National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Esophageal Cancer

V.2.2010

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NCCN Esophageal Cancer Panel Members

* Jaffer A. Ajani, MD/Chair † ¤
The University of Texas
M. D. Anderson Cancer Center

James S. Barthel, MD ¤ Þ
H. Lee Moffitt Cancer Center &
Research Institute

Tanios Bekaii-Saab, MD †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital and
Solove Research Institute

David J. Bentrem, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Thomas A. D'Amico, MD ¶
Duke Comprehensive Cancer Center

Prajnan Das, MD, MS, MPH §
The University of Texas
M. D. Anderson Cancer Center

Crystal Denlinger, MD †
Fox Chase Cancer Center

Charles S. Fuchs, MD, MPH †
Dana-Farber/Brigham and Women's Cancer
Center

Hans Gerdes, MD ¤ Þ
Memorial Sloan-Kettering Cancer Center

James A. Hayman, MD, MBA §
University of Michigan
Comprehensive Cancer Center

Lisa Hazard, MD §
Huntsman Cancer Institute
at the University of Utah

Wayne L. Hofstetter, MD ¶
The University of Texas
M. D. Anderson Cancer Center

David H. Ilson, MD, PhD † Þ
Memorial Sloan-Kettering Cancer Center

Rajesh N. Keswani, MD ¤
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

Lawrence R. Kleinberg, MD §
The Sidney Kimmel Comprehensive Cancer
Center at Johns Hopkins

Michael Korn, MD
UCSF Helen Diller Family
Comprehensive Cancer Center

Kenneth Meredith, MD ¶
H. Lee Moffitt Cancer Center &
Research Institute

Mary F. Mulcahy, MD ‡
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

Mark B. Orringer, MD ¶
University of Michigan
Comprehensive Cancer Center

Raymond U. Osarogiagbon, MD † Þ ‡
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

James A. Posey, MD †
University of Alabama at Birmingham
Comprehensive Cancer Center

Aaron R. Sasson, MD ¶
UNMC Eppley Cancer Center at
The Nebraska Medical Center

Walter J. Scott, MD ¶
Fox Chase Cancer Center

Stephen Shibata, MD †
City of Hope Comprehensive Cancer Center

Vivian E. M. Strong, MD ¶
Memorial Sloan-Kettering Cancer Center

Mary Kay Washington, MD, PhD ≠
Vanderbilt-Ingram Cancer Center

Christopher Willett, MD §
Duke Comprehensive Cancer Center

Douglas E. Wood, MD ¶
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Cameron D. Wright, MD ¶
Massachusetts General Hospital

Gary Yang, MD §
Roswell Park Cancer Institute

† Medical oncology
¤ Gastroenterology
¶ Surgery/Surgical oncology
Þ Internal medicine
§ Radiotherapy/Radiation oncology
‡ Hematology/Hematology oncology
≠ Pathology
*Writing committee member

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NCCN Esophageal Cancer Sub-Committee Members

Principles of Surgery

Thomas A. D'Amico, MD ¶/Lead
Duke Comprehensive Cancer Center

Wayne L. Hofstetter, MD ¶
The University of Texas
M. D. Anderson Cancer Center

Mark B. Orringer, MD ¶
University of Michigan
Comprehensive Cancer Center

Walter J. Scott, MD ¶
Fox Chase Cancer Center

Douglas E. Wood, MD ¶
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Cameron D. Wright, MD ¶
Massachusetts General Hospital

Principles of Radiation Therapy

Gary Yang, MD §/Lead
Roswell Park Cancer Institute

Prajnan Das, MD, MS, MPH §
The University of Texas
M. D. Anderson Cancer Center

James A. Hayman, MD, MBA §
University of Michigan
Comprehensive Cancer Center

Lisa Hazard, MD §
Huntsman Cancer Institute
at the University of Utah

Lawrence R. Kleinberg, MD §
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Christopher Willett, MD §
Duke Comprehensive Cancer Center

Principles of Best Supportive Care

James S. Barthel, MD ¤ Þ/Lead
H. Lee Moffitt Cancer Center &
Research Institute

James A. Hayman, MD, MBA §
University of Michigan
Comprehensive Cancer Center

Lisa Hazard, MD §
Huntsman Cancer Institute
at the University of Utah

Mary F. Mulcahy, MD ‡
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

¤ Gastroenterology
¶ Surgery/Surgical oncology
Þ Internal medicine
§ Radiotherapy/Radiation oncology
‡ Hematology/Hematology oncology

*Writing committee member

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

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

See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines Updates

The 2.2010 version of the Esophageal Cancer guidelines represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

Summary of changes in the 1.2010 version of the Esophageal Cancer guidelines from the 1.2009 version include:

(ESOPH-1):
- **Workup:**
  - **Second bullet: "Esophagogastroduodenoscopy to visualize upper GI tract, if possible" changed to "Esophagogastroduodenoscopy".**
  - **Third bullet: Clarified as "Chest/abdominal CT with oral and IV contrast".**
  - **"Barium swallow (optional)" was removed.**
- **Additional Evaluation:**
  - **"Multidisciplinary evaluation is encouraged" changed to "Multidisciplinary evaluation".**
  - **The following bullets were removed, "Barium enema or colonoscopy if colon interposition or bypass planned," and "Arteriogram (optional); Consider if performing colon interposition".**

(ESOPH-2):
- **Tis or T1a; Primary Treatment; EMR or Ablation: "Ablation" was removed. "Periodic endoscopic surveillance" was added.**
- **Footnotes "j" and "k" regarding the definition for "Tis or T1a" and "T1b" tumors is new to the page.**
- **Footnote "l" regarding resectable T4 tumors was revised.**
- **Footnote regarding ablation techniques was removed from the page.**

(ESOPH-3):
- **Definitive chemoradiation pathway changed to now include recommendations for "Response Assessment," "Outcome" and "Adjuvant Treatment".**
- **The phrase "surgery" changed to "esophagectomy".**

(ESOPH-3)--continued:
- **Preoperative chemoradiation pathway; Under Response assessment:**
  - **First bullet: Changed to "CT scan with contrast (not required if PET-CT is done)".**
  - **"PET-CT" changed from "preferred" to category 2B.**
- **After Unresectable or Metastatic disease: "Palliative chemotherapy and/or Best supportive care" were removed. These patients are now directed to the "Palliative therapy" recommendations on page ESOPH-7.**
- **Footnote "t": "Assessment ³ 4 weeks..." changed to "Assessment ≥ 5 weeks..."**

(ESOPH-4):
- **Postoperative Treatment**
  - **T2, N0 and T3, N0: Now includes the following recommendation, "ECF if received preoperatively (category 1)".**
  - **Node positive; Adenocarcinoma proxial or mid esophagus; Postoperative Treatment: "Chemoradiation (fluoropyrimidine-based)" changed from category 2B to category 2A.**

(ESOPH-5):
- **Primary Treatment:**
  - **Tis or T1a: "Chemoradiation" was added.**
  - **Medically unfit for surgery or surgery not elected and patient medically able to tolerate chemotherapy...: "RT" was added.**
  - **Medically unfit for surgery and patient unable to tolerate chemotherapy: "Palliative RT" was added.**

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

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Summary of the Guidelines Updates

Summary of changes in the 1.2010 version of the Esophageal Cancer guidelines from the 1.2009 version include:

(ESOPH-6)
- **Follow-up:**
  - **H&P changed from "every 4 mo for 1 y, every 6 mo for 2 y then annually" to "every 3-6 mo for 1-3 y, every 6 mo for 3-5 y, then annually."**
  - **"Endoscopy as clinically indicated" was clarified as "Upper GI endoscopy as clinically indicated."**

(ESOPH-A): Principles of Multidisciplinary Team Approach
- **Sentence that states, "The NCCN panel believes in an infrastructure that discourages unilateral treatment decision-making..." changed to "The NCCN panel believes in an infrastructure that encourages multidisciplinary treatment decision-making."**

(ESOPH-B): Principles of Surgery
- **The entire Principles of Surgery page was revised.**

(ESOPH-C): Principles of Systemic Therapy
- **Definitive Chemoradiation: "Paclitaxel plus cisplatin (category 2B)" changed to "Paclitaxel plus cisplatin or carboplatin (category 2B)".**
- **Metastatic or Locally advanced cancer: "Trastuzumab" with corresponding footnote that states "Used in combination with systemic chemotherapy for the treatment of patients with GE junction adenocarcinoma that is HER-2-positive as determined by a standardized method" was added.**
- **Footnote that states "Leucovorin or levoleucovorin is indicated with certain infusional 5-FU-based regimens" changed to "Leucovorin is indicated with..."**

(ESOPH-D): Principles of Radiation Therapy
- **Supportive Therapy; Fourth bullet: Intravenous hyperalimentation was removed from the first sentence. "Nasogastric feeding tube" was added to the second sentence.**
- **New bullet added that states "Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery".**

(ESOPH-E) Principles of Best Supportive Care
- **Added a new section for "Nausea and Vomiting".**

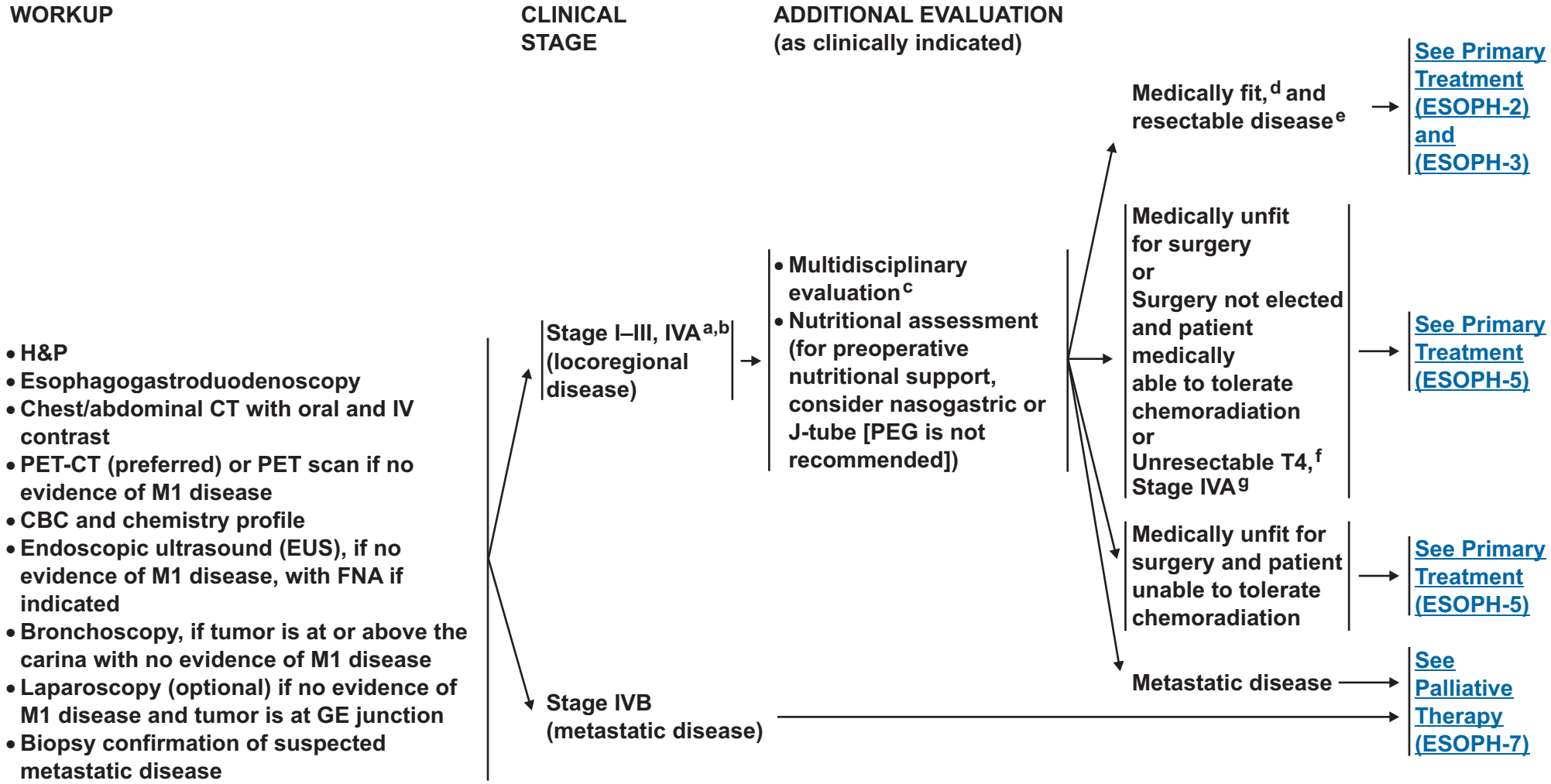
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[a] Celiac nodal involvement in cancers of the gastroesophageal junction may still be considered for combined modality therapy.
[b] Resectable Stage IVA: Patients with distal esophageal cancer with resectable celiac nodes and no involvement of celiac artery, aorta, or other organs.
[c] See Principles of Multidisciplinary Team Approach (ESOPH-A).
[d] Medically able to tolerate major abdominal and/or thoracic surgery.
[e] See Principles of Surgery (ESOPH-B).
[f] Unresectable T4: Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[g] Unresectable Stage IVA: Tumors of the lower esophagus with unresectable celiac nodes, involvement of celiac artery, aorta, or other organs including liver, pancreas, lung, and spleen are unresectable.

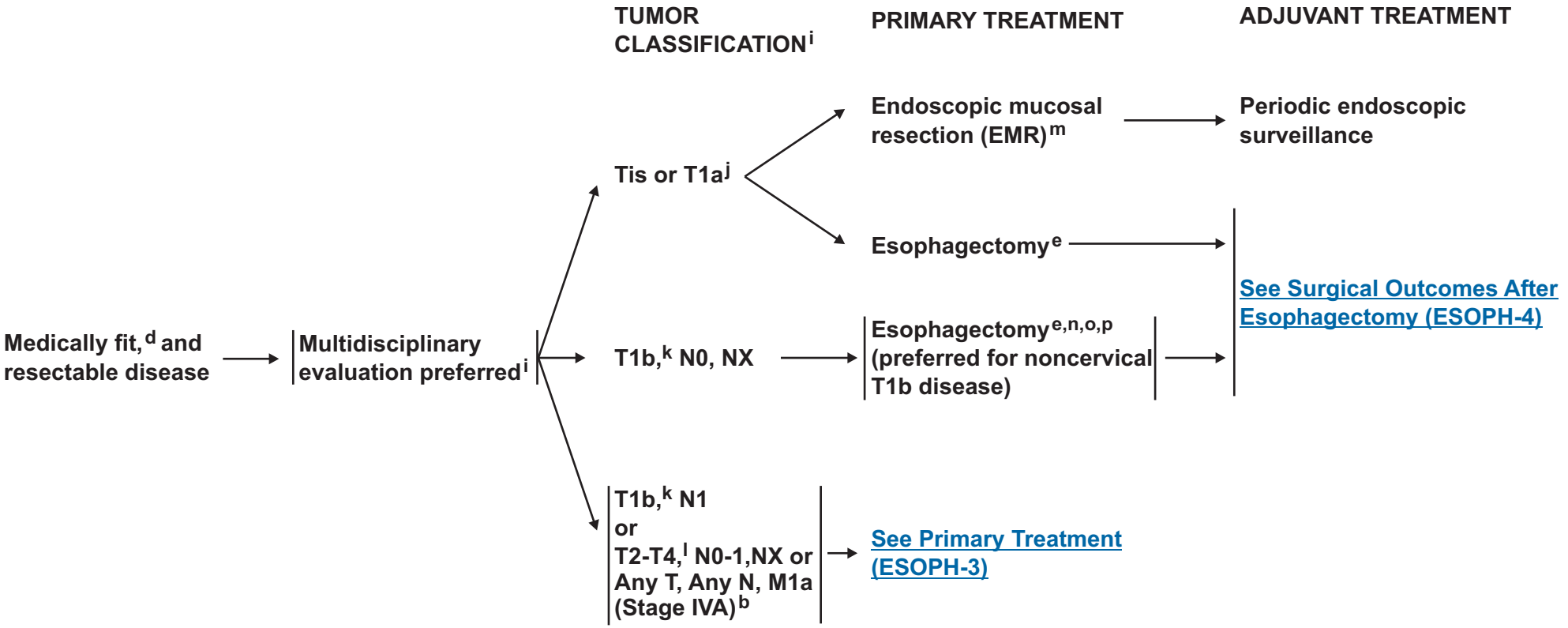
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[b] Resectable Stage IVA: Patients with distal esophageal cancer with resectable celiac nodes and no involvement of celiac artery, aorta, or other organs.
[d] Medically able to tolerate major abdominal and/or thoracic surgery.
[e] See Principles of Surgery (ESOPH-B).
[h] See Principles of Multidisciplinary Team Approach (ESOPH-A).
[i] See Staging (ST-1).
[j] Tis or T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[k] T1b: Tumors invading the submucosa.
[l] Resectable T4: involvement of pericardium, pleura or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases (N1).
[m] May be applied to Tis or T1a, defined as tumor involving the mucosa, but not invading the submucosa.
[n] Chemoradiotherapy is the preferred modality for cervical esophageal carcinoma.
[o] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[p] Feeding jejunostomy for postoperative nutritional support, generally preferred.

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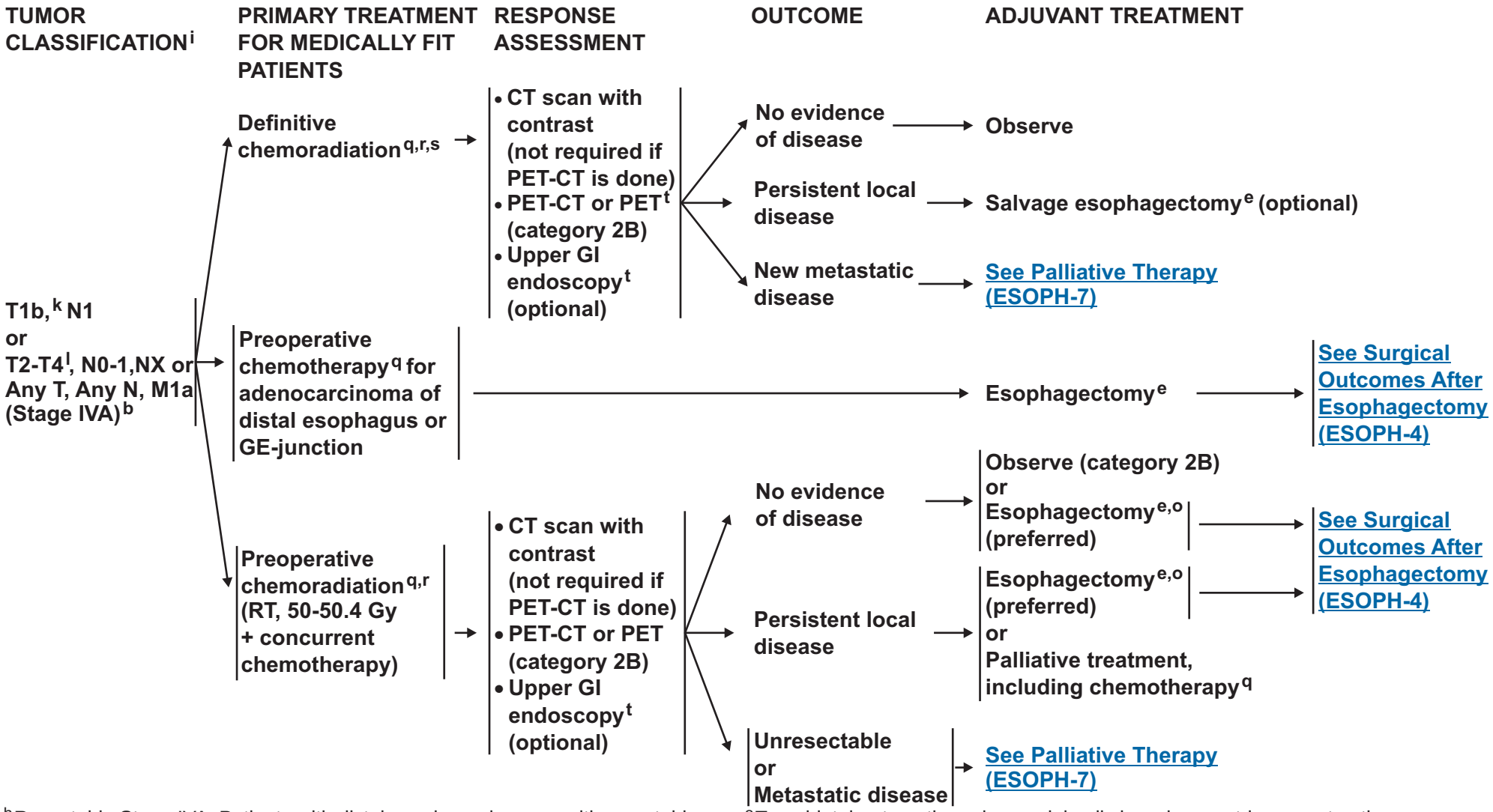
Follow-up (See ESOPH-6)

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[b] Resectable Stage IVA: Patients with distal esophageal cancer with resectable celiac nodes and no involvement of celiac artery, aorta, or other organs.

[e] See Principles of Surgery (ESOPH-B).

[k] T1b: Tumors invading the submucosa.

[l] Resectable T4: Involvement of pericardium, pleura or diaphragm. T1-T3 tumors are resectable even with regional nodal metastases (N1).

[i] See Staging (ST-1).

[o] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.

[q] See Principles of Systemic Therapy (ESOPH-C).

[r] See Principles of Radiation Therapy (ESOPH-D).

[s] Surgery is preferred for adenocarcinomas. Chemoradiation can be considered for squamous cell carcinoma.

[t] Assessment ≥ 5 weeks, endoscopy with biopsy and brushings.

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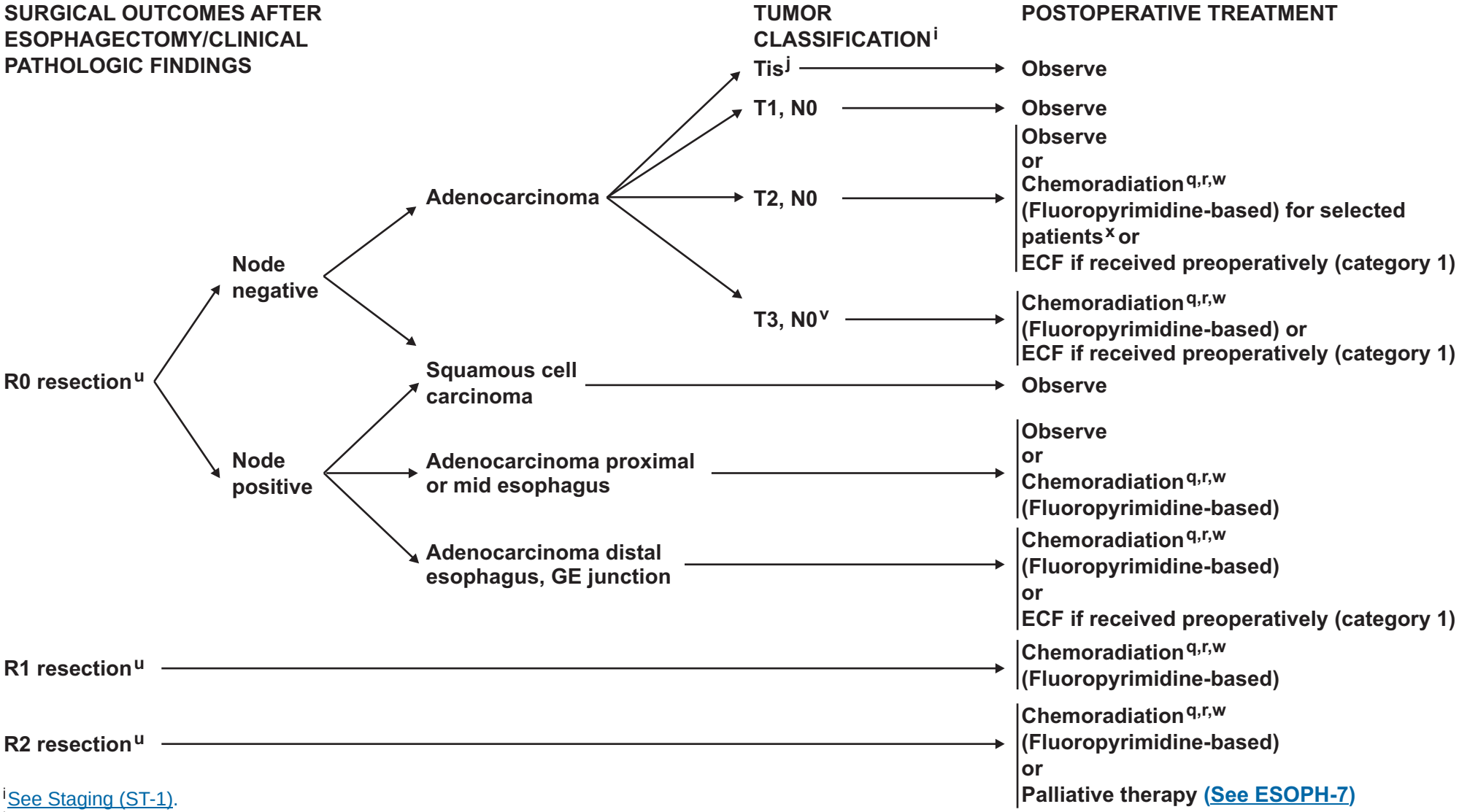
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[i] See Staging (ST-1).

[j] Tis or T1a: Defined as tumors involving the mucosa, but not invading the submucosa.

[q] See Principles of Systemic Therapy (ESOPH-C).

[r] See Principles of Radiation Therapy (ESOPH-D).

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

[v] Consider observation for non GE-junction tumors.

[w] Postoperative chemoradiation only if not received preoperatively.

[x] For higher risk patients such as poorly differentiated histology, lymphovascular invasion, neurovascular invasion or young patients. Limit to lower esophageal or GE junction patients.

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Follow-up (See ESOPH-6)

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PRIMARY TREATMENT FOR MEDICALLY UNIFIT PATIENTS

Tis or T1a[j] →
- **EMR**
- **or**
- **Chemoradiation[r]**

Medically unfit for surgery
or
Surgery not elected and patient medically able to tolerate chemotherapy
or
Unresectable T4,[f] or Stage IVA[g] →
- **50-50.4 Gy of RT + concurrent chemotherapy (Fluoropyrimidine-based) (preferred)[q,r]**
- **or**
- **Chemotherapy[q]**
- **or**
- **RT**
- **or**
- **Best supportive care[y]**

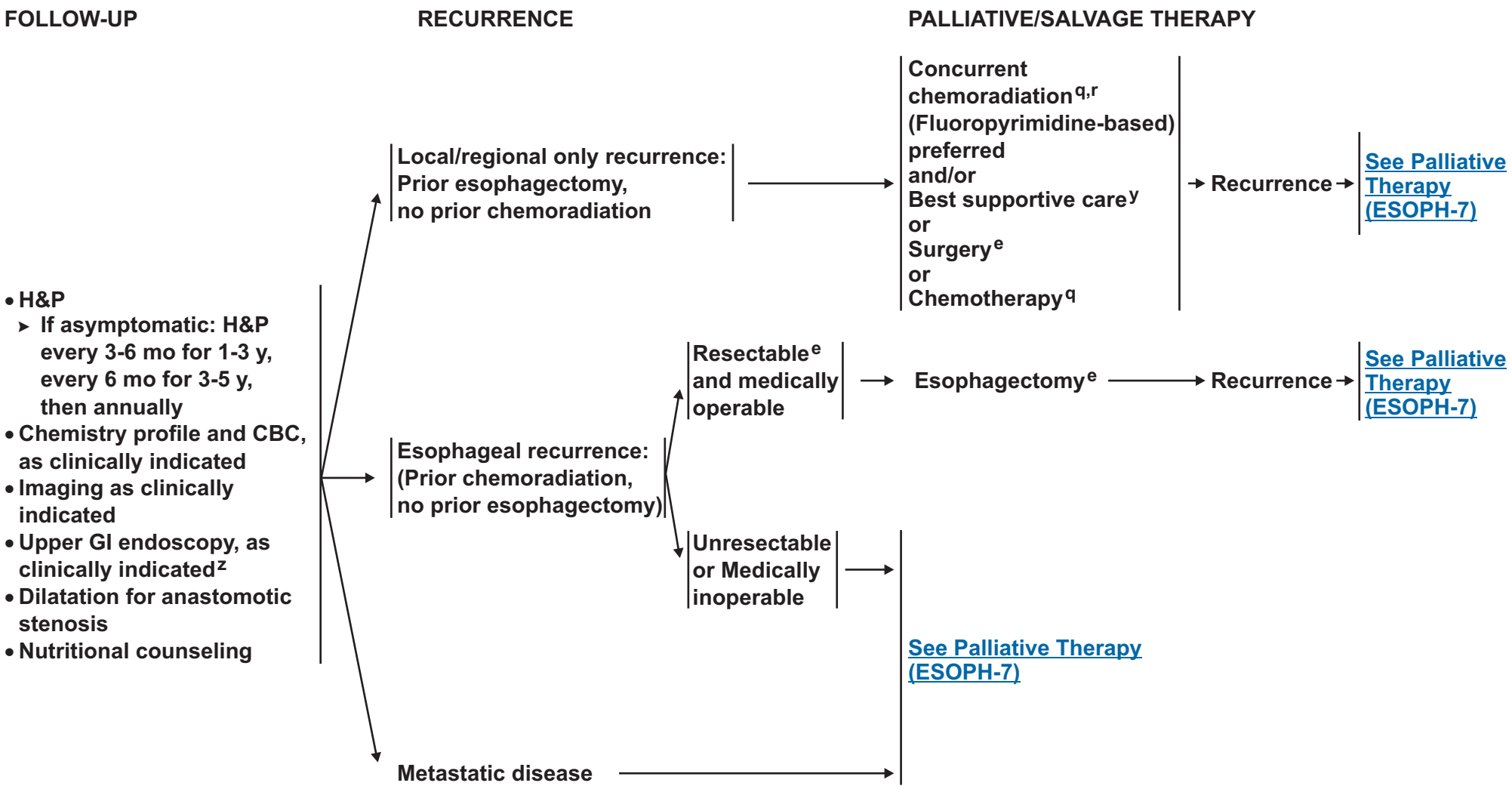
Medically unfit for surgery and patient unable to tolerate chemotherapy →
- **Palliative RT[r]**
- **or**
- **Best supportive care[y]**

[f]Unresectable T4: Involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
[g]Unresectable Stage IVA: Tumors of the lower esophagus with unresectable celiac nodes, involvement of celiac artery, aorta, or other organs including liver, pancreas, lung, and spleen are unresectable.
[j]Tis or T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[q]See Principles of Systemic Therapy (ESOPH-C).
[r]See Principles of Radiation Therapy (ESOPH-D).
[y]See Principles of Best Supportive Care (ESOPH-E).

Follow-up (See ESOPH-6)

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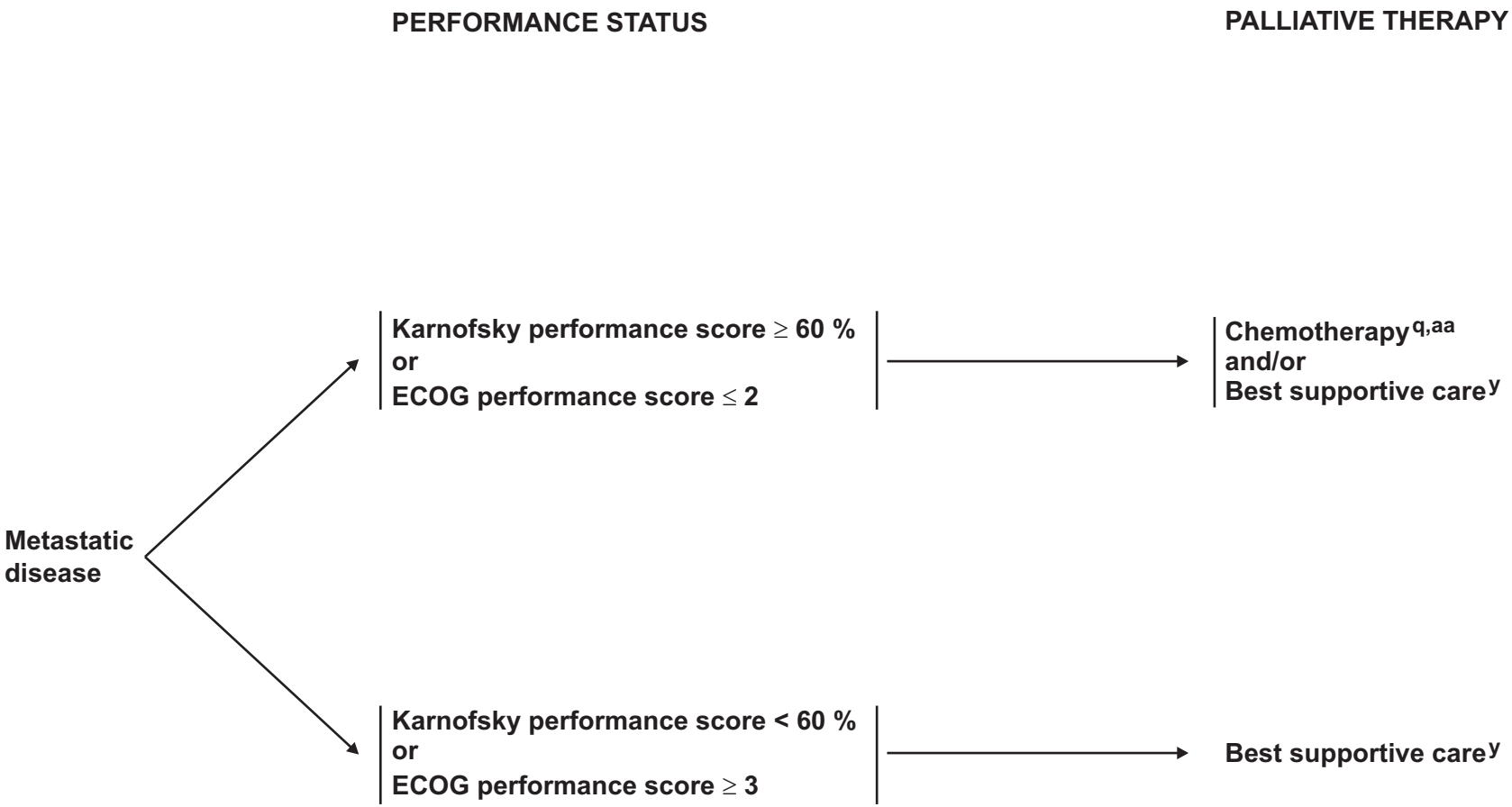
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[e] See Principles of Surgery (ESOPH-B).
[q] See Principles of Systemic Therapy (ESOPH-C).
[r] See Principles of Radiation Therapy (ESOPH-D).
[y] See Principles of Best Supportive Care (ESOPH-E).
[z] Patients with Tis or T1a who undergo EMR should have endoscopic surveillance every 3 months for one year, then annually.

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Back to Follow-up and Recurrence (ESOPH-6)

q See Principles of Systemic Therapy (ESOPH-C).
y See Principles of Best Supportive Care (ESOPH-E).
aa Further treatment after two sequential regimens should be dependent upon performance status and availability of clinical trials.

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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR GASTROESOPHAGEAL CANCERS

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

The combined modality therapy for patients with localized gastroesophageal 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.**
- **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, and other supporting disciplines are also desirable.**
- **All long-term therapeutic strategies are best developed after adequate staging procedures are completed, but ideally prior to any therapy that is rendered.**
- **Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions.**
- **A brief documentation of the consensus recommendation(s) by the multidisciplinary team for an individual patient may prove useful.**
- **The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient.**
- **Re-presentation of select patient outcomes after therapy is rendered may be an effective educational method for the entire multidisciplinary team.**
- **A periodic formal review of relevant literature during the course of the multidisciplinary meeting is highly encouraged.**

[1] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.
[2] Cooper JS, Guo MD, Herskovic A, M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281(17):1623-1627.
[3] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730.

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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 surgery all patients should be assessed by an esophageal surgeon for physiologic ability to undergo esophageal resection.[1] Esophageal resection should be considered for all physiologically fit patients with resectable esophageal cancer (> 5 cm from cricopharyngeus)

- Cervical or cervicothoracic esophageal carcinomas < 5 cm from the cricopharyngeus should be treated with definitive chemoradiation.

- Resectable esophageal or gastroesophageal junction cancer:
  - Tis (T1a) tumors, defined as tumors involving the mucosa but not invading the submucosa, may be considered for EMR or esophagectomy in experienced centers.[2,3,4,5,6]
  - Tumors in the submucosa (T1b) or deeper may be treated with esophagectomy.
  - T1-T3 tumors are resectable even with regional nodal metastases (N1)
  - T4 tumors with involvement of pericardium, pleura or diaphragm are resectable.
  - Stage IVA is resectable in patients with distal esophageal cancer with resectable celiac nodes and no involvement of celiac artery, aorta, or other organs

- Unresectable esophageal cancer:
  - T4 tumors with involvement of the heart, great vessels, trachea or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
  - Stage IVA tumors of the lower esophagus with unresectable celiac nodes, involvement of celiac artery, aorta, or other organs including liver, pancreas, lung, and spleen are unresectable.
  - Stage IVB tumors with systemic metastases or non-regional lymph node metastases 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, a feeding jejunostomy or a nasogastric feeding tube are preferred to a gastrostomy.

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PRINCIPLES OF SURGERY

- **Acceptable operative approaches for resectable esophageal or gastroesophageal junction cancer:**
  - **Ivor Lewis esophagogastrectomy (laparotomy + right thoracotomy)**
  - **McKeown esophagogastrectomy (right thoracotomy + laparotomy + cervical anastomosis)**
  - **Transhiatal esophagogastrectomy (laparotomy + cervical anastomosis)**
  - **Minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy + limited right thoracotomy)[7, 8]**
  - **Minimally invasive McKeown esophagogastrectomy (right thoracoscopy + limited 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:[9]**
  - **Standard**
  - **Extended (En-Bloc)**

- **In patients undergoing esophagectomy without neoadjuvant chemoradiation, at least 15 lymph nodes should be removed to achieve adequate nodal staging. The optimum number of nodes after preoperative chemoradiation is unknown.[10]**

- **Patients who develop localized, resectable esophageal recurrence after definitive chemoradiation can be considered for salvage esophagectomy if they do not have distant recurrence.[11]**

- **Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation. Esophageal resection, endoscopic mucosal resection, and other ablative techniques should be performed in high volume esophageal centers by experienced surgeons and endoscopists.[12,13]**

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PRINCIPLES OF SYSTEMIC THERAPY FOR ESOPHAGEAL OR GASTROESOPHAGEAL JUNCTION CANCER

- For localized esophageal carcinoma, the listed regimens include participating institution preferences mainly in the context of phase II trials, and these regimens may not be superior to category 1 regimens listed.
- For metastatic esophageal carcinoma, phase III trials have not been performed for many years. Some regimens listed below are derived from the gastric adenocarcinoma phase III trials that have included patients with lower esophageal cancer and/or gastroesophageal junction cancer.
- Please refer to the original reports for toxicity, doses, schedule, and dose modifications.
- Please refer to the Principles of Radiation Therapy for the radiation therapy administration details. (ESOPH-D)
- Prior to recommending chemotherapy, the requirements for adequacy of organ function and performance status should be met.
- The schedule, toxicity, and potential benefits should be thoroughly discussed with the patient and caregivers. Patient education should also include the discussion of precautions and measures to reduce the severity and duration of complications.
- Patients should be observed closely and treated for any complications during chemotherapy. Appropriate blood work should be monitored.
- Upon completion of chemotherapy, patients should be assessed for response and monitored for any long-term complications.

Preoperative and Postoperative Chemotherapy
(Only for adenocarcinoma of the distal esophagus or gastroesophageal junction):
- ECF (Epirubicin, cisplatin and 5-FU) (category 1)[1]
- ECF modifications (category 1)[1,2]

Preoperative Chemoradiation:
- Cisplatin plus fluoropyrimidine (5-FU or capecitabine)[3,4]
- Irinotecan plus cisplatin (category 2B)[5,6]
- Paclitaxel plus cisplatin or carboplatin (category 2B)[6,7,8]
- Docetaxel plus cisplatin (category 2B)
- Docetaxel or paclitaxel plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[9]
- Oxaliplatin plus fluoropyrimidine (5-FU† or capecitabine) (category 2B)[10]

Definitive Chemoradiation:
- Cisplatin-5FU (category 1)[11,12]
- Irinotecan plus cisplatin (category 2B)
- Paclitaxel plus cisplatin or carboplatin (category 2B)
- Docetaxel plus cisplatin (category 2B)
- Docetaxel or paclitaxel plus fluoropyrimidine (5-FU or capecitabine) (category 2B)
- Oxaliplatin plus fluoropyrimidine (5-FU† or capecitabine) (category 2B)[13]

Postoperative Chemoradiation:
(Only for adenocarcinoma or gastroesophageal junction)
- Fluoropyrimidine (5-FU or capecitabine) (category 1)[14]

Metastatic or Locally Advanced Cancer [where chemoradiation is not recommended]
- DCF (Docetaxel, cisplatin and 5-FU) (category 1)[15]
- ECF (category 1)[16]
- ECF modifications (category 1)[17,18,19]
- Irinotecan plus cisplatin (category 2B)[20]
- Oxaliplatin plus fluoropyrimidine (5-FU† or capecitabine). (category 2B)[19,21]
- DCF modifications (category 2B)[19,22,23]
- Irinotecan plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[24,25,26]
- Paclitaxel-based regimen (category 2B)[27,28,29]
- Trastuzumab††,[30]

†Leucovorin is indicated with certain infusional 5-FU-based regimens.
††Used in combination with systemic chemotherapy for the treatment of patients with GE junction adenocarcinoma that is HER-2-positive as determined by a standardized method.

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PRINCIPLES OF SYSTEMIC THERAPY-FOR ESOPHAGEAL OR GASTROESOPHAGEAL JUNCTION CANCER

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PRINCIPLES OF SYSTEMIC THERAPY-FOR ESOPHAGEAL OR GASTROESOPHAGEAL JUNCTION CANCER

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PRINCIPLES OF RADIATION THERAPY

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.[1,2] The uncertainties arising from respiratory motion should also be taken into consideration.

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

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

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PRINCIPLES OF RADIATION THERAPY (2 of 2)

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PRINCIPLES OF BEST SUPPORTIVE CARE FOR ESOPHAGEAL CANCER (1 of 2)[1,2,3,4]

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

Dysphagia

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

Obstruction:

- Complete esophageal obstruction
  - Endoscopic lumen restoration
  - Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
    - Surgical placement of jejunal feeding tube (if esophagectomy planned)
    - Placement of gastrostomy tube (if esophagectomy is not planned)
      -Retrograde endoscopic lumen restoration may be attempted through the gastrostomy site.
  - External beam radiation therapy
    - Brachytherapy may be considered in place of external beam radiation when feasible
  - Chemotherapy, when appropriate, may be considered
  - Surgery
- Severe esophageal obstruction
  - Endoscopic lumen enhancement
    - Guide wire or balloon dilation
    - Temporary placement of small diameter removable covered stents (8 mm – 16 mm diameter)
      -Placement of large diameter stents in patients with severe esophageal obstruction may result in uncontrollable chest pain, bleeding and perforation
    - Other measures as stated above
- Moderate esophageal obstruction (able to swallow semisolid food)
  - Intermittent endoscopic lumen enhancement as necessary
    - Measures stated above may be considered

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PRINCIPLES OF BEST SUPPORTIVE CARE FOR ESOPHAGEAL CANCER (2 of 2)[1,2,3,4]

Pain

- If patient is experiencing tumor related pain, then the pain should be assessed and treated in accordance with PAIN-1 Section of NCCN Adult Cancer Pain Guidelines.
  - Severe uncontrolled pain following esophageal stent placement should be treated emergently 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 Antiemesis Guidelines.

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Staging

Table 1

American Joint Committee on Cancer (AJCC) TNM Classification of Carcinoma of the Esophagus*

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Tumors of the lower thoracic esophagus:

M1a	Metastasis in celiac lymph nodes
M1b	Other distant metastasis

Tumors of the midthoracic esophagus:

M1a	Not applicable
M1b	Nonregional lymph nodes and/or other distant metastasis

Tumors of the upper thoracic esophagus:

M1a	Metastasis in cervical nodes
M1b	Other distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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Discussion

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, gastroesophageal (GE) junctions, and stomach, constitute a major health problem around the world. An estimated 37,640 new cases of and 25,070 deaths from upper GI cancers will occur in the United States in 2010.[1] A dramatic shift in the location of upper GI tumors has occurred in the United States.[2,3] Changes in histology and location of upper GI tumors have also been observed in some parts of Europe.[4] In Western Hemisphere countries, the most common site of esophageal cancer is in the lower third of the esophagus, where it often involves the GE junction.

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide.[5] An estimated 16,640 new cases and 14,500 deaths from esophageal cancer will occur in United States in 2010.[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] Esophageal adenocarcinoma 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 background 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.[10,11,12] Risk of SCC decreases substantially after smoking cessation; unlike in SCC, the risk for adenocarcinoma remains unchanged even after several years of smoking cessation.[13] Obesity and high body mass index (BMI) have been established as strong risk factors for esophageal adenocarcinoma.[11,14,15] Individuals in the highest quartile for BMI had a 7.6-fold increased risk of developing esophageal

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adenocarcinoma compared to those in the lowest quartile, whereas SCC was not associated with BMI.[16,17]

Gastroesophageal reflux disease (GERD) and Barrett's esophagus are the other two major risk factors for adenocarcinoma of the esophagus.[18-21] 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.[22] Patients with Barrett's esophagus have 30 to 60 times greater risk of developing esophageal adenocarcinoma than the general population.[20] Despite this, only a minority of patients with Barrett's esophagus will progress to esophageal adenocarcinoma.[23,24] 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.[25,26] These preliminary results warrant further prospective evaluation as predictors of risk for the development of high grade dysplasia and esophageal adenocarcinoma in patients with Barrett's esophagus.

Patients with SCC of the esophagus and esophageal adenocarcinoma are also at increased risk of developing second primary cancers such as head and neck and lung cancers.[27]

Staging

Current staging of esophageal cancer is based on the new tumor/node/metastasis (TNM) classification developed by the American Joint Committee on Cancer (Table 1). This classification is based on the review of pathology in the surgical specimen in patients who had surgery as primary therapy. This new classification may not work well for baseline clinical staging or in patients who received preoperative therapy. Patient outcomes may correlate with the initial clinical stage of the cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage. Although surgical pathology yields the most accurate staging, the advent of better imaging techniques, including endoscopic ultrasound (EUS), has improved preclinical staging.[28]

Combined use of EUS and EUS-guided fine needle aspiration (EUS-FNA) has a greater accuracy than does EUS alone in the evaluation of lymph node metastasis, especially celiac lymph nodes.[29,30] 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.[31] Direct surgical resection was contraindicated in 77% of evaluable patients due to advanced locoregional/metastatic disease.

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.

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

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showed that preoperative chemoradiation (CALGB 9781) and perioperative chemotherapy (MAGIC trial, predominantly a gastric cancer trial including a small group of patients with lower esophageal and GE junction cancers) significantly improved survival in patients with resectable esophageal and gastroesophageal cancer.[32,33]

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 surgery.

Stage I, II, and III cancers are assumed to be potentially resectable. Modern preoperative staging procedures such as EUS, EUS-FNA, combined PET and CT scans, and molecular biologic techniques may result in improved prognostic stratification, improved patient selection for surgical therapy, and improved overall survival. A recent study reported that serum c-reactive protein levels, change in body weight and clinical TNM staging before treatment can be combined in an index to predict the prognosis of patients with esophageal cancer.[34,35] C-reactive protein needs to be further investigated before its routine incorporation into initial staging. Pretreatment weight loss is a documented prognostic factor.

Surgical Approaches

Several approaches (transthoracic, transhiatal, or minimally invasive) are acceptable for esophagogastrectomy in patients with resectable esophageal cancer or GE junction cancers (ESOPH-B).[36] The type of esophageal resection is dictated by the size and location of the primary tumor, as well as the surgeon's experience and preference and the patient's preference. The optimal location of the anastomosis has been debated. 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 include a lower incidence of anastomotic leak and lower stricture rate. In a prospective randomized trial, cervical and thoracic anastomoses after esophageal resection were equally safe when performed in a standardized way.[37] Gastric conduit is preferred for esophageal reconstruction and it is used by majority of the surgeons to replace the esophagus after esophagogastrectomy.[38] Colon interposition is usually reserved for patients who have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[39]

Ivor Lewis esophagogastrectomy (right thoracotomy and laparotomy), and the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis) are the two variants of transthoracic esophagogastrectomy. Ivor-Lewis esophagogastrectomy, the most frequently used procedure for transthoracic esophagogastrectomy, uses abdominal and right thoracic incisions, with upper thoracic esophagogastric anastomosis (at or above the azygos vein).[40] Mobilization of the stomach for use as the conduit is performed, with dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries. This approach may be used for lesions at any thoracic location, but margins may be inadequate for tumors in the middle esophagus.

Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[41] 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 mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be

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hazardous. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy.[42] 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.[43]

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision, through the eighth intercostal space.[44] Mobilization of the stomach for use as the conduit is performed as described previously, and esophagectomy is accomplished through the left thoracotomy. Esophagogastric anastomosis is performed in the left chest, usually just superior to the inferior pulmonary vein, although it may be performed higher if the conduit is tunneled under the aortic arch. This approach may be used for lesions in the distal esophagus.[44]

Minimally invasive esophagectomy (MIE) is associated with decreased morbidity and shorter recovery times when compared with open procedures. 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.[45] 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 morbidity from 1.5% to 1.8%.[46] No randomized trials have assessed whether MIE improves survival when compared with open procedures. Open esophagectomy is still preferred in many settings (eg, large and bulky tumors, concerns about the location of positive margins, concerns that the gastric conduit may not be useable, patient has undergone multiple previous upper abdominal surgeries). In the absence of prospective trials with longer follow up, MIE remains an investigational and still evolving treatment for patients with esophageal cancer.[47] Open surgery should remain the standard for many patients. MIE may be useful for older patients.[48]

Endoscopic mucosal resection (EMR) represents a major advance in minimally invasive approaches in the gastrointestinal tract. EMR is used widely for treating superficial early SCC of esophagus in Japan and it is gaining acceptance in the Western countries.[49,50] EMR has been reported to accurately determine the depth of tumor invasion before surgical resection.[51] Indications for EMR for esophageal cancer include well and/or moderately differentiated SCC confined to lamina propria with no evidence of venous or lymphatic involvement. No randomized studies have compared EMR with other surgical techniques for GI cancers. Nevertheless, EMR continues to evolve as a promising technology in the diagnosis and treatment of esophageal and gastric cancers.

Principles of Surgery

Surgical resection for esophageal cancer is performed either with a curative intent or as part of palliative care. Selecting 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. Palliative resections 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.

All patients should be assessed for physiologic ability to undergo esophageal resection.[52] Esophageal resection may be appropriate for all physiologically fit patients with localized resectable thoracic esophageal cancer in the thorax (greater than 5 cm from

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cricopharyngeus) and intraabdominal esophagus or GE junction cancer (ESOPH-B). Cervical or cervicothoracic esophageal carcinomas less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Palliative esophagectomy can be considered for patients who develop localized, resectable esophageal recurrence after definitive chemoradiation if there is no distant recurrence.[53]

Clinical staging using EUS (with FNA, if indicated), chest and abdomen CT scan, and PET-CT scan (preferred over PET alone) should be performed before surgery to assess resectability.[54] Lymph node dissections can be performed using the standard or extended (en-bloc) technique.[55] In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the Surveillance Epidemiology and End Results (SEER) database, overall and disease-free survival were significantly longer in patients who had 11 or more lymph nodes examined.[56] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[57,58] 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.[58] In patients undergoing esophagectomy without preoperative chemoradiation, the guidelines recommend that at least 15 lymph nodes should be removed for adequate nodal staging (ESOPH-B).The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown.

Tis or T1a tumors (defined as those involving the mucosa but not invading the submucosa) should be considered for EMR, and esophagectomy should be reserved for unsuccessful EMR. These procedures are best performed in centers with experienced physicians.[59,60] Tumors in the submucosa or deeper may be treated with resection. T1-T3 tumors are resectable even in the presence of regional nodal metastases (N1). T4 tumors with involvement of pericardium, pleura or diaphragm may be resectable. Stage IVA tumors in the lower esophagus with resectable celiac nodes and no involvement of the celiac artery, aorta or other organs, are considered potentially resectable. T4 tumors (with involvement of heart, great vessels, trachea or adjacent organs including liver, pancreas, lung and spleen) are considered unresectable. Stage IVA tumors in the lower esophagus with unresectable celiac nodes and involvement of the celiac artery, aorta or other organs, including liver, pancreas, lung and spleen are unresectable. Stage IVB tumors with systemic metastases or non-regional lymph node involvement are considered unresectable.

Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation. Esophageal resection and EMR should be performed in high volume esophageal cancer centers by experienced physicians.[61]

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%.[62-64] 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.[65] 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/d with conventional techniques, all patients died of cancer by 3 years.[66,67] Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

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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.[68-72] 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 do not show a survival advantage for preoperative or postoperative RT alone.[73-75] A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative radiation.[76]

Principles of Radiation Therapy

RT (definitive, preoperative, postoperative or palliative) can be an integral part of treatment for esophageal cancer. 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. 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.

The panel recommends a dose range of 50-50.4 Gy delivered in fractions of 1.8-2 Gy per day. 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. Optimal dose ranges for these vital organs are included in ESOPH-D. Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients with esophageal cancer. Optimal criteria for DVH parameters are being actively developed in NCCN institutions.

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 on a prophylactic basis 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.[77] 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.[78] 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

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intraluminal brachytherapy to radiation or combined modality therapy, although reasonable, remains unclear.

Combined Modality Treatments: Concomitant 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.[79] Concomitant 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.[80]

Primary Chemoradiation Therapy

In the RTOG 85-01 trial, patients with SCC or adenocarcinoma received 4 cycles of 5-fluorouracil and cisplatin.[67,80] 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).[81] In this trial, 218 patients with either SCC (85%) or adenocarcinoma (15%) 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 (13.0 vs.18.1 months), 2-year survival (31% vs. 40%), and local/regional failure or local/regional persistence of cancer (56% vs. 52%) between the high dose and standard dose RT arms.

After the results of these studies, primary chemoradiation therapy with 5-fluooruracil and cisplatin using the RT dose of 50.4 Gy was established as the standard of care for patients with esophageal cancer.

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational.[82] The results of two meta-analysis showed 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.[83,84] In another 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).[85] Another recent meta-analysis (1,209 patients,10 randomized comparisons of preoperative chemoradiation vs. surgery alone), showed a significant survival benefit for preoperative chemoradiation in patients with resectable adenocarcinoma of the esophagus.[86]

Preoperative chemoradiation therapy has also been shown to be promising for localized esophageal cancer in phase I and II studies.[87-97] However, randomized trials comparing preoperative combined modality therapy with surgery alone in patients with clinically resectable cancer have shown conflicting results.[98-106] Recent results from a recent multicenter phase III randomized trial (CROSS study) showed that carboplatin and paclitaxel with concurrent radiotherapy improved

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overall survival compared to surgery alone in patients with resectable (T2-3, N0-1, M0) esophageal or esophagogastric junction cancers[107] whereas 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 stage I or II esophageal cancer compared with surgery alone.[108] 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.[33] The study fell short of its accrual goals with only 56 patients enrolled. Those 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.[109,110] Stahl et al. randomized 172 patients to either induction chemotherapy followed by chemoradiation therapy and surgery or induction chemotherapy followed by chemoradiation therapy.[109] Two-year progression-free survival (PFS) was better in the surgery group (64.3%) than in the chemoradiation therapy group (40.7%). However, there was no difference was seen 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.[111] 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.[110] However, this trial suffers from suboptimal design and low number of patients.

Postoperative Chemoradiation Therapy

Macdonald et al. investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or GE junction.[112] This study randomly assigned 556 patients with resected adenocarcinoma of the stomach or GE junction were randomly assigned to surgery plus postoperative chemoradiation (5-flurouracil/leucovorin) or surgery alone. 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 survival rates (50% vs. 41%) and 3-year relapse-free survival (RFS) rates (48% vs.31%) than the surgery only group. Postoperative chemoradiation therapy significantly improved overall survival and RFS for all patients at high risk for recurrence of adenocarcinoma of the stomach or GE junction. One major criticism of this trial is that 54% of patients had a D0 resection (with sub optimal dissection of N1 lymph nodes) and only 36% of patients had a D1 resection. However, surgery was not an integral part of this protocol and eligible patients were randomized only after surgery was completed.

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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.[113] 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.[114] Although preoperative chemotherapy decreased the incidence of R1 resection (4% compared with 15% in the surgery only group), no improvement was seen in the 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.[115] In this trial, patients were randomly assigned to receive either 2 cycles of preoperative 5-fluorouracil (1000 mg/m^2 per day by continuous infusion for 4 days) and cisplatin (80 mg/m^2 on day 1) repeated every 21 days followed by surgery, or surgery alone. 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.[116] 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.[116] However, the two large 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 (FNLCC ACCORD07-FFCD 9703), compared preoperative chemotherapy [5-fluorouracil and cisplatin (FP)] with surgery alone in patients with adenocarcinoma of the stomach and lower esophagus.[117] This study randomized 224 patients between surgery alone and preoperative chemotherapy (FP) followed by surgery. Post-operative FP was recommended for patients responding to preoperative FP. At a median follow-up of 5.7 years, 3 and 5-year disease free survival rates were 40% and 34% respectively for patients who received preoperative FP compared with 25% and 21% respectively for those treated with surgery alone. The preoperative chemotherapy group also had better 3- and 5-year overall survival rates (48% and 38% respectively) compared with the surgery alone group (35% and 24%, respectively). This trial was prematurely terminated due to low accrual.

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.[118]

Perioperative Chemotherapy

The British Medical Research Council performed the first well powered phase III trial (MAGIC trial) for perioperative chemotherapy.[32] This trial evaluated the effect of perioperative chemotherapy with the ECF (epirubicin, cisplatin and 5-fluorouracil) regimen given before and after surgery in resectable gastroesophageal cancer. Most (74%) of the patients had stomach cancer, whereas a small group of patients had

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adenocarcinoma of the lower esophagus (14%) and cancer of esophagogastric junction (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 PFS and overall survival in patients with operable gastric and lower esophageal adenocarcinomas.

Chemotherapy for Advanced Disease

Combination chemotherapy for metastatic esophageal cancer continues to evolve. Compared with adenocarcinoma, SCC seems to be more sensitive to chemotherapy, chemoradiation, and RT, but the long-term outcome appears to be the same. In randomized clinical trials, no consistent benefit was seen for any specific chemotherapy regimen and chemotherapy showed no survival benefit compared with best supportive care for patients with advanced esophageal cancer.[119] Adequately powered phase III studies are lacking. 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.[120]

Cisplatin is one of the most active agents, with a single agent response rate consistently in the range of 20% or greater.[121] Older agents that are active include 5-fluorouracil, mitomycin, bleomycin, methotrexate, mitoguazone, doxorubicin, and vindesine.[122] Newer agents such as irinotecan, docetaxel, paclitaxel and oxaliplatin have shown activity in advanced esophageal cancer.[123-126]

Fluorouracil plus cisplatin is the most investigated and most commonly used regimen for patients with esophageal cancer. Reported response rates to this combination vary between 20-50%. Paclitaxel and cisplatin with or without 5-fluorouracil has demonstrated activity in patients with locally advanced or metastatic esophageal cancer.[127, 128,129] Docetaxel in combination with cisplatin and 5-fluorouracil (DCF) was evaluated in a randomized multinational phase III study (V325). Majority of the patients had advanced gastric cancer and 19-25% of patients had GE junction cancer. In this study, 445 untreated patients were randomized to receive either DCF (every 3 weeks) or the combination of cisplatin and fluorouracil (CF).[130] Time to progression was significantly longer with DCF compared with CF (5.6 vs. 3.7 months). Various modifications of DCF regimen with the intent to improve tolerability are being evaluated in clinical trials for patients with advanced esophagogastric cancer.[131-136]

In addition, the combination of irinotecan and cisplatin is active, particularly against SCC of the esophagus.[137] Cisplatin in combination with gemcitabine has also been evaluated in phase II studies in patients with metastatic and advanced esophageal cancer.[138,139] Median survival was 7.3 months in patients with patients with metastatic esophageal cancer. In patients with advanced esophageal cancer the combination of gemcitabine and cisplatin yielded a 45% response rate. In a prospective randomized study, the combination of mitomycin, cisplatin and protracted intravenous infusion of fluorouracil (PVI 5-FU) [MCF] was equally efficient to the combination of epirubicin, cisplatin and PVI 5-FU (ECF) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.[140]

Capecitabine is an orally administered fluoropyrimidine that is converted to 5-flurouracil preferentially in the tumor tissue. Capecitabine has been evaluated in combination with other agents in advanced esophagogastric cancers.[141] 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.[142] Patients with histologically confirmed adenocarcinoma, SCC or

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undifferentiated cancer of the esophagus, GE junction 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 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.

In phase II studies, non-cisplatin containing regimens have shown activity in patients with advanced esophageal cancer.[143,144-148] The combination of 5-fluorouracil, leucovorin and irinotecan was found to be active in primary refractory or untreated locally advanced esophagogastric cancer as well as in patients with locally advanced unresectable and metastatic adenocarcinoma and SCC of the esophagus.[143,144,145] 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.[144] Median survival was 20 months and 10 months respectively for patients with adenocarcinoma and SCC. Capecitabine in combination with irinotecan was active in patients with metastatic esophagogastric cancer that has progressed on platinum-based chemotherapy. The results of a recent randomized study also showed that capecitabine and irinotecan was comparable in efficacy and activity to cisplatin and irinotecan.[147] The combination of carboplatin and paclitaxel regimen was moderately active with a response rate of 43% in patients with advanced esophageal cancer. However, 52% of patients had neutropenia (grade 3-4).[148]

Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend towards improved median PFS (5.8 v 3.9 months) compared to fluorouracil, leucovorin and cisplatin (FLP) in patients with metastatic gastroesophageal cancer.[149] 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 PFS (6.0 vs. 3.1 months), and an improved overall survival (13.9 vs. 7.2 months) compared with FLP, respectively.

Targeted Therapies

The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and HER2 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 (an anti-VEGFR antibody) and have been evaluated in treatment of patients with advanced esophageal cancer and GE junction adenocarcinoma.[150]

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-positive gastric and GE junction adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[151] The results of this study confirmed that trastuzumab plus standard chemotherapy is superior to chemotherapy alone in patients with HER2-positive advanced gastric and GE junction adenocarcinoma. Five hundred and ninety four patients with HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive trastuzumab plus chemotherapy (5-fluorouracil

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or capecitabine and cisplatin) or chemotherapy alone. There was a significant improvement in the median OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone (13.5 vs. 11.1 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 HER-2-expressing advanced gastric and GE junction adenocarcinoma. Further understanding regarding the relevance of HER2 testing in gastroesophageal cancer and the subgroup of patients with "HER2-positive" tumor that would benefit from targeted therapy is needed.

The safety and efficacy of cetuximab,[152-158] erlotinib[159,160] and bevacizumab[161,162] 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 GE junction cancers.

Treatment Guidelines

The management of esophageal cancer requires the expertise of several disciplines (thoracic surgery, radiation oncology, medical oncology, nutritional and pulmonary support, and endoscopy). Hence, the panel believes that multidisciplinary evaluation is preferred for the treatment of patients with esophagogastric cancer. The guidelines have now included a section on Principles of Multidisciplinary Team Approach for Gastroesophageal Cancers (ESOPH-A). The panel encourages a face-to-face multidisciplinary evaluation.

Esophagogastric Junction

Sierwert et al classified the adenocarcinoma of the esophagogastric (AEG) junction into three types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass. [163] If the epicenter of the tumor or more than 66% of the tumor mass is located more than 1 cm above the anatomic esophagogastric junction, 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 esophagogastric junction, 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 esophagogastric junction, the tumor is classified as adenocarcinoma of the esophagogastric junction, type III.[163]

In 2000, the classification was changed slightly.[164] Adenocarcinoma of the distal esophagus (AEG type I) includes tumors with a center that is 5-cm proximal or distal to the anatomic cardia and these tumors arise from an area with specialized intestinal metaplasia of the esophagus (i.e., Barrett esophagus) and may infiltrate the esophagogastric junction from above. AEG type II tumors or true carcinoma of the cardia arise immediately at the esophagogastric junction. AEG type III tumors or subcardiac gastric carcinoma infiltrate the esophagogastric junction from below.

Various techniques used to determine this include barium esophagography, esophagoscopy, and CT. 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 and specific requirements for local control.

Workup

Newly diagnosed patients should undergo a complete history, physical examination, and endoscopy of the entire upper GI tract (ESOPH-1). Histological confirmation of cancer is required. For patients in whom the upper GI tract cannot be visualized, a double contrast barium study of

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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. At this point, if metastatic cancer is not evident, EUS with fine needle aspiration is recommended if indicated. If the cancer is located at or above the cardia, bronchoscopy (including biopsy of any abnormality and cytology of the washings) should be performed. In addition, if the cancer is located at the GE junction, laparoscopic staging of the peritoneal cavity is optional.[165] Suspicions for metastatic cancer should be confirmed by biopsy.

Combined PET-CT imaging has many advantages over PET scan alone and it significantly improves the diagnostic accuracy.[166] PET-CT scans are useful in the initial staging and evaluation of patients after chemoradiation prior to surgical resection.[167] They may be useful for the detection of distant lymphatic and hematogenous metastases.[168] PET-CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer.[169] It was also shown to be an independent predictor of overall survival in patients with non-metastatic esophageal cancer.[170] In addition, a recent study in patients with esophageal cancer reported that combined PET-CT scans are more accurate than esophageal ultrasound-fine needle aspiration and CT scan for predicting nodal status and complete response after neoadjuvant therapy.[171] 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-CT scans are useful if there is no evidence of metastatic disease.

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. Nasogastric 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: patients with apparent locoregional cancer (stages I-III, IVA) and those with metastatic cancer (stage IVB). Patients with locoregional cancer are further classified into the following groups after additional evaluation (ESOPH-1):

- Medically fit with resectable disease in medically fit patients
- Medically unfit for surgery or surgery not elected and medically able to tolerate chemotherapy or those with unresectable disease (T4 or stage IVA)
- Medically unfit for surgery and unable to tolerate chemoradiation
- Metastatic disease

Resectable Esophageal Cancer

Treatment for Medically Fit Patients

Esophagectomy or EMR is the primary treatment option Tis or T1a tumors (ESOPH-2). Esophagectomy is the preferred treatment option patients with non-cervical T1b, N0, NX tumors, whereas

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chemoradiation therapy is the preferred modality for cervical ≥T1b tumors.

Primary treatment options for patients with resectable T1b, N1 or T2-T4, N0-1, NX, or stage IVA (any T, any N, M1a) tumors include definitive chemoradiation, preoperative concurrent chemoradiation or rarely preoperative chemotherapy (ESOPH-3). 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.[79] While definitive chemoradiation is an option for patients with SCC, surgery is the preferred treatment for patients with adenocarcinoma.

Post chemoradiation PET scan has been shown to predict the pathologic complete response and outcome after definitive or preoperative chemoradiation therapy.[172-176] In a prospective multicenter study (SAKK 75/02), a decrease in 18-fluorodeoxyglucose (FDG) tumor uptake of less than 40% was prospectively hypothesized as a predictor for histopathological non-response after chemoradiation therapy.[177] Swisher et al also showed that a post-chemoradiation FDG uptake value of 4 or less was found to be the only preoperative factor to correlate with decreased survival.[178] The 2-year survival rate was 60% for patients with a post-chemoradiation PET SUV of less than 4 and 34% for those with a PET SUV of 4 or more. In patients receiving preoperative or definitive chemoradiation therapy, CT scan with contrast or PET-CT scan can be considered before surgery or initiation of postoperative treatment. However, PET scans could not distinguish patients with microscopic residual disease and complete pathological response.[174,177] Therefore, PET scans should not be used for the selection of patients to surgery following preoperative chemoradiation.

Following definitive chemoradiation, patients with no evidence of disease can be observed and salvage esophagectomy is an option for those with persistent local disease. Esophagectomy is the preferred treatment option for all patients following preoperative chemotherapy and for those with no evidence of disease and as well as those with persistent local disease with no metastases following preoperative chemoradiation therapy (ESOPH-3). Alternatively, patients, particularly with SCC, with no evidence of disease following chemoradiation may be observed (category 2B) and those with persistent local disease can be given palliative treatment including chemotherapy (ESOPH-3). Patients with unresectable or metastatic disease after definitive or preoperative chemoradiation should be considered for palliative therapy as described in ESOPH-7, depending on their performance status.

Postoperative treatment is based on the surgical margins, nodal status and histology (ESOPH-4). In patients with no residual disease at surgical margins (R0 resection), no further treatment is necessary for those with SCC, irrespective of their nodal status. In patients with node negative adenocarcinoma, no further treatment is essential for those Tis, T1, N0 and T2, N0 tumors, whereas fluoropyrimidine-based chemoradiation is recommended for T2, N0 tumors in selected patients with high-risk features such as poorly differentiated histology, younger patients, and lymphovascular or neurovascular invasion and for all patients with T3, N0 tumors. In patients with positive nodes, fluoropyrimidine-based chemoradiation is recommended for patients with adenocarcinoma of proximal or mid esophagus or adenocarcinoma of the distal esophagus and GE junction. Postoperative chemoradiation is recommended only if not received preoperatively. Postoperative chemotherapy is recommended for patients who were treated with preoperative chemotherapy (category 1). Based on the results of the MAGIC trial, perioperative chemotherapy with ECF regimen (epirubicin, cisplatin and 5-fluorouracil) or its modifications is recommended for patients with completely resected node negative adenocarcinoma (T2-T3, N0) or node positive adenocarcinoma of the distal esophagus or GE junction.[32]

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Patients with microscopic (R1 resection) or macroscopic residual disease with no distant disease (R2 resection) should be treated with fluoropyrimidine-based chemoradiation, if they have not received preoperative chemoradiation. Palliative therapy as described in ESOPH-7 is an alternative option for patients with macroscopic residual disease.

The regimens included in the guidelines for preoperative or definitive chemoradiation are based on the preferences of the participating institutions mainly in the context of phase II trials. These regimens may not be superior to other regimens that are included with a category 1 recommendation. The following regimens are included in the guidelines for preoperative or definitive chemoradiation (ESOPH-C):

- Fluoropyrimidine (5-fluorouracil or capecitabine) in combination with cisplatin, oxaliplatin, docetaxel or paclitaxel
- Cisplatin in combination with irinotecan or docetaxel
- Paclitaxel in combination with cisplatin or carboplatin

Cisplatin in combination with 5-fluorouracil has a category 1 recommendation when used as definitive chemoradiation, whereas cisplatin plus 5-fluorouracil or capecitabine has a category 2A recommendation for preoperative chemoradiation. All of the other regimens are listed as category 2B recommendation. Leucovorin can be used with certain infusional 5-fluorouracil-based regimens.

Treatment for Medically Unfit Patients

EMR or chemoradiation is recommended for patients with Tis or T1a tumors. Fluoropyrimidine-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 (ESOPH-5). 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.

Unresectable or Non-metastatic Disease

In patients with advanced unresectable esophageal cancer, chemoradiation may be appropriate and occasionally can facilitate surgical resection in selected cases. In a recent randomized phase II trial, patients with inoperable esophageal cancer were randomized to definitive chemoradiation therapy with either FOLFOX 4 (5-fluorouracil, leucovorin and oxaliplatin) or 5-fluorouracil and cisplatin.[179] Median time to progression (TTP) was 15 months for FOLFOX arm compared to 9.5 months for 5-fluorouracil and cisplatin. Median event free survival (11.6 vs. 7.8 months) and median overall survival (22.7 vs.14.7 months) were 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.[180] Median overall survival and disease-free survival were was 17 months and 9 months respectively.

Fluoropyrimidine-based concurrent chemoradiation therapy is the preferred treatment option for patients with unresectable or non-metastatic cancer (T4 or stage IVA). Chemotherapy, RT or best supportive care are reasonable alternatives for patients with inoperable cancers (ESOPH-5).

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 1-3 years, then every 6 months for 3-5 years, and annually thereafter (ESOPH-6). CBC, multichannel

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serum chemistry evaluation, endoscopy 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.[181]

Recurrent and Metastatic Esophageal Cancer

Treatment for recurrent disease 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. Local or regional recurrence after esophagectomy can be treated with fluoropyrimidine-based concurrent chemoradiation therapy in patients who have not received prior chemoradiation (ESOPH-6). 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 for metastatic disease. Palliative therapy is also recommended for medically unfit patients and those who develop an unresectable recurrence.

Best supportive care is the appropriate treatment option for patients with metastatic cancer (ESOPH-7). 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.[182,183] 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 (Karnofsky performance score of 60 or more, or an ECOG performance score of 2 or less) may be offered chemotherapy along with best supportive care. Further treatment after two sequential regimens depends on the performance status and availability of clinical trials (ESOPH-7).

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 GE junction cancer. The following regimens are listed in the guidelines for metastatic or locally advanced cancer when chemoradiation is not an option (ESOPH-C):

- Docetaxel, cisplatin or 5-fluorouracil (DCF) or its modifications
- Epirubicin, cisplatin and 5-fluorouracil (ECF) or its modifications
- Irinotecan in combination with cisplatin or fluoropyrimidine (5-fluorouracil or capecitabine)
- Oxaliplatin in combination with fluoropyrimidine (5-fluorouracil or capecitabine)
- Paclitaxel-based regimens

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- Trastuzumab in combination with chemotherapy for patients with advanced GE junction adenocarcinoma that is HER-2-positive as determined by a standardized method.

ECF regimen or its modifications and DCF regimen have a category 1 recommendation. DCF modifications and all other regimens have a category 2B recommendation. Leucovorin can be used with certain infusional 5-fluorouracil-based regimens.

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 improvement in nutritional status, the sensation of well-being, and overall quality of life. Palliative interventions for the management of dysphagia (swallowing impairment), pain and GI bleeding are described in detail in ESOPH-E.

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. Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Available endoscopic palliative methods for the management of dysphagia include endoscopic lumen restoration (guide wire or balloon dilatation), placement of permanent or temporary self-expanding metal stents (SEMS), argon plasma coagulation, endoscopic injections of ethanol, RT, brachytherapy, laser therapy, photodynamic therapy and chemotherapy alone or in combination with a radiosensitizing agent.[184,185] Placement of jejunostomy or gastronomy tubes may be necessary to provide adequate hydration and nutrition.

Single dose brachytherapy was associated with fewer complications and better long-term relief of dysphagia compared with metal stents.[186] The combination of photodynamic therapy and the self-expanding stents provided excellent palliation of dysphagia for patients with obstructive adenocarcinoma of the esophagus.[187] Temporary placement of SEMS with concurrent radiation therapy was found to be beneficial for increasing survival rates compared with permanent stent placement.[188] Although SEMS is the preferred treatment for patients with tracheoesophageal fistula and those who are not candidates for chemoradiation, it is not an effective endoscopic approach.[189] Treatment options for the management of dysphagia should be individualized. A multimodality interdisciplinary approach is strongly recommended.

Pain

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

Bleeding

Bleeding in patients with esophageal cancer may be secondary to tumor related aorto-esophageal fistualization. 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.

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Management of 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. Endoscopy is performed on patients with severe symptoms of gastroesophageal reflux, especially those with a family history of Barrett's esophagus or esophageal cancer. Endoscopic surveillance is performed to evaluate progression from metaplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD), or adenocarcinoma. However, controversy exists when recommending a surveillance schedule for patients with Barrett's metaplasia. Once the diagnosis of metaplasia is established, routine endoscopic screening with 4-quadrant biopsy every 1 to 3 years is indicated.[190] The screening interval is decreased to 6 to 12 months if LGD is present. For patients with metaplasia or LGD, acid reflux is controlled with histamine receptor antagonists or proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole).

If HGD is discovered during surveillance, a second pathologist should provide pathologic confirmation. Among patients found to have HGD, adenocarcinoma actually may be present in up to 50% of patients In a study of 15 patients preoperatively diagnosed with HGD who underwent esophagogastrectomy, the final pathologic study showed carcinoma-in-situ in 3 patients (20%) and invasive cancer in 8 (53%).[191] A meta-analysis of published results of 119 patients undergoing resection showed a 2.6% operative mortality rate, a 47% incidence of invasive cancer, and an 82% 5-year survival rate in patients with invasive cancer. Surgical resection should be the preferred treatment for Barrett's esophagus with high-grade dysplasia. Many alternatives to surgical resection are being investigated.

Alternative strategies for patients with HGD include mucosal ablation or further surveillance every 3 months. Mucosal ablation can be achieved with photodynamic therapy, argon beam coagulation, thermal laser ablation, or EMR.[192,193,194] Among these methods of mucosal ablation, photodynamic therapy is superior for achieving ablation of metaplastic and dysplastic epithelium as well as for obviating the need for further interventions.[191,195,196] However, more recently, the use of photodynamic therapy as an endoscopic therapy for esophageal diseases is losing popularity due to long-term consequences. However, lifelong surveillance with deep biopsies is still required for patients with HGD who are treated with photodynamic therapy or EMR. 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.

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 GE junction.

Esophagectomy or EMR is the primary treatment option for patients with Tis or T1a tumors, whereas esophagectomy is considered the preferred primary treatment option for medically fit patients with

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resectable T1b, N0, or NX tumors. In medically fit patients with more advanced disease (T1b, N1 to T4, N0-1, NX, or stage IVA), primary treatment options include definitive chemoradiation, preoperative chemotherapy (rarely), or chemoradiation followed by esophagectomy. Medically unfit patients may be offered definitive chemoradiation therapy.

Postoperative treatment is based on histology, surgical margins, and nodal status. In patients with SCC who have no residual disease at surgical margins (R0 resection), no further treatment is recommended, irrespective of their nodal status. Fluoropyrimidine-based chemoradiation is recommended for all patients with node-positive adenocarcinoma and for those with node negative adenocarcinoma who have T2, N0 tumors with high-risk features and T3, N0 tumors. Postoperative chemotherapy is recommended (only if they had received preoperative chemotherapy) for patients with completely resected node negative adenocarcinoma (T2-T3, N0) and node positive adenocarcinoma of the lower esophagus and GE junction. All patients with residual disease at surgical margins (R1 and R2 resections) may be treated with fluoropyrimidine-based chemoradiation.

Concurrent chemoradiation with a fluoropyrimidine-based regimen 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 gastroesophageal junction cancers. Based on the results of the ToGA trial, the NCCN panel has included trastuzumab plus chemotherapy as a new treatment option for patients with HER2-positive advanced GE junction adenocarcinoma.

Best supportive care is an integral part of treatment, especially in patients with locally advanced disease. Assessing 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 Esophageal Cancer Guidelines emphasize that considerable advances have been made in the treatment of locoregional esophageal cancer. Novel therapeutic modalities, such as targeted therapies, vaccines, gene therapy, and antiangiogenic agents, are being studied in clinical trials for patients with esophageal cancer. The panel encourages patients with esophageal cancer to participate in well designed clinical trials to enable further advances.

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