# NCCN Guidelines® Version 2.2012 Panel Members

## Esophageal and Esophagogastric Junction Cancers

### NCCN Guidelines Panel Disclosures

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Affiliation</th>
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<tr>
<td>Jaffer A. Ajani, MD</td>
<td>Chair</td>
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<td>David J. Bentrem, MD</td>
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<td>Stephen Besh, MD</td>
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<td>Thomas A. D'Amico, MD</td>
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<td>Prajnan Das, MD, MS, MPH</td>
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<td>Crystal Denlinger, MD</td>
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<td>Charles S. Fuchs, MD, MPH</td>
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<td>Hans Gerdes, MD</td>
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<td>Robert E. Glasgow, MD</td>
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<td>James A. Hayman, MD, MBA</td>
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<td>Wayne L. Hofstetter, MD</td>
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<td>David H. Ilson, MD, PhD</td>
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<td>Rajesh N. Keswani, MD</td>
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<td>Lawrence R. Kleinberg, MD</td>
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<td>W. Michael Korn, MD</td>
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<td>A. Craig Lockhart, MD, MHS</td>
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<td>Kenneth Meredith, MD</td>
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<td>Mary F. Mulcahy, MD</td>
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<td>Mark B. Orringer, MD</td>
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<td>James A. Posey, MD</td>
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<td>Aaron R. Sasson, MD</td>
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<td>Walter J. Scott, MD</td>
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<td>Vivian E. M. Strong, MD</td>
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<td>Thomas K. Varghese, Jr, MD</td>
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<td>Mary Kay Washington, MD</td>
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<td>Christopher Willett, MD</td>
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<td>Cameron D. Wright, MD</td>
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</tbody>
</table>

### NCCN Guidelines Panel Members' Affiliations

- **† Medical oncology**
- **‡ Surgery/Surgical oncology**
- **§ Radiotherapy/Radiation oncology**
- **∥ Gastroenterology**
- **¶ Hematology/Hematology oncology**
- **¥ Internal medicine**
- **× Pathology**
- *** Writing committee member**

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The NCCN Guidelines® for Esophageal and Esophagogastric Junction Cancers do not include the proximal 5cm of the stomach.
The 2012 version of the Esophageal and Esophagogastric Junction Cancers Guidelines represents the addition of the updated Discussion text (MS-1).

Updates in version 1.2.2012 of the Esophageal and Esophagogastric Junction Cancers Guidelines from version 2.2.2011 include:

Global Change:

- The definitive chemoradiation dose changed from “45-50.4 Gy” to “50-50.4 Gy” throughout the algorithm.

**ESOPH-1**

- Workup:
  - “Endoscopic mucosal resection (EMR) may contribute to accurate staging of early stage cancers” was added as a recommendation.
  - “Smoking cessation advice, counseling, and pharmacotherapy” was added as a recommendation.
  - 11th bullet: “Biopsy confirmation of suspected metastatic disease” changed to “Biopsy of metastatic disease as clinically indicated”.
  - 12th bullet: HER2-neu testing if metastatic disease is documented/suspected changed to “HER2-neu testing if metastatic adenocarcinoma is documented/suspected”. A similar change was made on page ESOPH-8.
  - 13th bullet: “Assess Siewert category” changed to “Assign Siewert category”.
- Fourth column at top: “Medically fit, and resectable disease” was clarified as “Medically fit and locoregional disease”.

**ESOPH-2**

- T1a: The recommendation “EMR and ablation” is now listed as “preferred”.
- A separate pathway was added for T1b, N0 tumors with “Esophagectomy” recommended as primary treatment.
- The pathway “T1b, Any N” changed to “T1b, N+”.
- The phrase “cervical cancer” was clarified as “cervical esophagus”.
- The “T2 or higher, Any (regional) N” pathway changed to “T2-T4a, Any (regional) N” and a separate pathway was added for “T4b” tumors.

**ESOPH-3**

- T2-T4a, Any (regional) N: Primary Treatment Options: Preoperative chemoradiation is now “preferred”. Esophagectomy was clarified as being for “(low risk lesions, < 2cm, well differentiated lesions)”. Preoperative chemotherapy was clarified as “(only for adenocarcinoma of distal esophagus or EGJ)”.
- T4b pathway: Definitive chemoradiation was listed as primary treatment.

**ESOPH-4**

- Primary Treatment for Medically fit patients: For patients who received “Preoperative chemoradiation”, the recommendation “Upper GI endoscopy and biopsy” for Response assessment is now listed as “optional”.

**ESOPH-5**

- The column heading was clarified as follows, “Surgical Outcomes/Clinical Pathologic Findings (Patients Have Not Received Preoperative Chemoradiation or Chemotherapy)”. Previously it was entitled, “...Have Not Received Preoperative Therapy”.
- R0 resection; Node negative; Adenocarcinoma of distal esophagus or EGJ: Postoperative treatment:
  - T2, N0: “Consider chemoradiation for select patients” was added as an option for postoperative treatment. A corresponding footnote “aa” was added that states, “Consider chemoradiation for patients with high risk distal esophagus or EGJ adenocarcinoma. High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age”.
  - T4a, N0: This is a new pathway with “Observe or Chemoradiation (fluoropyrimidine-based)” added as treatment options.
- R0 resection; Node positive; Adenocarcinoma of proximal or mid esophagus: The recommendation “Chemoradiation (preferred) (fluoropyrimidine-based)” was removed as an option for postoperative treatment.
ESOPH-6
• The column heading was clarified as follows, “Surgical Outcomes/Clinical Pathologic Findings (Patients Received Preoperative Chemoradiation or Chemotherapy)”. Previously it was entitled, “... Received Preoperative Therapy”.
• R0 resection; Node negative; Adenocarcinoma of distal esophagus or EGJ; Postoperative Treatment:
  ▶ T3, N0; T4a, N0: “Chemoradiation (fluoropyrimidine-based)” was removed as an option for postoperative treatment.
• R0 resection; Node positive:
  ▶ For both Adenocarcinoma of proximal or mid esophagus and Adenocarcinoma of distal esophagus or EGJ, the recommendation “Chemoradiation (fluoropyrimidine-based)” was removed as an option for postoperative treatment.

ESOPH-7
• A new pathway for “Superficial T1b” tumors was added. Primary treatment for these patients include “EMR and ablation or Consider chemoradiation for tumors with poor prognostic features”.
• Footnote “cc” that states, Poor prognostic features include lymphovascular invasion (LVI), poorly differentiated histology, positive margin(s), and/or maximum tumor diameter 2cm or more,” is new to the algorithm.

ESOPH-9
• Metastatic disease: After the “Karnofsky performance score ≥ 60 %” pathway, the following recommendation was added, “Confirm HER2-neu testing has been done if metastatic adenocarcinoma is suspected”.

ESOPH-A: Principles of Endoscopic Staging and Therapy
• Diagnosis; 4th bullet: After the second sentence, a new sentence was added that states, “EMR can be therapeutic/diagnostic”.

ESOPH-B (3 of 4): Principles of Pathologic Review and HER2-neu Testing
• The first paragraph was revised as follows: “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.”
• Table 3: In the” 2+” overexpression row, the last column was revised as follows, “Equivocal (FISH is recommended)”.
• Footnote “#” was revised as follows, “The NCCN Guidelines panel recommends that cases showing less than 3+ overexpression 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.”

ESOPH-D: Principles of Surgery
• The 2nd bullet was revised as follows, “Prior to starting therapy all patients should be assessed by an esophageal surgeon...”. Previously this stated, “Prior to starting surgery...”
• Four new bullets were added regarding the definition of Siewert category tumors and how to treat them.
• A new bullet regarding positive peritoneal cytology was added.
ESOPH-E: Principles of Systemic Therapy

1 of 14:
- The third bullet was clarified as, “The use of three-drug cytotoxic regimens for advanced...”
- 9th bullet: The following statement was added, “Preoperative chemotherapy is an option only for distal esophagus and EGJ adenocarcinoma”.

2 of 14: Under Postoperative Chemoradiation (only for adenocarcinoma) the recommendation for “5-FU (bolus) and leucovorin (category 1)” was removed.

3 of 14:
- First line therapy: The statement, Two-drug regimens or single agent preferred. Three-drug regimens should be reserved for medically fit patients...” changed to “Two-drug regimens preferred. Three-drug cytotoxic regimens should be reserved...”
- Alternative regimens to be considered: Cetuximab was removed as an option. The corresponding dose recommendations on page 11 of 14 were also removed.

7 of 14: For Postoperative Chemoradiation, the dosing recommendations for “5-FU (bolus) and leucovorin” were removed.

8 of 14: Under Definitive Chemotherapy for Metastatic or Locally Advanced Cancer; First line therapy: A new dose for Trastuzumab (with chemotherapy) was added as follows, “Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days”. The same dose was also added for Second-line therapy 10 of 14.

ESOPH-F: Principles of Radiation Therapy

1 of 3: 4th bullet: The following statement was added, “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”.

2 of 3:
- Under Dose, the range “45-50.4 Gy (1.8-2 Gy/day)” was clarified as:
  - Preoperative or Postoperative Therapy: 45-50.4 Gy (1.8-2 Gy/day)
  - Definitive Therapy: 50-50.4 Gy (1.8-2 Gy/day)
- Footnote “a” added the following sentence, Important considerations may also include plans for post-treatment surgery, pretreatment pulmonary function, and relevant co-morbidities.
## Workup

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

## Clinical Stage

### Stage I–IIId,e (locoregional disease)

- Multidisciplinary evaluation\(^f\)
- Nutritional assessment
  - Consider nasogastric or J-tube for preoperative nutritional support; PEG is not recommended

### Stage IV (metastatic disease)

- Medically fit,\(^g\) and locoregional disease
- Medically unfit for surgery or surgery not elected and patient medically able to tolerate chemotherapy or chemoradiation or T4b ( unresectable)\(^i\)

## Additional Evaluation (as clinically indicated)

- Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
- T4a (resectable): involvement of pericardium, pleura or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases (N+).
- See Principles of Multidisciplinary Team Approach (ESOPH-C)

\(^a\) See Principles of Endoscopic Staging and Therapy (ESOPH-A).

\(^b\) See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).


\(^d\) Medically able to tolerate major abdominal and/or thoracic surgery.

\(^e\) See Principles of Surgery (ESOPH-D).

\(^f\) T4b ( unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
**Esophageal and Esophagogastric Junction Cancers**

### Tumor Classification

- **Tis**: Defined as high-grade dysplasia or carcinoma in situ.
- **T1a**: Defined as tumors involving the mucosa, but not invading the submucosa.
- **T1b**: Tumors invading the submucosa.
- **T2-T4a**, Any (regional) N<sup>e,n</sup>
- **T4b**: Involved in submucosa.

### Primary Treatment Options

- **Endoscopic mucosal resection (EMR)<sup>o</sup> or Ablation<sup>p</sup>** or ablation<sup>p</sup> (preferred)
- **Esophagectomy<sup>h</sup>**
- **Esophagectomy<sup>h,q,r</sup>** for noncervical esophagus<sup>s</sup>
- **Chemoradiation<sup>t,u</sup>** for cervical esophagus

### Clinical Trials

- NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**PRIMARY TREATMENT OPTIONS**

**T2-T4a, Any (regional) N**

\[\text{Medically fit,}^g\text{ and locoregional disease}\]

- Multidisciplinary evaluation preferred\(^f\)

**T2-T4a, Any (regional) N**

- Preoperative chemoradiation\(^t,u,v\) (preferred)
  - (RT, 45-50.4 Gy + concurrent chemotherapy)

- Definitive chemoradiation\(^t,u,w\)
  - (RT, 50-50.4 Gy + concurrent chemotherapy)
  - (Preferred for cervical esophagus)

- Preoperative chemotherapy\(^t\)
  - (only for adenocarcinoma of distal esophagus or EGJ)

**T4b**

- Definitive chemoradiation\(^t,u\)
  - (RT, 50-50.4 Gy + concurrent chemotherapy)

\(^e\) T4a (resectable): involvement of pericardium, pleura or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases (N+).

\(^f\) See Principles of Multidisciplinary Team Approach (ESOPH-C).

\(^g\) Medically able to tolerate major abdominal and/or thoracic surgery.

\(^h\) See Principles of Surgery (ESOPH-D).

\(^i\) T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.

\(^n\) Preclinical staging cannot establish the number of positive nodes.

\(^t\) See Principles of Systemic Therapy (ESOPH-E).

\(^u\) See Principles of Radiation Therapy (ESOPH-F).

\(^v\) Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (Gaast AV, van Hagen P, Hulshof M, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study. J Clin Oncol (Meeting Abstracts). 2010;28:4004.)

\(^w\) Surgery is preferred for adenocarcinomas. Chemoradiation can be considered for squamous cell carcinoma.

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## Esophageal and Esophagogastric Junction Cancers

## PRIMARY TREATMENT FOR MEDICALLY FIT PATIENTS

### RESPONSE ASSESSMENT

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<thead>
<tr>
<th>Outcome</th>
<th>ADJUVANT TREATMENT</th>
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<tbody>
<tr>
<td>No evidence of disease</td>
<td>Esophagectomy(^h,q) (preferred) or Observe (category 2B)</td>
</tr>
<tr>
<td>Persistent local disease</td>
<td>Esophagectomy(^h,q) (preferred) or Palliative therapy, including chemotherapy(^t)</td>
</tr>
<tr>
<td>Unresectable or Metastatic disease</td>
<td>See Palliative Therapy (ESOPH-9)</td>
</tr>
<tr>
<td>No evidence of disease</td>
<td>Observe</td>
</tr>
<tr>
<td>Persistent local disease</td>
<td>Salvage esophagectomy(^h)</td>
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### OUTCOME

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<td>Observe</td>
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<tr>
<td>Persistent local disease</td>
<td>Salvage esophagectomy(^h)</td>
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### ADJUVANT TREATMENT

- **Preoperative chemoradiation\(^t,u,v\):**
  - CT scan with contrast (not required if PET/CT is done)
  - PET/CT or PET\(^x\) (category 2B)
  - Upper GI endoscopy and biopsy\(^y\) (optional)

- **Definitive chemoradiation\(^t,u\):**
  - CT scan with contrast (not required if PET/CT is done)
  - PET/CT or PET\(^x\) (category 2B)
  - Upper GI endoscopy and biopsy\(^y\)

- **Preoperative chemotherapy\(^t\):**
  - for adenocarcinoma of distal esophagus or EGJ

\(^h\) See Principles of Surgery (ESOPH-D).
\(^q\) Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
\(^t\) See Principles of Systemic Therapy (ESOPH-E).
\(^u\) See Principles of Radiation Therapy (ESOPH-F).
\(^v\) Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (Gaast AV, van Hagen P, Hulshof M, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study. J Clin Oncol (Meeting Abstracts). 2010;28:4004-.)
\(^x\) 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).

### 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.

**See Surgical Outcomes After Esophagectomy (ESOPH-6)**

**See Surgical Outcomes After Esophagectomy (ESOPH-6)**

**Follow-up (See ESOPH-8)**
**NCCN Guidelines Version 2.2012**

**Esophageal and Esophagogastric Junction Cancers**

**SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS**

(Patients Have Not Received Preoperative Chemoradiation or Chemotherapy)

- **Tumor Classification**
  - Tis\(^k\) and T1, N0 → Observe
  - T2, N0 → Observe or Consider chemoradiation\(^t,u\) for select patients\(^aa\)
  - T3, N0 → Observe or Chemoradiation\(^t,u\) (Fluoropyrimidine-based)
  - T4a, N0 → Observe

**Postoperative Treatment**

- **R0 resection\(^z\)**
  - Node negative:
    - Adenocarcinoma of proximal or mid esophagus → Observe
    - Squamous cell carcinoma → Observe
    - Adenocarcinoma of distal esophagus or EGJ → Chemoradiation\(^t,u\) (Fluoropyrimidine-based)
  - Node positive:
    - Adenocarcinoma of proximal or mid esophagus → Observe
    - Adenocarcinoma of distal esophagus or EGJ → Chemoradiation\(^t,u\) (Fluoropyrimidine-based)
    - Squamous cell carcinoma → Observe

- **R1 resection\(^z\)**
  - Chemoradiation\(^t,u\) (Fluoropyrimidine-based) or Palliative therapy (See ESOPH-9)

- **R2 resection\(^z\)**
  - Chemoradiation\(^t,u\) (Fluoropyrimidine-based) or Palliative therapy (See ESOPH-9)

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\(^a^a\)Consider chemoradiation for patients with high risk distal esophagus or EGJ adenocarcinoma. High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age.

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\(^j\)See Staging (ST-1).

\(^k\)Tis: Defined as high-grade dysplasia or carcinoma in situ.

\(^u\)See Principles of Systemic Therapy (ESOPH-E).

\(^z\)R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.

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**Follow-up**

(See ESOPH-8)
SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS (Patients Received Preoperative Chemoradiation or Chemotherapy)

TUMOR CLASSIFICATION

POSTOPERATIVE TREATMENT

Adenocarcinoma of distal esophagus or EGJ

Adenocarcinoma of proximal or mid esophagus

Squamous cell carcinoma

Adenocarcinoma of distal esophagus or EGJ

Squamous cell carcinoma

Adenocarcinoma of proximal or mid esophagus

Node negative

Node positive

R0 resection

R1 resection

R2 resection

T2, N0

T3, N0

T4a, N0

ECF or its modifications† if received preoperatively (category 1)

Observe

Observe

Observe

Observe

Observe

Observe

ECF or its modifications† if received preoperatively (category 1)

Chemoradiation†, u, bb (Fluoropyrimidine-based)

Chemoradiation†, u, bb (Fluoropyrimidine-based)

Chemoradiation†, u, bb (Fluoropyrimidine-based)

Palliative therapy (See ESOPH-9)

Follow-up (See ESOPH-8)

See Staging (ST-1).

See Principles of Systemic Therapy (ESOPH-E).

See Principles of Radiation Therapy (ESOPH-F).

R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1B.

†Postoperative chemoradiation only if not received preoperatively.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**Definitive Chemoradiation**  
(50-50.4 Gy of RT + concurrent chemotherapy)  
(Fluoropyrimidine- or taxane-based) (preferred)  
or  
Chemotherapy  
or  
RT  
or  
Best supportive care

Medically unfit for surgery  
or  
Surgery not elected and patient medically able to tolerate chemotherapy or chemoradiation  
or  
T4b (unresectable)

**Medically unfit for surgery and patient unable to tolerate chemotherapy or chemoradiation**

**Palliative RT**  
or  
Best supportive care

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See Principles of Endoscopic Staging and Therapy (ESOPH-A).  
Tis: Defined as high-grade dysplasia or carcinoma in situ.  
T4b (unresectable): Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.  
T1a: Defined as tumors involving the mucosa, but not invading the submucosa.  
See Principles of Systemic Therapy (ESOPH-E).  
See Principles of Radiation Therapy (ESOPH-F).  
See Principles of Best Supportive Care (ESOPH-G).
FOLLOW-UP

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
- Dilatation for anastomotic stenosis
- Nutritional counseling
- Confirm that HER2-neu testing has been done if metastatic adenocarcinoma was present at diagnosis

Chemistry profile and CBC, as clinically indicated
Imaging as clinically indicated
Upper GI endoscopy and biopsy as clinically indicated
Dilatation for anastomotic stenosis
Nutritional counseling
Confirm that HER2-neu testing has been done if metastatic adenocarcinoma was present at diagnosis

H&P

Recurrence

Locoregional only recurrence:
Prior esophagectomy, no prior chemoradiation

Recurrent

Locoregional only recurrence:
Prior esophagectomy, no prior chemoradiation

Recurrent

Resectable and medically operable

Recurrent

Esophagectomy

Recurrent

Unresectable or Medically inoperable

Recurrent

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

See Palliative Therapy (ESOPH-9)

See Palliative Therapy (ESOPH-9)

See Palliative Therapy (ESOPH-9)
**PERFORMANCE STATUS**

<table>
<thead>
<tr>
<th>Karnofsky performance score ≥ 60 % or ECOG performance score ≤ 2</th>
<th>Confirm HER2-neu testing has been done if metastatic adenocarcinoma is suspected(^a)</th>
<th>Chemotherapy(^{t,ee}) and/or Best supportive care(^{dd})</th>
</tr>
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<tbody>
<tr>
<td>Karnofsky performance score &lt; 60 % or ECOG performance score ≥ 3</td>
<td></td>
<td>Best supportive care(^{dd})</td>
</tr>
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**Metastatic disease**

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\(^a\) See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).

\(^t\) See Principles of Systemic Therapy (ESOPH-E).

\(^{dd}\) See Principles of Best Supportive Care (ESOPH-G).

\(^{ee}\) Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

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Back to Follow-up and Recurrence (ESOPH-8)
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, 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.
- Multiple biopsies, six to eight, 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. Endoscopic mucosal resection (EMR) can be therapeutic/diagnostic. 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.
- Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment.
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).

- 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 trachea, aorta, liver correlates with infiltration of tumor into surrounding organs (T4 disease).

- 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. 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.

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

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**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. 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.
- 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. 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 and brushings 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. Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.
- 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. 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.
PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

(REFERENCES)

### TABLE 1  Pathologic Review

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Analysis/Interpretation/Reporting&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **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)”<sup>b,c,d</sup>  
  - Histologic type<sup>e</sup>  
  - Grade<sup>f</sup>  
  - Presence or absence of Barrett's esophagus                                                                 |
| **Endoscopic mucosal resection**       | Include in pathology report:  
  - Invasion, if present<sup>b,d</sup>  
  - Histologic type<sup>e</sup>  
  - Grade<sup>f</sup>  
  - 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<sup>g</sup>  
  - 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 |

<sup>a</sup>Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at [http://www.cap.org](http://www.cap.org)) for reporting pathologic findings is recommended.

<sup>b</sup>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.<sup>1</sup>

<sup>c</sup>Biopsies showing Barrett's esophagus with suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.<sup>2</sup>

<sup>d</sup>Invasion of a thickened and duplicated muscularis mucosae should not be misinterpreted as invasion of the muscularis propria in Barrett's esophagus.<sup>3</sup>

<sup>e</sup>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.<sup>1</sup>

<sup>f</sup>Pathologic grade is needed for stage grouping in the AJCC TNM 7th edition.<sup>1</sup>

<sup>g</sup>Tumors arising in the proximal stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.<sup>1</sup>

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<sup>Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.</sup>
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 and squamous cell carcinoma of the esophagus.

Although grading systems for tumor response in esophageal cancer have not been uniformly adopted, in general, three-category systems provide good reproducibility among pathologists. The following system developed specifically for esophagus by Wu, et al 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), 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

<table>
<thead>
<tr>
<th>Tumor Regression Grade</th>
<th>Wu et al. Description</th>
<th>Ryan et al. Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Complete response)</td>
<td>No residual cancer cells</td>
<td>No cancer cells</td>
</tr>
<tr>
<td>1 (Moderate response)</td>
<td>1% to 50% residual cancer; rare individual cancer cells or minute clusters of cancer cells</td>
<td>Single cells or small groups of cancer cells</td>
</tr>
<tr>
<td>2 (Minimal response)</td>
<td>More than 50% residual cancer cells, often grossly identifiable at primary site</td>
<td>Residual cancer cells outgrown by fibrosis</td>
</tr>
<tr>
<td>3 (Poor response)</td>
<td>Minimum or no treatment effect; extensive residual cancer</td>
<td></td>
</tr>
</tbody>
</table>

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Continue
**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\(^\text{10}\) are recommended:

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

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

\(\text{The NCCN Guidelines panel recommends that cases showing less than 3+ overexpression 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 \(\geq 2\)) are considered positive.}\)

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

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Continue
PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

(REFERENCES)

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. The NCCN panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients.

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

- The involved institution and individuals from relevant disciplines are committed to jointly reviewing the detailed data on patients on a regular basis. Frequent meetings (either once a week or once every two weeks) are encouraged.

- Optimally at each meeting, all relevant disciplines should be encouraged to participate and these may include: surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines are also desirable.

- All long-term therapeutic strategies are best developed after adequate staging procedures are completed, but ideally prior to any therapy that is rendered.

- Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions.

- A brief documentation of the consensus recommendation(s) by the multidisciplinary team for an individual patient may prove useful.

- The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient.

- Re-presentation of select patient outcomes after therapy is rendered may be an effective educational method for the entire multidisciplinary team.

- A periodic formal review of relevant literature during the course of the multidisciplinary meeting is highly encouraged.


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PRINCIPLES OF 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. 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). Siewert Type I: adenocarcinoma of the distal 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 distal 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. Laparoscopy may be useful in select patients in detecting radiographically occult metastatic disease, especially in patients with Siewert II and III tumors.

- 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.
  - 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.
  - T4 tumors with involvement of pericardium, pleura or diaphragm are resectable.

- Unresectable esophageal cancer:
  - T4 tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
  - Most patients with 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.
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.\(^{16}\)

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PRINCIPLES OF SURGERY


Rusch VW. Are Cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several. Semin Oncol 2004; 31:444-449


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 co-morbidities, toxicity profile and HER2-neu expression (for adenocarcinoma only)

The use of three-drug cytotoxic regimens for advanced disease should be reserved for patients who are medically fit, with a good performance status (ECOG performance status of 0 or 1), and with access to frequent toxicity assessment.

Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated) with evidence supporting 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 5-FU and capecitabine may be used interchangeably (except as indicated). Infusion is the preferred route compared with bolus 5-FU.

Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile

For localized EGJ adenocarcinoma, preoperative chemoradiation is the preferred approach. Preoperative chemotherapy is an option only for distal esophagus and EGJ adenocarcinoma.

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)
**PRINCIPLES OF SYSTEMIC THERAPY**

### Preoperative Chemoradiation:
- Paclitaxel and carboplatin (category 1)
- Cisplatin and fluoropyrimidine (5-FU or capecitabine) (category 1)
- Oxaliplatin and fluoropyrimidine (5-FU or capecitabine)
- Paclitaxel and cisplatin
- Carboplatin and 5-FU (category 2B)
- Irinotecan and cisplatin (category 2B)
- Docetaxel or paclitaxel and fluoropyrimidine (5-FU or capecitabine) (category 2B)
- Oxaliplatin, docetaxel, and capecitabine (category 2B)

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

### Sequential Chemotherapy and Chemoradiation
- Irinotecan and cisplatin
- Paclitaxel and cisplatin
- Docetaxel and cisplatin
- 5-fluorouracil and cisplatin; 5-fluorouracil and paclitaxel

### Definitive Chemoradiation:
- Cisplatin and fluoropyrimidine (5-FU or capecitabine)
- Oxaliplatin and fluoropyrimidine (5-FU or capecitabine)
- Paclitaxel or docetaxel and cisplatin
- Paclitaxel and carboplatin (category 2B)
- Irinotecan and cisplatin (category 2B)
- Docetaxel or paclitaxel and fluoropyrimidine (5-FU or capecitabine) (category 2B)
- Oxaliplatin, docetaxel, and capecitabine (category 2B)

### Postoperative Chemoradiation:
(Only for adenocarcinoma)
- LV5FU2 before and after infusion 5-FU or capecitabine with radiation (preferred)

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† Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, please see [Discussion](#).

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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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Definitive Chemotherapy for Metastatic or Locally Advanced Cancer [where chemoradiation is not indicated]

First Line Therapy

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

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

\(^\text{†}\)Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, please see (Discussion).

Second Line Therapy

Dependent on prior therapy and performance status (PS):

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

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

- Gemcitabine, 5-FU, and leucovorin\(^\text{68}\)
- Pegylated liposomal doxorubicin, cisplatin and 5-FU\(^\text{69}\)
- Mitomycin and irinotecan\(^\text{70}\)
- Mitomycin, cisplatin, and 5-FU\(^\text{39}\)
- Mitomycin and 5-FU\(^\text{†}\)\(^\text{71}\)
- Etoposide\(^\text{72,73}\)
- Erlotinib\(^\text{74,75}\)

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

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**PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES**

### PREOPERATIVE CHEMORADIATION

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

- **Cisplatin and fluoropyrimidine**
  - Cisplatin 75-100 mg/m² IV on Days 1 and 29
  - 5-FU 750-1000 mg/m² IV continuous infusion over 24 hours daily on Days 1-4 and 29-32
  - 35-Day cycle

- **Cisplatin 30 mg/m² IV on Day 1**
  - Capecitabine 800 mg/m² PO BID on Days 1-5
  - Weekly for 5 weeks

- **Cisplatin 15 mg/m² IV daily on Days 1-5**
  - 5-FU 800 mg/m² IV continuous infusion over 24 hours daily on Days 1-5
  - Cycled every 21 days for 2 cycles

- **Oxaliplatin and fluoropyrimidine**
  - Oxaliplatin 45 mg/m² IV on Day 1 weekly for 5 weeks
  - 5-FU 225 mg/m² IV continuous infusion over 24 hours daily on Days 1-33

- **Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses**
  - 5-FU 180 mg/m² IV daily on Days 1-33

- **Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses**
  - Capecitabine 625 mg/m² PO BID on Days 1-5 for 5 weeks

### Taxane and cisplatin
- **Paclitaxel 60 mg/m² IV on Days 1, 8, 15, and 22**
- **Cisplatin 75 mg/m² IV on Day 1**
  - Given for 1 cycle

### Carboplatin and 5-FU
- **Carboplatin AUC 6 IV on Days 1 and 22**
- **5-FU 200 mg/m² IV daily on Days 1-42**

### Irinotecan and cisplatin
- **Irinotecan 65 mg/m² IV on Days 1, 8, 22, 29**
- **Cisplatin 30 mg/m² IV on Days 1, 8, 22, 29**

### Taxane and fluoropyrimidine
- **Paclitaxel 45-50 mg/m² IV on Day 1**
- **Capecitabine 625-825 mg/m² PO BID on Days 1-5**
  - Weekly for 5 weeks

- **Docetaxel 20 mg/m² IV on Day 1**
  - 5-FU 200-300 mg/m² IV daily on Days 1-5
  - Weekly for 5 weeks

- **Docetaxel 20 mg/m² IV on Day 1**
  - Capecitabine 625-825 mg/m² PO BID on Days 1-5
  - Weekly for 5 weeks

- **Oxaliplatin, docetaxel, and capecitabine**
  - Oxaliplatin 40 mg/m² IV on Days 1, 8, 15, 22, and 29
  - Docetaxel 20 mg/m² IV on Days 1, 8, 15, 22, and 29
  - Capecitabine 1000 mg/m² PO BID on Days 1-7, 15-21, and 29-35
  - Given for 1 cycle

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

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PERIOPERATIVE CHEMOTHERAPY (INCLUDING EG JUNCTION)

**ECF (epirubicin, cisplatin, and 5-FU)**
- Epirubicin 50 mg/m² IV on Day 1
- Cisplatin 60 mg/m² IV on Day 1
- 5-FU 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

**ECF modifications**
- Epirubicin 50 mg/m² IV on Day 1
- Oxaliplatin 130 mg/m² IV on Day 1
- 5-FU 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

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

**DEFINITIVE CHEMORADIATION (NON-SURGICAL)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Taxane and cisplatin</th>
<th>Taxane and fluoropyrimidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin and fluoropyrimidine</td>
<td>Paclitaxel 60 mg/m² IV on Days 1, 8, 15, and 22</td>
<td>Paclitaxel 45-50 mg/m² IV on Day 1</td>
</tr>
<tr>
<td>Cisplatin 75-100 mg/m² IV on Day 1</td>
<td>Cisplatin 75 mg/m² IV on Day 1</td>
<td>Cisplatin 625-825 mg/m² PO BID on Days 1-5</td>
</tr>
<tr>
<td>5-FU 750-1000 mg/m² IV continuous infusion</td>
<td>Given for 1 cycle</td>
<td>Weekly for 5 weeks 13, 14</td>
</tr>
<tr>
<td>over 24 hours daily on Days 1-4</td>
<td></td>
<td>Docetaxel 20 mg/m² IV on Day 1</td>
</tr>
<tr>
<td>Cycled every 28 days for 2-4 cycles with radiation</td>
<td></td>
<td>5-FU 200-300 mg/m² IV daily on Days 1-5</td>
</tr>
<tr>
<td>followed by 2 cycles without radiation</td>
<td></td>
<td>Weekly for 5 weeks 15, 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel 20 mg/m² IV on Day 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-FU 200-300 mg/m² IV daily on Days 1-5</td>
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<tr>
<td></td>
<td></td>
<td>weekly for 5 weeks 14, 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel 20 mg/m² IV on Day 1</td>
</tr>
<tr>
<td>Cisplatin 30 mg/m² IV on Day 1</td>
<td>Cisplatin 60-80 mg/m² IV on Days 1 and 22</td>
<td>Capecitabine 625-825 mg/m² PO BID on Days 1-5</td>
</tr>
<tr>
<td>Capecitabine 800 mg/m² PO BID on Days 1-5</td>
<td>Given for 1 cycle</td>
<td>Weekly for 5 weeks 14, 16</td>
</tr>
<tr>
<td>Weekly for 5 weeks 5</td>
<td></td>
<td>Docetaxel 20 mg/m² IV on Day 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-FU 200-300 mg/m² IV daily on Days 1-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weekly for 5 weeks 14, 16</td>
</tr>
<tr>
<td>Oxaliplatin and fluoropyrimidine</td>
<td>Docetaxel 20-30 mg/m² IV on Day 1</td>
<td>Oxaliplatin 40 mg/m² IV on Days 1, 8, 15, 22, and 29</td>
</tr>
<tr>
<td>Oxaliplatin 45-50 mg/m² IV on Day 1</td>
<td>Cisplatin 20-30 mg/m² IV on Day 1</td>
<td>Docetaxel 20 mg/m² IV on Days 1, 8, 15, 22, and 29</td>
</tr>
<tr>
<td>on Day 1 weekly for 5 weeks</td>
<td>Given for 5 weeks 26</td>
<td>Capcitabine 1000 mg/m² PO BID on Days 1-7, 15-21, and 29-35</td>
</tr>
<tr>
<td>5-FU 225 mg/m² IV continuous infusion over 24 hours</td>
<td>Paclitaxel 50 mg/m² IV on Day 1</td>
<td>Given for 1 cycle 16</td>
</tr>
<tr>
<td>daily on Days 1-33</td>
<td>Carboplatin AUC 2 IV on Day 1</td>
<td></td>
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<tr>
<td></td>
<td>Weekly for 5 weeks 3</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29</td>
<td>Irinotecan and cisplatin</td>
<td></td>
</tr>
<tr>
<td>on 5-FU 180 mg/m² IV daily on Days 1-33</td>
<td>Irinotecan 65 mg/m² IV on Days 1, 8, 22, 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin 30 mg/m² IV on Days 1, 8, 22, 29</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m² IV on Days 1, 15, 29 for 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine 625 mg/m² PO BID on Days 1-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly for 5 weeks 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29</td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Weekly for 5 weeks 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m² IV on Day 1</td>
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<td></td>
</tr>
<tr>
<td>Leucovorin 400 mg/m² IVP on Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU 400 mg/m² IVP on Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU 600 mg/m² IV continuous infusion over 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hours daily on Days 1 and 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycled every 14 days for 3 cycles with radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>followed by 3 cycles without radiation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF SYSTEMIC THERAPY FOR ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCERS

POSTOPERATIVE CHEMORADIATION (INCLUDING EG JUNCTION)

LV5FU2 before and after infusional 5-FU or capecitabine (preferred)
1 cycle before and 2 cycles after radiation
Leucovorin 400 mg/m² IV on Days 1 and 15 or Days 1, 2, 15, and 16
5-FU 400 mg/m² IVP on Days 1 and 15 or Days 1, 2, 15, and 16
5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1, 2, 15, and 16
Cycled every 28 days

With radiation
5-FU 200-250 mg/m² IV continuous infusion over 24 hours daily on Days 1-5 or 1-7
Weekly for 5 weeks

With radiation
Capecitabine 625-825 mg/m² PO BID on Days 1-5 or 1-7
Weekly for 5 weeks

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

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

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

### FIRST-LINE THERAPY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trastuzumab (with chemotherapy)</strong></td>
<td>Docetaxel 50 mg/m² IV on Day 1, Oxaliplatin 85 mg/m² IV on Day 1, 5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>DCF (docetaxel, cisplatin, and 5-FU)</strong></td>
<td>Docetaxel 60 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, 5-FU 750 mg/m² IV continuous infusion over 24 hours daily on Days 1-4, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>ECF modifications</strong></td>
<td>Epirubicin 50 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, Capecitabine 625 mg/m² PO BID on Days 1-21, Cycled every 21 days.</td>
</tr>
</tbody>
</table>

### DCF modifications

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCF (docetaxel, cisplatin, and 5-FU)</strong></td>
<td>Docetaxel 50 mg/m² IV on Day 1, Oxaliplatin 85 mg/m² IV on Day 1, 5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>DCF modifications</strong></td>
<td>Docetaxel 60 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, 5-FU 750 mg/m² IV continuous infusion over 24 hours daily on Days 1-4, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>ECF modifications</strong></td>
<td>Epirubicin 50 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, Capecitabine 625 mg/m² PO BID on Days 1-21, Cycled every 21 days.</td>
</tr>
</tbody>
</table>

### DCF modifications--continued

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCF (docetaxel, cisplatin, and 5-FU)</strong></td>
<td>Docetaxel 50 mg/m² IV on Day 1, Oxaliplatin 85 mg/m² IV on Day 1, 5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>DCF modifications--continued</strong></td>
<td>Docetaxel 60 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, 5-FU 750 mg/m² IV continuous infusion over 24 hours daily on Days 1-4, Cycled every 21 days.</td>
</tr>
<tr>
<td><strong>ECF modifications</strong></td>
<td>Epirubicin 50 mg/m² IV on Day 1, Cisplatin 60 mg/m² IV on Day 1, Capecitabine 625 mg/m² PO BID on Days 1-21, Cycled every 21 days.</td>
</tr>
</tbody>
</table>

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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Continue
PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES

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

FIRST-LINE THERAPY---continued

Fluoropyrimidine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
5-FU 400 mg/m² IVP on Day 1
5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
5-FU 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days

5-FU and irinotecan
Irinotecan 80 mg/m² IV on Day 1
Leucovorin 500 mg/m² IV on Day 1
5-FU 2000 mg/m² IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 1 week off treatment

Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
5-FU 400 mg/m² IVP on Day 1
5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days

Fluoropyrimidine
Leucovorin
5-FU 400 mg/m² IVP on Day 1
5-FU 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days

5-FU 800 mg/m² IV continuous infusion over 24 hours daily on Days 1-5
Cycled every 28 days

Capecitabine 1000 mg/m² PO BID on Days 1-14
Cycled every 21 days

Docetaxel 75-100 mg/m² IV on Day 1
Cycled every 21 days

Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days

Paclitaxel with cisplatin or carboplatin
Paclitaxel 135 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 2
Cycled every 21 days

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

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 6 IV on Day 1
Cycled every 21 days

Docetaxel and cisplatin
Docetaxel 70-85 mg/m² IV on Day 1
Cisplatin 70-75 mg/m² IV on Day 1
Cycled every 21 days

Docetaxel and irinotecan
Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days

Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days

Paclitaxel 135-175 mg/m² IV on Day 1
Cycled every 21 days

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

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

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

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

**SECOND-LINE THERAPY**

| Regimen Description | First Dose | Second Dose | Third Dose | Fourth Dose | Fifth Dose | Sixth Dose | Seventh Dose | Eighth Dose | Ninth Dose | Tenth Dose | Eleventh Dose | Twelfth Dose | Thirteenth Dose | Fourteenth Dose | Fifteenth Dose | Sixteenth Dose | Seventeenth Dose | Eighteenth Dose | Nineteenth Dose | Twentieth Dose | Twenty-first Dose | Twenty-second Dose | Twenty-third Dose | Twenty-fourth Dose | Twenty-fifth Dose | Twenty-sixth Dose | Twenty-seventh Dose | Twenty-eighth Dose | Twenty-ninth Dose | Thirtieth Dose | Thirty-first Dose | Thirty-second Dose | Thirty-third Dose | Thirty-fourth Dose | Thirty-fifth Dose | Thirty-sixth Dose | Thirty-seventh Dose | Thirty-eighth Dose | Thirty-ninth Dose | Fortieth Dose | Forty-first Dose | Forty-second Dose | Forty-third Dose | Forty-fourth Dose | Forty-fifth Dose | Forty-sixth Dose | Forty-seventh Dose | Forty-eighth Dose | Forty-ninth Dose | Fiftieth Dose | Fiftieth-fifth Dose | Fiftieth-sixth Dose | Fiftieth-seventh Dose | Fiftieth-eight Dose | Fiftieth-ninth Dose | Fiftieth-ten Dose | Fiftieth-ten Dose | Fiftieth-tenth Dose | Fiftieth-ten Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth Dose | Fiftieth-tenth D0054

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

---

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PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES

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

**Gemcitabine, 5-FU, and leucovorin**
- Gemcitabine 1000 mg/m² IV on Days 1, 8, and 15
- Leucovorin 20 mg/m² IV on Days 1, 8, and 15
- 5-FU 500 mg/m² IV on Days 1, 8, and 15
- Cycled every 28 days

**Pegylated liposomal doxorubicin, cisplatin, and 5-FU**
- Pegylated liposomal doxorubicin 20 mg/m² IV on Day 1
- Cisplatin 50 mg/m² IV on Day 1
- 5-FU 400 mg/m² IVP on Day 1
- 5-FU 600 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
- Cycled every 14 days

**Mitomycin and irinotecan**
- Mitomycin 10 mg/m² IV on Days 1 and 22
- Leucovorin 500 mg/m² IV on Day 1
- 5-FU 2600 mg/m² IV continuous infusion over 24 hours on Day 1
- Weekly for 6 weeks followed by 2 weeks off treatment

**Etoposide**
- Etoposide 90-120 mg/m² IV on Days 1-3
- Cycled every 28 days

**Erlotinib**
- Erlotinib 150 mg PO daily

ALTERNATIVE REGIMENS FOR CONSIDERATION

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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Sharma R, Yang GY, Nava HR, et al. A single institution experience with neoadjuvant chemoradiation (CRT) with irinotecan (I) and cisplatin (C) in locally advanced esophageal carcinoma (LAEC). J Clin Oncol (Meeting Abstracts) 2009;27:e15619-.


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PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES


33 Shah MA, Shibata S, Stoller RG, et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE). J Clin Oncol (Meeting Abstracts) 2010;28:4014-


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Continued
PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

General Radiation Information

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

Simulation and Treatment Planning

- Use of CT simulation and 3D treatment planning is strongly encouraged.
- When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily 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. The relative risk of nodal metastases at a specific nodal location is dependent on the site of origin of the primary tumor. The planning target volume (PTV) should include the tumor plus a nominal 5 cm cephalad and caudal margin, and a 1.5 to 2 cm radial margin. 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.
- 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.

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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 or Postoperative Therapy: 45-50.4 Gy (1.8-2 Gy/day)
- Definitive Therapy: 50-50.4 Gy (1.8-2 Gy/day)\(^3\)

Supportive Therapy
- Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks.
- During irradiation, patients are seen for status check at least once a week with notation of vital signs, weight and blood counts.
- Antiemetics should be given on a prophylactic basis when appropriate. Antacid and antidiarrheal medications may be prescribed when needed.
- If estimated caloric intake is < 1500 kcal/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.

\(^a\)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.
PRINCIPLES OF RADIATION THERAPY

(References)


PRINCIPLES OF BEST SUPPORTIVE CARE\textsuperscript{1,2,3,4,5,6}

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

Dysphagia

\begin{itemize}
  \item Assess the extent of disease, the functional degree of swallowing impairment and confirm the etiology of dysphagia
  \item Functional Degrees of Swallowing Impairment
    \begin{itemize}
      \item Unable to swallow saliva
      \item Able to swallow liquids only
      \item Able to swallow semisolid food (consistency of baby food)
      \item Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed
      \item Able to eat solid food without special attention to bite size or chewing (dysphagia symptoms may be intermittent)
    \end{itemize}
  \end{itemize}

\textbullet Dysphagia arising from esophageal cancer most often is due to obstruction, but on occasion may be primarily due to tumor related dysmotility.

Obstruction:

\begin{itemize}
  \item Complete esophageal obstruction
    \begin{itemize}
      \item Endoscopic lumen restoration
      \item Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
      \item Surgical or radiologic placement of jejunal or gastrostomy tube
    \end{itemize}
  \item Moderate esophageal obstruction (able to swallow semisolid food)
    \begin{itemize}
      \item Endoscopic lumen enhancement as necessary
      \item Measures stated above may be considered
    \end{itemize}
  \item Severe esophageal obstruction (able to swallow liquids only)
    \begin{itemize}
      \item Endoscopic lumen enhancement
        \begin{itemize}
          \item Wire guided dilation or balloon dilation
          \item Endoscopy or fluoroscopy-guided placement of covered expandable metal stents.
        \end{itemize}
      \item Other measures as stated above
    \end{itemize}
  \item Moderate esophageal obstruction (able to swallow semisolid food)
    \begin{itemize}
      \item Endoscopic lumen enhancement as necessary
    \end{itemize}
\end{itemize}
PRINCIPLES OF BEST SUPPORTIVE CARE

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

**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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**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.
**Table 1**

**American Joint Committee on Cancer (AJCC)**

**TNM Classification of Carcinoma of the Esophagus and Esophagogastric Junction (7th ed, 2010)**

**Primary Tumor (T)**

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

*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)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>N4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1–2 regional lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 3–6 regional lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in seven or more regional lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

**Anatomic Stage/Prognostic Groups**

**Squamous Cell Carcinoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Grade</th>
<th>Tumor Location**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis (HGD)</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>2–3</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2–3</td>
<td>N0</td>
<td>M0</td>
<td>1, X</td>
<td>Lower, X</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2–3</td>
<td>N0</td>
<td>M0</td>
<td>2–3</td>
<td>Upper, middle</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1–2</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4a</td>
<td>N1–2</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

*Or mixed histology including a squamous component or NOS.

**Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus.
### Table 1---Continued

#### Anatomic Stage/Prognostic Groups

**Adenocarcinoma**

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

#### 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

Esophageal and Esophagogastric Junction Cancers

NCCN Categories of Evidence and Consensus

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

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach, constitute a major health problem around the world. An estimated 38,780 new cases of and 25,610 deaths from upper GI tract cancers will occur in the United States in 2012.1 A dramatic shift in the location of upper GI tract tumors has occurred in the United States.2, 3 Changes in histology and location of upper GI tract tumors have also been observed in some parts of Europe.4 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.5 An estimated 17,460 new cases and 15,070 deaths from esophageal cancer will occur in United States in 2012.1 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 malignancies 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.2

Tobacco and alcohol abuse are major risk factors for SCC whereas the use of tobacco is a moderate established risk factor for adenocarcinoma.10-12 Risk of SCC decreases substantially after smoking cessation; unlike in SCC, the risk for adenocarcinoma remains unchanged even after several years of smoking cessation.13,14 Obesity and high body mass index (BMI) have been established as strong risk
Factors for adenocarcinoma of the esophagus. 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.

Gastroesophageal reflux disease (GERD) and Barrett’s esophagus are the other two major risk factors for adenocarcinoma of the esophagus. GERD is associated with high body mass index 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. Patients with Barrett’s esophagus have 30 to 60 times greater risk of developing adenocarcinoma of the esophagus than the general population. Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett’s esophagus are strongly associated with higher grades of dysplasia.

These preliminary results 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.

Staging

The tumor (T), node (N) and metastasis (M) classification developed by the American Joint Committee on Cancer (AJCC) in 2002 was based on the pathological review of the surgical specimen in patients who had surgery as primary therapy. The revised 2010 AJCC staging classification (Table 1) is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) in 4,627 patients who were treated with primary esophagectomy without preoperative or postoperative therapy. In the data reported by WECC, the survival decreased with increasing depth of tumor invasion (pT), presence of regional lymph node metastases (pN) and the presence of distant metastases (pM). In addition, survival was somewhat worse for pT1b (submucosal) tumors than for pT1a (intramucosal) tumors. Survival was worse for SCC than adenocarcinomas. The revised staging system includes separate stage groupings for SCC and adenocarcinoma. The revised staging system is for the esophageal and EGJ cancers, including the cancer within the first 5 cm of the stomach that extend into the EGJ or distal thoracic esophagus. However, this new classification may not work well for baseline clinical staging or in patients who received preoperative therapy. This new classification has several other shortcomings including: inclusion of proximal 5 cm of 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. 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. 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.\(^3^0\) 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.\(^3^0\)

In 2000, the classification was changed slightly.\(^3^1\) Siewert Type I tumors are defined as the adenocarcinoma of the distal esophagus with the tumor center located within 1-5 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 2-5 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 extend into the EGJ or esophagus (Siewert Types I and II) are classified as adenocarcinoma of the esophagus for the purposes of staging.\(^2^7\) 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.

**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.\(^2^7\) 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 endoscopic mucosal resection (EMR) or esophageal resection specimens, the depth of tumor invasion and the status of mucosal and deep margins should also be recorded. In an esophageal resection specimen, Barrett’s esophagus with HGD is reported as carcinoma-in-situ (Tis).\(^2^7\) Biopsies showing Barrett’s esophagus with a suspected dysplasia should be reviewed by a second expert gastrointestinal pathologist for confirmation.\(^3^2\) 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 or ulcer bed after preoperative therapy without grossly obvious residual tumor.
Assessment of Treatment Response

The prognostic significance of complete pathological response and histological tumor regression after neoadjuvant therapy in patients with adenocarcinoma and SCC of the esophagus has been demonstrated in several studies. Post-therapy 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.

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. Tumor regression remained a significant predictor of disease-free survival 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)]. The overall survival 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, overall survival 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). 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 Principles of Pathologic Review and HER2-neu Testing-Assessment of Treatment Response-Table 2 in the guidelines.

Assessment of HER2-neu Overexpression

Human epidermal growth factor receptor 2 gene (HER2, also known as HER2-neu) is a member of the human epidermal growth factor receptor (EGFR) family and is implicated in the development of various solid tumour types. HER2-neu amplification and overexpression are more frequent in adenocarcinoma of the esophagus (15-30%) than SCC of esophagus (5-13%). HER2-neu overexpression in esophagogastric cancers varies widely (2-45%). HER2-neu-positivity has been reported to be higher in EGJ cancers than in gastric cancers. In the Trastuzumab for Gastric Cancer (ToGA) trial which evaluated the addition of trastuzumab to chemotherapy in HER2-neu-positive advanced gastric cancer, HER2-neu-positivity rates were 33% and 21% respectively, for patients with EGJ and gastric cancers. 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. HER2-neu overexpression seems to be associated with poorer survival, especially in patients with SCC of the esophagus.

For patients with unresectable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or EGJ, assessment of HER2-neu overexpression should be performed using immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH), following the 4-tier HER2-neu scoring system developed by Hoffman et al, which was also used in the ToGA trial (Table 1). In a subsequent validation study, this scoring system was also found to be reproducible between different pathologists. Surgical and biopsy specimens with intense immunoreactivity in less than 10% of cancer cells (IHC score = 0) and those with faint or barely perceptible membranous reactivity in 10% or more of cancer cells (IHC score = 1)
are considered negative for HER2-neu overexpression. Specimens with strong complete, basolateral or lateral membranous reactivity in 10% or more of cancer cells (IHC score = 3) in resection specimens, or in a cluster of 5 or more tumor cells in biopsy specimens, are considered positive for HER2-neu overexpression. In cases showing weak to moderate complete, basolateral or lateral membranous reactivity in more than 10% of cancer cells (IHC score = 2), the HER2-neu overexpression is considered equivocal. The panel recommends that cases showing less than 3+ overexpression of HER2-neu by IHC should be additionally confirmed by FISH or other in situ hybridization methods.

To summarize, it is better to request IHC first; if the IHC score is 3+ then there is no need to request FISH; however, if the IHC score is 2+, FISH should be requested and if there is evidence of HER2-neu amplification by FISH, trastuzumab can be recommended. Trastuzumab is not recommended if IHC score is 0 or 1+.

**Surgery**

Surgery is a major component of treatment for resectable disease. One of the major developments in the surgical therapy of esophageal cancer has been the marked reduction in surgical morbidity and mortality as a result of improvements in staging techniques, patient selection, support systems and surgical experience. Recent randomized trials have showed that preoperative chemoradiation (CROSS study) and perioperative chemotherapy (MAGIC trial, predominantly a gastric cancer trial including a small group of patients with lower esophageal and EGJ cancers) significantly improved survival in patients with resectable esophageal and 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 positron emission tomography (PET) and computed tomography (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 overall survival.

**Surgical Approaches**

Several strategies and approaches are acceptable for esophagogastrectomy in patients with resectable esophageal cancer or EGJ cancers. 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) and the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis) 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). Mobilization of the stomach for use as the conduit is performed, with dissection of the celiac and left gastric lymph nodes.
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. 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 esophagogastrectomy 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. In the largest population based study which assessed outcomes after transthoracic and transhiatal esophagectomy for esophageal cancer, transhiatal esophagectomy offered an early survival advantage, but long term survival was not different between the two surgical approaches.

**Transthoracic or Thoracoabdominal Esophagogastrectomy**

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision, through the eighth intercostal space. Mobilization of the stomach for use as the conduit is performed as described previously, and esophagectomy is accomplished through the left thoracotomy. Esophagogastrectomy 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.

**Minimally Invasive Esophagectomy**

Minimally invasive esophagectomy (MIE) strategies include numerous techniques, including minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy and limited thoracotomy or thoracoscopy) and minimally invasive McKeown esophagogastrectomy (thoracoscopy, limited laparotomy or laparoscopy, and cervical incision). MIE strategies may be associated with decreased morbidity and shorter recovery times. In a study of MIE (mainly using thoracoscopic mobilization) in 222 patients, 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. 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%. 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. Open esophagectomy should remain the standard for many patients. MIE may be useful for older patients.
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. Gastric conduit is preferred for esophageal reconstruction and it is preferred by majority of esophageal surgeons. Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.

Principles of Surgery

All patients should be assessed for physiologic ability to undergo esophageal resection. 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. 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 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 esophagus 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.

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 that described in the NCCN Guidelines for Gastric cancer. 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. Positive peritoneal cytology in the
absence of overt peritoneal metastases is associated with poor prognosis in patients with EGJ adenocarcinoma. Patients with advanced tumors, clinical stage T3 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 overall survival. Selected patients with stage III disease may have resectable tumor as well. T4 tumors with involvement of pericardium, pleura or diaphragm may be resectable. EGJ tumors with supraclavicular lymph node involvement, stage IV tumors with distant metastases including non regional lymph node involvement and T4 tumors with involvement of heart, great vessels, trachea or adjacent organs including liver, pancreas, lung and spleen are considered unresectable. Esophagectomy, EMR and other ablative techniques should be performed in high volume esophageal cancer centers by experienced surgeons and endoscopists.

Lymph node dissections (or lymphadenectomy) can be performed using the standard or extended (en-bloc) technique. In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the Surveillance Epidemiology and End Results (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. The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy. A recent report from the Worldwide Esophageal Cancer Collaboration 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. 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

Endoscopic mucosal resection (EMR) and endoscopic ablation procedures [cryoablation, radiofrequency ablation (RFA) and photodynamic therapy (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 in the GI tract. EMR is used widely for treating superficial early SCC of esophagus in Japan and it is gaining acceptance in the Western countries for the treatment of Barrett’s esophagus and superficial adenocarcinomas. While EMR of visible lesions suspicious of malignancy is effective, it is also associated with a high rate of recurrence. Complete Barrett’s eradication endoscopic mucosal resection (CBE-EMR) has been shown to be a highly effective long-term treatment for patients with Barrett’s esophagus and HGD. Diagnostic EMR has been reported to accurately determine the depth of tumor invasion and therefore influence surgical planning before surgical resection.

PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett’s esophagus and
HGD. 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. 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.

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 cancers. 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. 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, 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. The 5-year survival rate was significantly higher for patients with a tumor length of 2 cm or less (78% vs. 29% 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, vascular and/or lymphatic invasion. 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.

**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). Mediastinal and perigastric lymph nodes are readily identified by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well circumscribed, rounded structures in these areas indicates the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of...
features, but also confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment. \(^{108}\)

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. \(^{109, 110}\) In a study conducted by the Mayo clinic 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. \(^{111}\) 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, lateral spread and ruling out multifocal disease. EUS staging prior to proceeding with EMR in the setting of carcinoma is recommended. \(^{102}\) 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. \(^{112, 113}\) 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 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. \(^{114}\) Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease. \(^{115}\)

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. \(^{116}\) EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.
Endoscopic surveillance after ablative therapy or EMR of early esophageal cancer should continue after completion of treatment. Biopsies of the 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 low-grade dysplasia (LGD) using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett's esophagus is not recommended.

**Barrett's Esophagus**

Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar or glandular epithelium that is predisposed to malignancy. 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 LGD and HGD. The 5-year cumulative incidence of cancer was 4% for patients with LGD compared to 59% for those with HGD. 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. 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. 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.

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. In recent years, many alternatives to surgical resection are being investigated. Alternative strategies for patients with Barrett's esophagus and HGD include EMR and endoscopic ablation with PDT, RFA, or cryoablation. 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. 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. 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.
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. 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.

**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%. 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. However, in the Radiation Therapy Oncology Group (RTOG) 85-01 trial, in which patients in the RT alone arm received 64 Gy at 2 Gy per day with conventional techniques, all patients died of cancer by 3 years. Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

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

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

**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 45-50.4 Gy delivered in fractions of 1.8-2 Gy per day. The panel recommends a multidisciplinary team, which should include medical, radiation and surgical oncologists, radiologists, gastroenterologists and pathologists. The panel encourages the use of CT simulation and 3D treatment planning. 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. The planning target volume (PTV) should include the tumor plus a cephalad and caudal margin of 5 cm, and a radial margin of 1.5-2 cm. Every effort should be made to reduce unnecessary radiation doses to vital organs such as liver, kidneys, spinal cord, heart (especially the left ventricle) and lungs. Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients with esophageal cancer treated with concurrent chemotherapy.
and radiation. 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 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 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 heart and lungs. In designing IMRT plans, for structures such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses.

Close patient monitoring and aggressive supportive care are essential during radiation treatment. Management of acute toxicities is necessary to avoid treatment interruptions or dose reductions. Antiemetics should be given 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 from Sur et al., no significant difference was seen in local control or survival with high dose brachytherapy compared with external beam. In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 combined modality regimen (5-fluorouracil and cisplatin with 50 Gy of external beam RT) followed by an intraluminal boost. Local failure was 27%, and acute toxicity included 58% with grade 3, 26% with grade 4, and 8% with grade 5. The cumulative incidence of fistula was 18% per year, and the crude incidence was 14%. Therefore, the additional benefit of adding intraluminal brachytherapy to radiation or combined modality therapy, although reasonable, remains unclear.

Combined Modality Treatments: Concurrent Chemotherapy and Radiation Therapy

Multiple modalities have been employed for the treatment of esophageal cancer because of the overall poor survival rates of patients who have been treated with resection alone.

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. In this trial, patients with SCC or adenocarcinoma with clinical stage T1-3, N0-1, M0 received 4 cycles of 5-fluorouracil and cisplatin. RT (50 Gy at 2 Gy/d) was given concurrent with day 1 of chemotherapy. The control arm was RT alone, albeit a higher dose (64 Gy) than in the combined modality therapy arm. Patients who were randomly assigned to receive combined modality therapy showed a significant improvement in both median survival (14 vs. 9 months) and 5-year overall survival (27% vs. none) with a 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, comparing 2 different RT doses used with the same chemotherapy regimen (5-fluorouracil and cisplatin). 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 same chemotherapy regimen (5-fluorouracil and cisplatin). No significant difference was observed in median survival (13 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 5-fluorouracil and cisplatin using the RT dose of 50.4 Gy as the standard of care for patients with esophageal cancer.

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

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational. 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. Another recent meta-analysis (1,854 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. Swisher et al also reported that preoperative chemoradiation was associated with increased pathologic
complete response (28% vs. 4%) and 3-year overall survival (48% vs. 29%) compared with preoperative chemotherapy in patients with locally advanced esophageal cancer. \(^{152}\) In a retrospective analysis of 363 patients with adenocarcinoma of the lower esophagus, the overall survival after preoperative chemoradiation was significantly shorter for patients with Barrett’s esophagus compared to those without Barrett’s esophagus (32 months vs. 51 months respectively). \(^{153}\)

Preoperative chemoradiation therapy using two drug combination regimens including paclitaxel, docetaxel or irinotecan with oxaliplatin or cisplatin, 5-fluorouracil or capecitabine has also been shown to be promising for localized esophageal cancer or EGJ adenocarcinoma in non-randomized phase I and II studies. \(^{154-167}\) In a recent phase I/II study, preoperative chemoradiation with a three drug regimen including docetaxel, oxaliplatin and capecitabine was safe and effective in patients with locoregional esophageal or EGJ cancers. \(^{168}\) At a median follow-up of 116 weeks, median disease-free and overall survival were 16 and 24 months, respectively and the corresponding survival rates were 45% and 52%, respectively.

However, randomized trials comparing surgery alone with preoperative chemoradiation followed by surgery in patients with clinically resectable cancer have shown conflicting results. \(^{169-177}\) Results from a recent, multicenter phase III randomized trial (CROSS study), largest trial in its class, showed that preoperative chemoradiation therapy with carboplatin and paclitaxel improved overall survival compared to surgery alone in patients with resectable (T2-3, N0-1, M0) esophageal or EGJ cancers. \(^{52}\) R0 resection rate was higher in the chemoradiation arm compared to the surgery alone arm (92% and 65% respectively). Median survival was 49 months in the chemoradiation arm compared to 26 months in the surgery alone arm. The 1-, 2- and 3-year survival rates were 82%, 67% and 59% respectively in the chemoradiation arm and 70%, 52% and 48% respectively in the surgery alone arm.

In contrast to the results of the CROSS study, the results of an interim analysis of another phase III randomized controlled study (FFCD 9901) showed that preoperative chemoradiation therapy with cisplatin and fluorouracil did not improve overall survival but enhanced postoperative mortality rate for patients with localized stage I or II esophageal cancer compared with surgery alone. \(^{178}\) Full publications of these data are awaited.

The CALGB 9781 trial was a prospective randomized intergroup trial comparing trimodality therapy with surgery alone for the treatment of stage I-III esophageal cancer. \(^{179}\) 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 5-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.

The effect of adding surgery to chemoradiation therapy in patients with locally advanced SCC of the esophagus has been evaluated in randomized trials. \(^{180,181}\) Stahl et al randomized 172 patients to either induction chemotherapy followed by chemoradiation therapy and surgery or induction chemotherapy followed by chemoradiation therapy. \(^{180}\) Two-year progression-free survival rate was better in the surgery group (64.3%) than in the chemoradiation therapy group.
(40.7%). However, there was no difference in overall survival 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. The Stahl trial was prematurely terminated due to lack of accrual.

Bedenne et al (FFCD 9102 trial) also showed that adding surgery to chemoradiation provided no benefit compared with treatment with additional chemoradiation, especially in patients with locally advanced SCC of the esophagus who experience response to initial chemoradiation therapy. However, this trial suffers from suboptimal design and low number of patients.

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. The median progression-free survival was 26 and 14 months for chemotherapy and chemoradiation respectively (p = 0.37). The corresponding median overall survival was 32 months and 30 months respectively (p = 0.83). However, the histopathological response rate (31% vs. 8%; p = 0.01) and R1 resection rate (0% vs. 11%; p = 0.04) 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. 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. Patients with locally advanced adenocarcinoma of the lower esophagus or EGJ were randomized between two treatment groups: chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiotherapy followed by surgery (arm B). Patients in arm B had a significantly higher probability of showing pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection. Preoperative chemoradiation therapy improved 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 chemoradiotherapy 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. R0 resection was achieved in 65% of patients. Median survival and the actuarial 2-year survival rate were 14.5 months and 35% respectively. 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 overall and event-free-survival were 36.5 months and 22.8 months respectively.

In a more recent phase II trial which 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. Pathologic complete response was achieved in 16% of patients. Median overall survival was 31.7 months.

**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. 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; 5-fluorouracil and leucovorin before and after concurrent chemoradiation with 5-fluorouracil and leucovorin, delivered in five monthly cycles of bolus chemotherapy (5-fluorouracil and leucovorin) with RT (45 Gy) concurrent with cycles 2 and 3) or surgery alone (n=275). Patients were at high risk for relapse; more than two thirds of them had T3 or T4 tumors and 85% of patients had node positive disease. Resection of all detectable disease was required for participation in the trial. Postoperative chemoradiation was offered for all patients with tumors T1 or higher, with or without lymph node metastases. Postoperative chemoradiation therapy significantly improved overall survival and relapse-free survival for all patients at high risk for recurrence. Median overall survival in the surgery only group was 27 months, as compared with 36 months in the chemoradiation group. The hazard ratio for death was 1.35. The chemoradiation group had better 3-year overall (50% vs. 41%) and relapse-free survival rates (48% vs. 31%) than the surgery only group.

With more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric or EGJ adenocarcinoma treated with postoperative chemoradiation. No increases in late toxic effects were noted. It should be noted that surgery was not part of this protocol and patients were eligible for the study only after recovery from surgery. One major criticism of this trial is that 54% of patients had a D0 resection (with sub optimal dissection of N1 lymph nodes) and 36% of patients had a D1 resection and only 10% of patients had a D2 dissection. D2 lymph-node dissection was not recommended and patients were not excluded on the basis of the extent of lymphadenectomy. Nevertheless, the results of this study have established postoperative chemoradiation as a reasonable option for patients with adenocarcinoma of distal esophagus or EGJ.

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

In a phase II non-randomized trial which evaluated postoperative concurrent chemoradiation with cisplatin and 5-fluorouracil in patients with poor prognosis esophageal and EGJ adenocarcinoma, the projected rates of 4-year overall survival, freedom from recurrence, distant metastatic control and locoregional control were 51%, 50%, 56% and 86% respectively for patients with node-positive tumors (T3 or T4), which are better than the historical outcomes with surgery alone. 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. RTOG 8911 (Intergroup 0113) trial randomized patients with potentially resectable esophageal cancer of both histologic types to receive either preoperative chemotherapy (5-fluorouracil plus cisplatin) or undergo surgery alone. The preliminary results of this study did not show any survival benefit between the two groups. 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. Although preoperative chemotherapy decreased the incidence of R1 resection (4% compared with 15% in the surgery only group), there was no improvement in overall survival between the two groups.

The Medical Research Council (MRC) published their trial (MRC OEO2), which involved 802 patients with potentially resectable esophageal cancer. In this trial, patients were randomly assigned to receive either 2 cycles of preoperative 5-fluorouracil (1000 mg/m² per day by continuous infusion for 4 days) and cisplatin (80 mg/m² on day 1) repeated every 21 days followed by surgery, or surgery alone. However, this trial had several clinical methodology problems. Nearly 10% of patients received off protocol preoperative 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. At a median follow-up of 6 years, disease-free and overall survival were significantly longer for the preoperative chemotherapy group. The difference in survival favoring the preoperative chemotherapy group (23% vs.17% for surgery) was consistent in patients with adenocarcinoma and SCC. However, the two histologic subtypes (SCC and adenocarcinoma) that constituted more than 97% of total patients analyzed, had no treatment effect suggesting limited or no benefit from preoperative chemotherapy.

The phase III study conducted by the French Study group (FNLC ACCORD07-FFCD 9703), compared preoperative chemotherapy [5-fluorouracil and cisplatin (FP)] with surgery alone in patients with adenocarcinoma of the stomach and lower esophagus. This study randomized 224 patients between surgery alone and preoperative chemotherapy (FP) followed by surgery. Postoperative FP was recommended for patients responding to preoperative FP. At a median follow-up of 5.7 years, the 5-year disease free survival rate was 34% for patients who received preoperative FP compared to 19% for those treated with surgery alone. The 5-year overall survival rate was also better in the preoperative chemotherapy 38% compared to 24% in the surgery alone group. This trial was prematurely terminated due to low accrual.

Long-term results of another randomized trial also showed that preoperative chemotherapy with a combination of etoposide and cisplatin significantly improved overall and disease-free survival in patients (n = 169) with SCC of the esophagus. Median overall survival 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 overall and disease-free survival benefit favoring preoperative chemotherapy over surgery alone. A 4% increase in 5-year overall and disease-free survival favored the preoperative chemotherapy group. The results of an updated meta-analysis that included 1,981 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.

Perioperative Chemotherapy

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

Chemotherapy for Advanced Disease

Chemotherapy for metastatic esophageal cancer continues to evolve and patients with advanced adenocarcinoma of the esophagus and EGJ can be treated using the regimens included in the NCCN Guidelines for Gastric cancer for advanced 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 chemoradiation showed no survival benefit compared with best supportive care for patients with advanced esophageal cancer. 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. 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. Cisplatin plus fluorouracil is the most investigated and most commonly used regimen for patients with esophageal cancer, resulting in response rates of 20-50%. Newer agents such as irinotecan, docetaxel, paclitaxel and etoposide have also shown activity in patients with advanced esophageal cancer.

Cisplatin plus paclitaxel or docetaxel, with or without 5-fluorouracil has demonstrated activity in patients with locally advanced EGJ or metastatic esophageal cancers. 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). 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 < 0.001). The median overall survival was significantly longer for DCF compared with CF (9.2 months vs. 8.6 months; p = 0.02), 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 = 0.01). Various modifications of DCF regimen with the intent to improve tolerability are...
Discussion

Esophageal and Esophagogastric Junction Cancers

being evaluated in clinical trials for patients with advanced esophagogastric cancer.221-226

The combination of cisplatin with irinotecan is active, particularly against SCC of the esophagus.227 In a prospective randomized study, the combination of mitomycin, cisplatin and 5-fluorouracil (protracted intravenous infusion) was equally efficient to the combination of epirubicin, cisplatin and 5-fluorouracil (protracted intravenous infusion) (ECF) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.228 Cisplatin in combination with gemcitabine has shown significant activity in phase II studies in patients with metastatic and advanced esophageal cancer.229, 230

Capecitabine is an orally administered fluoropyrimidine that is converted to 5-fluorouracil preferentially in the tumor tissue. 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.231 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, 5-fluorouracil (EOF), epirubicin, cisplatin and capecitabine (ECX) and epirubicin, oxaliplatin and capecitabine (EOX)]. Median follow-up was 17.1 months. Results from this study suggest that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated advanced esophagogastric cancer. 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 5-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 5-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.232-235 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.233 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.236-239 In a phase II study, the combination of irinotecan and docetaxel, resulted in an overall response rate of 31% (4% CR and 27% PR) among chemotherapy naïve patients (n = 29) with unresectable or metastatic SCC or adenocarcinoma of the esophagus; there were two PRs and one CR among the pretreated patients (n = 15).236 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.237 The results of a recent randomized study also showed that capecitabine and irinotecan was comparable in efficacy and activity to cisplatin and irinotecan.238 Mitomycin and irinotecan
combination was also effective in patients with advanced esophageal or EGJ adenocarcinoma.\(^{239}\)

The combination of carboplatin and paclitaxel regimen was moderately active with a response rate of 43% in patients with advanced esophageal cancer.\(^{240}\) However, 52% of patients had neutropenia (grade 3-4). Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend towards improved median progression-free survival (5.8 v 3.9 months) compared to fluorouracil, leucovorin and cisplatin (FLP) in patients with metastatic esophagogastric cancer.\(^{241}\) However, no significant differences were seen in median overall survival (10.7 vs. 8.8 months, respectively) between the FLO and FLP. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), and progression-free survival (6.0 vs. 3.1 months), and an improved overall survival (13.9 vs. 7.2 months) compared with FLP, respectively. The combination of gemcitabine, fluorouracil and leucovorin has also shown activity in patients with locally advanced or metastatic SCC or adenocarcinoma.\(^{242,243}\)

**Targeted Therapies**

The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and HER2-neu has been associated with poor prognosis in patients with gastric and esophageal cancers. In clinical trials, EGFR inhibitors including cetuximab and erlotinib, trastuzumab (anti-HER2 antibody), and bevacizumab (anti-VEGFR antibody) and have been evaluated in treatment of patients with advanced esophageal cancer and EGJ adenocarcinoma.\(^{244}\)

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-neu-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.\(^{49}\) The results of this study confirmed that trastuzumab plus standard chemotherapy is superior to chemotherapy alone in patients with HER2-neu-positive advanced gastric and EGJ adenocarcinoma. In this study, 594 patients with HER2-neu-positive esophagogastric and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) or chemotherapy alone. Median follow-up was 19 in the trastuzumab plus chemotherapy group and 17 months in the chemotherapy alone group. There was a significant improvement in the median overall survival with the addition of trastuzumab to chemotherapy compared to chemotherapy alone (14 vs. 11 months, respectively). Safety profiles were similar with no unexpected adverse events in the trastuzumab. There was also no difference in symptomatic congestive heart failure between arms. This establishes that trastuzumab plus chemotherapy as a new standard of care for the treatment of patients with a HER2-neu expressing advanced gastric and EGJ adenocarcinoma.

The safety and efficacy of cetuximab,\(^{245-249}\) erlotinib\(^{250-252}\) and bevacizumab\(^{253-255}\) have been evaluated in multiple phase II studies. Ongoing trials are evaluating the efficacy and safety of the above mentioned agents in combination with chemotherapy for the treatment of patients with advanced esophageal and EGJ cancers.

**Treatment Guidelines**

The management of esophageal and EGJ cancers requires the expertise of several disciplines 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. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of any discipline taking care of patients with esophagealgastric 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, and endoscopy with biopsy of the entire upper GI tract. Histological confirmation of cancer is required. 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 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. EMR may contribute to accurate staging of early stage cancers. At this point, if metastatic cancer is not evident, EUS with fine needle aspiration is recommended if indicated. 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. If the cancer is located at or above the cardia, bronchoscopy (including biopsy of any abnormality and cytology of the washings) should be performed. Laparoscopic staging of the peritoneal cavity should be considered (optional) if there is no evidence of metastatic disease (M1) or if the cancer is located at the EGJ. Metastatic cancer should be confirmed by biopsy.

In the revised staging system for the esophageal and EGJ cancers, tumors whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extend into the EGJ or distal thoracic esophagus (Siewert Types I and II) are classified as adenocarcinoma of the esophagus. The guidelines recommended assessment of Siewert tumor type as part of initial work up in all patients with adenocarcinomas involving the EGJ. See the section “Esophagogastric Junction”.

Combined PET/CT has many advantages over PET scan alone and it significantly improves the diagnostic accuracy. PET/CT scans are useful for initial staging and evaluation of patients after chemoradiation prior to surgery. They may be useful for the detection of distant lymphatic and hematogenous metastases. PET/CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer. It was also shown to be an independent predictor of overall survival in patients with non-metastatic esophageal cancer. In addition, a recent study in patients with esophageal cancer 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. When used alone, PET/CT and CT suggest targets for biopsy; however, false positive results are common. Combined PET/CT scans are emerging and seem to be useful for restaging patients and monitoring response to primary therapy. Additional studies are needed to assess the efficacy of combined PET/CT scan in esophageal cancer. PET evaluation is preferred if there is no evidence of metastatic disease (PET/CT is preferred over PET scan).
Additional Evaluation

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

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

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

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

Primary Treatment

EMR or ablation is the primary treatment option for patients with Tis tumors (high-grade dysplasia or carcinoma-in-situ). Esophagectomy is the standard treatment option for patients with superficial T1 tumors.262, 263

Endoscopic therapies (EMR and ablation) may be appropriate options for patients with superficial T1a invading the mucosa but not invading the submucosa.84-87 The panel has included EMR and ablation (preferred) or esophagectomy for patients with superficial T1a tumors. Ablation may not be needed for squamous lesions that are completely excised. Esophagectomy is recommended as the primary treatment option for patients with T1b tumors invading the submucosa.

In the case of T1b, N+ tumors, esophagectomy is the preferred treatment option for patients with resectable noncervical esophageal cancer, whereas chemoradiation is the preferred modality for those with cervical esophageal cancer. Retrospective studies have shown that concurrent chemoradiation is an effective treatment option for patients with cervical and upper thoracic esophageal cancer.264-267

Primary treatment options for patients with locally advanced resectable disease (T2-T4a, any regional N tumors) include preoperative chemoradiation (preferred), definitive chemoradiation (preferred for cervical esophageal cancer), preoperative chemotherapy (only for adenocarcinoma of the distal esophagus or EGJ) or esophagectomy (for patients with low-risk and well-differentiated lesions less than 2 cm in size). Preoperative chemoradiation is preferred over preoperative chemotherapy for patients with adenocarcinoma of the distal esophagus or EGJ.52, 152, 186 In randomized trials, definitive chemoradiation therapy has been demonstrated as the curative
approach for patients with SCC of the esophagus whereas its role is not established in patients with adenocarcinoma. While definitive chemoradiation is an option for patients with SCC, surgery is the preferred treatment for patients with adenocarcinoma. Fluoropyrimidine-or taxane-based regimens are recommended for preoperative and definitive chemoradiation. See “Principles of Systemic Therapy” section of the guidelines for list of specific regimens.

Definitive chemoradiation is the preferred treatment for patients with T4b (unresectable) tumors. Fluoropyrimidine-based or taxane-based concurrent chemoradiation may be appropriate and occasionally can facilitate surgical resection in selected cases.

Response Assessment
The prognostic value of metabolic response defined by PET scan after preoperative chemotherapy has been evaluated in retrospective and prospective studies. While some studies have reported that PET scan could predict histopathological complete response and outcome after definitive or preoperative chemoradiation in patients with locally advanced esophageal cancer, other studies have shown conflicting results.

The cut-off points for the reduction in the 18-fluorodeoxyglucose (FDG) standard uptake value (SUV) between pre- and post-treatment PET scans (35%-80%) and the timing of post-treatment PET before surgery (2 -6 weeks) 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. 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 overall survival was not reached in metabolic responders, whereas the median overall survival was 25.8 months in non-responders (p=0.015). Median event-free survival was 29.7 months and 14 months respectively, for metabolic responders non-responders (p=0.002). Major histological remissions (<10% of residual cancer) were noted in 58% of metabolic responders but none 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. But the specific uptake value used as a cutoff in these series also varied from 2.5-4. 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. 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.

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.
Additional Treatment

Esophagectomy is the preferred treatment option for all patients with adenocarcinoma of the distal esophagus or EGJ following preoperative chemotherapy whereas patients who received preoperative or definitive chemoradiation should undergo restaging [CT scan with contrast, if PET/CT is not done, PET/CT or PET, upper GI endoscopy and biopsy (optional after preoperative chemoradiation)] after completion of primary treatment. Response assessment with PET/CT or PET scan (category 2B) should be done 5-6 weeks after completion of preoperative therapy. 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. 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.

Esophagectomy is the preferred treatment option for patients with no evidence of disease and as well as those with persistent local disease following preoperative chemoradiation. Alternatively, patients, particularly with SCC, 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.

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. 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 distal esophagus or EGJ. The efficacy of postoperative treatment has not been established in randomized trials for patients with esophageal cancer.

For patients who have not received preoperative therapy

No further treatment is necessary for patients with SCC, adenocarcinoma of the proximal or mid esophagus (irrespective of their nodal status) and node negative adenocarcinoma of the distal esophagus and EGJ, if there is no residual disease at surgical margins (R0 resection). Alternatively, selected patients with node negative adenocarcinoma of the distal esophagus and EGJ [T2 tumors and high-risk features (poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age) and T3-T4a tumors] can be treated with fluoropyrimidine-based chemoradiation. Based on the results of the INT-0116 trial, the panel has included fluoropyrimidine-based chemoradiation for all patients with node positive adenocarcinoma of the distal esophagus or EGJ, following R0 resection.

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

No further treatment is necessary for those with SCC or adenocarcinoma of the proximal or mid esophagus (irrespective of their nodal status), if there is no residual disease at surgical margins (R0 resection). Based on the results of the MAGIC trial,\(^5\) postoperative chemotherapy with ECF or its modifications (category 1), if received preoperatively is recommended for all patients with adenocarcinoma of the distal esophagus or EGJ, irrespective of the nodal status, if there is no residual disease at surgical margins (R0 resection). Alternatively, patients with node negative adenocarcinoma (T2-T4a tumors) can be observed, if there is no residual disease at surgical margins.

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

Medically unfit Patients with Locoregional Cancer

EMR or ablation is recommended for patients with Tis tumors whereas EMR and 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.\(^2\)\(^9\)\(^6\) 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.\(^2\)\(^9\)\(^6\), \(^2\)\(^9\)\(^7\) Chemoradiation is included as an option for this group of patients.

Fluoropyrimidine-based or taxane-based concurrent 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 are unable to tolerate chemotherapy or chemoradiation.

Follow-up after Resection or Definitive Chemoradiation

All patients should be followed systematically. For asymptomatic patients, follow-up should include a complete history and physical examination every 3-6 months for 1-2 years, then every 6-12 months for 3-5 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 counseling may be extremely valuable.

Recurrent Esophageal Cancer

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

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 relapse is resectable. If both criteria are met, esophagectomy remains an option. When patients experience another relapse after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described below for metastatic disease.

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

**Metastatic Esophageal Cancer**

Best supportive care is the appropriate treatment option for patients with metastatic cancer. Patients’ performance status should determine whether chemotherapy is added to best supportive care. Several scales are available to measure performance status in patients with cancer. Karnofsky scale of Performance Status (KPS) and Eastern Cooperative Group Performance Status (ECOG PS) are the two commonly used scales.\(^{298, 299}\) KPS is an ordered scale with 11 levels (0 to 100) and the general functioning and survival of a patient is assessed based on their health status (activity, work and self-care). Low Karnofsky scores are associated with poor survival and more serious illnesses (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 Karnofsky performance score of 60 or less or an ECOG performance 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 metastatic esophageal cancer have not been performed for many years. The regimens listed in the guidelines are derived from the gastric adenocarcinoma phase III trials that have included patients with lower esophageal and/or EGJ cancer. Some of the regimens listed in the guidelines are based on institutional preferences that have support only from phase II studies. Two drug regimens or single agents are preferred. Three-drug regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation. DCF modifications are preferred over DCF. The use of trastuzumab in combination with an anthracycline is not recommended. Leucovorin can be used with certain infusional 5-fluorouracil-based regimens.

The following regimens are listed in the guidelines for metastatic or locally advanced esophageal or EGJ cancers (See “Principles of Systemic Therapy” section of the guidelines for list of specific regimens):

**First-line therapy**

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

**Second-line Therapy**

• Trastuzumab with chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients who are HER2-neu-positive, if not used as first-line therapy
• Docetaxel or paclitaxel (category 2B)
• Irinotecan-based single agent or combination therapy (category 2B)

**Leucovorin Shortage**

There is currently a shortage of leucovorin in the United States. 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/m² is equivalent to 400 mg/m² 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. Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in fluorouracil dose (in the range of 10%) may be considered.

**Best Supportive Care**

The goal of best supportive care is to prevent and relieve suffering and improve quality of life for patients and their caregivers regardless of 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. Temporary placement of SEMS with concurrent RT was found to be beneficial for increasing survival rates compared with permanent stent placement. 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. 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. 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 gastrostomy 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 reobstruction rate with the larger diameter, there may be a higher risk of stent-related complications.\textsuperscript{306}

\textbf{Pain}

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

\textbf{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.

\textbf{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.

\textbf{Summary}

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

Adenocarcinoma and SCC are the 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 established risk factor for adenocarcinoma. Barrett’s esophagus, obesity, and GERD seem to be the major risk factors for development of adenocarcinoma of the esophagus or EGJ.

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

Postoperative treatment is based on histology, surgical margins and nodal status. In patients with SCC or adenocarcinoma of the proximal or mid esophagus (irrespective of their nodal status), no further treatment is necessary if there is no residual disease at surgical margins (R0 resection). For patients who have not received preoperative therapy, based on the results of the INT-0116 trial, the panel has included fluoropyrimidine-based chemoradiation for all patients with node positive adenocarcinoma of the distal esophagus or EGJ and for selected patients with node negative adenocarcinoma of the distal esophagus and EGJ, following R0 resection. Based on the results of the MAGIC trial, perioperative chemotherapy with ECF or its modifications is recommended following R0 resection for all patients with adenocarcinoma of the distal esophagus or EGJ, 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 EGJ adenocarcinoma. HER2-neu testing is recommended if metastatic disease is documented or suspected. The efficacy VEGFR and EGFR inhibitors in combination with chemotherapy for patients with advanced EGJ cancers are being evaluated in ongoing randomized phase III trials.

Best supportive care is an integral part of treatment, especially in patients with locally advanced disease. 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. Metastatic disease in patients with good performance status can be treated with chemotherapy plus best supportive care, whereas best supportive care is recommended for those with poor performance status. Endoscopic palliation of esophageal cancer has improved substantially because of improving technology.

The NCCN Guidelines for Esophageal and EGJ Cancers emphasize that considerable advances have been made in the treatment of patients with locoregional cancer. The NCCN Guidelines 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.
# Table 1. Guidelines for Assessment of *HER2-neu* Overexpression

<table>
<thead>
<tr>
<th>Score/ <em>HER2-neu</em> Overexpression</th>
<th>Surgical Specimen</th>
<th>Biopsy Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/Negative</td>
<td>No reactivity or membranous reactivity in &lt;10% of cancer cells</td>
<td>No reactivity or no membranous reactivity in any cancer cells</td>
</tr>
<tr>
<td>1+/Negative</td>
<td>Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane</td>
<td>Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive</td>
</tr>
<tr>
<td>2+/Equivocal²</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in &gt;10% of cancer cells</td>
<td>Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</td>
</tr>
<tr>
<td>3+/Positive</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells</td>
<td>Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of the percentage of cancer cells positive</td>
</tr>
</tbody>
</table>

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


222. Shankaran V, Mulcahy MF, Hochster HS, et al. Docetaxel, oxaliplatin, and 5-fluorouracil for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinomas: Preliminary results of a phase II study. Gastrointestinal Cancers Symposium 2009;Abstract 47. Available at:


