia
- Functional Degrees of Swallowing Impairment
  - Unable to swallow saliva
  - Able to swallow liquids only
  - Able to swallow semisolid food (consistency of baby food)
  - Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed
  - Able to eat solid food without special attention to bite size or chewing (dysphagia symptoms may be intermittent)
- Dysphagia arising from esophageal cancer most often is due to obstruction, but on occasion may be primarily due to tumor related dysmotility.

Obstruction:

- Complete esophageal obstruction
  - Endoscopic lumen restoration
  - Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
    - Surgical or radiologic placement of jejunal or gastrostomy tube
  - External beam radiation therapy
    - Brachytherapy may be considered in place of external beam radiation if lumen can be restored using appropriate applicators during the delivery of brachytherapy to decrease excessive dose deposition on mucosal surfaces. Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.
  - Chemotherapy
  - Surgery
    - May on occasion be useful in carefully selected patients.
- Severe esophageal obstruction (able to swallow liquids only)
  - Endoscopic lumen enhancement
    - Wire guided dilation or balloon dilation (caution should be exercised when dilating malignant strictures as this may be associated with an increased risk of perforation)
    - Endoscopy or fluoroscopy-guided placement of covered expandable metal stents.
      -While there are data suggesting a lower migration and re-obstruction rate with the larger diameter covered expandable metal stents, they may be associated with a higher risk of other complications. If possible, the distal end of the stent should remain above the GEJ to reduce symptoms of reflux and risk of aspiration.
    - Other measures as stated above
- Moderate esophageal obstruction (able to swallow semisolid food)
  - Endoscopic lumen enhancement as necessary
    - Measures stated above may be considered

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PRINCIPLES OF BEST SUPPORTIVE CARE[1-7]

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 treatedwith endoscopic removal of the stent once uncontrollable nature of pain is established.**

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**
- **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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NCCN Guidelines Version 2.2013 Staging Esophageal and Esophagogastric Junction Cancers

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Discussion

Table 1

American Joint Committee on Cancer (AJCC)
TNM Classification of Carcinoma of the Esophagus and Esophagogastric Junction (7th ed, 2010)

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis High-grade dysplasia*
T1 Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a Tumor invades lamina propria or muscularis mucosae
T1b Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades adventitia
T4 Tumor invades adjacent structures
T4a Resectable tumor invading pleura, pericardium,or diaphragm
T4b Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

*High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–2 regional lymph nodes
N2 Metastasis in 3–6 regional lymph nodes
N3 Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

Squamous Cell Carcinoma*

Stage	T	N	M	Grade	Tumor Location**
Stage 0	Tis (HGD)	N0	M0	1, X	Any
Stage IA	T1	N0	M0	1, X	Any
Stage IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
Stage IIA	T2–3	N0	M0	1, X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
Stage IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
Stage IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Stage IIIB	T3	N2	M0	Any	Any
Stage IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IV	Any	Any	M1	Any	Any

*Or mixed histology including a squamous component or NOS.
**Location of the primary cancer site is defi ned by the position of the upper (proximal) edge of the tumor in the esophagus.

Continue...

Table 1---Continued

Anatomic Stage/Prognostic Groups

Adenocarcinoma

Stage	T	N	M	Grade
Stage 0	Tis (HGD)	N0	M0	1, X
Stage IA	T1	N0	M0	1-2, X
Stage IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
Stage IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
Stage IV	Any	Any	M1	Any

Histologic Grade (G)

GX	Grade cannot be assessed – stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated – stage grouping as G3 squamous

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 noted.

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Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach, constitute a major health problem around the world. A dramatic shift in the location of upper GI tract tumors has occurred in the United States.[1,2] Changes in 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.

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide.[4] In 2013, an estimated 17,990 people will be diagnosed and 15,210 people will eventually die of their disease in the United States.[5] It is endemic in many parts of the world, particularly in the developing nations. The incidence of esophageal cancer represents one of the widest variations, with a 60-fold difference between high- and low-incidence regions.[6] High prevalence areas include Asia, southern and eastern Africa, and Northern France.[7]

Esophageal cancers are histologically classified as squamous cell carcinoma (SCC) or adenocarcinoma.[8] Adenocarcinoma of the esophagus may be associated with a better long-term prognosis after resection than SCC.[9] However, more concrete data are desirable for such an assertion. SCC is most common in the endemic regions of the world and adenocarcinoma is most common in nonendemic areas, such as North America and many Western European countries. Both SCC and adenocarcinoma are more common in men. SCCs have become increasingly less common, accounting for fewer than 30% of all esophageal cancers in the United States and Western Europe. Adenocarcinoma is diagnosed predominantly in white men in whom the incidence has risen more steeply. However, adenocarcinoma is gradually increasing in men of all ethnic backgrounds and also in women.[1]

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

Gastroesophageal reflux disease (GERD) and Barrett's esophagus are the other two major risk factors for adenocarcinoma of the esophagus.[19-22] 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.[23] Patients with Barrett's esophagus have 30 to 60 times greater risk of developing adenocarcinoma of the esophagus than the general population.[21] Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with higher grades of dysplasia.[24,25] These preliminary findings warrant further prospective evaluation as predictors of risk for the development of high-grade dysplasia (HGD) and adenocarcinoma of the esophagus in patients with Barrett's esophagus.

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

Staging

The tumor (T), node (N) and metastasis (M) classification developed by the AJCC in 2002 was based on the pathologic review of the surgical specimen in patients who had surgery as primary therapy. The revised 2010 AJCC staging classification is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for 4627 patients who were treated with primary esophagectomy without preoperative or postoperative therapy.[27] In the data reported by the WECC, survival decreased with increasing depth of tumor invasion (pT), presence of regional lymph node metastases (pN) and the presence of distant metastases (pM).[28] In addition, survival was somewhat worse for pT1b (submucosal) tumors than for pT1a (intramucosal) tumors and survival was worse for SCC than for adenocarcinomas.

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

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 preclinical staging.[29] In North America and many western European countries, where screening programs for early detection of esophageal cancer are not in use or practical because of low incidence, the diagnosis is often made late in the disease course. At diagnosis, nearly 50% of patients have cancer that extends beyond the local regional confines of the primary. Fewer than 60% of patients with locoregional cancer 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 the adenocarcinoma of the EGJ into three types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass.[30] If the epicenter of the tumor or more than 66% of the tumor mass is located more than 1 cm above the anatomic EGJ, then the tumor is classified as an adenocarcinoma of the distal esophagus, type I. If the epicenter of the tumor or tumor mass is located within 1 cm proximal and 2 cm distal to the anatomic EGJ, this adenocarcinoma is classified as type II. If the epicenter of the tumor or more than 66% of the tumor mass is located more than 2 cm below the anatomic EGJ, the tumor is classified as type III.[30]

In 2000, the classification was changed slightly.[31] Siewert Type I tumors are defined as the 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 the true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ. Siewert Type III is defined as the subcardial carcinoma with the tumor center between 2 to 5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below.

In the revised AJCC staging system, tumors whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extends into the EGJ or esophagus (Siewert Types I and II) are classified as adenocarcinoma of the esophagus for the purposes of staging.[27] All other cancers with a midpoint in the stomach lying more than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into the EGJ or esophagus (Siewert Type III) are staged using the gastric cancer staging system. This approach remains a subject of disagreement, some confusion and debate. An individualized therapeutic approach may be preferred for specific patients and tumor locations, based on thorough pretreatment staging. Therapeutic decisions may be refined according to the location of the individual tumor, nodal distribution, and specific requirements for local control.

Barrett's Esophagus

Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar or glandular epithelium that is predisposed to malignancy.[23] Patients with Barrett's esophagus are at a greater risk of developing adenocarcinoma of the esophagus than the general population and the risk of malignancy increases with the development of low-grade dysplasia (LGD) and HGD.[21] The 5-year cumulative incidence of cancer was 4% for patients with LGD compared to 59% for those with HGD.[32] Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with the progression of Barrett's esophagus to adenocarcinoma of the esophagus.[24,25,33] Biomarkers such as aneuploidy and loss of heterozygosity of *p53* have been associated with increased risk of progression to HGD and/or adenocarcinoma of the esophagus.[33] 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 is performed on patients with severe symptoms of GERD, especially those with a family history of Barrett's esophagus or esophageal cancer. The location, length and circumferential involvement should be characterized in accordance with the Prague classification and mucosal nodules should be carefully documented.[34]

Medical management of patients with Barrett's esophagus continues to evolve and is based on the symptomatic control of gastroesophageal reflux using histamine receptor antagonists or proton pump inhibitors. Surgical resection has been the preferred treatment for patients with Barrett's esophagus and HGD. Alternative strategies for patients with Barrett's esophagus and HGD include endoscopic mucosal resection (EMR), cryoablation and endoscopic ablation with radiofrequency ablation (RFA) or photodynamic therapy (PDT).[35] For patients with metaplasia or LGD, acid reflux is controlled with histamine receptor antagonists or proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole).

Endoscopic surveillance is performed to evaluate the progression from metaplasia to LGD, HGD, or adenocarcinoma. However, controversy exists when recommending a surveillance schedule for patients with Barrett's esophagus. Recent studies suggest that the rate of progression of Barrett's esophagus to adenocarcinoma of the

esophagus is much lower than previously reported.[36,37] 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.[38] 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.[38] For patients who are at high risk for cancer or refuse EMR, continued surveillance every 3 months is an option if definitive therapy would be offered for those who develop adenocarcinoma.

Principles of Pathology

Biopsy

A specific diagnosis of SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the TNM system for SCC.[27] In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade (required for stage grouping). In addition to the above mentioned elements, the pathology report of the biopsy specimen should also include the presence or absence of Barrett's esophagus.

In the case of EMR or esophageal resection specimens, the depth of tumor invasion and the status of mucosal and deep margins should also be recorded. In an esophageal resection specimen, Barrett's esophagus with HGD is reported as carcinoma-in-situ (Tis).[27] Biopsies showing Barrett's esophagus with a suspected dysplasia should be reviewed by a second expert GI pathologist for confirmation.[38]

The pathology report of the biopsy of surgical specimen should also document the location of the tumor in relationship to the EGJ, lymph node status and the number of lymph nodes recovered. In the case of esophagectomy with prior chemoradiation, tumor site should be thoroughly sampled including the entire EGJ after preoperative therapy without grossly obvious residual tumor.

Assessment of HER2-neu Overexpression

Human epidermal growth factor receptor 2 (*HER2*) gene and/or HER2 protein expression has been implicated in the development of gastric and EGJ adenocarcinomas.[39] *HER2-neu* amplification and overexpression are more frequent in adenocarcinoma of the esophagus (15% to 30%) than SCC of esophagus (5% to13%).[40-42] HER2-neu overexpression in esophagogastric cancers varies widely (2% to 45%).[43] HER2-neu-positivity has been reported to be higher in patients with EGJ cancers than in patients with gastric cancers.[44,45] In the Trastuzumab for Gastric Cancer (ToGA) trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2-neu-positive advanced gastric cancer, HER2-neu-positivity rates were 33% and 21% respectively, for patients with EGJ and gastric cancers.[46]

However, unlike in breast cancer, the prognostic significance of *HER2-neu* expression in patients with esophageal cancer is not clear. It has been demonstrated that *HER2-neu* overexpression correlates with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[43] *HER2-neu* overexpression seems to be associated with poorer survival, especially in patients with SCC of the esophagus.[40]

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

According to the HER2 scoring system for breast cancer proposed by the American Society of Clinical Oncology/College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to two major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many gastric cancer patients who could otherwise be candidates for anti-HER2 therapy.[47,48] Results from two separate series also demonstrated that the HER2 scoring system for breast cancer identified a significantly lower percentage of patients with gastric cancer meeting the criteria for HER2-positivity by IHC (5.4% vs.11% in the ToGA trial).[49,50]

In 2008, Hoffmann et al developed a modified 4-tier HER2 scoring system specific 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.[47] In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[48] This modified HER2 scoring system was also used in the ToGA trial.[49]

HER2 testing is now recommended for all patients with metastatic EGJ adenocarcinoma at the time of diagnosis. The guidelines recommend that assessment for HER2 status should be performed first using IHC following the modified scoring system used in the ToGA trial).[47,49] A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in-situ hybridization techniques (Table 1). The panel recommends FISH only for patients with an IHC score of 2+, although some institutions routinely perform both IHC and FISH on all patients.

Assessment of Treatment Response

The prognostic significance of complete pathologic response and histologic tumor regression after neoadjuvant therapy in patients with adenocarcinoma and SCC of the esophagus has been demonstrated in several studies.[51-56] 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.[57]

Several tumor regression grading (TRG) systems have been developed to assess the pathologic response to preoperative neoadjuvant therapy. Mandard et al proposed a 5-tiered grading system based on the percentage of residual cancer cells and the extent of fibrosis.[58] Tumor regression remained a significant predictor of disease-free survival (DFS) after preoperative chemoradiation and surgery. Chirieac et al used a 4-tiered classification system based on the extent of residual cancer (0%, 1% 10%, 11%-50% and more than 50% [gross residual carcinoma]).[57] The overall survival (OS) was significantly better for patients with no residual carcinoma (133 months) than it was for those

with more than 50% residual carcinoma (10.5 months). However, OS was not significantly different between patients with 1%-10% and 11%-50% residual carcinoma. Based on these results Wu et al developed a 3-tiered classification system: P0 (0% residual carcinoma), P1 (1% to 50% residual carcinoma), and P2 (more than 50% residual carcinoma).[59] Although grading systems for tumor response in esophageal cancer have not been uniformly adopted, in general, the 3-tiered system proposed by Wu et al has been reported to have an excellent interobserver agreement among pathologists on grading the extent of residual carcinoma in patients with esophageal and EGJ cancers. See the Principles of Pathologic Review and *HER2-neu* Testing-Assessment of Treatment Response-Table 2 in the guidelines.

Role of PET Scans in the Assessment of Treatment Response

The prognostic significance of metabolic response defined by PET scans after preoperative chemotherapy has been evaluated in retrospective [60-70] and prospective studies.[71-85] While some studies have reported that PET scans could predict histopathologic complete response and outcome after definitive or preoperative chemoradiation in patients with locally advanced esophageal cancer,[60,61,63,66,67,70-77,79-81] other studies have shown conflicting results.[62,65,69,78,82-85]

The cut-off points for the reduction in the 18-fluorodeoxyglucose (FDG) standardized uptake value (SUV) between pre and posttreatment PET scans (35%-80%)[71-73,81] and the timing of posttreatment PET before surgery (2 to 6 weeks) [71,75,79,81] have varied widely across the studies. In addition, the prospective studies that have shown the positive predictive value of PET scan after preoperative therapy are limited by the small sample size with the exception of the MUNICON II study which included 110 patients with locally advanced adenocarcinoma of the EGJ.[81] In this study, metabolic responders were defined as those with a decrease of 35% or more 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 0% in metabolic non-responders.

In some retrospective studies, FDG uptake on a single post-treatment 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 2.5-4.[60,64] Swisher et al showed that the 2-year survival rate was 60% for patients with a post chemoradiation FDG uptake of less than 4 and 34% for those with a FDG uptake of 4 or more; PET scans, however, could not distinguish patients with microscopic residual disease.[60] In a more recent retrospective study using the same cut-off value (FDG uptake of less than 4), Bruzzi et al. reported that PET scan has only 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. Other studies have also reported that the accuracy of PET for detecting non-responders is very low to justify the use of PET scans to determine early discontinuation of preoperative therapy in patients with potentially resectable esophageal cancer.[83,85]

Based on the available evidence, the guidelines recommend consideration of PET/CT or PET only for the assessment of response to preoperative or definitive chemoradiation therapy before surgery or initiation of postoperative treatment (category 2B). However, the guidelines emphasize that PET scans should not be used for the selection of patients to surgery following preoperative chemoradiation. In patients who are treated with preoperative chemoradiation,

RT-induced ulceration has been associated with false-positive results on PET/CT, precluding accurate detection of residual esophageal tumor.[86] 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.[86]

Surgery

Surgery is a major component of treatment for resectable disease. One of the major developments in the surgical therapy of esophageal cancer has been the marked reduction in surgical morbidity and mortality as a result of improvements in staging techniques, patient selection, support systems and surgical experience. Recent randomized trials have shown that preoperative chemoradiation (CROSS study)[87] and perioperative chemotherapy (MAGIC trial, predominantly a gastric cancer trial that included a small group of patients with lower esophageal and EGJ cancers) [88] significantly improved survival in patients with resectable esophageal and esophagogastric cancer. With the incidence of esophageal cancer, particularly adenocarcinoma of the distal esophagus increasing dramatically, the hope is that surveillance programs will continue to detect earlier stage disease, thus increasing the number of patients who can benefit from therapy.

Currently, staging studies such as 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 disease, lymph node involvement has been shown to be a strong independent predictor of poor survival with surgery alone. These patients are therefore considered for preoperative therapy followed by surgery. In the future, molecular biologic techniques may result in improved prognostic stratification, improved patient selection for surgical therapy, and improved OS.[89-91]

Surgical Approaches

Several operative techniques are acceptable for esophagogastrectomy in patients with resectable esophageal cancer or EGJ cancers.[92] Transthoracic and transhiatal esophagogastrectomy are the two most common surgical approaches. Acceptable operative techniques and the choice of conduit are described below.

Transthoracic Esophagogastrectomy

Ivor Lewis esophagogastrectomy (right thoracotomy and laparotomy),[93] and the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis)[94] are the two standard options to achieve transthoracic esophagogastrectomy. Ivor-Lewis esophagogastrectomy, the most frequently used procedure for transthoracic esophagogastrectomy, uses laparotomy and right thoracotomy, with upper thoracic esophagogastric anastomosis (at or above the azygos vein).[93] 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 at any thoracic location, but proximal esophageal margin will be inadequate for tumors in the middle esophagus.

Transhiatal Esophagogastrectomy

Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[95] 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.[96] In the largest population based study which assessed outcomes after transthoracic and transhiatal esophagectomy for esophageal cancer, transhiatal esophagectomy offered an early survival advantage. However, long-term survival was not different between the two surgical approaches.[97]

Transthoracic or Thoracoabdominal Esophagogastrectomy

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision, through the eighth intercostal space.[98] Mobilization of the stomach for use as the conduit is performed as described previously, and esophagectomy is accomplished through the left thoracotomy. Esophagogastric anastomosis is performed in the left chest, usually just superior to the inferior pulmonary vein, although it may be performed higher if the conduit is tunneled under the aortic arch. This approach may be used for lesions in the distal esophagus.[98]

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 study of MIE (mainly using thoracoscopic mobilization) in 222 patients, mortality rate was only 1.4% and hospital stay was only 7 days, which is less than most open procedures; only 16 patients (7.2%) required conversion to an open procedure.[99] However, it is important to note that 62% of their patients had early stage disease. A recent report involving 56 patients also showed that MIE was comparable to open esophagectomy but the use of neoadjuvant treatment slightly increased the surgical mortality from 1.5% to 1.8%.[100] No randomized trials have assessed whether MIE improves outcomes when compared with open procedures.

Open esophagectomy may still be preferred over MIE for certain patients with previous abdominal surgery, large and bulky tumors, concerns that the gastric conduit may not be useable and difficulty with lymph node dissection. In the absence of prospective trials with longer follow-up, MIE remains investigational and is still an evolving treatment option for patients with esophageal cancer.[101,102] Open esophagectomy should remain the standard for many patients. MIE may be useful for older patients.[103]

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 leak. Advantages of a thoracic anastomosis may include lower incidence of anastomotic leak, lower stricture rate and lower rate of left recurrent nerve injury. In a prospective randomized trial, cervical and thoracic anastomoses after esophageal resection were equally safe when performed in a standardized way.[104] Gastric conduit is preferred for esophageal reconstruction and it is preferred by the majority of esophageal surgeons.[105] Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[106]

Principles of Surgery

All patients should be assessed for physiologic ability to undergo esophageal resection.[107] Selection of patients for surgery involves assessing whether they are medically fit (medically able to tolerate general anesthesia and major abdominal and/or thoracic surgery). Most patients with early stage cancer can tolerate resection. Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation.

Clinical staging using EUS (with FNA, if indicated), chest and abdomen CT scan, and PET scan (integrated PET/CT preferred over PET alone) should be performed before surgery to assess resectability.[108] Patients with locally advanced cancer should have access to medical and radiation oncology consults. Pretreatment nutritional support should be considered for patients with significant dysphagia and weight loss in order to support them during induction chemoradiation. Enteral nutrition is the best option and a jejunostomy feeding tube is preferred over gastrostomy feeding tube or percutaneous endoscopic gastrostomy (PEG) tube.

Surgery is usually performed with a curative intent, but it may be included as a component of palliative care. Palliative resections, however, should be avoided in patients with clearly unresectable or advanced cancer with comorbidities, including severe cardiac and pulmonary disease. These patients may benefit from noninvasive palliative interventions.

Esophagectomy should be considered for all physiologically fit patients with localized resectable thoracic esophageal cancer (greater than 5 cm from cricopharyngeus) and intraabdominal esophageal or EGJ cancer. The type of esophageal resection is dictated by the size, stage and location of the primary tumor, as well as the surgeon's experience and the patient's preference. Cervical or cervicothoracic esophageal cancers less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Salvage esophagectomy can be considered for patients who develop localized, resectable esophageal recurrence after definitive chemoradiation if there is no distant recurrence.[109]

The surgical approach for Siewert Type I and II EGJ tumors are similar to that described above. Siewert Type III tumors are considered as gastric cancers and the surgical approach for these tumors is similar to that described in the NCCN Guidelines for Gastric cancer.[30,110,111] 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.[112] Positive peritoneal cytology in the absence of overt peritoneal metastases is associated with a poor prognosis in patients with EGJ adenocarcinoma.[113] Patients with advanced tumors, clinical stage T3 tumors, or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

Patients with Tis or T1a tumors should have an option for EMR. Patients with tumors in the submucosa (T1b) or deeper may be treated with esophagectomy. Patients with T1-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 tumor as well. T4a tumors with involvement of the pericardium, pleura or diaphragm may be resectable. 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. Esophagectomy, EMR and other ablative techniques should be performed in high volume esophageal cancer centers by experienced surgeons and endoscopists.[114]

Lymph node dissections (or lymphadenectomy) can be performed using the standard or extended (en-bloc) technique.[115] In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the SEER database, patients who had more than 12 lymph nodes examined had significant reduction in mortality compared to those who had no lymph node evaluation and patients who had 30 or more lymph nodes examined had significantly lower mortality than any other groups.[116] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[117,118] A recent 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.[118] In patients undergoing esophagectomy without preoperative chemoradiation, the guidelines recommend that at least 15 lymph nodes should be removed for adequate nodal staging. The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.

Endoscopic Therapies

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

EMR represents a major advance in minimally invasive approaches for the management of patients with upper GI tract cancers.[119] EMR is used widely for treating superficial early SCC of the esophagus in Japan and is gaining acceptance in Western countries for the treatment of Barrett's esophagus and superficial adenocarcinomas.[119-122] While EMR of visible lesions suspicious of malignancy is effective, it is also associated with a high rate of recurrence. Diagnostic EMR has been reported to accurately determine the depth of tumor invasion and therefore influence surgical planning prior to surgical resection.[128] Complete Barrett's eradication EMR (CBE-EMR) has been shown to be a highly effective long-term treatment for patients with Barrett's esophagus and HGD.[123-127]

PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett's esophagus and HGD.[129,130] However, more recently, the use of PDT as an endoscopic therapy for esophageal cancers is losing popularity due to long-term consequences. Balloon-based RFA induces complete remissions in the majority of patients with Barrett's esophagus with or without HGD.[131] Endoscopic cryoablation has also been reported to be a safe and well tolerated therapy for patients with Barrett's esophagus with HGD and early stage esophageal cancers.[132,133]

Although there are no randomized studies that have compared EMR and endoscopic ablation procedures with other surgical techniques for GI cancers, there are retrospective studies that demonstrate that EMR and other endoscopic ablation procedures are complementary and provide effective therapeutic options for selected patients with Barrett's esophagus and early esophageal cancer.[134] These procedures are best performed in centers with experienced physicians.

Principles of Endoscopy

Endoscopy has become an important tool in the diagnosis, staging, treatment and surveillance of patients with esophageal cancer. Most endoscopy procedures are performed with the aid of conscious sedation or monitored anesthesia 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 endoscopies are performed to determine the presence and location of esophageal cancer and to biopsy any suspicious lesions. Multiple biopsies (6-8), using standard size endoscopy forceps should be performed to provide sufficient material for histologic interpretation. Larger forceps are recommended during surveillance endoscopy of Barrett's esophagus for the detection of dysplasia.[135] Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment.

The location of the tumor relative to the teeth and EGJ, the degree of obstruction, and the length and the extent of circumferential involvement of the tumor should be carefully recorded to assist with treatment planning. Esophageal tumor length, as assessed by preoperative endoscopy has been identified as an independent predictor of long-term survival in patients with adenocarcinoma of the esophagus.[136] The 5-year survival rate was significantly higher for patients with a tumor length of 2 cm or less (78% vs. 29% for those with a tumor length of more than 2 cm).

EMR can be therapeutic as well as diagnostic. EMR of focal nodules can be performed in the setting of early stage disease to provide accurate staging of the tumor including degree of differentiation and, vascular and/or lymphatic invasion.[137,138] High-resolution endoscopy and narrow-band imaging may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[139,140] EMR can be potentially therapeutic when a lesion less than 2 cm in diameter is removed and histopathologic assessment demonstrates well or moderate differentiation, no invasion beyond the muscularis mucosa, and no lymphovascular invasion.

Staging

EUS provides accurate initial staging of locoregional esophageal cancer. EUS performed prior to any treatment provides evidence of depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and occasionally signs of distant spread, such as lesions in surrounding organs (M).[141,142] 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 also confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[143] EMR of small lesions (3 cm or less) can provide accurate T staging, complementing the results of EUS.[144] The combined use of EUS and FNA (EUS-FNA) has a greater accuracy than EUS alone in the evaluation of lymph node metastasis, especially celiac lymph nodes.[145,146] 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.[147] Direct surgical resection was contraindicated in 77% of evaluable patients due to advanced locoregional/metastatic disease.

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. In certain cases, dilating the malignant stricture to allow completion of staging may be appropriate but there is increased risk of perforation after dilation. FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. The review of CT and PET scans prior to EUS is recommended to become familiar with the nodal distribution for a possible FNA biopsy.

Treatment

The goal of EMR and/or ablation is the complete removal of Barrett's esophagus in addition to the eradication of the malignancy.

Indications for therapeutic EMR for esophageal cancer include HGD or carcinoma in situ (Tis), well to moderately differentiated lesions confined to the mucosa (T1a) without evidence of lymphovascular invasion or lymph node metastases. Esophagectomy for Tis or T1a tumors should be reserved for unsuccessful EMR. All focal nodules should be resected rather than ablated. Tis or HGD needs to be fully characterized, including evaluating presence of nodularity and, lateral spread and ruling out multifocal disease. EUS staging prior to proceeding with EMR in the setting of carcinoma is recommended.[137] Ablative therapy of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed following EMR.

Long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG Laser, PDT and cryotherapy, or endoscopic and radiographic assisted insertion of expandable metal or plastic stents.[148,149] 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.

Surveillance

Assessment with endoscopy with biopsy and brushings should be done 5-6 weeks after completion of preoperative therapy. EUS performed after chemotherapy or RT has a reduced ability to accurately determine the present stage of disease.[150] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease.[151]

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 performed in conjunction with endoscopy exams has a high sensitivity for recurrent disease.[152] EUS-FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

Endoscopic surveillance after ablative therapy or EMR of early esophageal cancer should continue after completion of treatment. Biopsies of the neo-squamous mucosa are recommended 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 HGD and LGD using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett's esophagus is not recommended.

Radiation Therapy

Several historical series have reported results of using external beam radiation therapy (RT) alone. Most of these series included patients with unfavorable features, such as clinical T4 cancer and or patients who were not expected to withstand surgery. Overall, the 5-year survival rate for patients treated with conventional doses of RT alone is 0-10%.[153-155] 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.[156] 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 by 3 years.[157,158] Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

Alternative RT techniques, such as hypoxic cell sensitizers and hyperfractionation, have not resulted in a clear survival advantage. Experience with intraoperative RT as an alternative to external beam RT is limited.[159-163] Intensity modulated RT (IMRT) is currently being investigated. Retrospective studies comparing three dimensional (3D) conformal vs. IMRT for patients with esophagus cancer have generally shown superior dose conformity and homogeneity with IMRT and reduction of RT dose to the lungs and heart.

In the adjuvant setting, randomized trials have not shown a survival advantage for preoperative or postoperative RT alone.[164-166] A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative RT.[167]

Principles of Radiation Therapy

RT (definitive, preoperative, postoperative or palliative) can be an integral part of treatment for esophageal cancer. The panel recommends a dose range of 41.4 to 50.4 Gy (delivered in fractions of 1.8 to 2 Gy per day) for preoperative therapy. Patients who are not fit for surgery due to the presence of comorbidities or other risk factors should receive RT doses of 50 to 50.4 Gy because the lower dose may not be adequate. The recommended dose ranges for postoperative and definitive therapy are 45 to 50.4 Gy and 50 to 50.4 Gy respectively. For definitive therapy, higher doses (60 to 66 Gy) may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned. However there is no evidence from randomized trials to support the additional benefit of this dose range over 50 to 50.4 Gy.

The panel recommends a multidisciplinary team, which should include medical, radiation and surgical oncologists, radiologists, gastroenterologists and pathologists. In general, Siewert I and II tumors should be managed with RT guidelines applicable to esophageal and EGJ cancers. Siewert III tumors may be more appropriately managed with RT guidelines applicable to either esophageal, EGJ or gastric cancers. These recommendations may be modified depending on the location of the bulk of the tumor.

The panel encourages the use of CT simulation and 3D treatment planning. When four dimensional (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. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid target localization. Use of immobilization device is strongly recommended for reproducibility.

The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified by imaging studies such as CT scan, barium swallow, EUS and PET/CT scans. The clinical tumor volume (CTV) should include the areas at risk for microscopic disease

and elective nodal regions such as the celiac axis, depending on the location of the primary tumor within the esophagus. The planning target volume (PTV) should include the tumor plus a cephalad and caudal margin of 5 cm, and a radial margin of 1.5 to 2 cm.

Every effort should be made to reduce unnecessary RT doses to vital organs such as the liver, kidneys, spinal cord, heart (especially the left ventricle) and lungs. Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients treated with concurrent chemoradiation. Optimal criteria for DVH parameters are being actively developed in NCCN Member Institutions.

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

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

Brachytherapy

Brachytherapy alone is a palliative modality and results in a local control rate of 25-35% and in a median survival of approximately 5 months. In the randomized trial, Sur et al reported no significant difference in local control or survival with high dose brachytherapy compared with external beam RT.[168] In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 combined modality regimen (fluorouracil and cisplatin with 50 Gy of external beam RT) followed by an intraluminal boost.[169] 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.

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.[170]

Definitive Chemoradiation Therapy

Concurrent chemoradiation therapy versus RT, each without resection, was studied in the only randomized trial (RTOG 85-01) designed to deliver adequate doses of systemic chemotherapy with concurrent

RT.[171] In this trial, patients with SCC or adenocarcinoma with clinical stage T1-3, N0-1, M0 received 4 cycles of fluorouracil and cisplatin.[158,171] RT (50 Gy at 2 Gy/d) was given concurrently with day 1 of chemotherapy. The control arm was RT alone (64 Gy). Patients who were randomly assigned to receive combined modality therapy showed a significant improvement in both median survival (14 vs. 9 months) and 5-year OS (27% vs. none) with projected 8-year and 10-year survival rates of 22% and 20% respectively. The incidence of local failure as the first site of failure (defined as local persistence plus recurrence) was also lower in the combined modality arm (47% vs. 65%).

The INT 0123 trial was the follow-up trial to RTOG 85-01, that compared 2 different RT doses used with the same chemotherapy regimen (fluorouracil and cisplatin).[172] In this trial, 218 patients with either SCC (85%) or adenocarcinoma (15%) with clinical stage T1-4, N0-1, M0 were randomly assigned to a higher dose (64.8 Gy) of RT or the standard dose of 50.4 Gy used with the same chemotherapy regimen (fluorouracil and cisplatin). No significant difference was observed in median survival (13 months vs.18 months), 2-year survival (31% vs. 40%), and local/regional failure or locoregional persistence of cancer (56% vs. 52%) 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.

Recent reports have also confirmed the efficacy of definitive chemoradiation in patients with locally advanced esophageal cancer.[173-176] Definitive chemoradiation with docetaxel and cisplatin resulted in high ORR in patients with SCC (98%; 71% complete response). At the median follow-up of 18 months, the median OS time was 23 months.[173] The rate of locoregional progression-free survival (PFS), PFS and 3-year OS rates were 60%, 29% and 37%, respectively. Definitive chemoradiation with carboplatin and paclitaxel was also well tolerated resulting in superior OS, disease-specific survival, durable locoregional control and palliation in about half of the patients with unresectable esophageal cancer.[174,175] In a recent randomized phase III trial, 267 patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to definitive chemoradiation therapy with either FOLFOX 4 (fluorouracil, leucovorin and oxaliplatin) or fluorouracil and cisplatin.[176] The majority of patients had SCC. The median follow-up was 25.3 months. The 3-year PFS rate was 18.2% and 17.4% respectively for FOLFOX and fluorouracil and cisplatin. The median OS was 20.2 months and 17.5 months respectively.

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational.[177] The results of two meta-analyses have shown that preoperative chemoradiation therapy plus surgery significantly reduced 3-year mortality and locoregional recurrence, and preoperative chemoradiation therapy also downstaged the tumor when compared with surgery alone.[178,179] Another recent meta-analysis (1854 patients,12 randomized trials comparing preoperative chemoradiation vs. surgery alone), showed a significant survival benefit for preoperative chemoradiation in patients with resectable adenocarcinoma of the esophagus.[180] Swisher et al also reported that preoperative chemoradiation was associated with increased pathologic complete response (28% vs. 4%) and 3-year OS (48% vs. 29%) compared with

preoperative chemotherapy in patients with locally advanced esophageal cancer.[181] In a retrospective analysis of 363 patients with adenocarcinoma of the lower esophagus, the OS after preoperative chemoradiation was significantly shorter for patients with Barrett's esophagus compared to those without Barrett's esophagus (32 months vs. 51 months respectively).[182]

However, randomized trials comparing surgery alone with preoperative chemoradiation followed by surgery in patients with clinically resectable cancer have shown conflicting results.[87,183-189] Results from a recent, multicenter phase III randomized trial (CROSS study), the largest trial in its class, showed that preoperative chemoradiation with carboplatin and paclitaxel significantly improved OS and 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).[87] R0 resection rate was higher in the chemoradiation arm compared to the surgery alone arm (92% and 69% respectively). Median survival was 49 months in the chemoradiation arm compared to 24 months in the surgery alone arm. The 1-, 2-,3- and 5-year survival rates were 82%, 67%, 58% and 47% respectively in the chemoradiation arm compared to 70%, 50%, 44% and 34% respectively in the surgery alone arm. Pathologic complete response rate was higher for patients with SCC than for those with adenocarcinoma (49% and 23% respectively; P = .008) but the histologic type was not a prognostic factor for survival. In contrast to the results of the CROSS study, the results of an interim analysis of another phase III randomized controlled study (FFCD 9901) showed that preoperative chemoradiation therapy with cisplatin and fluorouracil did not improve OS but enhanced postoperative mortality rate for patients with localized stage I or II esophageal cancer compared with surgery alone.[189] Full publications of these data are awaited.

The effect of adding surgery to chemoradiation therapy in patients with locally advanced SCC of the esophagus has been evaluated in randomized trials.[190,191] Stahl et al randomized 172 patients to either induction chemotherapy followed by chemoradiation therapy and surgery or induction chemotherapy followed by chemoradiation therapy.[190] The 2-year PFS rate was better in the surgery group (64.3%) than in the chemoradiation group (40.7%). However, there was no difference in OS between the two groups. The surgery group had significantly higher treatment-related mortality than the chemoradiation therapy group (12.8% vs. 3.5%, respectively). Long term results with a median follow-up of 10 years also showed no clear difference in survival between the two groups.[192] The Stahl trial was prematurely terminated due to lack of accrual. Bedenne et al (FFCD 9102 trial) also showed that adding surgery to chemoradiation provides no benefit compared with treatment with additional chemoradiation, especially in patients with locally advanced SCC of the esophagus who experience response to initial chemoradiation therapy.[191] However, this trial suffers from suboptimal design and low number of patients.

The CALGB 9781 trial was a prospective randomized intergroup trial that evaluated trimodality therapy vs. surgery alone for the treatment of patients with stage I-III esophageal cancer.[193] The study fell short of its accrual goals with only 56 patients enrolled. Patients were randomized to undergo either surgery alone or receive concurrent chemoradiation therapy with cisplatin and fluorouracil. Median follow-up was 6 years. An intent-to-treat analysis showed a median survival of 4.5 years vs.1.8 years, favoring trimodality therapy. Patients receiving trimodality therapy also had a significantly better 5-year survival rate (39% vs.16%). Although the accrual rate was low, the observed difference in survival was significant and this study showed that trimodality therapy

might be an appropriate standard of care for patients with localized esophageal cancer.

In a recent phase II randomized study, preoperative chemoradiation with cisplatin and fluorouracil did not show any survival benefit over preoperative chemotherapy in patients (n = 75) with resectable adenocarcinoma of the esophagus and EGJ.[194] The median PFS was 26 and 14 months for chemotherapy and chemoradiation respectively (P =.37). The corresponding median OS was 32 months and 30 months respectively (P =.83). However, the histopathologic response rate (31% vs. 8%; P =.01) and R1 resection rate (0% vs. 11%; P =.04) favored chemoradiation therapy.

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Sequential preoperative chemotherapy followed by chemoradiation has also been evaluated in clinical studies for patients with locally advanced esophageal and EGJ cancers.[195-202]

In a phase III study, Stahl et al. compared preoperative chemotherapy (cisplatin, fluorouracil and leucovorin) with chemoradiation therapy using the same regimen in 119 patients with locally advanced EGJ adenocarcinoma.[199] Patients with locally advanced adenocarcinoma of the lower esophagus or EGJ were randomized to chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiotherapy followed by surgery (arm B). Patients in arm B had a significantly higher probability of achieving pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection. Preoperative chemoradiation therapy improved 3-year survival rate from 27.7% to 47.4%. Although the study was closed prematurely due to low accrual and statistical significance was not achieved, there was a trend towards survival advantage for preoperative chemoradiation compared with preoperative chemotherapy 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.[200] R0 resection was achieved in 65% of patients. Median survival and the actuarial 2-year survival rate were 14.5 months and 35% respectively.[200] In another multicenter phase II trial (SAKK 75/02), preoperative induction chemotherapy with docetaxel and cisplatin followed by chemoradiation with the same regimen was effective in patients with SCC or adenocarcinoma of the esophagus (66 patients and 57 underwent surgery). R0 resection was achieved in 52 patients. Median OS and EFS were 36.5 months and 22.8 months respectively.[201]

In a more recent phase II trial that evaluated preoperative induction chemotherapy followed by chemoradiation with irinotecan and cisplatin followed by surgery, 69% of patients with resectable SCC, adenocarcinoma of the esophagus or EGJ underwent R0 resection.[202] Pathologic complete response was achieved in 16% of patients. Median OS was 31.7 months.

Induction chemotherapy prior to preoperative chemoradiation may be appropriate in selected patients. However, this approach has not been evaluated in randomized clinical trials.

Postoperative Chemoradiation Therapy

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[203] In this trial 556 patients (20% of patients had EGJ adenocarcinoma) with

resected adenocarcinoma of the stomach or EGJ (stage IB-IV, M0 according to 1988 AJCC staging criteria) were randomly assigned to surgery plus postoperative chemoradiation (n=281; bolus fluorouracil and leucovorin before and after concurrent chemoradiation with 5-flurouracil and leucovorin) or surgery alone (n=275). The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%); only 31% of the patients had T1-T2 tumors and 14% of patients had node-negative tumors. Surgery was not part of the trial protocol but resection of all detectable disease was required for participation in the trial. Patients were eligible for the study only after recovery from surgery. Postoperative chemoradiation (offered to all patients with tumors T1 or higher, with or without lymph node metastases) significantly improved OS and RFS. Median OS in the surgery-only group was 27 months and was 36 months in the chemoradiation group (P = .005). The chemoradiation group had better 3-year OS (50% vs. 41%) and 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 more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric cancer or EGJ adenocarcinoma treated with postoperative chemoradiation. No increases in late toxic effects were noted.[204]

The results of the INT-0116 trial have established postoperative chemoradiation therapy as a standard of care in patients with completely resected gastric cancer who have not received preoperative therapy. However, the regimen used in this trial (bolus fluorouracil and leucovorin before and after chemoradiation with the same combination) 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 only 64% of patients completed treatment and 17% discontinued treatment due to toxicity. Three patients (1%) died as a result of chemoradiation-related toxic effects including pulmonary fibrosis, cardiac event and myelosuppression.

Although the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer, the recommended doses or schedule of chemotherapy agents as used in the INT-0116 trial are no longer used due to concerns regarding toxicity.

In retrospective analyses, the addition of postoperative chemoradiation has been associated with survival benefit in patients with lymph node positive locoregional esophageal cancer.[205,206] Data from a more recent retrospective analysis also showed that postoperative chemoradiation according to the Intergroup-0116 protocol resulted in improved DFS after curative resection in patients (n = 211) with EGJ adenocarcinomas and positive lymph nodes, who did not receive neoadjuvant chemotherapy.[207] The 3-year DFS rate after postoperative chemoradiation was 37% compared to 24% after surgery alone.

In a phase II non-randomized trial that evaluated postoperative concurrent 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 are better than the historical outcomes with surgery alone.[208]

However, the efficacy of postoperative chemoradiation compared to surgery alone has not been demonstrated in a randomized trial in patients with esophageal cancer.

Chemotherapy

Preoperative Chemotherapy

Chemotherapy alone has been investigated in the preoperative setting. The RTOG 8911 (Intergroup 0113) trial randomized patients with potentially resectable esophageal cancer of both histologic types to receive either preoperative chemotherapy (fluorouracil plus cisplatin) or undergo surgery alone. The preliminary results of this study did not show any survival benefit between the two groups.[209] Long-term results of this study showed that 63% of patients treated with chemotherapy followed by surgery underwent complete resection (R0) compared with 59% of patients treated with surgery alone.[210] Although preoperative chemotherapy decreased the incidence of R1 resection (4% compared with 15% in the surgery only group), there was no improvement in OS between the two groups.

In the MRC OEO2 trial conducted by the Medical Research Council, 802 patients with potentially resectable esophageal cancer were randomly assigned to either 2 cycles of preoperative fluorouracil (1000 mg/m^2 per day by continuous infusion for 4 days) and cisplatin (80 mg/m^2 on day 1) repeated every 21 days followed by surgery, or surgery alone.[211] However, this trial had several clinical methodology problems. Nearly 10% of patients received off protocol preoperative RT, and patients accrued in China were excluded. At a short median follow-up time of 2 years, the group treated with preoperative chemotherapy had a 3.5 month survival time advantage (16.8 vs.13.3 months). Long-term follow-up confirmed that preoperative chemotherapy improves survival in patients with resectable esophageal cancer.[212] At a median follow-up of 6 years, DFS and OS were significantly longer for the preoperative chemotherapy group. The difference in survival favoring the preoperative chemotherapy group (23% vs.17% for surgery) was consistent in patients with SCC and adenocarcinoma.[212]

Long-term results of another randomized trial also showed that preoperative chemotherapy with a combination of etoposide and cisplatin significantly improved OS and DFS in patients (n = 169) with SCC of the esophagus.[213] Median OS was 16 months for patients assigned to preoperative chemotherapy followed by surgery compared to 12 months for those who underwent surgery alone. The 5-year survival rates were 26% and 17%, respectively.

An individual patient data-based meta-analysis showed a small but significant OS and DFS benefit favoring preoperative chemotherapy over surgery alone. A 4% increase in 5-year OS and DFS favored the preoperative chemotherapy group.[214] The results of an updated meta-analysis that included 1981 patients from 9 randomized trials comparing preoperative chemotherapy vs. surgery alone, showed a survival benefit for preoperative chemotherapy in patients with resectable adenocarcinoma of the esophagus.[180]

Perioperative Chemotherapy

The British Medical Research Council performed the first well-powered phase III trial (MAGIC trial) that evaluated perioperative chemotherapy for patients with resectable gastroesophageal cancer.[88] In this trial,

503 patients were randomized to receive either surgery alone or perioperative chemotherapy (preoperative and postoperative chemotherapy) with epirubicin, cisplatin and fluorouracil (ECF) and surgery. Patients were randomized prior to surgical intervention. The majority (74%) of the patients had stomach cancer, whereas a small group of patients had adenocarcinoma of the lower esophagus (14%) and EGJ (11%). The majority of patients had T2 or higher tumors (12%

had T1 tumors, 32% of patients had T2 tumors and 56% of patients had T3-T4 tumors) and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5%, respectively). Perioperative chemotherapy significantly improved PFS (P < .001) and OS (P = .009). The 5-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

In a more recent FNCLCC/FFCD trial (n = 224; 75% of patients had adenocarcinoma of the lower esophagus or EGJ and 25% had gastric cancer), Ychou et al reported that perioperative chemotherapy with fluorouracil and cisplatin significantly increased the curative resection rate, DFS and OS in patients with resectable cancer.[215] At the median follow-up of 5.7 years, the 5-year OS rate was 38% for patients in the surgery plus perioperative chemotherapy group and 24% for patients in the surgery only group (P = .02). The corresponding 5-year DFS rates were 34% and 19% respectively. This trial was prematurely terminated due to low accrual.

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

Chemotherapy for Locally Advanced or Metastatic Disease

SCC seems to be more sensitive to chemotherapy, chemoradiation and RT than adenocarcinoma, but the long-term outcome appears to be the same. In randomized clinical trials, no consistent benefit was seen for any specific chemotherapy regimen and chemotherapy showed no survival benefit compared with best supportive care for patients with advanced esophageal cancer.[216] Palliative chemotherapy is not known to provide any survival advantage, but it may improve quality of life in patients with metastatic or unresectable esophageal cancer.[217] Adequately powered phase III studies are lacking.

Cisplatin is one of the most active agents, with a single agent response rate consistently in the range of 20% or greater.[218] Cisplatin plus fluorouracil is the most investigated and most commonly used regimen for patients with esophageal cancer, resulting in response rates of 20% to 50%. Newer agents such as irinotecan,[219-221] docetaxel,[222,223] paclitaxel[224-226] and etoposide[227] have also shown activity in patients with advanced esophageal cancer.

Cisplatin plus paclitaxel or docetaxel, with or without fluorouracil has demonstrated activity in patients with locally advanced EGJ or metastatic esophageal cancers.[228-233] In a randomized multinational phase III study (V325), 445 untreated patients were randomized to receive either DCF (every 3 weeks) or the combination of cisplatin and fluorouracil (CF).[232] The majority of patients had advanced gastric cancer and 19-25% of patients had EGJ cancer. At a median follow-up of 13.6 months, time to progression was significantly longer with DCF compared with CF (5.6 vs. 3.7 months; P < .001). The median OS was significantly longer for DCF compared with CF (9.2 months vs. 8.6 months; P =.02), at a median follow-up time of 23.4 months; the overall confirmed response rate was also significantly higher with DCF than CF ((37% and 25%, respectively; P =.01).[232] Various modifications of the DCF regimen with the intent to improve tolerability are being evaluated in clinical trials for patients with advanced esophagogastric cancer.[234-239]

The combination of cisplatin with irinotecan is active, particularly against SCC of the esophagus.[240] In a prospective randomized study, the combination of mitomycin, cisplatin and fluorouracil (protracted intravenous infusion) was equally efficient to ECF (protracted

intravenous infusion) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.[241] Cisplatin in combination with gemcitabine has shown significant activity in phase II studies in patients with metastatic and advanced esophageal cancer.[242,243]

The REAL-2 trial (30% of patients with esophageal cancer) was a randomized multicenter phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in 1002 patients with advanced esophagogastric cancer.[244] Patients with histologically confirmed adenocarcinoma, SCC or undifferentiated cancer of the esophagus, EGJ or stomach were randomized to receive one of the four epirubicin-based regimens (ECF; epirubicin, oxaliplatin, and fluorouracil [EOF]; epirubicin, cisplatin and capecitabine [ECX]; and epirubicin, oxaliplatin and capecitabine [EOX]). Median follow-up was 17.1 months. Results from this study suggest that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated advanced esophagogastric cancer. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy. The toxic effects from fluorouracil and capecitabine were not different.

Non cisplatin-containing regimens have also shown activity in patients with advanced esophageal cancer, in phase II studies. The combination of fluorouracil, leucovorin and irinotecan was found to be active in patients with primary refractory or untreated locally advanced EGJ cancer as well as in patients with locally advanced unresectable and metastatic adenocarcinoma and SCC of the esophagus.[245-248] In patients with locally advanced or metastatic esophageal cancer, partial response was achieved in 33% of evaluable patients (n=19); 38% had stable disease and 8% had progressive disease.[246] Median survival was 20 months and 10 months respectively for patients with adenocarcinoma and SCC.

The combination of irinotecan with docetaxel or capecitabine or mitomycin has also shown promising activity in patients with metastatic esophagogastric cancer as well as unresectable or metastatic SCC or adenocarcinoma of the esophagus.[249-252] In a phase II study, the combination of irinotecan and docetaxel, resulted in an ORR of 31% (4% complete response and 27% partial response) among chemotherapy naïve patients (n = 29) with unresectable or metastatic SCC or adenocarcinoma of the esophagus; there were two partial responses and one complete response among the pretreated patients (n = 15).[249] Median time to progression was similar in both chemotherapy naïve and pretreated patients (4 months and 3.5 months respectively) and the median survival was 9 and 11 months respectively for the two groups. Capecitabine in combination with irinotecan was active in patients with metastatic esophagogastric cancer that had progressed on platinum-based chemotherapy.[250] The results of a recent randomized study also showed that capecitabine and irinotecan was comparable in efficacy and activity to cisplatin and irinotecan.[251] Mitomycin and irinotecan combination was also effective in patients with advanced esophageal or EGJ adenocarcinoma.[252]

The combination of carboplatin and paclitaxel was moderately active with a response rate of 43% in patients with advanced esophageal cancer.[253] However, 52% of patients had neutropenia (grade 3-4). Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend towards improved median PFS (5.8 vs. 3.9 months) compared to fluorouracil, leucovorin and cisplatin (FLP) in patients with metastatic

esophagogastric cancer.[254] However, no significant differences were seen in median OS (10.7 vs. 8.8 months, respectively) between the FLO and FLP regimens. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), and PFS (6.0 vs. 3.1 months), and an improved OS (13.9 vs. 7.2 months) compared with FLP, respectively. The combination of gemcitabine, fluorouracil and leucovorin has also shown activity in patients with locally advanced or metastatic SCC or adenocarcinoma.[255,256]

Targeted Therapies

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-neu-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[49] In this trial, 594 patients with HER2-neu-positive (3+ on IHC or FISH positive [HER2:CEP17 ≥2]) locally advanced, recurrent, or metastatic gastric and EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone.[49] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 months and 17 months respectively, in the two groups. There was a significant improvement in the median OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone in patients with *HER2*-neu overexpression or amplification (13.8 vs.11 months, respectively; P = .046). This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with HER2-neu-positive advanced or metastatic gastric and EGJ adenocarcinoma.

However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3 + or IHC 2+ and FISH positive. There was no significant survival benefit for patients whose tumors were IHC 0 or 1+ and FISH positive.[49] In the post-hoc sub group analysis of the ToGA trial, 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; hazard ratio [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).

Ongoing trials are evaluating the efficacy and safety of EGFR inhibitors (cetuximab[257-261] and erlotinib [262-264]) and anti-VEGFR antibody (bevacizumab[265-267]) in combination with chemotherapy for the treatment of patients with advanced esophageal and EGJ cancers.

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, nursing, palliative care specialists, and other supporting disciplines are also desirable. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of any discipline taking care of patients with esophagogastric cancer. Optimally at each meeting, the panel encourages participation of all relevant disciplines. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient. See the section on “Principles of Multidisciplinary Team Approach for Esophagogastric Cancers” in the guidelines.

Workup

Newly diagnosed patients should undergo a complete history, physical examination, biopsy (to confirm histologic classification and metastatic cancer) and endoscopy with biopsy of the entire upper GI tract. If the cancer is located at or above the cardia, bronchoscopy (including biopsy of any abnormality 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 optional. A complete blood cell count (CBC), multichannel serum chemistry analysis, coagulation studies, and CT scan (with oral and IV contrast) of the chest and abdomen should also be performed. Pelvic CT should be obtained when clinically indicated. EUS and PET/CT evaluation is recommended, if metastatic cancer is not evident. HER2-neu testing is recommended if metastatic disease is documented or suspected. See the section on “Principles of Pathology”, for assessment of *HER2-neu* overexpression.

PET/CT scans are useful for initial staging and evaluation of patients after chemoradiation prior to surgery for the detection of distant lymphatic and hematogenous metastases.[268,269,270] PET/CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer.[271] It has also been shown to be an independent predictor of OS in patients with non-metastatic esophageal cancer.[272] In addition, a recent study reported that combined PET/CT scans are more accurate than EUS-FNA and CT scan for predicting nodal status and complete response after neoadjuvant therapy in patients with esophageal cancer.[273] When used alone, PET/CT and CT suggest targets for biopsy; however, false positive results are common. Combined PET/CT scans are emerging and seem to be useful for restaging patients and monitoring response to primary therapy.

The guidelines recommended assessment of Siewert tumor type as part of initial work up in all patients with adenocarcinomas involving the EGJ.[30,31] See the section titled “Esophagogastric Junction”.

Initial workup enables patients to be classified into two groups with the following characteristics:

- Locoregional cancer (stages I-III)
- Metastatic cancer (stage IV)

Additional Evaluation

In patients with apparent locoregional cancer, additional evaluations may be warranted to assess their medical condition and feasibility of resection, especially for patients with celiac-positive disease. These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. Nasoduodenal or jejunostomy tube should be considered for preoperative nutritional support. Percutaneous endoscopic gastronomy is not recommended. In patients with adenocarcinoma of the esophagus or EGJ, laparoscopic staging of the peritoneal cavity should be considered (optional) if there is no evidence of metastatic disease (M1).[112] Evaluation of the colon using barium radiograph or colonoscopy may be warranted if colon interposition is planned as part of the surgical procedure. A superior mesenteric artery angiogram should be considered only in selected cases when colon interposition is planned.

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

- Medically fit patients
- Medically unfit for surgery or surgery not elected and patients medically able to tolerate chemotherapy or chemoradiation

- Medically unfit for surgery and unable to tolerate chemotherapy or chemoradiation

Medically Fit Patients with Locoregional Cancer

Esophagectomy is the standard treatment option for patients with superficial T1 tumors.[274,275] Endoscopic therapies (EMR and ablation) may be appropriate options for patients with superficial T1a invading the mucosa but not invading the submucosa.[119-122] Retrospective studies have shown that concurrent chemoradiation is an effective treatment option for patients with cervical and upper thoracic esophageal cancer.[276-279]

In randomized trials, definitive chemoradiation therapy has been demonstrated as the curative approach for patients with locally advanced or unresectable SCC of the esophagus.[171,172,176] Preoperative chemoradiation is the preferred treatment for patients with localized adenocarcinoma of the thoracic esophagus or EGJ.[87,181,199] In a retrospective study, definitive chemoradiation was beneficial for patients with locally advanced adenocarcinoma of the esophagus. The 2-, 3- and 5-year survival rates were 44%, 33% and 19.5%, respectively, with a median survival of 21 months.[280] Perioperative chemotherapy is an alternate but less preferred approach.[88]

Primary Treatment for Squamous Cell Carcinoma

The guidelines include EMR or ablation as the primary treatment option for patients with Tis tumors (HGD or carcinoma-in-situ) whereas EMR followed by ablation (preferred) or esophagectomy are included as options for patients with superficial T1a tumors. Ablation may not be needed for lesions that are completely excised. Esophagectomy is the recommended primary treatment option for patients with T1b, N0 tumors invading the submucosa.

Primary treatment options for patients with T1b, N+ tumors and those with locally advanced resectable tumors (T2-T4a, any regional N) include preoperative chemoradiation (for non-cervical esophagus),[87] definitive chemoradiation (recommended for cervical esophageal cancer)[171,172] or esophagectomy (for non-cervical esophagus). Definitive chemoradiation is the preferred treatment for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in selected cases. Chemotherapy can be considered only in the setting of invasion of trachea, great vessels, or heart.

Fluoropyrimidine-or taxane-based regimens are recommended for preoperative and definitive chemoradiation. See the “Principles of Systemic Therapy” section of the guidelines for list of specific regimens.

Primary Treatment for Adenocarcinoma

Primary treatment options for patients with Tis tumors (HGD or carcinoma-in-situ), T1a tumors and T1b tumors are similar to those described above for patients with SCC.

Primary treatment options for patients with T1b, N+ and those with locally advanced resectable tumors (T2-T4a, any regional N) include preoperative chemoradiation (preferred),[87,199] definitive chemoradiation (only for patients who decline surgery or cannot withstand surgery), perioperative chemotherapy[88] or esophagectomy (for patients with low-risk and well-differentiated lesions less than 2 cm in size). Definitive chemoradiation is the preferred treatment for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in selected cases.

Fluoropyrimidine- or taxane-based regimens are recommended for preoperative and definitive chemoradiation. See the “Principles of Systemic Therapy” section of the guidelines for list of specific regimens.

Additional Treatment (SCC and Adenocarcinoma)

Restaging (ie, CT scan with contrast, if PET/CT is not done, PET/CT or PET, upper GI endoscopy and biopsy [optional after preoperative chemoradiation]), is recommended after completion of preoperative or definitive chemoradiation for all patients with SCC or adenocarcinoma. Response assessment with PET/CT or PET scan (category 2B) should be done 5-6 weeks after completion of preoperative therapy.

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

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

Patients with unresectable or metastatic disease after definitive or preoperative chemoradiation should be considered for palliative therapy, depending on their performance status.

Postoperative Treatment

Postoperative treatment is based on the surgical margins, nodal status and histology. The efficacy of postoperative treatment has not been established in randomized trials for patients with esophageal cancer. Available evidence for the use of postoperative chemoradiation (only for patients who have not received preoperative therapy) and perioperative chemotherapy for patients with adenocarcinoma of the distal esophagus or EGJ comes from prospective randomized clinical trials involving patients with gastric cancer that have included patients with adenocarcinoma of the distal esophagus or EGJ.[88,203]

For Patients with SCC Who Have Not Received Preoperative Therapy

No further treatment is necessary (irrespective of their nodal status), if there is no residual disease at surgical margins (R0 resection). Patients with microscopic (R1 resection) or macroscopic (R2 resection) residual disease should be treated with fluoropyrimidine-based chemoradiation. Palliative therapy is an alternative option for patients with macroscopic residual disease.

For Patients with Adenocarcinoma Who Have Not Received Preoperative Therapy

No further treatment is necessary for patients with Tis and T1, N0 tumors, if there is no residual disease at surgical margins (R0 resection). Based on the results of the INT-0116 trial, the panel has included postoperative fluoropyrimidine-based chemoradiation for all patients with T3-T4a tumors and node positive T1-T2 tumors.[203,204] Given the lack of evidence from randomized clinical trials showing any survival benefit for postoperative chemoradiation for patients with T2, N0 tumors, postoperative chemoradiation is recommended (category 2B) only for selected patients with high risk features (poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or age younger than 50 years), if there is no residual disease at surgical margins (R0 resection).[281] Alternatively, patients with node negative T2-T4a tumors can also be observed.

The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer.[203,204] However, the panel does not

recommend the doses or the schedule of chemotherapy agents as used in the INT-0116 trial due to concerns regarding toxicity. Instead, the panel recommends the use of fluoropyrimidine (infusional fluorouracil or capecitabine), before and after fluoropyrimidine-based chemoradiation.

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

For Patients with SCC Who Have Received Preoperative Therapy

No further treatment is necessary (irrespective of their nodal status), if there is no residual disease at surgical margins (R0 resection). Patients with microscopic (R1 resection) or macroscopic residual disease (R2 resection) should be treated with fluoropyrimidine-based chemoradiation, if they have not received preoperative chemoradiation. Alternatively, patients with microscopic residual disease (R1 resection) can be observed until progression and patients with macroscopic residual disease (R2 resection) can be treated with palliative therapy.

For Patients with Adenocarcinoma Who Have Received Preoperative Therapy

Postoperative chemotherapy (category 1), if received preoperatively is recommended for all patients (irrespective of the nodal status), if there is no residual disease at surgical margins (R0 resection).[88] Observation is an option for patients who have not received preoperative chemotherapy. Alternatively, patients with node positive adenocarcinoma could be treated with chemoradiation (category 2B), if not received preoperatively. However, this approach has not been evaluated in prospective studies.

Patients with microscopic (R1 resection) or macroscopic (R2 resection) residual disease should be treated with fluoropyrimidine-based chemoradiation, if they have not received preoperatively. Alternatively, patients with microscopic residual disease (R1 resection) can be observed until progression and patients with macroscopic residual disease (R2 resection) can be treated with palliative therapy.

Medically Unfit Patients with Locoregional Cancer

SCC and Adenocarcinoma

EMR or ablation is recommended for patients with Tis tumors whereas EMR followed by ablation is an appropriate option for patients with T1a and superficial T1b. The results of a recent retrospective analysis showed that endoscopic management may be appropriate for selected patients with superficial submucosal tumors who are unfit for surgery.[282] However, endoscopic therapies may not be suitable for selected patients who have superficial T1b tumors with poor prognostic features including lymphovascular invasion, positive margins, poorly differentiated histology and/or tumor diameter of 2 cm or more.[283,284] Chemoradiation is included as an option for this group of patients.

Fluoropyrimidine-based or taxane-based definitive chemoradiation is the preferred treatment option for all the other patients with technically resectable cancer who are medically unfit for surgery or for those who choose not to undergo surgery and are medically able to tolerate chemotherapy or chemoradiation. Alternatively, these patients can also be treated with chemotherapy or RT or best supportive care.

Palliative RT or best supportive care are the appropriate options for patients medically unfit for surgery and who are unable to tolerate chemotherapy or chemoradiation.

Follow-up after Resection or Definitive Chemoradiation

SCC and Adenocarcinoma

All patients should be followed systematically. For asymptomatic patients, follow-up should include a complete history and physical examination every 3 to 6 months for 1 to 2 years, then every 6 to 12 months for 3 to 5 years, and annually thereafter. CBC, multichannel serum chemistry evaluation, upper GI endoscopy with biopsy and imaging studies should be obtained as clinically indicated. Patients with Tis or T1a tumors who undergo EMR should undergo endoscopic surveillance every 3 months for one year and then annually. In addition, some patients may require dilatation of an anastomotic or a chemoradiation-induced stricture. Nutritional assessment and counseling may be extremely valuable. HER2-neu testing should be done if metastatic adenocarcinoma was present at diagnosis.

Recurrent Disease

SCC and Adenocarcinoma

Treatment for recurrent cancer can range from aggressive intervention with curative intent in patients with locoregional recurrence to therapy intended strictly for palliation in patients for whom cure is not a possibility.

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

When recurrence develops after chemoradiation therapy with no prior esophagectomy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option. When patients experience another recurrence after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described below for metastatic disease.

Palliative therapy is recommended for medically unfit patients and those who develop an unresectable or metastatic recurrence.

Locally Advanced or Metastatic Disease

SCC and Adenocarcinoma

Palliative therapy (chemotherapy, or clinical trial or best supportive care) is recommended for patients with locally advanced or metastatic cancer.

Best supportive care is the appropriate treatment option for patients with locally advanced or metastatic cancer. Patients' performance status should determine whether chemotherapy is added to best supportive care.

Several scales are available to measure performance status in patients with cancer. Karnofsky Performance Status Scale (KPS) and ECOG Performance Status (ECOG PS) are the two commonly used scales.[285,286] KPS is an ordered scale with 11 levels (0 to 100) and the general functioning and survival of a patient is assessed based on his or her health status (activity, work and self-care). Low Karnofsky scores are associated with poor survival and more serious illnesses (http://www.hospicepatients.org/karnofsky.html). ECOG PS is a 5-point scale (0-5) based on the level of symptom interference with normal activity. Patients with higher levels are considered to have poor performance status (http://www.ecog.org/general/perf_stat.html).

Patients with a KPS score of 60 or less or an ECOG PS score of 3 or more should probably be offered best supportive care. Patients with

better performance status (KPS score of 60 or more, or an ECOG PS score of 2 or less) may be offered chemotherapy along with best supportive care. Further treatment after two sequential regimens depends on the patient's performance status and availability of clinical trials.

Phase III trials for locally advanced or metastatic esophageal cancer have not been performed for many years. The regimens listed in the guidelines are derived from the gastric adenocarcinoma phase III trials that have included patients with lower esophageal and/or EGJ cancer.

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

Based on the results of the ToGA trial, the guidelines recommend trastuzumab with chemotherapy for patients with a tumor score of IHC 3+ and IHC 2+ with the evidence of *HER2* amplification by FISH (HER2:CEP17 ratio ≥ 2).[49] Trastuzumab is not recommended for patients with a tumor score of IHC 0 or 1+. The use of trastuzumab in combination with an anthracycline is not recommended. See the "Principles of Systemic Therapy" section of the guidelines for a list of specific regimens. Some of the chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published studies and institutional preferences that have support only from phase II studies.

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. 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 levo-leucovorin, which is commonly used in Europe. Levo-leucovorin 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 for all doses in all patients, since lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[287-289] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. A modest increase in fluorouracil dose (in the range of 10%) may be considered for patients who can tolerate this without grade II or higher toxicity.

Best Supportive Care

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

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Assessing the severity of the disease and swallowing impairment is essential to initiate appropriate interventions for long-term palliation of dysphagia in patients with esophageal cancer. Available palliative methods for the management of dysphagia include endoscopic lumen restoration or

enhancement, placement of permanent or temporary self-expanding metal stents (SEMS), RT, brachytherapy, chemotherapy or surgery.

Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Single dose brachytherapy was associated with fewer complications and better long-term relief of dysphagia compared with metal stents.[290] Temporary placement of SEMS with concurrent RT was found to be beneficial for increasing survival rates compared with permanent stent placement.[291] SEMS is the preferred treatment for patients with tracheoesophageal fistula and those who are not candidates for chemoradiation or those who failed to achieve adequate palliation with such therapy.[292] Membrane-covered stents have significantly better palliation than conventional bare metal stents because of decreased rate of tumor ingrowth which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[149] Treatment options for the management of dysphagia should be individualized. A multimodality interdisciplinary approach is strongly encouraged.

For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, external beam RT, chemotherapy or surgery. Surgical or radiologic placement of jejunostomy or gastronomy tubes may be necessary to provide adequate hydration and nutrition, if endoscopic lumen restoration is not undertaken or unsuccessful. Brachytherapy may be considered instead of RT, if lumen can be restored using appropriate applicators during the delivery of brachytherapy to decrease excessive dose on mucosal surfaces. Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy. For patients with severe esophageal obstruction (those able to swallow liquids only), the options include endoscopic lumen enhancement (wire-guided or balloon dilation), endoscopy or fluoroscopy-guided placement of covered expandable metal stents or other measure described above. While there are data suggesting a lower migration and re-obstruction rate with the larger diameter covered expandable metal stents, there may be a higher risk of stent-related complications.[293] Caution should be exercised when dilating malignant strictures as this may be associated with an increased risk of perforation.[294]

Pain

Patients experiencing tumor related pain should be assessed and treated according to the NCCN Guidelines for Adult Cancer Pain. Severe uncontrolled pain after stent placement of should be treated with its immediate removal.

Bleeding

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

Nausea 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.

Summary

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

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

EMR or ablation is the primary treatment option for medically fit patients with Tis tumors whereas those with T1a tumors should be treated with EMR followed by ablation or esophagectomy. 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 or higher, any N), primary treatment options include preoperative chemoradiation, definitive chemoradiation, preoperative chemotherapy (only for adenocarcinoma) or esophagectomy.

Postoperative treatment is based on histology, surgical margins and nodal status. For patients with SCC (irrespective of their nodal status), no further treatment is necessary if there is no residual disease at surgical margins (R0 resection). For patients with adenocarcinoma who have not received preoperative therapy, the panel has included postoperative fluoropyrimidine-based chemoradiation (following R0 resection) for all patients with Tis, T3-T4 tumors, node positive T1-T2 tumors and selected patients with T2, N0 tumors with high-risk features. Perioperative chemotherapy is recommended following R0 resection for all patients with adenocarcinoma, irrespective of the nodal status (category 1).

All patients with residual disease at surgical margins (R1 and R2 resections) may be treated with fluoropyrimidine-based chemoradiation. Fluoropyrimidine-based or taxane-based concurrent chemoradiation is recommended for unresectable disease and for patients with technically resectable disease who choose not to undergo surgery and for patients medically unfit for surgery and able to tolerate chemotherapy.

Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal and EGJ cancers. Based on the results of the ToGA trial, trastuzumab plus chemotherapy is included as an option for patients with HER2-neu-positive advanced or metastatic adenocarcinoma. HER2-neu testing is recommended if metastatic adenocarcinoma is documented or suspected.

Best supportive care is an integral part of treatment, especially in patients with locally advanced or metastatic disease. Patients with good performance status can be treated with chemotherapy plus best supportive care, whereas best supportive care alone is recommended for those with poor performance status.

Assessment of disease severity and related symptoms is essential to initiate appropriate palliative interventions that will prevent and relieve suffering and improve quality of life for patients and their caregivers. Endoscopic palliation of esophageal cancer has improved substantially because of improving technology.

The NCCN Guidelines for esophageal and EGJ cancers provide an evidence- and consensus-based systematic approach to the management of patients with esophageal and EGJ cancers. Novel therapeutic modalities, such as targeted therapies, vaccines and gene therapy are being studied in clinical trials. The panel encourages patients with esophageal and EGJ cancers to participate in well designed clinical trials to enable further advances.

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