National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Esophageal and Esophagogastric Junction Cancers

Version 2.2016

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

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

*Thomas A. D'Amico, MD/Vice Chair ¶
Duke Cancer Institute

Khaldoun Almhanna, MD, MPH †
Moffitt Cancer Center

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

Joseph Chao, MD †
City of Hope Comprehensive
Cancer Center

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

Crystal S. Denlinger, MD †
Fox Chase Cancer Center

Paul Fanta, MD ‡ †
UC San Diego Moores Cancer Center

Farhood Farjah, MD ¶
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

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

Hans Gerdes, MD ¤ Þ
Memorial Sloan Kettering
Cancer Center

NCCN
Nicole McMillian, MS
Hema Sundar, PhD

Michael Gibson, MD, PhD † ‡ Þ
Case Comprehensive Cancer
Center/University Hospitals
Seidman Cancer Center and
Cleveland Clinic Taussig
Cancer Institute

Robert E. Glasgow, MD ¶
Huntsman Cancer Institute
at the University of Utah

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

Steven Hochwald, MD ¶
Roswell Park Cancer Institute

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

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

Dawn Jaroszewski, MD
Mayo Clinic Cancer Center

Kimberly L. Johung, MD, PhD §
Yale Cancer Center/
Smilow Cancer Hospital

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

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

W. Michael Korn, MD ¤ †
UCSF Helen Diller Family
Comprehensive Cancer Center

Stephen Leong, MD †
University of Colorado
Cancer Center

Catherine Linn, MD Þ
Vanderbilt-Ingram Cancer Center

A. Craig Lockhart, MD, MHS †
Siteman Cancer Center
at Barnes-Jewish Hospital
and Washington University
School of Medicine

Quan P. Ly, MD ¶
Fred & Pamela Buffett
Cancer Center

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

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

Kyle A. Perry, MD ¶
The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute

George A. Poultsides, MD, MS ¶
Stanford Cancer Institute

Walter J. Scott, MD ¶
Fox Chase Cancer Center

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

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

Benny Weksler, MD, MBA ¶
The University of Tennessee
Health Science Center

Christopher G. Willett, MD §
Duke Cancer Institute

Cameron D. Wright, MD ¶
Massachusetts General Hospital
Cancer Center

Debra Zelman, JD ¥
Debbie's Dream Foundation:
Curing Stomach Cancer

Continue

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

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

Principles of Systemic Therapy
Mary F. Mulcahy, MD ‡ †/Lead
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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

Khaldoun Almhanna, MD, MPH †
Moffitt Cancer Center

Crystal S. Denlinger, MD †
Fox Chase Cancer Center

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

A. Craig Lockhart, MD, MHS †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Stephen Leong, MD †
University of Colorado Cancer Center

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

Principles of Surgery
Thomas A. D'Amico, MD ¶/Lead
Duke Cancer Institute

Robert E. Glasgow, MD ¶
Huntsman Cancer Institute at the University of Utah

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

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

Walter J. Scott, MD ¶
Fox Chase Cancer Center

Cameron D. Wright, MD ¶
Massachusetts General Hospital Cancer Center

Principles of Radiation Therapy
Lawrence R. Kleinberg, MD §/Lead
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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

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

Christopher G. Willett, MD §
Duke Cancer Institute

Principles of Palliative/Best Supportive Care
Rajesh N. Keswani, MD ¤ Þ/Lead
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Hans Gerdes, MD ¤ Þ
Memorial Sloan Kettering Cancer Center

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

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

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

Principles of Surveillance
Jaffer A. Ajani, MD, MS † ¤/Lead
The University of Texas
MD Anderson Cancer Center

Khaldoun Almhanna, MD, MPH †
Moffitt Cancer Center

Thomas A. D'Amico, MD¶
Duke Cancer Institute

Crystal S. Denlinger, MD †
Fox Chase Cancer Center

Hans Gerdes, MD ¤ Þ
Memorial Sloan Kettering
Cancer Center

Steven Hochwald, MD ¶
Roswell Park Cancer Institute

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

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

Stephen Leong, MD †
University of Colorado
Cancer Center

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

Christopher G. Willett, MD §
Duke Cancer Institute

Principles of Genetic Risk Assessment
Mary Kay Washington, MD, PhD ≠/Co-Lead
Vanderbilt-Ingram Cancer Center

Crystal S. Denlinger, MD †
Fox Chase Cancer Center

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

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

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

Squamous Cell Carcinoma and Adenocarcinoma Treatment
Christopher Willett, MD §/Lead
Duke Cancer Institute

Jaffer A. Ajani, MD, MS † ¤
The University of Texas
MD Anderson Cancer Center

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

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

Walter J. Scott, MD ¶
Fox Chase Cancer Center

Principles of Endoscopic Staging and Therapy
Hans Gerdes, MD ¤ Þ/Lead
Memorial Sloan Kettering Cancer Center

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

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

Principles of Pathologic Review and HER2-neu Testing
Mary Kay Washington, MD, PhD ≠
Vanderbilt-Ingram Cancer Center

Continue

NCCN Guidelines Panel Disclosures

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

NCCN Esophageal and Esophagogastric Junction Cancers Panel Members
NCCN Esophageal and Esophagogastric Junction Cancers Sub-Committee Members
Summary of the Guidelines Updates
Workup and Histologic Classification (ESOPH-1)

Squamous Cell Carcinoma

Locoregional Disease (ESOPH-2)
Primary Treatment Options for Medically Fit Patients (ESOPH-3) and (ESOPH-4)
Surgical Outcomes For Patients Who Have Not Received Preoperative Therapy (ESOPH-6)
Surgical Outcomes For Patients Who Have Received Preoperative Therapy (ESOPH-7)
Management of Non-Surgical Candidates (ESOPH-8)
Follow-up/Surveillance and Recurrence (ESOPH-9)
Palliative Management (ESOPH-10)

Adenocarcinoma

Locoregional Disease (ESOPH-11)
Primary Treatment Options for Medically Fit Patients (ESOPH-12) and (ESOPH-13)
Surgical Outcomes For Patients Who Have Not Received Preoperative Therapy (ESOPH-15)
Surgical Outcomes For Patients Who Have Received Preoperative Therapy (ESOPH-16)
Management of Non-Surgical Candidates (ESOPH-17)
Follow-up/Surveillance and Recurrence (ESOPH-18)
Palliative Management (ESOPH-19)

Squamous Cell Carcinoma and Adenocarcinoma

Principles of Endoscopic Staging and Therapy (ESOPH-A)
Principles of Pathologic Review and HER2-neu Testing (ESOPH-B)
Principles of Surgery (ESOPH-C)
Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers (ESOPH-D)
Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E)
Principles of Systemic Therapy (ESOPH-F)
Principles of Radiation Therapy (ESOPH-G)
Principles of Palliative/Best Supportive Care (ESOPH-H)
Principles of Surveillance (ESOPH-I)
Staging (ST-1)

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

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

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

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016 Updates Esophageal and Esophagogastric Junction Cancers

Updates in Version 2.2016 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 1.2016 include:

ESOPH-1

- **Workup: Fifth bullet revised, "Pelvic CT *with contrast* as clinically indicated".**

Squamous Cell Carcinoma

ESOPH-5 (Changes also made for Adenocarcinoma on ESOSPH-14)

- **Response assessment for "Preoperative chemoradiation" and "Definitive chemoradiation" pathways: First bullet revised, "*Chest/abdominal* CT scan with contrast ."**

ESOPH-9 (Changes also made for Adenocarcinoma on ESOSPH-18)

- **Locoregional recurrence; Prior esophagectomy pathway: After Palliative Management; "*Chest/abdominal CT with contrast*" was added.**
- **Locoregional recurrence; Prior chemoradiation pathway: After Esophagectomy, "*Chest/abdominal CT with contrast*" was added.**

ESOPH-F--Principles of Systemic Therapy

Page 3 of 12

- **Heading revised: "Systemic Therapy for Metastatic or Locally Advanced Cancer" changed to "Systemic Therapy for *Unresectable Locally Advanced, Recurrent* or Metastatic *Disease.*"**

ESOPH-H--Principles of Palliative/Best Supportive Care

- **This section was extensively revised.**

Continued

NCCN Guidelines Version 2.2016 Updates Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

Updates in Version 1.2016 of the NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers from Version 3.2015 include:

Global Changes

- **Notations for clinical (c), surgical (yp), and pathological (p) staging were added to the tumor classification as appropriate throughout the guidelines.**

ESOPH-1

- **Workup:**
  - **Eighth bullet revised: "Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers *(T1a or T1b)*"**
  - **Fourteenth bullet revised: "Smoking cessation advice, counseling, and pharmacotherapy *as indicated*."**
  - **Footnote e revised: ~~"Smoking cessation guidelines are available from the U.S. Public Health Service at: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf.~~ *See NCCN Guidelines for Smoking Cessation.*"**

Squamous Cell Carcinoma

ESOPH-2 (Changes also made for Adenocarcinoma on ESOPH-11)

- **Additional Evaluation: Recommendation revised "Consider nasogastric or J-tube *(preferred) or PEG* for preoperative nutritional support ~~PEG is not recommended~~"**
- **The pathways "Non-surgical candidate able to tolerate chemotherapy or chemoradiation" and "Non-surgical candidate unable to tolerate chemotherapy or chemoradiation" were combined and revised to "*Non-surgical candidate.*"**
- **Footnote k revised: "Medically able to tolerate major ~~abdominal and/or thoracic~~ surgery."**
- **Footnote l revised: "Medically ~~unfit patients~~ *unable to tolerate major surgery* or medically fit patients who decline surgery."**

ESOPH-4

- **Primary treatment for "cT1b, N+ cT2-T4a, N0-N+" revised: "Esophagectomy (non-cervical esophagus) (*T1b-T2* low-risk lesions: <2 cm, well differentiated ~~lesions~~)."**

ESOPH-5 (Changes also made for Adenocarcinoma on ESOSPH-14)

- **Response assessment for Preoperative chemoradiation: Revised "Upper GI endoscopy and biopsy (optional *if surgery is planned*)."**
- **Definitive chemoradiation pathway; Persistent local disease: Under "Additional Management" recommendation revised, "~~Salvage~~ Esophagectomy."**
- **New footnote "z" added: "*If surveillance is being considered for potentially operable patients, upper GI endoscopy and biopsy should be done.*"**

ESOPH-6

- **Column heading revised: "Surgical Outcomes/Clinical Pathologic Findings for Squamous Cell Carcinoma (Patients Have Not Received Preoperative Chemoradiation ~~or Chemotherapy~~)."**

ESOPH-7

- **Column heading revised: "Surgical Outcomes/Clinical Pathologic Findings for Squamous Cell Carcinoma (Patients Have Received Preoperative Chemoradiation ~~or Chemotherapy~~)."**
- **Footnote "bb" is new: "*The yp prefix is used to indicate cases in which staging is performed following preoperative therapy*."**

Continued

NCCN Guidelines Version 2.2016 Updates Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

Squamous Cell Carcinoma (continued)

ESOPH-8 (Changes also made for Adenocarcinoma on ESOSPH-17)

- Second column pathways revised: "Non-surgical candidate able to tolerate ~~chemotherapy or~~ chemoradiation" and "Non-surgical candidate unable to tolerate ~~chemotherapy or~~ chemoradiation."
- Management of Non-surgical Candidates with cT1b, N+, cT2-T4a, N0-N+, or cT4b (unresectable) disease:
  - Recommendation revised for "Non-surgical candidates able to tolerate chemoradiation": "Definitive Chemoradiation (50–50.4 Gy of RT + concurrent chemotherapy) (Fluoropyrimidine- or taxane-based) ~~(preferred)~~."
  - Options removed: Chemotherapy, RT, Palliative/Best supportive care.

ESOPH-9 (Changes also made for Adenocarcinoma on ESOSPH-18)

- Follow-up/Surveillance
  - Third bullet revised: "Imaging *studies* ~~as clinically indicated~~."
  - Fourth bullet revised: "Upper GI endoscopy and biopsy ~~as clinically indicated~~."
- Column heading revised: "Palliative/~~Salvage~~ Management."

Adenocarcinoma

ESOPH-12

- Footnote "gg" is new: "*Diagnostic ER can be considered to confirm the pathologic staging and for treatment in select patients.*"

ESOPH-13

- Primary Treatment Optioins for Medically Fit Patients
  - New "Perioperative chemotherapy" pathway added.
  - "Preoperative chemotherapy" pathway from ESOPH-14 was moved to this page.

ESOPH-16

- Postoperative Management
  - The "Observation" recommendation for all stages was clarified as "Observation *until progression (if received preoperative chemotherapy or chemoradiation)*."
  - The "Chemotherapy" recommendation was revised for the R0 resection pathways: "Chemotherapy if received ~~preoperatively~~ *perioperatively* (category 1)."
- Footnote "mm" reference added: "*Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.*"

Continued

NCCN Guidelines Version 2.2016 Updates
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

ESOPH-A Principles of Endoscopic Staging and Therapy

2 of 5

- **Staging; Second bullet revised: "Hypoechoic (dark) expansion of the esophageal wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal esophageal wall corresponding with greater depths of tumor penetration, correlating with higher T~~-stages~~ *categories*."**

4 of 5

- **Post-Treatment Surveillance**
  - **First bullet revised: "~~Assessment with~~ *Consider deferring assessment* endoscopy with biopsy ~~should be done ≥~~ to 6 weeks *or later* after completion of preoperative therapy in patients whom avoidance of surgery is being considered."**
  - **Sixth bullet revised: "~~For follow-up,~~ Patients who have received therapeutic endoscopic resection should have endoscopic surveillance and mucosal ablation where appropriate every 3 months for the first year. ~~and every 3 to 6 months the second year~~ *Follow-up as clinically indicated after two years. Follow-up for Barrett's esophagus alone may be required*."**

ESOPH-D Principles of Genetic Risk Assessment

1 of 2

- **Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Esophageal and EGJ Cancers**
  - **First bullet; Sub-arrow bullet revised: "~~This syndrome~~ *Tylosis with esophageal cancer (TEC)* is a very rare condition with an autosomal dominant pattern of inheritance and is *caused by germline mutations in the RHBDF2 gene.* ~~an as yet unknown gene named tylosis with esophageal cancer (TEC) mapped by linkage analysis to 17q25 and distal to the keratin 1 gene cluster.~~ ~~Patients with tylosis~~ *Individuals with germline RHBDF2 mutations* have an increased risk for squamous cell carcinoma (SCC) of the esophagus. PPK is divided into diffuse, punctate, or focal patterns of skin thickening on palms and soles. The non-epidermolytic PPK is associated with high risk of SCC of the middle and distal esophagus. ~~There is no gene marker to identify these individuals.~~"**
  - **Second bullet; Sub-arrow bullet revised: "Familial Barrett's esophagus (FBE) includes adenocarcinoma of the esophagus (EAC) and adenocarcinoma of the EGJ. Development of Barrett's esophagus (BE) is strongly associated with gastroesophageal reflux disease (GERD). FBE may be associated with one or more ~~rare~~ autosomally inherited dominant susceptibility alleles. ~~There is no gene marker to identify individuals with FBE~~ *Several candidate genes have been identified, but not validated.***

2 of 2

- **Esophageal Cancer, Tylosis with Non-epidermolytic Palmoplantar Keratosis (PPK) and Howel-Evans Syndrome; Gene revised: "~~*TEC (17q25)*~~ *RHBDF2"***
- **Familial Barrett's Esophagus (FBE); Gene revised: "~~unknown~~ Candidate genes have not been validated."**

Continued

NCCN Guidelines Version 2.2016 Updates
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

ESOPH-F: Principles of Systemic Therapy

1 of 12

- Third bullet revised: "~~For metastatic adenocarcinoma trastuzumab can be added to chemotherapy if tumor overexpresses HER2-neu.~~ *Trastuzumab should be added to chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma*."

2 of 12

- Perioperative Chemotherapy
  - ECF (epirubicin, cisplatin, and fluorouracil) changed from category 1 to category 3.
  - ECF modifications changed from category 2A to category 3 for all modifications
- New section added: "*Preoperative Chemotherapy (Only for adenocarcinoma of the thoracic esophagus or EGJ).*"
  - "*Fluorouracil and cisplatin (2 cycles) (category 2B)*" added as an option based on the results of the OEO5 trial.

3 of 12 Systemic Therapy for Metastatic or Locally Advanced Cancer (where local therapy is not indicated)

- First-Line Therapy; Preferred Regimens
  - "DCF (docetaxel, cisplatin, and fluorouracil) (category 1)" removed as an option.
  - The following were removed from the list of "Preferred Regimens" and added to the list of "Other Regimens"
    - ◊ ECF (epirubicin, cisplatin, and fluorouracil) (category 1)
    - ◊ ECF modifications (category 1)
- First-Line Therapy; Other regimens
  - Docetaxel and irinotecan removed as an option.
- The "Alternative Regimens for Consideration" section was removed along with the following systemic therapies:
  - Mitomycin and irinotecan
  - Mitomycin and fluorouracil

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

- The Regimen and dosing schedules pages were update to reflect the changes on ESOPH- 2 of 12 and ESOPH-F 3 of 12.

10 of 12

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

ESOPH-G Principles of Radiation

- General Guidelines
  - Fourth bullet revised: "In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal and esophagogastric junction (EGJ) cancers. ~~Depending on the clinical situation~~, Siewert III tumors *patients may receive perioperative chemotherapy or preoperative chemoradiation depending on institutional preference,* ~~may be~~ and are generally more appropriately managed with radiation ~~therapy~~ *according to* guidelines applicable to ~~either esophageal and EGJ or~~ gastric cancers. These recommendations may be modified depending on the location of the bulk of the tumor."
- Simulation and Treatment Planning
  - First bullet revised: "Use of CT simulation and 3-D treatment planning is strongly encouraged. Intensity-modulated radiation therapy (IMRT) ~~may be used~~ *is appropiate* in clinical settings where reduction in dose to organs at risk (eg, heart, lungs) is required that cannot be achieved by 3-D techniques."
  - Second bullet revised: "The patient should be instructed to avoid intake of a heavy meal 3 hours before simulation and treatment *for lesions requiring therapy of the proximal stomach.*"

ESOPH-I 2 of 4 Principles of Surveillance

- Table 1: Recommendation revised throughout table "(PET-CT or CT chest/abdomen *with contrast unless contraindicated*)."

ESOPH-I 3 of 4 Principles of Surveillance

- Table 2: Under: Trimodality therapy" for T2-T4, N0-N+, T4b, recommendation revised: "(PET-CT ~~preferred over~~ or CT *with contrast unless contraindicated*).

NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

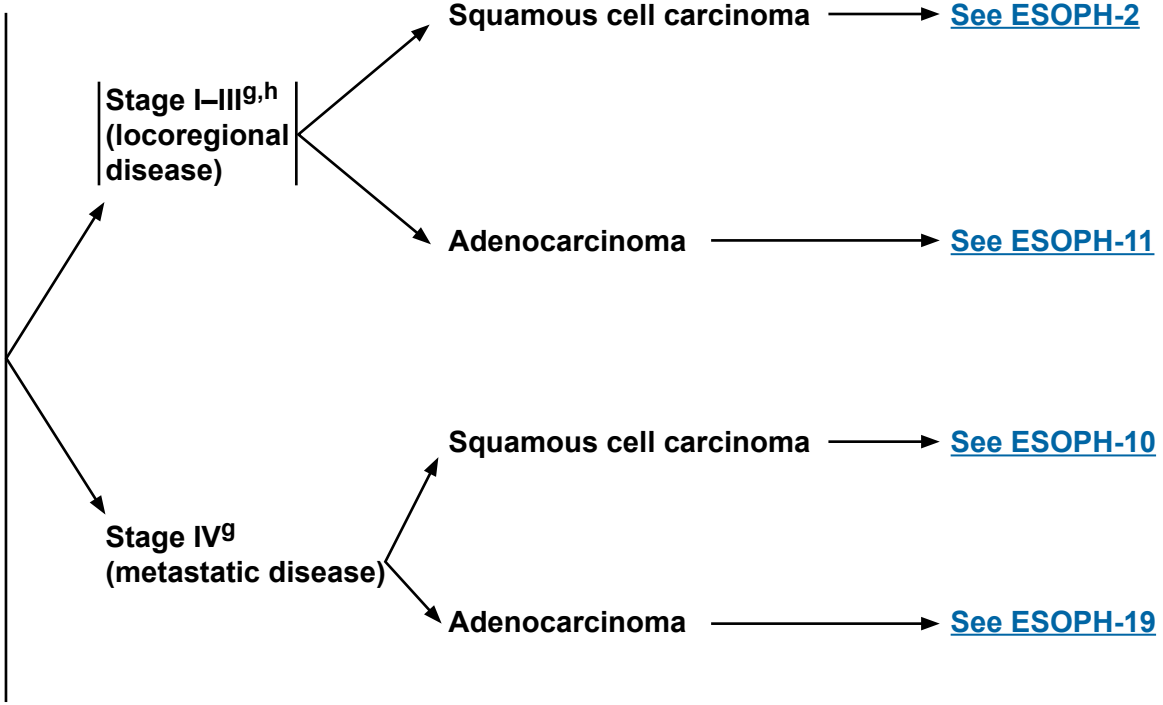
NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

WORKUP

- **H&P**
- **Upper GI endoscopy and biopsy[a]**
- **Chest/abdominal CT with oral and IV contrast**
- **Pelvic CT with contrast as clinically indicated**
- **PET-CT evaluation if no evidence of M1 disease**
- **CBC and comprehensive chemistry profile**
- **Endoscopic ultrasound (EUS), if no evidence of M1 disease**
- **Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b)[a,b]**
- **Biopsy of metastatic disease as clinically indicated**
- **HER2-neu testing if metastatic adenocarcinoma is documented/suspected[c]**
- **Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease**
- **Assign Siewert category[d]**
- **Nutritional assessment and counseling**
- **Smoking cessation advice, counseling, and pharmacotherapy as indicated[e]**
- **Screen for family history[f]**

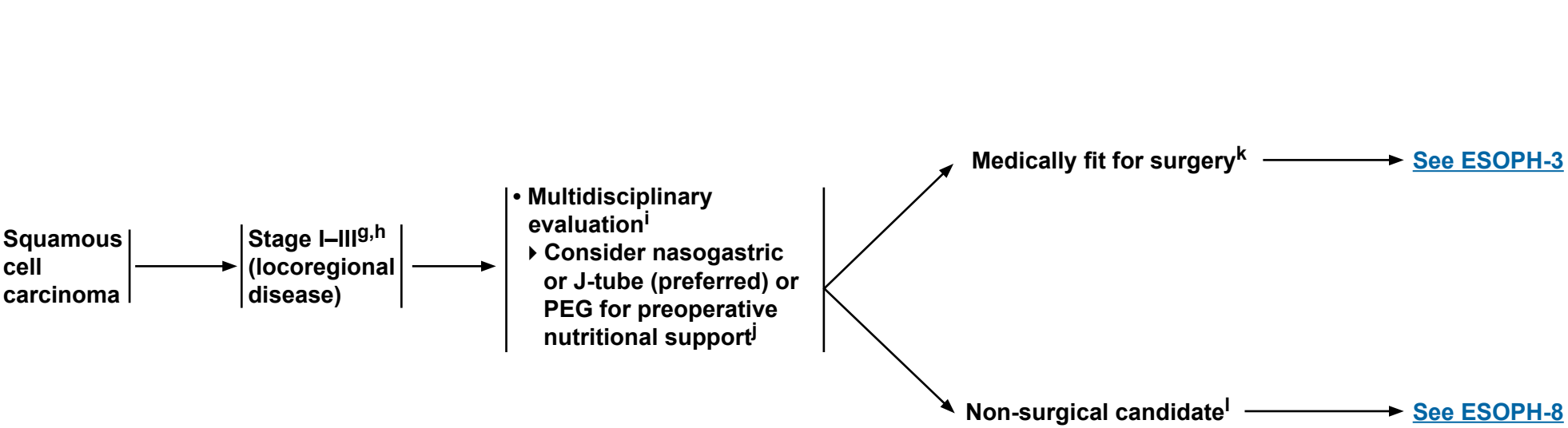
CLINICAL STAGE[g]

HISTOLOGIC CLASSIFICATION[c]



[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[b] ER may also be therapeutic for early-stage cancers.
[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[e] See NCCN Guidelines for Smoking Cessation.
[f] See Principles of Genetic Risk Assessment for Esophageal and Esophagogastric Junction (EGJ) Cancers (ESOPH-D). Also see NCCN Guidelines for Colorectal Cancer Screening, Genetic/Familial High-Risk Assessement: Colorectal, and Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.

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

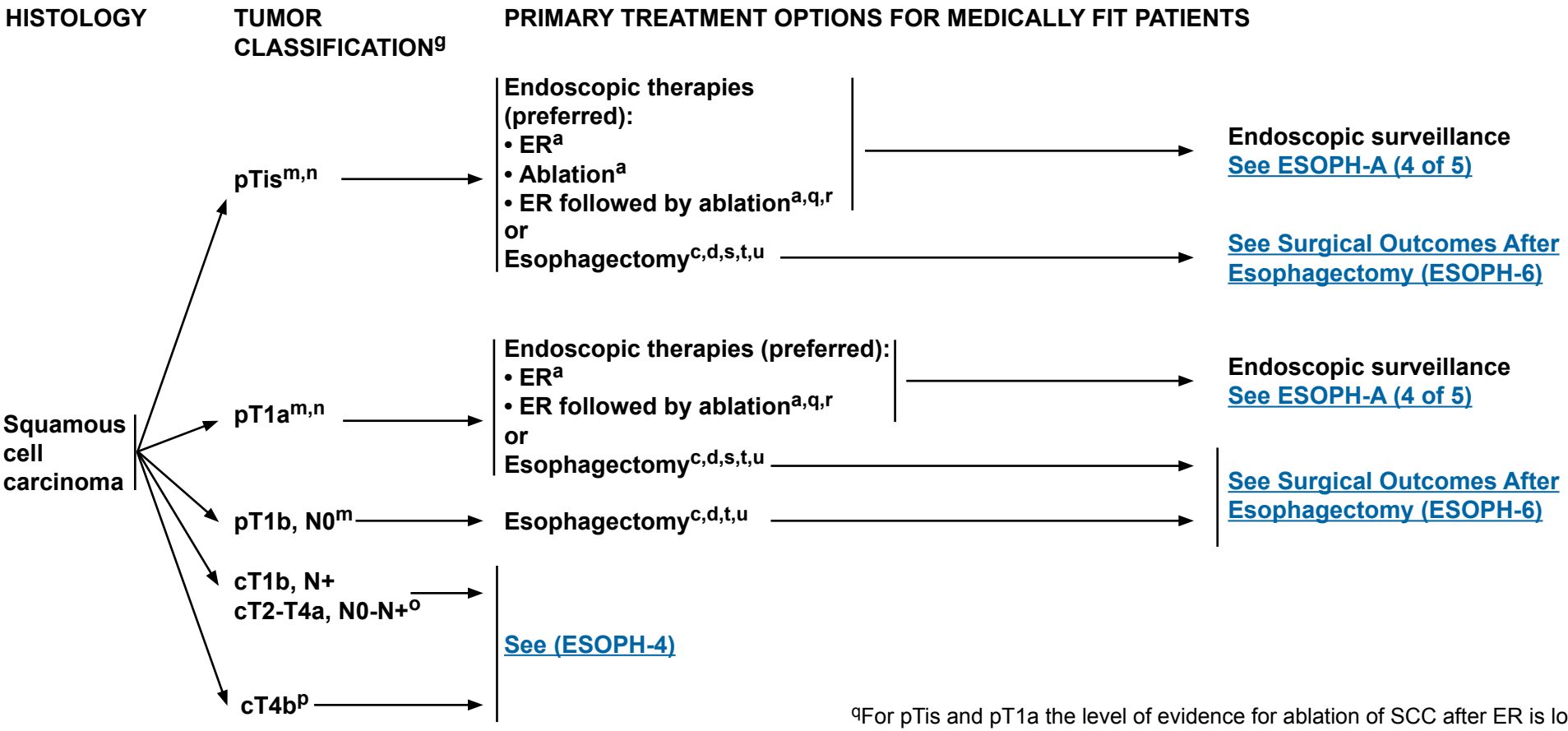


[g] See Staging (ST-1) for tumor classification.
[h] Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
[i] See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[j] Percutaneous endoscopic gastrostomy (PEG) may be considered for patients with cervical esophagus receiving definitive chemoradiation.
[k] Medically able to tolerate major surgery.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.

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.

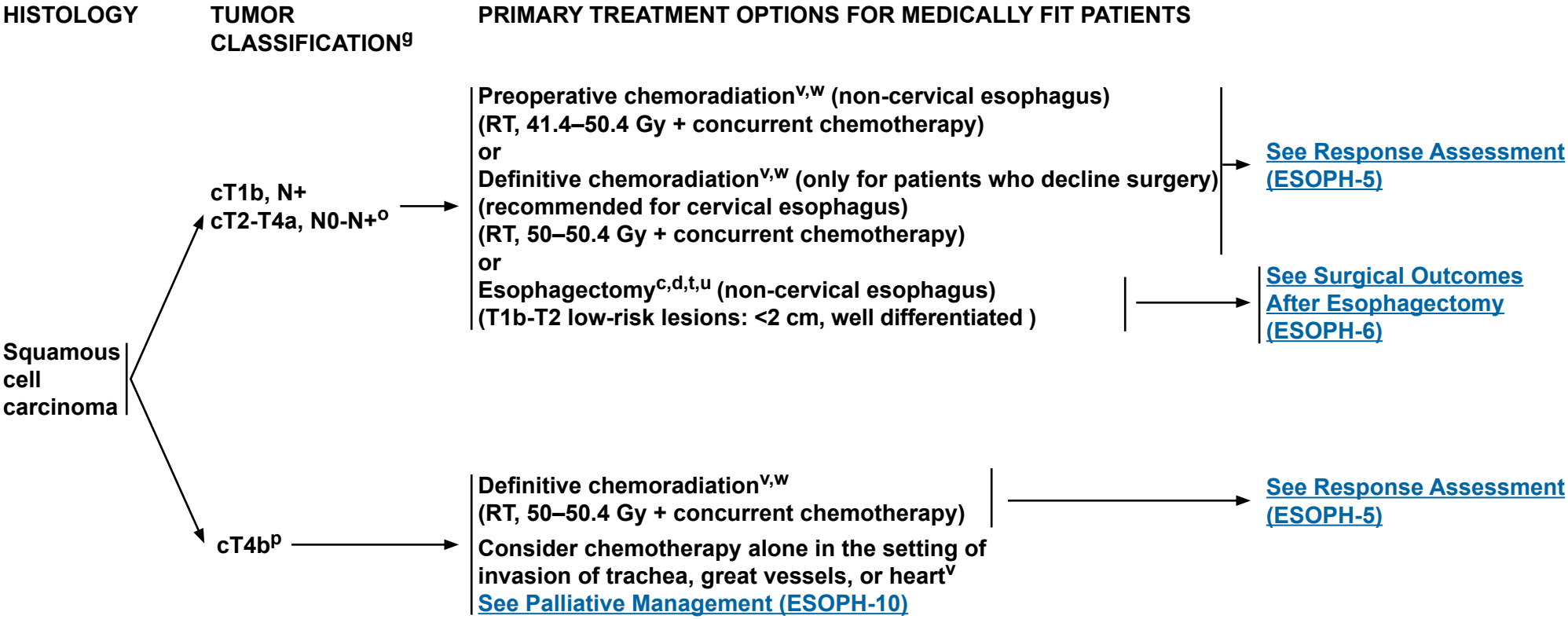
NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion



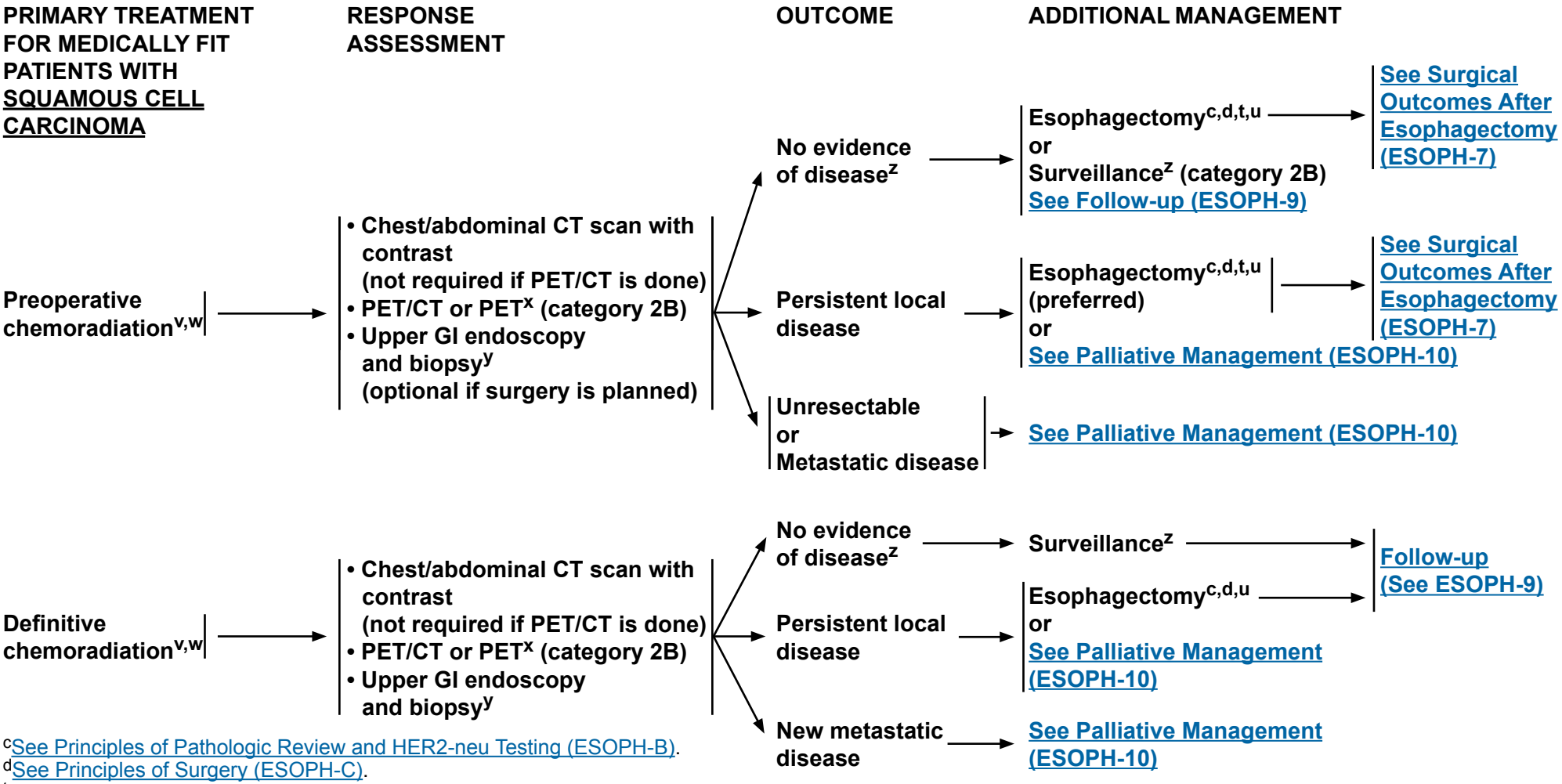
[a]See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c]See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d]See Principles of Surgery (ESOPH-C).
[g]See Staging (ST-1) for tumor classification.
[m]pTis, pT1a, and pT1b tumor classifications are defined by pathology of the diagnostic ER specimen. See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n]The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o]Preclinical staging cannot establish the number of positive nodes.
[p]Consider endoluminal stenting when appropriate.
[q]For pTis and pT1a the level of evidence for ablation of SCC after ER is low. However, additional ablation may be needed if there is multifocal high-grade dysplasia/carcinoma in situ. Ablation may not be needed if all lesions are completely excised. For references, see Principles of Endoscopic Staging and Therapy (ESOPH-A).
[r]ER followed by ablation may be used to completely eliminate residual dysplasia.
[s]Esophagectomy is indicated for patients with extensive carcinoma in situ (pTis or HGD) or pT1a, especially nodular disease that is not adequately controlled by ablation or ER followed by ablation.
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.

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.



[c]See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d]See Principles of Surgery (ESOPH-C).
[g]See Staging (ST-1) for tumor classification.
[o]Preclinical staging cannot establish the number of positive nodes.
[p]Consider endoluminal stenting when appropriate.
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v]See Principles of Systemic Therapy (ESOPH-F).
[w]See Principles of Radiation Therapy (ESOPH-G).

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



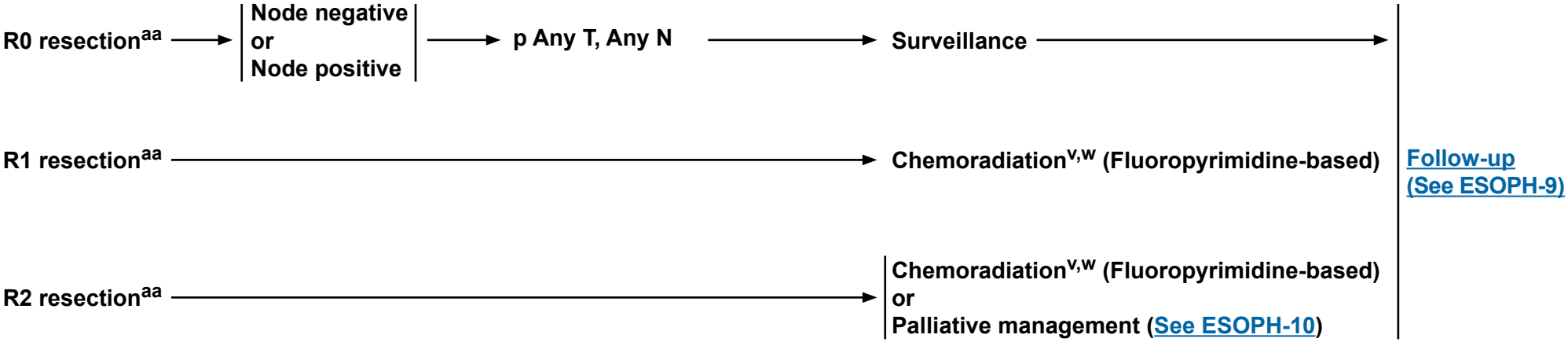
[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[x] Assessment ≥5–6 weeks after completion of preoperative therapy.
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[z] If surveillance is being considered for potentially operable patients, upper GI endoscopy and biopsy should be done.

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.

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

TUMOR CLASSIFICATION[g]

POSTOPERATIVE MANAGEMENT



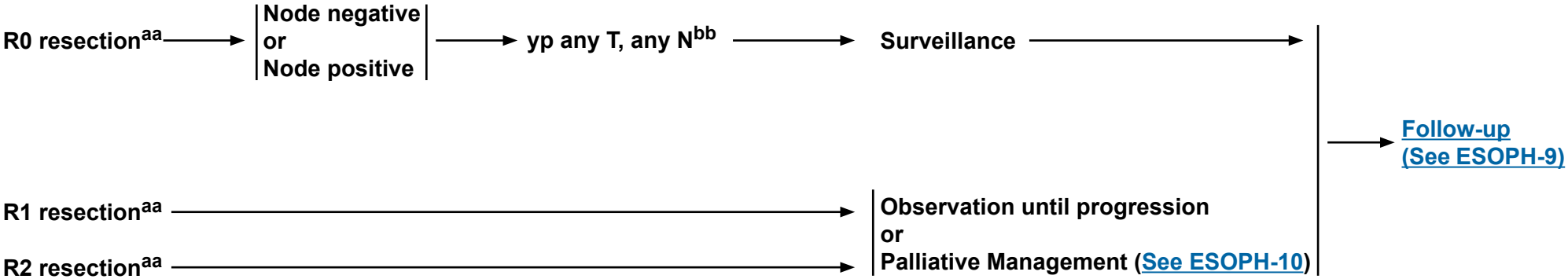
[g] See Staging (ST-1) for tumor classification.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[aa] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1.

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.

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

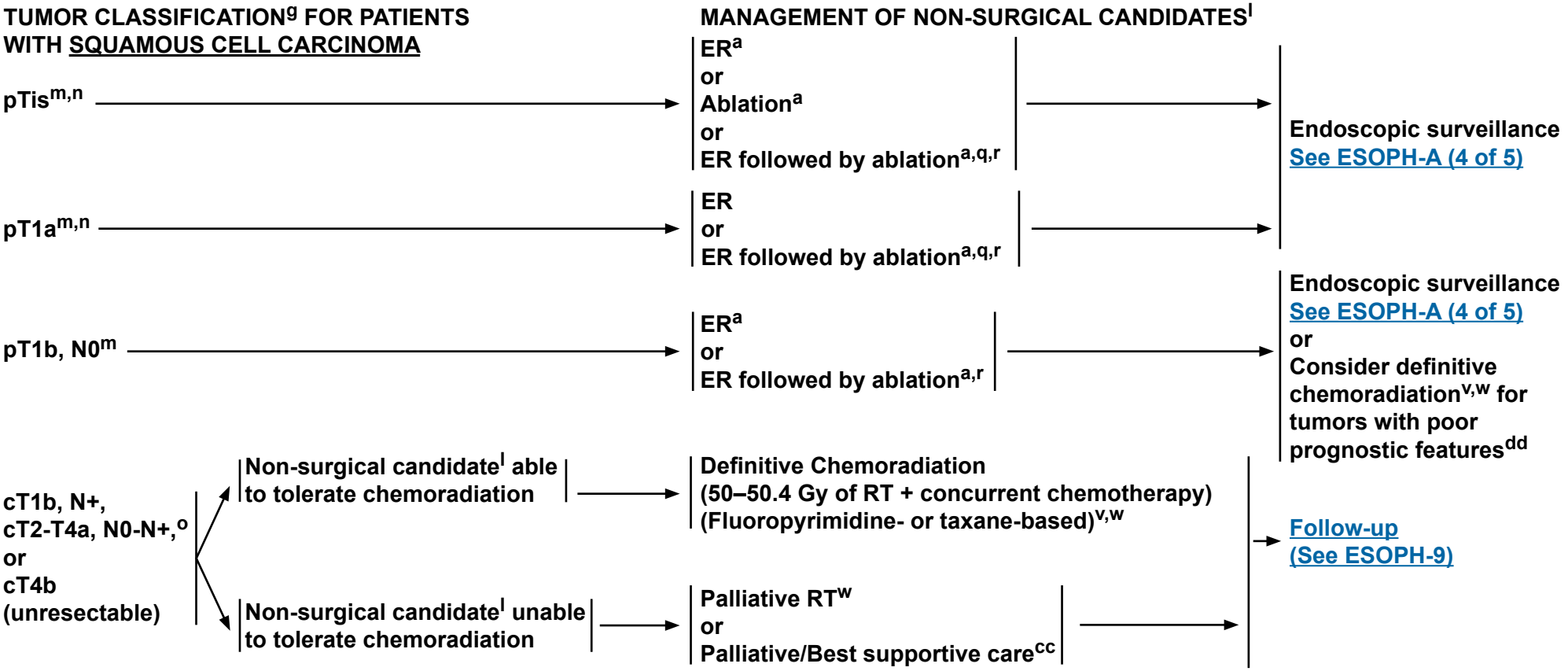
TUMOR CLASSIFICATION[g,bb]

POSTOPERATIVE MANAGEMENT



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

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



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

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.

FOLLOW-UP/SURVEILLANCE FOR RECURRENCE
SQUAMOUS CELL CARCINOMA[ee]

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

Locoregional recurrence: Prior esophagectomy, no prior chemoradiation → **PALLIATIVE MANAGEMENT**

Locoregional recurrence (Prior chemoradiation, no prior esophagectomy)

- **Resectable and medically operable** → **Esophagectomy[c,d,t,u]** → **Chest/abdominal CT with contrast** → **Recurrence** → **See Palliative Management (ESOPH-10)**
- **Unresectable or medically inoperable** → **See Palliative Management (ESOPH-10)**

Metastatic disease → **See Palliative Management (ESOPH-10)**

PALLIATIVE MANAGEMENT

Concurrent chemoradiation[v,w] (Fluoropyrimidine- or taxane-based) preferred
or
Surgery[c,d]
or
Chemotherapy[v]
or
Palliative/Best supportive care[cc]

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

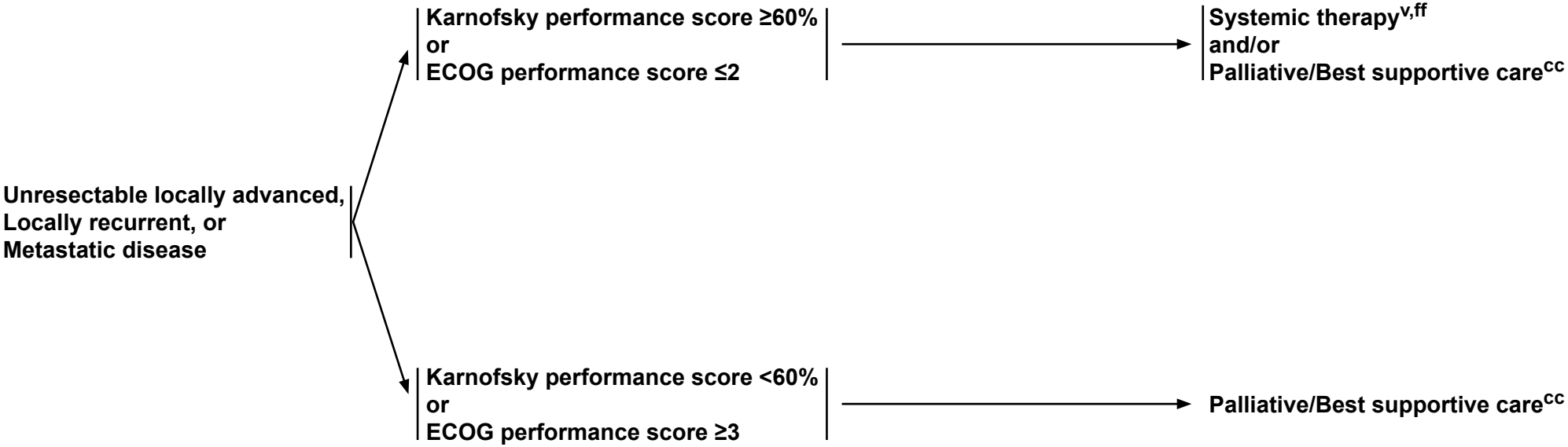
[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[cc] See Principles of Palliative/Best Supportive Care (ESOPH-H).
[ee] See Principles of Surveillance (ESOPH-I).

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

FOR SQUAMOUS CELL CARCINOMA

PERFORMANCE STATUS

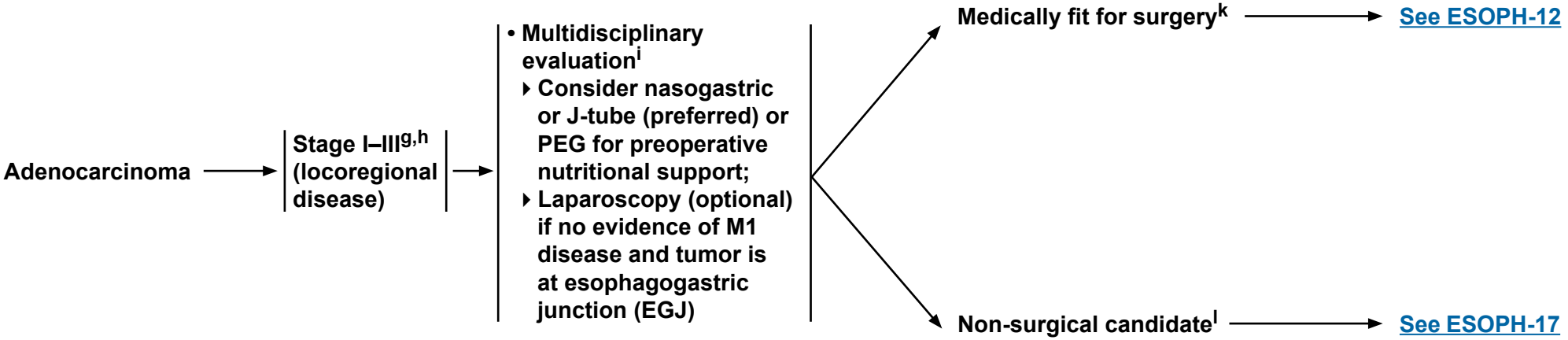
PALLIATIVE MANAGEMENT



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

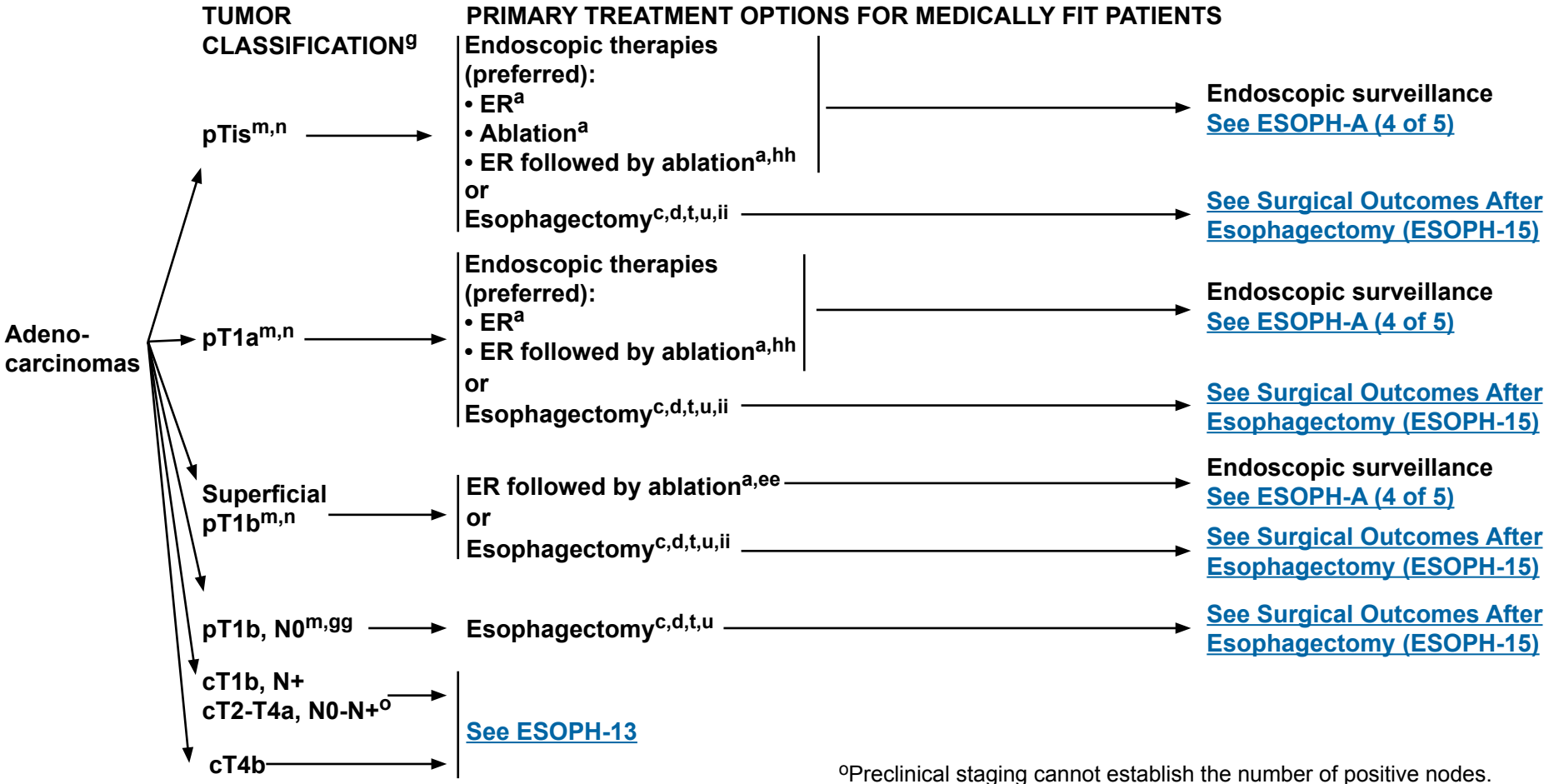
Back to Follow-up and Recurrence (ESOPH-9)

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



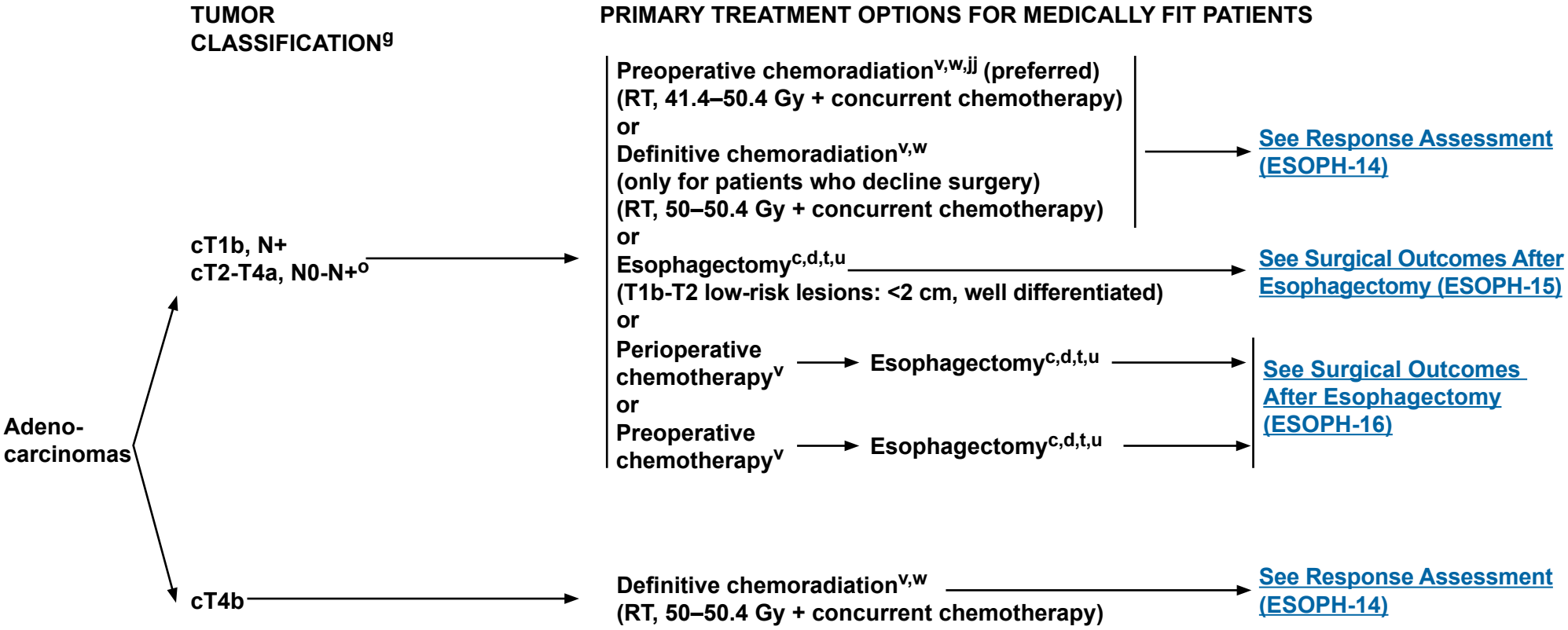
[g]See Staging (ST-1) for tumor classification.
[h]Celiac nodal involvement in cancers of the esophagogastric junction may still be considered for combined modality therapy.
[i]See Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (ESOPH-E).
[k]Medically able to tolerate major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

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



[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[g] See Staging (ST-1) for tumor classification.
[m] pTis, pT1a, superficial pT1b, pT1b, N0 tumor classifications are defined by pathology of the diagnostic ER specimen See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[n] The initial diagnostic ER procedure may prove therapeutic for some patients, but for others additional therapy may be necessary prior to the start of surveillance.
[o] Preclinical staging cannot establish the number of positive nodes.
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[gg] Diagnostic ER can be considered to confirm the pathologic staging and for treatment in select patients.
[hh] ER followed by ablation to completely eliminate residual dysplasia or Barrett's epithelium.
[ii] Esophagectomy is indicated for patients with extensive carcinoma in situ (pTis or HGD), pT1a, or superficial pT1b, especially nodular disease that is not adequately controlled by ablation or ER followed by ablation.

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.

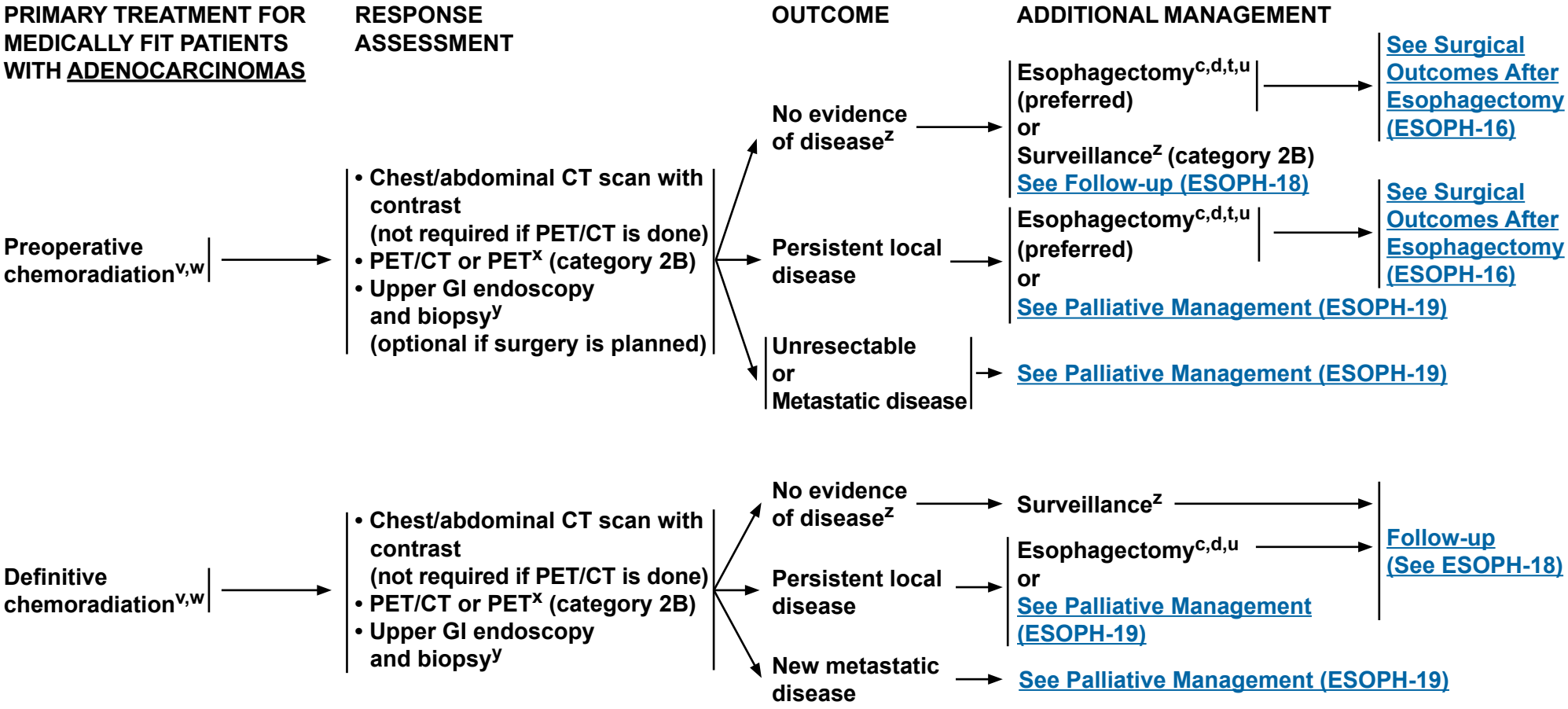


[c]See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d]See Principles of Surgery (ESOPH-C).
[g]See Staging (ST-1) for tumor classification.
[o]Preclinical staging cannot establish the number of positive nodes.
[t]Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u]Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v]See Principles of Systemic Therapy (ESOPH-F).
[w]See Principles of Radiation Therapy (ESOPH-G).
[jj]Preoperative chemoradiation (category 1) is preferred over preoperative chemotherapy for EGJ. (van Hagen P, Hulshof MC, van Lanschot JJ, et al, CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084)

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.

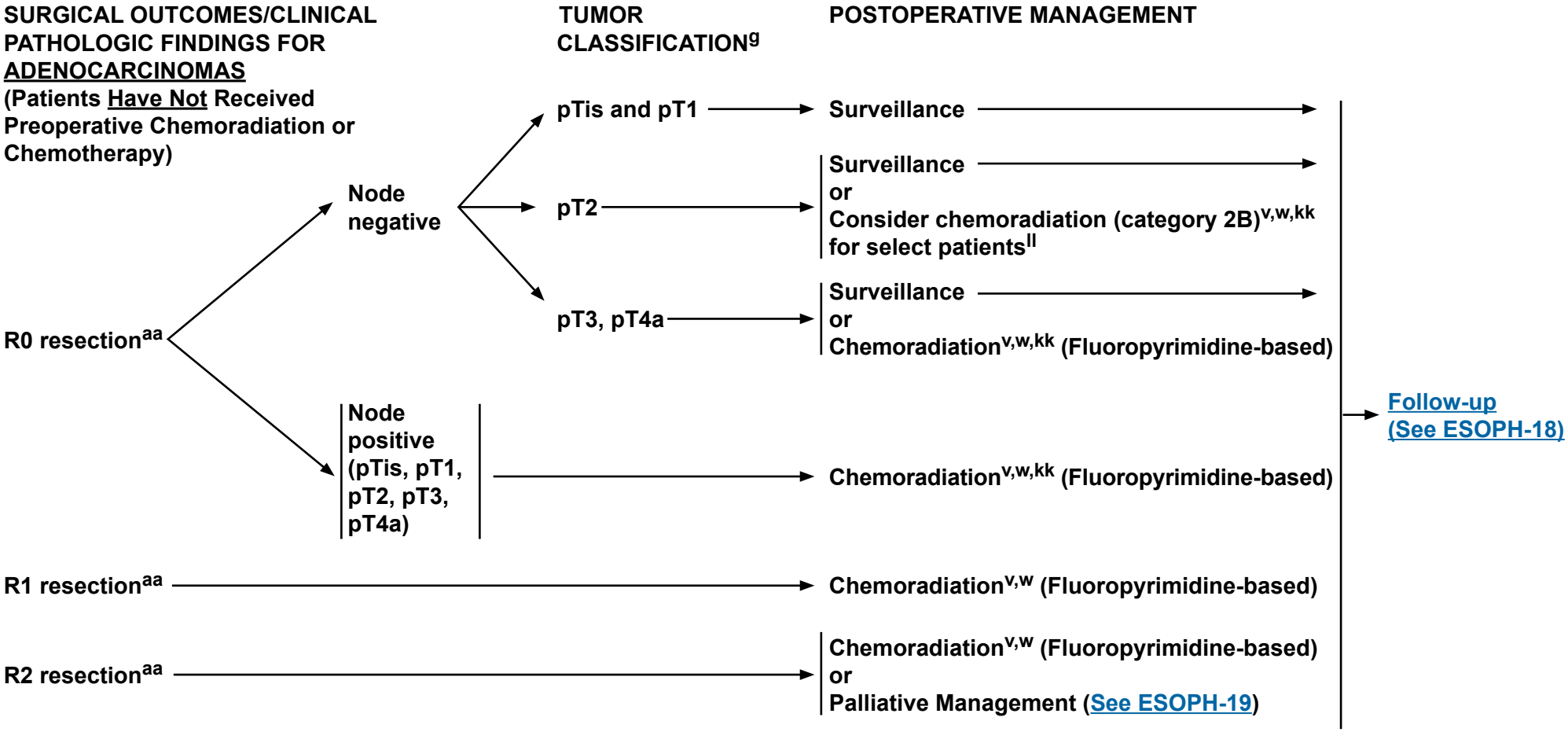
NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion



[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[x] Assessment ≥5–6 weeks after completion of preoperative therapy.
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[z] If surveillance is being considered for potentially operable patients, upper GI endoscopy and biopsy should be done.

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



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

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.

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

POSTOPERATIVE MANAGEMENT

R0 resection[aa]

- **Node negative (yp Any T)[bb]** →
  - **Observation until progression (if received preoperative chemotherapy or chemoradiation)**
  - **or**
  - **Chemotherapy[mm] if received perioperatively (category 1)[v]**
- **Node positive (yp Any T)[bb]** →
  - **Observation until progression (if received preoperative chemotherapy or chemoradiation)**
  - **or**
  - **Chemoradiation[v,w] (Fluoropyrimidine-based), only if not received preoperatively (category 2B)**
  - **or**
  - **Chemotherapy[mm] if received perioperatively (category 1)[v]**

R1 resection[aa] →
- **Observation until progression (if received preoperative chemotherapy or chemoradiation)**
- **or**
- **Chemoradiation[v,w] (Fluoropyrimidine-based), only if not received preoperatively**

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

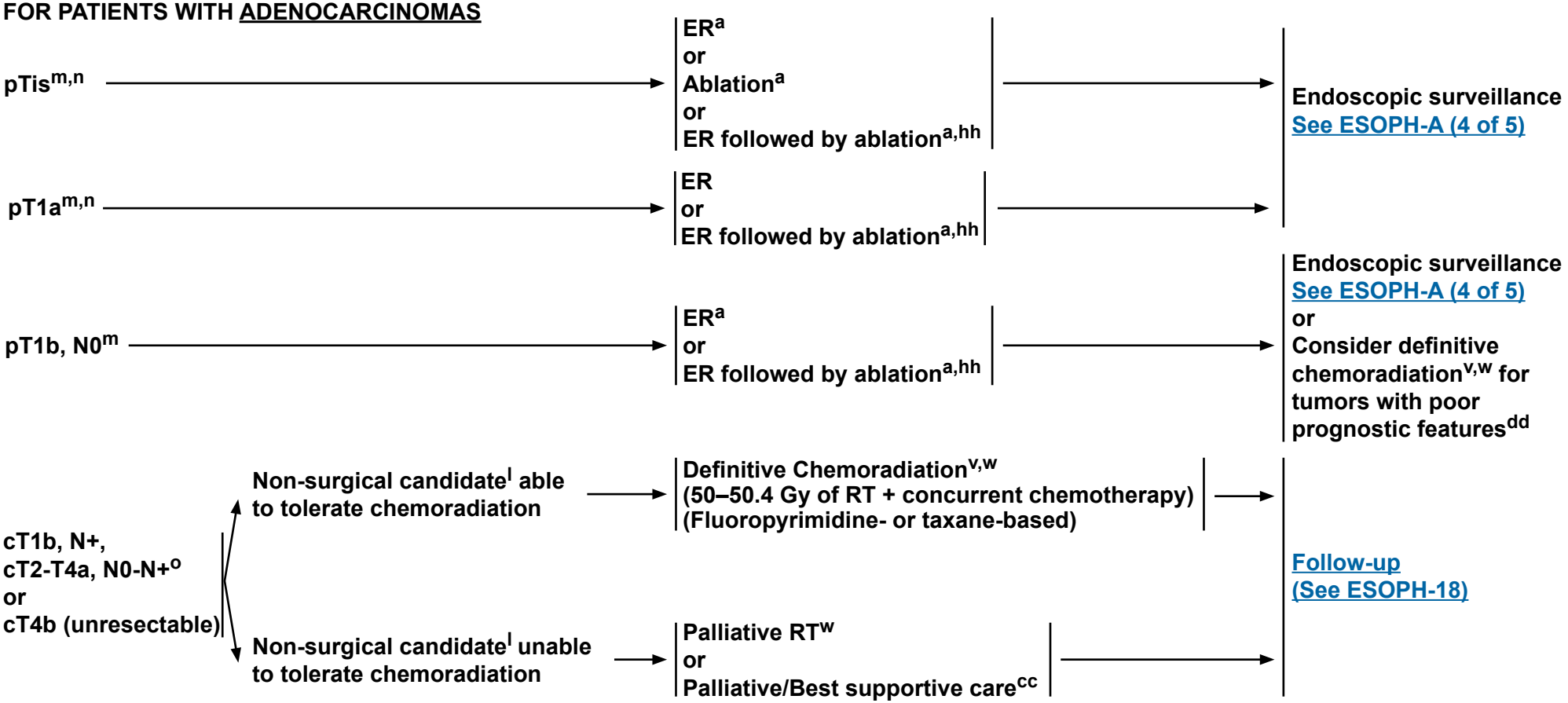
→ **Follow-up (See ESOPH-18)**

[g] See Staging (ST-1) for tumor classification.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[aa] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1.
[bb] The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.
[mm] Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.

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

TUMOR CLASSIFICATION[g] FOR PATIENTS WITH ADENOCARCINOMAS

MANAGEMENT OF NON-SURGICAL CANDIDATES[l]

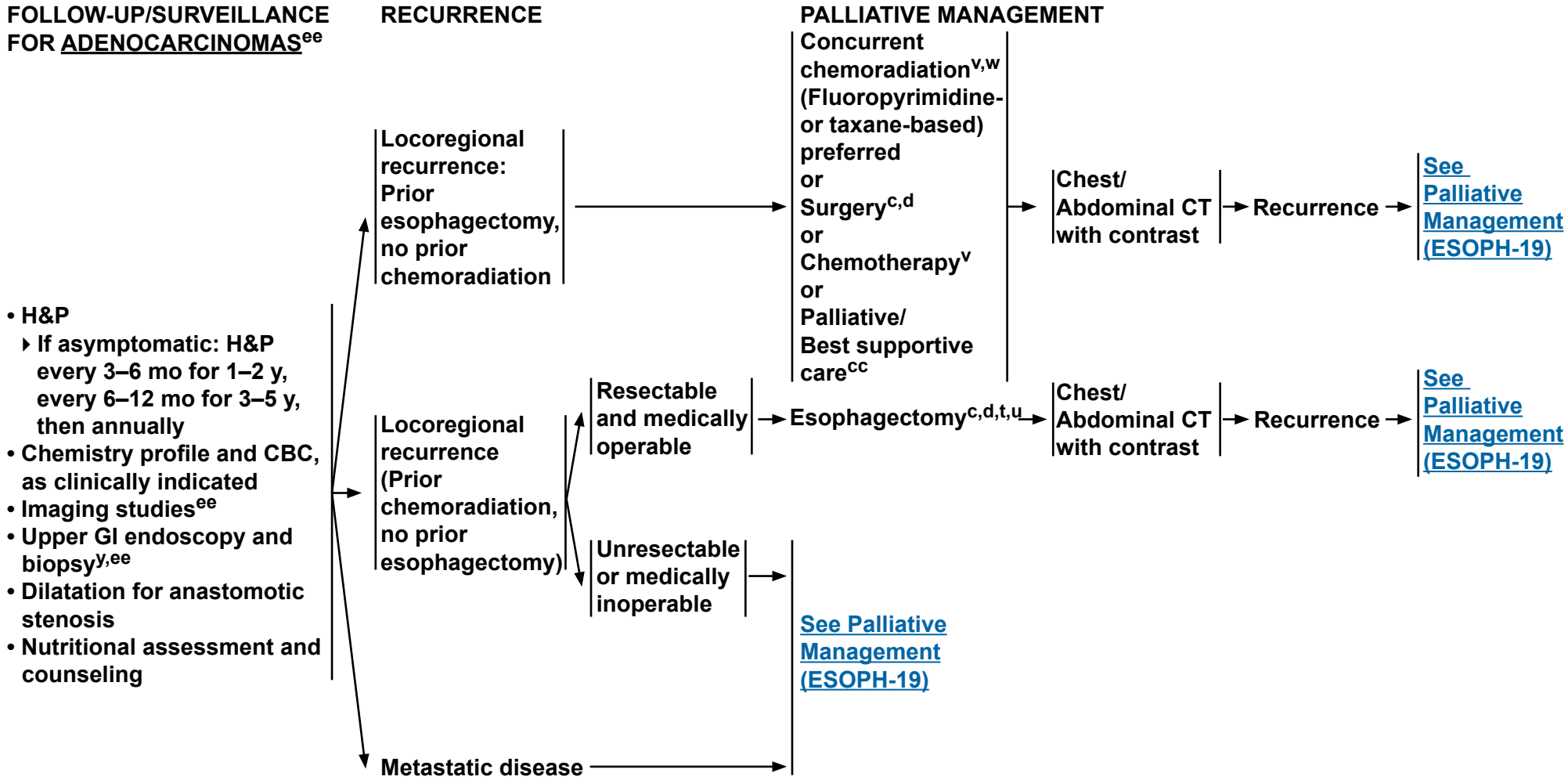


[a] See Principles of Endoscopic Staging and Therapy (ESOPH-A).
[g] See Staging (ST-1) for tumor classification.
[l] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[m] pTis, pT1a, and pT1b tumor classification are defined by pathology of the diagnostic ER specimen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

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.

NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

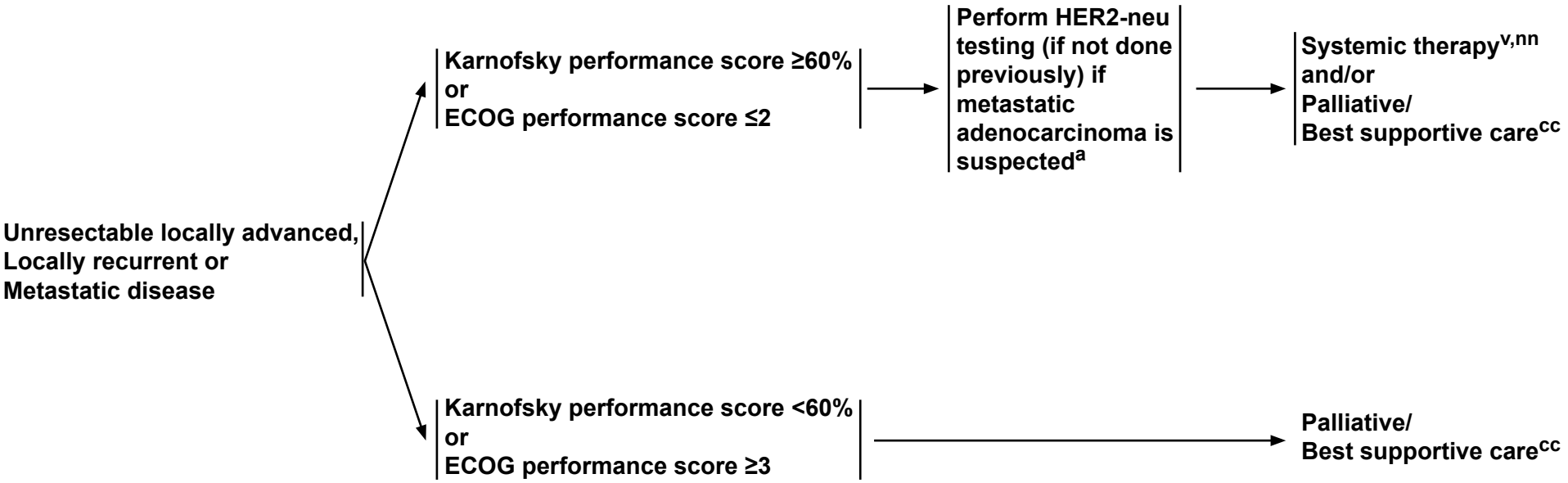
NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion



[c] See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B).
[d] See Principles of Surgery (ESOPH-C).
[t] Transhiatal or transthoracic, or minimally invasive; gastric reconstruction preferred.
[u] Feeding jejunostomy for postoperative nutritional support, generally preferred.
[v] See Principles of Systemic Therapy (ESOPH-F).
[w] See Principles of Radiation Therapy (ESOPH-G).
[y] See Post-Treatment Surveillance--Principles of Endoscopic Staging and Therapy (ESOPH-A 4 of 5).
[cc] See Principles of Palliative/Best Supportive Care (ESOPH-H)
[ee] See Principles of Surveillance (ESOPH-I).

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

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



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

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

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

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

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

DIAGNOSIS

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

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

STAGING

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

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

PRIMARY TREATMENT

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

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

TREATMENT OF SYMPTOMS

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

POST-TREATMENT SURVEILLANCE

- Consider deferring assessment endoscopy with biopsy to 6 weeks or later after completion of preoperative therapy in patients whom avoidance of surgery is being considered.[28]
- EUS exams performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the present stage of disease.[29] Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.[28]
- Endoscopic surveillance following definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging.
- Endoscopic surveillance after ablative therapy or ER of early-stage esophageal cancer should continue after completion of treatment. Biopsies should be taken of the neosquamous mucosa even in the absence of mucosal abnormalities as dysplasia may occasionally be present beneath the squamous mucosa.
- Endoscopic surveillance should also include a search for the presence of Barrett's esophagus and four-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent high-grade and low-grade dysplasia using RFA or cryoablation should be considered. Ablation of non-dysplastic Barrett's esophagus is not recommended.
- Patients who have received therapeutic ER should have endoscopic surveillance and mucosal ablation where appropriate every 3 months for the first year. Follow up as clinically indicated after two years. Follow-up for Barrett’s esophagus alone may be required.

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

Continued

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY (REFERENCES)

[1]Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C & M Criteria Gastroenterology 2006;131;1392-1399.

[2]Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Endoscopy 2010;42:351-359.

[3]Graham DY Schwartz JT, Cain GD, et al. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982 Feb;82:228-231.

[4]Komanduri S, Swanson G, Keefer L, Jakate S. Use of a new jumbo forceps improves tissue acquisition of Barrett's esophagus surveillance biopsies. Gastrointest Endosc 2009;70:1072-1078 e1071.

[5]Thomas T, Singh R, Ragunath K. Trimodal imaging-assisted endoscopic mucosal resection of early Barrett's neoplasia. Surg Endosc 2009;23:1609-1613.

[6]Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005;446:497-504.

[7]Ancona E et al, Prediction of Lymph Node Status in Superficial Esophageal Carcinoma. Ann Surg Oncol 2008;15(11):3278-88

[8]Pennathur A, Farkas A, Krasinskas AM, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg 2009;87:1048-1054.

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

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

[11]Keswani RN, Early DS, Edmundowicz SA, et al. Routine positron emission tomography does not alter nodal staging in patients undergoing EUS-guided FNA for esophageal cancer. Gastrointest Endosc 2009;69:1210-1217.

[12]Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277-2288.

[13]Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010;71:680-685.

[14]Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007;66:460-468.

[15]Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57:1200-1206.

[16]Bergman JJ, Zhang YM, He S, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus.Gastrointest Endosc 2011;74:1181-1190.

[17]Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146:652-660.

[18]Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 2011;141:460-468.

[19]Chadwick G Groene O, Markar SR, et al., Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointestinal Endoscopy 2014;79:718-731.

[20]Nentwich MF, von Loga K, Reeh M, et al. Depth of submucosal tumor infiltration and its relevance in lymphatic metastasis formation for T1b squamous cell and adenocarcinomas of the esophagus. J Gastrointest Surg 2014;18:242-249; discussion 249.

[21]Leggett CL, Lewis JT, Wu TT, et al. Clinical and histological determinants of mortality for patients with Barrett's esophagus-related T1 esophageal adenocarcinoma. Clin Gastroenterol Hepatol 2014.

[22]Lee L, Ronellenfitsch U, Hofstetter WL, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg 2013;217:191-199.

[23]van Vilsteren FG et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial, Gut 2011;60:765-773.

[24]van Vilsteren FG, Alvarez HL, Pouw RE, et al. Radiofrequency ablation for the endscopic eradication of esophageal squamous high grade intraepithelial neoplasia and mucosal squamous cell carcinoma. Endoscopy 2011;43:282-290.

[25]Becker V, Bajbouj M, Schmid RM, et al. Multimodal endoscopic therapy for multifocal intraepithelial neoplasia and superficial esophageal squamous cell carcinoma - a case series. Endoscopy 2011;43:360-364.

[26]Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gastrointest Endosc 1995;42:507-512.

[27]Vakil N, Morris AI, Marcon N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. Am J Gastroenterol 2001;96:1791-1796.

[28]Sarkaria IS, Rizk NP, Bains MS, et al. Post-treatment endoscopic biopsy is a poor-predictor of pathologic response in patients undergoing chemoradiation therapy for esophageal cancer. Ann Surg 2009;249:764-767.

[29]Ribeiro A, Franceschi D, Parra J, et al. Endoscopic ultrasound restaging after neoadjuvant chemotherapy in esophageal cancer. Am J Gastroenterol 2006;101:1216-1221.

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.

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

TABLE 1 Pathologic Review

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

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

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

Continued

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of treatment response

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

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

TABLE 2

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

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

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

Continued

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

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

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or esophagogastric junction (EGJ) for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization methods is recommended. The following criteria used in the ToGA trial[11] are recommended:

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

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

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

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

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

Continued

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

[1]Edge SE, Byrd DR, Carducci MA, Compton CC. AJCC TNM Staging Manual. 7th ed. New York, NY: Springer 2009.
[2]Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. AM J Gastroenterol 2008;103:788-97.
[3]Abraham SC, Krasinskas AM, Correa AM, et al. Duplication of the muscularis mucosae in Barrett esophagus: an underrecognized feature and its implication for staging of adenocarcinoma. AM J Surg Pathol 2007;31:1719-25.
[4]Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer 2005;103:1347-55.
[5]Rohatgi PR, Swisher SG, Correa AM, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. Cancer 2005;104:1349-55.
[6]Wu T-T, Chirieac LR, Abraham SC, et al. Excellent interobserver agreement on grading the extent of residual carcinoma after preoperative chemoradiation in esophageal and esophagogastric junction carcinoma: a reliable predictor for patient outcome. AM J Surg Pathol 2007;31:58-64.
[7]Brucher BLDM, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. Cancer 2006 May 15;106:2119-27.
[8]Ryan R, Gibbons D, Hyland JMP, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005;47:141-6.
[9]Washington K, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with carcinoma of the esophagus. College of American Pathologists Cancer Protocols 2009; 1-16. (available at http://www.cap.org).
[10]Gu Y, Swisher SG, Ajani JA, et al, The number of lymph nodes with metastasis predicts survival in patients with esophageal or esophagogastric junction adenocarcinoma who receive preoperative chemoradiation. Cancer 2006;106:1017-25.
[11]Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376(9742):687-697.

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.

PRINCIPLES OF SURGERY

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

Continued on next page

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.

PRINCIPLES OF SURGERY

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

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

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

- Acceptable lymph node dissections:[13]
  - Standard
  - Extended (En-Bloc)

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

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

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

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

Continued

PRINCIPLES OF SURGERY

[1]Steyerberg EW, Neville BA, Kopper LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 2006;24:4277-4284.
[2]Siewert JR, Stein HJ. Adenocarcinoma of the gastroesophageal junction: classification, pathology and extent of resection. Dis Esophagus 1996;9:173-182.
[3]Siewart JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction. Results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg 2000;232:353-361.
[4]Rusch VW. Are Cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several. Semin Oncol 2004; 31:444-449
[5]Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophagogastric junction. Scan J Surg 2006; 95:260-269.
[6]Fujita H, Sueyoshi S, Yamana H, et al. Optimum treatment strategy for superficial esophageal cancer: Endoscopic mucosal resection versus radical esophagectomy. World J Surg 2001;25:424-431.
[7]Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360: 2277-2289.
[8]Larghi A, Lightdale CJ, Ross AS, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high-grade dysplasia and intramucosal carcinoma. Endoscopy 2007;39:1086-1091.
[9]Lopes CV, Hela M, Pesenti C, et al. Circumferential endoscopic resection of Barrett's esophagus with high-grade dysplasia or early adenocarcinoma. Surg Endosc 2007;21: 820-824.
[10]Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc 2008;68:35-40.
[11]Levy RM , Wizorek J Shende M, Lukethich JD. Laparoscopic and thoracoscopic esophagectomy. Adv Surg 2010;44:101-116.
[12]Decker G, Coosemans W, DeLeyn P, et al. Minimally invasive esophagectomy for cancer. Eur J Cardiothorac Surg 2009;35:13-21.
[13]Hofstetter WL. Lymph Node Dissection in Esophageal Cancer. Current Therapies in Thoracic and Cardiovascular Surgery, edited by SC Yang and DE Cameron. Mosby, Inc., Philadelphia, Pennsylvania, pp. 360-363, 2004.
[14]Risk NP, Ishwaran H, Rice T, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg 2010;251:46-50.
[15]Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123:175-183.
[16]Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-1137.

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.

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

Criteria for Further Risk Evaluation for High-Risk Syndromes:

- Referral to a cancer genetics professional is recommended for an individual with a known high-risk syndrome associated with esophageal and EGJ cancers.
- Although early age of onset, multiple family members with the same or related cancer, and individuals with multiple primary cancers are all signs of hereditary cancer, specific referral guidelines for esophageal and EGJ cancers risk assessment are not possible at this time.

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

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

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

Continued

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

Surveillance Recommendations

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

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

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

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

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

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

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

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

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

PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status (PS), comorbidities, and toxicity profile.**
- **Trastuzumab should be added to chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising efficacy.[1]**
- **Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.**
- **Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.**
- **Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusional fluorouracil is preferred over bolus fluorouracil.[2]**
- **Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.**
- **Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.[3] Perioperative chemotherapy is an alternative option.[4,5]**
- **Induction chemotherapy may be appropriate as clinically indicated.**
- **In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.**

[1]Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.
[2]Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903-2909.
[3]van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.
[4]Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.
[5]Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation

Infusional fluorouracil can be replaced with capecitabine

- **Preferred Regimens:**
  - **Paclitaxel and carboplatin (category 1)[1]**
  - **Fluorouracil and cisplatin (category 1)[2,3]**
  - **Fluorouracil† and oxaliplatin (category 1)[4,5]**
- **Other Regimens:**
  - **Irinotecan and cisplatin (category 2B)[6]**
  - **Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]**

Perioperative Chemotherapy

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

- **Fluorouracil and cisplatin (category 1)[8]**
- **ECF (epirubicin, cisplatin, and fluorouracil) (category 3)[9]**
- **ECF modifications (category 3 for all modifications)[10,11]**
  - **Epirubicin, oxaliplatin, and fluorouracil**
  - **Epirubicin, cisplatin, and capecitabine**
  - **Epirubicin, oxaliplatin, and capecitabine**

Preoperative chemotherapy (2 cycles)

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

- **Fluorouracil and cisplatin (category 2B)[12]**

Definitive Chemoradiation

Infusional fluorouracil can be replaced with capecitabine

- **Preferred Regimens:**
  - **Fluorouracil and cisplatin (category 1)[13]**
  - **Fluorouracil† and oxaliplatin (category 1)[4,5]**
  - **Paclitaxel and carboplatin[1]**
- **Other Regimens:**
  - **Cisplatin with docetaxel or paclitaxel[14-16]**
  - **Irinotecan and cisplatin (category 2B)[6]**
  - **Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]**

Postoperative Chemoradiation

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

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see (Discussion MS-33).

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

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

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

- **Trastuzumab should be added to first-line chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma** (See Principles of Pathologic Review and HER2-neu Testing [ESOPH-B])
  - **Combination with fluoropyrimidine and cisplatin (category 1)[18]**
  - **Combination with other chemotherapy agents (category 2B)**
  - **Trastuzumab is not recommended for use with anthracyclines**

First-Line Therapy

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

- **Preferred Regimens:**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[19-22] (category 1)**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[20,23,24]**
  - **DCF modifications**
    - ◊ **Docetaxel, cisplatin, and fluorouracil†[,25]**
    - ◊ **Docetaxel, oxaliplatin, and fluorouracil[26]**
    - ◊ **Docetaxel, carboplatin, and fluorouracil (category 2B)[27]**
- **Other Regimens:**
  - **Paclitaxel with cisplatin or carboplatin[28-30]**
  - **Docetaxel with cisplatin[31,32]**
  - **Fluoropyrimidine[21,33,34] (fluorouracil† or capecitabine)**
  - **Docetaxel[35,36]**
  - **Paclitaxel[37,38]**
  - **Fluorouracil† and irinotecan (category 1)[39]**
  - **ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[40]**
  - **ECF modifications (category 1)[10,11]**
    - ◊ **Epirubicin, oxaliplatin, and fluorouracil**
    - ◊ **Epirubicin, cisplatin, and capecitabine**
    - ◊ **Epirubicin, oxaliplatin, and capecitabine**

Second-Line Therapy

Dependent on prior therapy and PS:

- **Preferred Regimens:**
  - **Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[41]**
  - **Docetaxel (category 1)[35,36]**
  - **Paclitaxel (category 1)[37,38,42]**
  - **Irinotecan (category 1)[42-45]**
  - **Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[46]**
- **Other Regimens:**
  - **Irinotecan and cisplatin[23,47]**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and irinotecan[48] (category 2B)**
  - **Docetaxel and irinotecan[49] (category 2B)**

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see (Discussion MS-33).

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

Continued

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

PREOPERATIVE CHEMORADIATION

PREFERRED REGIMENS

Paclitaxel and carboplatin

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

Fluorouracil and cisplatin

Cisplatin 75–100 mg/m² IV on Days 1 and 29
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4 and 29–32
35-day cycle[2]

Cisplatin 15 mg/m² IV daily on Days 1–5
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for 2 cycles[3]

Fluorouracil and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation and 3 cycles after radiation[4]

Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m² IV continuous infusion over 24 hours daily on Days 1–33[5]

PREFERRED REGIMENS

Capecitabine and cisplatin

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

Capecitabine and Oxaliplatin

Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID on Days 1–5 for 5 weeks[51]

OTHER REGIMENS

Irinotecan and cisplatin

Irinotecan 65 mg/m² IV on Days 1, 8, 22, and 29
Cisplatin 30 mg/m² IV on Days 1, 8, 22, and 29[6]

Paclitaxel and fluoropyrimidine

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

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

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

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

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

Continued

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

PERIOPERATIVE CHEMOTHERAPY (INCLUDING EGJ)

Fluorouracil and cisplatin
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cisplatin 75–80 mg/m² IV on Day 1
Cycled every 28 days for 2–3 cycles preoperatively and 3–4 cycles postoperatively for a total of 6 cycles[8]

ECF (epirubicin, cisplatin, and fluorouracil)
Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[9]

ECF modifications
Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[10]

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[10]

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[10,11]

PREOPERATIVE CHEMOTHERAPY

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Fluorouracil and cisplatin
Fluorouracil 1000 mg/m² IV continuous infusion over 24 hours daily on Days 1-4
Cisplatin 80 mg/m² IV on Day 1
Cycled every 21 days for 2 cycles preoperatively[12]

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

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

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

Continued

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

DEFINITIVE CHEMORADIATION (NON-SURGICAL)

PREFERRED REGIMENS

Fluorouracil and cisplatin
Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days for 2–4 cycles for 2 cycles with radiation followed by 2 cycles without radiation[13]

Fluorouracil and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m² IV daily on Days 1–33[5]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation followed by 3 cycles without radiation[4]

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

Capecitabine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID on Days 1–5 weekly for 5 weeks[51]

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

OTHER REGIMENS

Taxane and cisplatin
Paclitaxel 60 mg/m² IV on Days 1, 8, 15, and 22
Cisplatin 75 mg/m² IV on Day 1
Given for 1 cycle[14]

Docetaxel 60 mg/m² IV on Days 1 and 22
Cisplatin 60–80 mg/m² IV on Days 1 and 22
Given for 1 cycle[15]

Docetaxel 20–30 mg/m² IV on Day 1
Cisplatin 20–30 mg/m² IV on Day 1
Weekly for 5 weeks[16]

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

OTHER REGIMENS--continued

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

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

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

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

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

Continued

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

POSTOPERATIVE CHEMORADIATION (INCLUDING EGJ)

Fluorouracil (bolus) and leucovorin (category 1)[17,52]
Cycles 1, 3, and 4 (before and after radiation)
Leucovorin 20 mg/m² IV Push on Days 1– 5
Fluorouracil 425 mg/m² IV Push daily on Days 1–5
Cycled every 28 days

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

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[17,52] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE ABOVE SPECIFIED DOSES OR SCHEDULE OF CYTOTOXIC AGENTS BECAUSE OF CONCERNS REGARDING TOXICITY.
THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

- **1 cycle before and 2 cycles after chemoradiation**
  Capecitabine 750–1000 mg/m² PO BID on Days 1–14
  Cycled every 28 days[53]

- **1 cycle before and 2 cycles after chemoradiation**
  Leucovorin 400 mg/m² IV on Days 1 and 15 OR Days 1, 2, 15, and 16
  Fluorouracil 400 mg/m² IV Push on Days 1 and 15 OR Days 1, 2, 15, and 16
  Fluorouracil 600 mg/m² IV continuous infusion over 22 hours daily on Days 1, 2, 15, and 16
  Cycled every 28 days[54]

With radiation
Fluorouracil 200–250 mg/m² IV continuous infusion over 24 hours daily on Days 1–5 or 1–7
Weekly for 5 weeks[55]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5 or 1–7
Weekly for 5 weeks[56]

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

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

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

Continued

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

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

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

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

PREFERRED REGIMENS

Fluoropyrimidine and cisplatin

Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous
infusion over 24 hours daily on Days 1–4
Cycled every 28 days[19]

Cisplatin 50 mg/m² IV daily on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion
over 24 hours daily on Day 1
Cycled every 14 days[20,21]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[22]

PREFERRED REGIMENS--continued

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[23]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion
over 24 hours on Day 1
Cycled every 14 days[20]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[24]

PREFERRED REGIMENS--continued

DCF modifications

Docetaxel 40 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV on Day 1
Fluorouracil 1000 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cisplatin 40 mg/m² IV on Day 3
Cycled every 14 days[25]

Docetaxel 50 mg/m² IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[26]

Docetaxel 75 mg/m² IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m² IV continuous infusion
over 24 hours daily on Days 1–3
Cycled every 21 days[27]

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

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

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

Continued

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

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

OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135–200 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 2
Cycled every 21 days[28]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[29]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[30]

Docetaxel and cisplatin

Docetaxel 70–85 mg/m² IV on Day 1
Cisplatin 70–75 mg/m² IV on Day 1
Cycled every 21 days[31,32]

Fluoropyrimidine

Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[21]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[33]

Capecitabine 1000–1250 mg/m² PO BID on Days 1–14
Cycled every 21 days[34]

OTHER REGIMENS--continued

Taxane

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[35,36]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[37]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[38]

Fluorouracil and irinotecan

Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days
(only for adenocarcinoma)[39]

Irinotecan 80 mg/m² IV on Day 1
Leucovorin 500 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[57]

OTHER REGIMENS--continued

ECF

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[40]

ECF modifications

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[10,11]

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[10,11]

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[10,11]

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

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

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

Continued

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

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

PREFERRED REGIMENS

Ramucirumab and paclitaxel (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m^2 on Days 1, 8, and 15
Cycled every 28 days[41]

Taxane
Docetaxel 75–100 mg/m^2 IV on Day 1
Cycled every 21 days[35,36]

Paclitaxel 135–250 mg/m^2 IV on Day 1
Cycled every 21 days[37]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[38]

Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15
Cycled every 28 days[42]

PREFERRED REGIMENS--continued

Irinotecan
Irinotecan 250–350 mg/m^2 IV on Day 1
Cycled every 21 days[44]

Irinotecan 150–180 mg/m^2 IV on Day 1
Cycled every 14 days[42,43]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[45]

Ramucirumab (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[46]

OTHER REGIMENS

Irinotecan and cisplatin
Irinotecan 65 mg/m^2 IV on Days 1 and 8
Cisplatin 25–30 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[23,47]

Fluoropyrimidine and irinotecan
Irinotecan 250 mg/m^2 IV on Day 1
Capecitabine 1000 mg/m^2 PO BID on Days 1–14
Cycled every 21 days[48]

Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IV Push on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days
(only for adenocarcinoma)[39]

Docetaxel and irinotecan
Docetaxel 35 mg/m^2 IV on Days 1 and 8
Irinotecan 50 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[49]

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

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

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

[1]van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.
[2]Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092.
[3]Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-1168.
[4]Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-314.
[5]Khushalani NI, Leichman CG, Proulx G, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. J Clin Oncol 2002;20:2844-2850.
[6]Sharma R, Yang GY, Nava HR, et al. A single institution experience with neoadjuvant chemoradiation (CRT) with irinotecan (I) and cisplatin (C) in locally advanced esophageal carcinoma (LAEC) [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract e15619.
[7]Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol 2006;24:3953-3958.
[8]Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.
[9]Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
[10]Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005;92:1976-1983.
[11]Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
[12]Alderson D, Langley RE, Nankivell MG, et al. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072) [abstract]. J Clin Oncol 2015;33 (15_suppl):Abstract 4002.
[13]Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174.
[14]Urba SG, Orringer MB, Ianettonni M, et al. Concurrent cisplatin, paclitaxel, and radiotherapy as preoperative treatment for patients with locoregional esophageal carcinoma. Cancer 2003;98:2177-2183.
[15]Li QQ, Liu MZ, Hu YH, et al. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. Dis Esophagus 2010;23:253-259.
[16]Day FL, Leong T, Ngan S, et al. Phase I trial of docetaxel, cisplatin and concurrent radical radiotherapy in locally advanced oesophageal cancer. Br J Cancer 2011;104:265-271.
[17]Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333.
[18]Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-697.
[19]Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009;20:1667-1673.
[20]Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.
[21]Bouche O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. J Clin Oncol 2004;22:4319-4328.
[22]Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009;20:666-673.
[23]Enzinger PC, Burtness B, Hollis D, et al. CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 4006.
[24]Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 2012;48:518-526.
[25]Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. J Clin Oncol 2015;33:3874-3879.
[26]Shankaran V, Mulcahy MF, Hochster HS, et al. Docetaxel, oxaliplatin, and 5-fluorouracil for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinomas: Preliminary results of a phase II study. Gastrointestinal Cancers Symposium 2009:Abstract 47.
[27]Elkerm YM, Elsaid A, AL-Batran S, Pauligk C. Final results of a phase II trial of docetaxel-carboplatin-FU in locally advanced gastric carcinoma [abstract]. Presented at the Gastrointestinal Cancers Symposium 2008. Abstract 38.
[28]Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000;6:316-323.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

[29]Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998;78:511-514.
[30]Gadgeel SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol 2003;26:37-41.
[31]Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005;23:5660-5667.
[32]Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010;66:31-36.
[33]Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 2003;21:54-59.
[34]Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol 2004;15:1344-1347.
[35]Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007;24:407-412.
[36]Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78-86.
[37]Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994;86:1086-1091.
[38]Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898-902.
[39]Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014;32:3520-3526.
[40]Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20:1996-2004.
[41]Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;1224-1235.
[42]Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 Trial. J Clin Oncol 2013;31:4438-4444.
[43]Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481-488.
[44]Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-2314.
[45]Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 2003;21:807-814.
[46]Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39.
[47]Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22-25.
[48]Leary A, Assersohn L, Cunningham D, et al. A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol 2009;64:455-462.
[49]Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. Ann Oncol 2009;20:1242-1248.
[50]Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. Jpn J Clin Oncol 2007;37:829-835.
[51]Javle MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. Cancer Invest 2009;27:193-200.
[52]Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730.
[53]Jansen EP, Boot H, Saunders MP, et al. A phase I-II study of postoperative capecitabine-based chemoradiotherapy in gastric cancer. Int J Radiat Oncol Biol Phys 2007;69:1424-1428.
[54]Andre T, Quinaux E, Louvet C, et al. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol 2007;25:3732-3738.
[55]Leong T, Joon DL, Willis D, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the trans-tasman radiation oncology group. Int J Radiat Oncol Biol Phys 2011;79:690-695.
[56]Lee HS, Choi Y, Hur WJ, et al. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. World J Gastroenterol 2006;12:603-607.
[57]Wolff K, Wein A, Reulbach U, et al. Weekly high-dose 5-fluorouracil as a 24-h infusion and sodium folinic acid (AIO regimen) plus irinotecan in patients with locally advanced nonresectable and metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus: a phase II trial. Anticancer Drugs 2009;20:165-173.

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

Continued

PRINCIPLES OF RADIATION THERAPY

General Guidelines

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

Simulation and Treatment Planning

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

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

Continued

PRINCIPLES OF RADIATION THERAPY

Target Volume (General Guidelines):

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

Normal Tissue Tolerance Dose-Limits

- **Treatment planning is essential to reduce unnecessary dose to organs at risk, including liver (60% of liver <30 Gy, 25 Gy mean dose), kidneys (at least 2/3 of one kidney <20 Gy), spinal cord (<45 Gy), and heart (1/3 of heart <40 Gy, and effort should be made to keep the left ventricle doses to a minimum).**
- **Lung dose may require particular attention, especially in the preoperatively treated patient.[a] Normal lung (more than 2 cm outside the target volume) should not receive more than 40 Gy. To reduce the incidence of postoperative pulmonary complications (as well as symptomatic pneumonitis) a guideline is to limit the proportion of total lung receiving 20 Gy or more to 25% and 5 Gy or more to 50%.**
- **It is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.**

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

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

Continued

PRINCIPLES OF RADIATION THERAPY

Dose

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

Supportive Care

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

[b]Patients who are at risk for not having surgery due to comorbidities or other risk factors should receive radiation doses of 50–50.4 (1.8–2 Gy/d) because the lower preoperative therapy dose may not be adequate.

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

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.

References on next page

PRINCIPLES OF RADIATION THERAPY
(References)

[1]Gao XS, Qiao X, Wu F, et al. Pathological analysis of clinical targetvolume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma. Int J Radiat Oncol Biol Phys 2007;67:389–396.
[2]Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174.

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.

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

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

Dysphagia

- **Assess the extent of disease and the functional degree of swallowing impairment, preferably through a standardized scoring scale and confirm the etiology of dysphagia**
- **Dysphagia grading scale[8]**
  - **Grade 0: Able to eat solid food without special attention to bite size or chewing**
  - **Grade 1: Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed**
  - **Grade 2: Able to swallow semisolid food (consistency of baby food)**
  - **Grade 3: Able to swallow liquids only**
  - **Grade 4: Unable to swallow liquids or saliva**
- **Dysphagia arising from esophageal cancer most often is due to obstruction, but on occasion may be primarily due to tumor-related dysmotility.**

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

Continued on next page

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

Obstruction

- Complete esophageal obstruction
  - Endoscopic lumen restoration, generally performed via simultaneous retrograde (via a gastrostomy tract) and antegrade endoscopy
  - Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
    - ◊ Surgical or radiologic placement of jejunal or gastrostomy tube
  - External beam radiation therapy
  - Brachytherapy may be considered in place of external beam radiation if a lumen can be restored that allows for the use of appropriate applicators. Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.
  - Photodynamic therapy can effectively treat esophageal obstruction, but is less commonly performed due to associated photosensitivity and costs. [9]
  - Chemotherapy
  - Surgery may on occasion be useful in carefully selected patients.
- Severe esophageal obstruction (able to swallow liquids only)
  - Wire-guided dilation or balloon dilation (caution should be exercised when dilating malignant strictures as this may be associated with an increased risk of perforation)
  - Endoscopy or fluoroscopy-guided placement of partially or fully covered expandable metal stents.
    - ◊ There are data suggesting a lower migration and stent occlusion rates with the larger diameter covered expandable metal stents, but an increased risk of other complications such as bleeding and esophago-respiratory fistula.[10]
    - ◊ If possible, the distal end of the stent should remain above the EGJ to reduce symptoms of reflux and risk of aspiration.
  - External beam radiation therapy[11] and brachytherapy both effectively treat malignant dysphagia
    - ◊ The onset of symptom relief for radiotherapy (EBRT or brachytherapy) is slower compared to endoscopic palliation but is also likely to be more durable.[12,13]
  - Other measures as stated above
- Moderate esophageal obstruction (able to swallow semisolid food)
  - Measures stated above may be considered, but should be balanced with the associated risks

Pain

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

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.

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

Bleeding

- **Acute bleeding from esophageal cancer may represent a pre-terminal event secondary to tumor-related aorto-esophageal fistualization. Endoscopic assessment and intervention may lead to precipitous exsanguination, and therefore should be undertaken cautiously.**
  - **If bleeding appears to be primarily from tumor surface, then endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation may be useful for control of bleeding; however, limited data suggest that while endoscopic therapies may initially be effective, the rate of recurrent bleeding is very high.[14]**
- **Chronic blood loss from esophageal cancer**
  - **External beam radiation therapy**

Nausea/Vomiting

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

[1]Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004;364:1497-1504.
[2]Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999;17:3270-3275.
[3]Ross WA, Alkassab F, Lynch PM, et al. Evolving role of self-expanding metal stents in the treatment of malignant dysphagia and fistulas. Gastrointest Endosc 2007;65:70-76.
[4]Shin JH, Song HY, Kim JH, et al. Comparison of temporary and permanent stent placement with concurrent radiation therapy in patients with esophageal carcinoma. J Vasc Interv Radiol 2005;16:67-74.
[5]Vakil N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. Am J Gastroenterol 2001;96:1791–1799.
[6]Verschuur EM, Morris AL, Marcon N, et al. New design esophageal stents for the palliation of dysphagia from esophageal or gastric cardia cancer: a randomized trial. Am J Gastroenterol 2008;103:304-312.
[7]Fan Y, Song HY, Kim JH, et al. Evaluation of the incidence of esophageal complications associated with balloon dilation and their management in patients with malignant esophageal strictures. AJR Am J Roentgenol 2012;198:213-218.
[8]Blazeby JM, Williams MH, Brookes ST, et al. Quality of life measurement in patients with oesophageal cancer. Gut 1995;37:505-508.
[9]Petersen BT, Chuttani R, Croffie J, et al. Photodynamic therapy for gastrointestinal disease. Gastrointest Endosc. 2006 Jun;63:927-932.
[10]White RE, Chepkwony R, Mwachiro M, et al. Randomized Trial of Small-diameter Versus Large-diameter Esophageal Stents for Palliation of Malignant Esophageal Obstruction. J Clin Gastroenterol 2015;49:660-665.
[11]Murray LJ, Din OS, Kumar VS, et al. Palliative radiotherapy in patients with esophageal carcinoma: A retrospective review. Pract Radiat Oncol 2012;2:257-264.
[12]Hanna WC, Sudarshan M, Roberge D, et al. What is the optimal management of dysphagia in metastatic esophageal cancer? Curr Oncol 2012;19:e60-66.
[13]Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004;364:1497-504.
[14]Sheibani S, Kim JJ, Chen B, et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. Aliment Pharmacol Ther 2013;38:144-150.

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.

PRINCIPLES OF SURVEILLANCE

The surveillance strategies after successful local therapy for esophageal and EGJ cancers remain controversial, with little prospective data to construct appropriate algorithms that balance the benefits and risks (including cost) within a population.

The goal of this document is to provide guidance for stage-specific surveillance based on the currently available retrospectively analyzed literature[1-6] and the expertise of the panel members to individualize surveillance recommendations. It is hoped that prospective data will emerge and we will be able to propose surveillance recommendations based on the evidence.

It should be noted that although the majority (~90%) of relapses occur within the first two years after completion of local therapy, potentially actionable relapses have been recognized sometimes more than 5 years after local therapy. Metachronous malignancy (a second cancer in the residual esophagus or in the case of squamous cell carcinoma in a different organ) is also a consideration in long-term survivors.

The recommendations outlined below are following completion of local therapy.

pStage 0-I (Tis, T1a, T1b and Superficial T1b)

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

See Table 1 for specific surveillance recommendations.

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

PRINCIPLES OF SURVEILLANCE

Table 1

Tumor Classification	Type of therapy rendered	Surveillance recommendations
Tis	**Endoscopic resection (ER)/ablation**	Upper GI endoscopy (EGD) every 6 months for 1 to 2 years, then annually for 3 more years. Further surveillance or therapy will be determined if either Barrett's esophagus (BE) or cancer relapse is diagnosed. Imaging studies as a surveillance tool are not recommended.
	Esophagectomy	EGD as needed based on symptoms. Although the goal of the resection would be to resect all areas of Tis and BE, patients with incompletely resected BE should undergo ablation and endoscopic surveillance every 6 months for 1 to 2 years. Routine imaging is not required.
T1a with or without BE	**ER/ablation**	EGD every 3 months for the first year, every 4–6 months for the second year, then annually for 3 more years.
T1a	**Esophagectomy**	Imaging studies as a surveillance tool are not recommended. EGD as needed based on symptoms. Although the goal of the resection would be to resect all areas of T1a and BE, patients with incompletely resected BE should undergo ablation and endoscopic surveillance every 3 months for the first year, every 4–6 months for the second year, then annually for 3 more years.
Superficial pT1b (N0 based on EUS)	**ER/ablation**	Imaging (PET-CT or CT chest/abdomen with contrast unless contraindicated) every 4–6 months for 2 years and then annually for at least one additional year. EGD every 3 months for the first year, every 4–6 months for the second year, annually for 3 more years.
T1b, N0 (N0 based on EUS)	**ER/ablation (Non-surgical candidates)**	EGD every 3 months for the first year; every 4–6 months for the second year, annually for 3 more years. Further surveillance or therapy will be determined if either BE or cancer relapse is diagnosed. Imaging (PET-CT or CT chest/abdomen with contrast unless contraindicated) may be considered every 12 months for up to 3 years and then as clinically warranted.
T1b, Any N	**Esophagectomy**	Imaging (PET-CT or CT chest/abdomen with contrast unless contraindicated) can be considered starting at 6–12 months for up to 3 years, then as clinically warranted. EGD as needed based on symptoms and radiographic findings. Although the goal of the resection would be to resect all areas of T1b and BE, patients with incompletely resected BE should undergo ablation and endoscopic surveillance every 3 months for the first year, every 4–6 months for the second year, then annually for 3 more years.
	Chemoradiation (Non-surgical candidate)	EGD every 6–12 months for first 2 years then annually for 3 more years. Imaging (PET-CT or CT chest/abdomen with contrast unless contraindicated) should be considered every 6–9 months for the first 2 years, then annually up to 5 years.
	Chemoradiation (Candidate for salvage esophagectomy)	EGD every 6–12 months for first 2 years then annually for 3 more years. Imaging (PET-CT or CT chest/abdomen with contrast unless contraindicated) should be considered every 6 to 9 months for the first 2 years, then annually up to 5 years. In this group, EUS/FNA may be warranted based on imaging studies.

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.

PRINCIPLES OF SURVEILLANCE

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

Literature suggests that local/regional relapses are common after bimodality therapy.[3] Therefore, EGD is a valuable surveillance tool in these patients. Most relapses (95%) occur within 24 months. Thus, surveillance for at least 24 months is recommended for these patients.[3]

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

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

See Table 2 for specific surveillance recommendations.

Table 2

Tumor Classification	Type of Therapy Rendered	Surveillance Recommendations
T2-T4, N0-N+, T4b	**Bimodality therapy (chemoradiation)**	Imaging studies are complementary. EGD every 3–4 months for the first 2 years, every 6 months for the third year, then as clinically warranted. The value of carcinoembryonic antigen (CEA) and other tumor markers is unknown.
T2-T4, N0-N+, T4b	**Trimodality therapy**	Imaging studies (PET-CT or CT chest/abdomen with contrast unless contraindicated) are recommended. Frequency of surveillance may be every 4–6 months in the first 12 months and every 6–9 months in the next 24 months. Unscheduled evaluation is recommended if a patient becomes symptomatic. The value of CEA and other tumor markers is unknown. EGD as a surveillance tool is not recommended.

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.

PRINCIPLES OF SURVEILLANCE

References

[1]Dorth JA, Pura JA, Palta M, et al. Patterns of recurrence after trimodality therapy for esophageal cancer. Cancer 2014;120:2099-2105.

[2]Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 2014;32:385-391.

[3]Sudo K, Xiao L, Wadhwa R, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol 2014;32:3400-3405.

[4]Sudo K, Taketa T, Correa AM, et al. Locoregional failure rate after preoperative chemoradiation of esophageal adenocarcinoma and the outcomes of salvage strategies. J Clin Oncol 2013;31:4306-4310.

[5]Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol 2013;8:1558-1562.

[6]Taketa T, Sudo K, Correa AM, et al. Post-chemoradiation surgical pathology stage can customize the surveillance strategy in patients with esophageal adenocarcinoma. J Natl Compr Canc Netw 2014;12:1139-1144.

[7]Katada C, Muto M, Manabe T, et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005;61:219-225.

[8]Haidry RJ, Butt MA, Dunn J, et al. Radiofrequency ablation for early oesophageal squamous neoplasia: outcomes form United Kingdom registry. World J Gastroenterol 2013;19:6011-6019.

[9]Perry KA, Walker JP, Salazar M, et al. Endoscopic management of high-grade dysplasia and intramucosal carcinoma: experience in a large academic medical center. Surg Endosc 2014;28:777-782.

[10]Yasuda K, Choi SE, Nishioka NS, et al. Incidence and predictors of adenocarcinoma following endoscopic ablation of Barrett's esophagus. Dig Dis Sci 2014;59:1560-1566.

[11]Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol 2014;12:1840-1847 e1841.

[12]Manner H, Rabenstein T, Pech O, et al. Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study). Endoscopy 2014;46:6-12.

[13]Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146:652-660.

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

Table 1

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

Primary Tumor (T)

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

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Squamous Cell Carcinoma*

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

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

Continue...

Table 1--Continued

Anatomic Stage/Prognostic Groups

Adenocarcinoma

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

Histologic Grade (G)

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Esophageal/EGJ Table of Contents
Discussion

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/23/15.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview MS-2
Literature Search Criteria and Guidelines Update Methodology MS-3
Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Esophageal and EGJ Cancers MS-3
Tylosis with Esophageal Cancer MS-3
Familial Barrett's Esophagus MS-3
Bloom Syndrome MS-4
Fanconi Anemia MS-4
Staging MS-4
Esophagogastric Junction MS-5
Barrett's Esophagus MS-6
Principles of Pathology MS-7
Biopsy MS-7
Assessment of HER2-neu Overexpression MS-7
Assessment of Treatment Response MS-8
Surgery MS-10
Surgical Approaches MS-10
Principles of Surgery MS-12
Endoscopic Therapies MS-13
Principles of Endoscopy MS-14
Radiation Therapy MS-16
Principles of Radiation Therapy MS-17
Combined Modality Therapy MS-18
Definitive Chemoradiation Therapy MS-18
Preoperative Chemoradiation Therapy MS-19
Preoperative Sequential Chemotherapy and Chemoradiation Therapy MS-21
Postoperative Chemoradiation Therapy MS-22
Chemotherapy MS-23
Preoperative Chemotherapy MS-23
Perioperative Chemotherapy MS-24
Chemotherapy for Locally Advanced or Metastatic Cancer MS-24
Targeted Therapies MS-26
Treatment Guidelines MS-27
Workup MS-27
Additional Evaluation MS-28
Management of Locoregional Cancer in Medically Fit Patients MS-28
Management of Locoregional Cancer in Non-surgical Candidates MS-31
Surveillance MS-31
Management of Metastatic, or Recurrent Cancer MS-32
Leucovorin Shortage MS-34
Best Supportive Care MS-34
Summary MS-35
References MS-37

Overview

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

Esophageal cancer is the 6th most common cause of cancer deaths worldwide and is more common in men.[4] It is an endemic in many parts of the world, particularly in the developing nations, where it is the 4th most common cause of cancer deaths.[4] In 2015, an estimated 16,980 people will be diagnosed with esophageal cancer and 15,590 people will eventually die of their disease in the United States.[5] 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] Both are more common in men. SCC is the most common histology in Eastern Europe and Asia, and adenocarcinoma is most common in North America and most Western European countries. SCCs have become increasingly less common in the West, accounting for fewer than 30% of all esophageal cancers in the United States and Western Europe. Adenocarcinoma is diagnosed predominantly in white men in whom the incidence has risen more steeply. However, adenocarcinoma is gradually increasing in men of all ethnic backgrounds and also in women.[1] SCC seems to be more sensitive to chemotherapy, chemoradiation, and RT than adenocarcinoma, but the long-term outcome appears to be the same. 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.

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

Gastroesophageal reflux disease (GERD) and Barrett's esophagus are the other two major risk factors for adenocarcinoma of the esophagus.[19-22] GERD is associated with a high BMI and is also a risk factor for Barrett's esophagus, a condition in which the normal squamous epithelium of the esophagus that is damaged by GERD is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to malignancy.[23] Patients with Barrett's esophagus have 30 to 60 times greater risk of developing adenocarcinoma of the esophagus than the general population.[21] Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with higher grades of dysplasia.[24,25] These preliminary findings warrant further prospective evaluation of predictors of risk for the development of high-grade dysplasia (HGD) and adenocarcinoma of the esophagus in patients with Barrett's esophagus.

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Esophageal and EGJ Cancers an electronic search of the PubMed database was performed to obtain key literature in Esophageal and EGJ Cancers published between 06/27/2013 and 06/27/2014, using the following search terms: esophageal cancer, esophageal squamous cell, esophageal adenocarcinoma, esophagogastric junction, gastroesophageal junction, PET scans, endoscopic treatment, endoscopic resection (ER), ablation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[27]

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

The PubMed search resulted in 76 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

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

Tylosis with Esophageal Cancer

Tylosis (also known as non-epidermolytic Palmoplantar Keratosis or Howel-Evans syndrome) is a very rare autosomal dominant syndrome characterized by palmoplantar keratoderma (PPK), a complex group of hereditary syndromes. PPK is classified into diffuse, punctate, and focal forms according to the patterns of skin thickening on palms and soles. The diffuse PPK is further divided into epidermolytic and non-epidermolytic forms. The non-epidermolytic PPK is associated with a high risk of developing SCC of the middle and distal esophagus.[28] In individuals with tylosis, the average age at diagnosis of SCC of the esophagus is 45 years. The risk of developing SCC of the esophagus has been reported to be 40% to 90% by the age of 70 years.[29,30] The locus of the hitherto unknown gene *TEC* (tylosis with esophageal cancer) has been mapped by linkage analysis to a region on chromosome 17q25 that is distal to the keratin 1 gene cluster, which also has been implicated in the development of sporadic SCC of the esophagus.[31-34] However, the causative gene is yet to be identified.[34]

Surveillance by upper GI endoscopy is recommended for family members with tylosis after 20 years of age.[28]

Familial Barrett's Esophagus

Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to the development of adenocarcinoma of the esophagus.[23] Development of Barrett's

esophagus is strongly associated with GERD. The familial aggregation of Barrett's esophagus, adenocarcinoma of the esophagus and EGJ is termed as familial Barrett's esophagus (FBE).[35-37] In one cohort study, family history was identified as an independent predictor for the presence of Barrett's esophagus, adenocarcinoma of the esophagus, or EGJ, after adjusting for age, sex, and the presence of obesity 10 or more years prior to study enrollment.[36] FBE may be associated with one or more rare autosomally inherited dominant susceptibility alleles.[38] Recent reports have identified germline mutations in a variety of susceptibility genes that may be associated with the development of Barrett's esophagus.[39,40] However, at the present time there are no specific gene markers to identify individuals with FBE.

Potential family history of Barrett's esophagus, adenocarcinoma of the esophagus, or EGJ should be determined for patients presenting with GERD, especially Caucasian males older than 40 years of age.

Bloom Syndrome

Bloom syndrome (BS) is a rare autosomal recessive syndrome belonging to a group of "chromosomal breakage syndromes." BS is characterized by mutations in the *BLM* gene at 15q26.1 and strikingly elevated sister chromatid exchanges that are associated with an increased predisposition to a wide variety of malignancies.[41] Acute myeloid leukemia (AML), acute lymphoblastic leukemia, lymphoid neoplasms, and Wilms tumor are the predominant cancers diagnosed before 25 years of age, whereas carcinomas of different anatomic sites including SCC of the esophagus are diagnosed after 20 years of age.[28,42] Individuals with BS are often diagnosed with cancers at an earlier age than that of the general population. Chromosomal quadraradials with breakage may be used for the diagnosis of BS.[28]

Screening for GERD with or without endoscopy after 20 years of age may be considered to detect cancer early.

Fanconi Anemia

Fanconi anemia (FA) is an autosomal recessive disorder characterized by congenital malformations, progressive pancytopenia, and an increased predisposition to the development of hematologic malignancies as well as solid tumors.[28] FA is caused by mutations in one of 15 genes (*FANC*) encoding the FA pathway, with *FANCA, FANCC, FANCG*, and *FANCD2* being the most common ones.[43] AML is the most common cancer type in patients with FA. However, patients with FA are also at an increased risk of developing SCC of head, neck and esophagus, cervical cancer, and brain tumors.[28,44,45] Individuals with FA are identified by pancytopenia and chromosome breakage and hematologic abnormalities, including anemia, bleeding, and easy bruising. Karyotyping does not identify individuals with FA, but enhanced mitomycin C-induced chromosomal breakage analysis can identify homozygotes but not heterozygotes.[28,46]

Endoscopy of the esophagus may be considered as a surveillance strategy in individuals identified with FA.

Staging

The tumor (T), node (N), and metastasis (M) classification developed by the AJCC in 2002 was based on the pathologic review of the surgical specimen in patients who had surgery as primary therapy. The revised 2010 AJCC staging classification is based on the risk-adjusted random forest analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for 4627 patients who were treated with primary esophagectomy without preoperative or postoperative therapy.[47] In the data reported by the WECC, survival decreased with increasing depth of tumor invasion (pT), presence of regional lymph node metastases (pN), and the presence of distant metastases (pM).[48] In addition, survival was

somewhat worse for pT1b (submucosal) tumors than for pT1a (intramucosal) tumors and survival was worse for SCC than for adenocarcinomas.

The revised staging system includes separate stage groupings for SCC and adenocarcinoma. The revised staging system is for esophageal and EGJ cancers, including cancer within the first 5 cm of the stomach that extends into the EGJ or distal thoracic esophagus.[47] However, this new classification may not work well for baseline clinical staging or for patients who received preoperative therapy. This new classification has several other shortcomings, including: inclusion of proximal 5 cm of the stomach, lack of guidance for regional resectable and unresectable cancer, and the emphasis on the number of nodes rather than their anatomic locations and significance. The size of the lymph node is also not addressed.

Patient outcomes may correlate with the clinical stage of the cancer at diagnosis, but the best correlation with survival is associated with the surgical pathologic stage (whether or not patient has received preoperative therapy). Although surgical pathology yields the most accurate staging, the advent of better imaging techniques has improved preclinical staging.[49] In North America and many western European countries, where screening programs for early detection of esophageal and EGJ cancers are not in use or practical because of low incidence, the diagnosis is often made late in the disease course. At diagnosis, nearly 50% of patients have cancer that extends beyond the locoregional confines of the primary. Fewer than 60% of patients with locoregional cancer can undergo a curative resection. Approximately 70% to 80% of resected specimens harbor metastases in the regional lymph nodes. Thus, clinicians are often dealing with an advanced-stage, incurable cancer in newly diagnosed patients.

Esophagogastric Junction

Siewert et al classified the EGJ adenocarcinoma into three types based purely on the anatomic location of the epicenter of the tumor or the location of the tumor mass.[50] If the epicenter of the tumor or more than 66% of the tumor mass is located more than 1 cm above the anatomic EGJ, then the tumor is classified as an adenocarcinoma of the distal esophagus, type I. If the epicenter of the tumor or tumor mass is located within 1 cm proximal and 2 cm distal to the anatomic EGJ, this adenocarcinoma is classified as type II. If the epicenter of the tumor or more than 66% of the tumor mass is located more than 2 cm below the anatomic EGJ, the tumor is classified as type III.[50]

In 2000, the classification was slightly changed.[51] Siewert Type I tumors are defined as the adenocarcinoma of the distal esophagus with the tumor center located within 1 to 5 cm above the anatomic EGJ. Siewert Type II tumors are defined as the true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ. Siewert Type III is defined as the subcardial carcinoma with the tumor center between 2 to 5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below.

In the revised AJCC staging system, tumors whose midpoint is in the lower thoracic esophagus, EGJ, or within the proximal 5 cm of the stomach that extends into the EGJ or esophagus (Siewert Types I and II) are classified as adenocarcinoma of the esophagus for the purposes of staging.[47] All other cancers with a midpoint in the stomach lying more than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into the EGJ or esophagus (Siewert Type III) are staged using the gastric cancer staging system. This approach remains a subject of disagreement, some confusion, and debate. An individualized therapeutic approach may be preferred for specific

patients and tumor locations, based on thorough pretreatment staging. Therapeutic decisions may be refined according to the location of the individual tumor, nodal distribution, and specific requirements for local control.

Barrett's Esophagus

Barrett's esophagus is a condition in which the normal squamous epithelium of the esophagus is replaced by a metaplastic, columnar, or glandular epithelium that is predisposed to the development of adenocarcinoma of the esophagus.[23] Patients with Barrett's esophagus are at a greater risk of developing adenocarcinoma of the esophagus than the general population. Barrett's esophagus can progress to low-grade dysplasia (LGD) or HGD and in some cases to adenocarcinoma of the esophagus.[21] Age, male gender, long-standing GERD, hiatal hernia size, and the length of the Barrett's esophagus are strongly associated with the progression of Barrett's esophagus to adenocarcinoma of the esophagus.[24,25,52] Biomarkers such as aneuploidy and loss of heterozygosity of *p53* have been associated with increased risk of progression to HGD and/or adenocarcinoma of the esophagus.[52] These preliminary results warrant further prospective evaluation as predictors of risk for the development of HGD and adenocarcinoma of the esophagus in patients with Barrett's esophagus. Endoscopy is performed on patients with severe symptoms of GERD, especially those with a family history of Barrett's esophagus or esophageal cancer. The location, length, and circumferential involvement should be characterized in accordance with the Prague classification and mucosal nodules should be carefully documented.[53]

ER and mucosal radiofrequency ablation (RFA) has become the preferred treatment for most patients with Barrett's esophagus and HGD. Alternative strategies include cryoablation or photodynamic therapy (PDT).[54-56] Surgical resection is reserved for patients with HGD and characteristics that are unfavorable for non-surgical therapy, such as nodularity or long-segment involvement. For patients with metaplasia or LGD, gastroesophageal reflux is controlled with histamine receptor antagonists or proton pump inhibitors.

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

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

randomized trial, endoscopic therapy is recommended for patients with confirmed HGD.[61] A recent randomized study suggests that endoscopic therapy may be useful for patients with confirmed LGD.[62]

Principles of Pathology

Biopsy

A specific diagnosis of SCC or adenocarcinoma should be established for staging and treatment purposes. Mixed adenosquamous carcinomas and carcinomas not otherwise classified are staged using the TNM system for SCC.[47] In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade (required for stage grouping). In addition to the above mentioned elements, the pathology report of the biopsy specimen should also include the presence or absence of Barrett's esophagus.

In the case of ER or esophageal resection specimens, the depth of tumor invasion and the status of mucosal and deep margins should also be recorded. In an esophageal resection specimen, Barrett's esophagus with HGD is reported as carcinoma in situ (Tis).[47] Biopsies showing Barrett's esophagus with a suspected dysplasia should be reviewed by a second expert GI pathologist for confirmation.[60]

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

Assessment of HER2-neu Overexpression

Human epidermal growth factor receptor 2 (*HER2*) gene and/or HER2 protein expression has been implicated in the development of gastric and EGJ adenocarcinomas.[63] *HER2-neu* amplification and overexpression are more frequent in adenocarcinoma of the esophagus (15%–30%) than SCC of the esophagus (5%–13%).[64-66] HER2-neu overexpression in esophagogastric cancers varies widely (2%–45%).[67] HER2-neu-positivity has been reported to be higher in patients with EGJ cancers than in patients with gastric cancers.[68,69] In the ToGA trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2-neu-positive advanced gastric cancer, HER2-neu-positivity rates were 33% and 21%, respectively, for patients with EGJ and gastric cancers.[70]

However, unlike in breast cancer, the prognostic significance of *HER2-neu* expression in patients with esophageal cancer is not clear. It has been demonstrated that *HER2-neu* overexpression correlates with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis.[67] *HER2-neu* overexpression seems to be associated with poorer survival, especially in patients with SCC of the esophagus.[64]

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

According to the HER2 scoring system for breast cancer proposed by the ASCO/College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to two major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many gastric cancer patients who could otherwise be candidates for anti-HER2 therapy.[71,72] Results from two separate series also demonstrated that the HER2 scoring system for breast cancer identified a significantly lower percentage of patients with gastric cancer meeting the criteria for HER2-positivity by IHC (5.4% vs.11% in the ToGA trial).[73,74]

In 2008, Hoffmann et al developed a modified 4-tier HER2 scoring system specific for gastric cancer by using the assessment area cut-off of at least 10% stained tumor cells for resection specimens and omitting this area cut-off for biopsy specimens.[71] In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[72] This modified HER2 scoring system was also used in the ToGA trial.[73]

HER2 testing is now recommended for all patients with metastatic EGJ adenocarcinoma at the time of diagnosis. The guidelines recommend that assessment for HER2 status should be performed first using IHC following the modified scoring system used in the ToGA trial).[71,73] A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in-situ hybridization techniques. The panel recommends FISH only for patients with an IHC score of 2+, although some institutions routinely perform both IHC and FISH on all patients.

Assessment of Treatment Response

The prognostic significance of pathologic complete response (pCR) and histologic tumor regression after induction therapy in patients with adenocarcinoma and SCC of the esophagus has been demonstrated in several studies.[75-81] Posttreatment pathologic stage was the best predictor of survival outcome for patients with locoregional carcinoma of the esophagus or EGJ who underwent preoperative chemoradiation followed by esophagectomy.[82]

Several tumor regression grading systems have been developed to assess the pathologic response to preoperative neoadjuvant therapy. Mandard et al proposed a 5-tiered grading system based on the percentage of residual cancer cells and the extent of fibrosis.[83] Tumor regression remained a significant predictor of disease-free survival (DFS) after preoperative chemoradiation and surgery. Chirieac et al used a 4-tiered classification system based on the extent of residual cancer (0%, 1%–10%, 11%–50% and more than 50% [gross residual carcinoma]).[82] The overall survival (OS) was significantly better for patients with no residual carcinoma (133 months) than it was for those with more than 50% residual carcinoma (10.5 months). However, OS was not significantly different between patients with 1% to 10% and 11% to 50% residual carcinoma. Based on these results, Wu et al developed a 3-tiered classification system: P0 (0% residual carcinoma), P1 (1% to 50% residual carcinoma), and P2 (more than 50% residual carcinoma).[84] Although grading systems for tumor response in esophageal cancer have not been uniformly adopted, in general, the 3-tiered system proposed by Wu et al has been reported to have an excellent interobserver agreement among pathologists on grading the

extent of residual carcinoma in patients with esophageal and EGJ cancers.[84] See the *Principles of Pathologic Review and HER2-neu Testing-Assessment of Treatment Response-Table 2* in the guidelines.

Role of PET Scans in the Assessment of Treatment Response

The prognostic significance of metabolic response after preoperative therapy as defined by PET scans has been evaluated in retrospective[85-95] and prospective studies[96-111] in patients with locally advanced esophageal cancer. However, the timing of posttreatment PET before surgery (2 to 6 weeks)[96,100,104,106] and the cut-off values for the reduction in the 18-fluorodeoxyglucose (FDG) standardized uptake value (SUV) between pre and posttreatment PET scans (35%–80%)[96-98,106] have varied widely across the studies. In addition, the prospective studies that have shown the positive predictive value of PET scan after preoperative therapy are limited by the small sample size with the exception of the MUNICON II study, which included 110 patients with locally advanced adenocarcinoma of the EGJ.[106] In this study, metabolic responders were defined as those with a decrease of 35% or more SUV after 2 weeks of induction chemotherapy. After a median follow-up of 2.3 years, median OS was not reached in metabolic responders, whereas the median OS was 25.8 months in non-responders (P = .015). Median event-free survival (EFS) was 29.7 months and 14 months, respectively, for metabolic responders and non-responders (P = .002). Major histologic remissions (<10% of residual cancer) were noted in 58% of metabolic responders but in 0% of metabolic non-responders.

In some retrospective studies, FDG uptake on a single post-treatment PET scan was the only predictive factor that correlated with pathologic response and survival. However, the specific uptake value used as a cutoff in these series also varied from 2.5 to 4.[85,89] Swisher et al showed that the 2-year survival rate was 60% for patients with a post chemoradiation FDG uptake of less than 4 and 34% for those with a FDG uptake of 4 or more; PET scans, however, could not distinguish patients with microscopic residual disease.[85] In a more recent retrospective study using the same cut-off value (FDG uptake of less than 4), Bruzzi et al reported that PET scan has only a limited utility for assessing therapeutic response, although it was useful in the detection of distant metastases in patients with locally advanced, potentially resectable esophageal cancer. Other studies have also reported that the accuracy of PET for detecting non-responders is very low to justify the use of PET scans to determine early discontinuation of preoperative therapy in patients with potentially resectable esophageal cancer.[108,110]

In patients who are treated with preoperative chemoradiation, RT-induced ulceration has been associated with false-positive results on PET/CT, precluding accurate detection of residual esophageal tumor.[112] However, PET/CT when used in combination with endoscopy was found to be useful in identifying patients with a high risk of residual tumor following preoperative chemoradiation.[112]

Surgery provides a significant survival benefit in patients with locally advanced esophageal cancer achieving clinical response to preoperative chemoradiation.[113,114] In a recent prospective study that compared the outcomes of surveillance vs. surgical resection in patients with esophageal cancer achieving complete clinical response after preoperative chemoradiation, surgical resection was independently associated with less recurrence (32.7% vs. 50.8%; P = .021) and better median survival (83 months vs. 31 months; P = .001).[113] The guidelines recommend consideration of PET/CT or PET only for the assessment of response to preoperative or definitive chemoradiation therapy before surgery or initiation of postoperative treatment (category 2B). However, the guidelines emphasize that PET

scans should not be used for the selection of patients to surgery following preoperative chemoradiation.

Surgery

Surgery is a major component of treatment for resectable disease. One of the major developments in the surgical therapy of esophageal cancer has been the marked reduction in surgical morbidity and mortality as a result of improvements in staging techniques, patient selection, support systems, and surgical experience. Recent randomized trials have shown that preoperative chemoradiation (CROSS study)[115] and perioperative chemotherapy (MAGIC trial, predominantly a gastric cancer trial that included a small group of patients with lower esophageal and EGJ cancers)[116] significantly improved survival in patients with resectable esophageal and esophagogastric cancer. With the incidence of esophageal cancer, particularly adenocarcinoma of the distal esophagus increasing dramatically, the hope is that surveillance programs will continue to detect earlier stage cancer, thus increasing the number of patients who can benefit from therapy.

Currently, staging studies such as endoscopic ultrasound (EUS) and integrated PET/CT scans are utilized to select patients for surgery, to exclude metastatic disease and to identify and quantify lymph node involvement. For patients with locally advanced cancer, lymph node involvement has been shown to be a strong independent predictor of poor survival with surgery alone. These patients are therefore considered for preoperative therapy followed by surgery. In the future, molecular biologic techniques may result in improved prognostic stratification, improved patient selection for surgical therapy, and improved OS.[117-119]

Surgical Approaches

Several operative techniques are acceptable for esophagogastrectomy in patients with resectable esophageal or EGJ cancers.[120] Transthoracic and transhiatal esophagogastrectomy are the two most common surgical approaches. Acceptable operative techniques and the choice of conduit are described below.

Transthoracic Esophagogastrectomy

Ivor Lewis esophagogastrectomy (right thoracotomy and laparotomy),[121] and the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis)[122] are the two standard options for transthoracic esophagogastrectomy. Ivor Lewis esophagogastrectomy, the most frequently used procedure for transthoracic esophagogastrectomy, uses laparotomy and right thoracotomy, with upper thoracic esophagogastric anastomosis (at or above the azygos vein).[121] Mobilization of the stomach for use as the conduit is performed, with dissection of the celiac and left gastric lymph nodes, division of the left gastric artery, and preservation of the gastroepiploic and right gastric arteries. This approach may be used for lesions in the distal thoracic location, but proximal esophageal margin will be inadequate for tumors in the middle esophagus. McKeown esophagectomy, with an anastomosis in the cervical region, is similar in conduct, but with the advantage of being applicable for tumors in the upper, middle, and lower thoracic esophagus.

Transhiatal Esophagogastrectomy

Transhiatal esophagogastrectomy (laparotomy and cervical anastomosis) is performed using abdominal and left cervical incisions.[123] The mobilization of the stomach for use as the conduit is performed as in the Ivor-Lewis esophagogastrectomy. This procedure is completed through the abdominal incision, and the gastric conduit is

drawn through the posterior mediastinum and exteriorized in the cervical incision for the esophagogastric anastomosis. This approach may be used for lesions at any thoracic location; however, transhiatal dissection of large, middle esophageal tumors adjacent to the trachea is difficult and may be hazardous. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy.[124] In the largest population based study, which assessed outcomes after transthoracic and transhiatal esophagectomy for esophageal cancer, transhiatal esophagectomy offered an early survival advantage. However, long-term survival was not different between the two surgical approaches.[125] Though survival differences have not been demonstrated, many believe that the lower lymph node retrieval associated with transhiatal esophagectomy represents a less effective oncologic approach.

Transthoracic or Thoracoabdominal Esophagogastrectomy

Left transthoracic or thoracoabdominal esophagogastrectomy uses a contiguous abdominal and left thoracic incision through the eighth intercostal space.[126] 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, particularly bulky tumors.[126]

Minimally Invasive Esophagectomy

Minimally invasive esophagectomy (MIE) strategies include minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy and limited thoracotomy or thoracoscopy) and minimally invasive McKeown esophagogastrectomy (thoracoscopy, limited laparotomy or laparoscopy, and cervical incision). MIE strategies may be associated with decreased morbidity and shorter recovery times. In a study of MIE (mainly using thoracoscopic mobilization) in 222 patients, mortality rate was only 1.4% and hospital stay was only 7 days, which is less than most open procedures; only 16 patients (7.2%) required conversion to an open procedure.[127] However, it is important to note that 62% of their patients had early-stage disease. A recent report involving 56 patients also showed that MIE was comparable to open esophagectomy but the use of neoadjuvant treatment slightly increased the surgical mortality from 1.5% to 1.8%.[128] No randomized trials have assessed whether MIE improves outcomes when compared with open procedures. Open esophagectomy may still be preferred over MIE for certain patients with previous abdominal surgery, large and bulky tumors, concerns that the gastric conduit may not be useable, and difficulty with lymph node dissection. MIE is still an evolving treatment option for patients with esophageal cancer, although it is reasonable to replace thoracotomy with thoracoscopy when possible, especially in older patients and those with significant comorbidity.[129-131]

Anastomosis and Choice of Conduit

The optimal location of the anastomosis has been debated. Potential advantages of a cervical anastomosis include more extensive resection of the esophagus, possibility of avoiding thoracotomy, less severe symptoms of reflux, and less severe complications related to anastomotic leak. Advantages of a thoracic anastomosis may include lower incidence of anastomotic leak, lower stricture rate, and lower rate of left recurrent nerve injury. In a prospective randomized trial, cervical and thoracic anastomoses after esophageal resection were equally safe when performed in a standardized way.[132] Gastric conduit is preferred for esophageal reconstruction by the majority of esophageal surgeons.[133] Colon interposition is usually reserved for patients who

have undergone previous gastric surgery or other procedures that might have devascularized the stomach.[134]

Principles of Surgery

All patients should be assessed for physiologic ability to undergo esophageal resection.[135] Selection of patients for surgery involves assessing whether they are medically fit (medically able to tolerate general anesthesia and major abdominal and/or thoracic surgery). Most patients with early-stage cancer can tolerate resection. Patients with potentially resectable esophageal cancer should undergo multidisciplinary evaluation.

Clinical staging using EUS with fine-needle aspiration (FNA), if indicated, chest and abdomen CT scan, and PET scan (integrated PET/CT preferred over PET alone) should be performed before surgery to assess resectability.[136] Patients with locally advanced cancer (T3 or N1) should have access to medical and radiation oncology consults. Pretreatment nutritional support should be considered for patients with significant dysphagia and weight loss in order to support them during induction chemoradiation. Enteral nutrition is the best option and a jejunostomy feeding tube is preferred over gastrostomy feeding tube or percutaneous endoscopic gastrostomy (PEG) tube.

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

Esophagectomy should be considered for all physiologically fit patients with localized, resectable, thoracic esophageal cancer (greater than 5 cm from cricopharyngeus) and intraabdominal esophageal or EGJ cancer. Esophagectomy should be performed in high-volume esophageal cancer centers by experienced surgeons.[137] The type of esophageal resection is dictated by the size, stage, and location of the primary tumor, as well as the surgeon's experience and the patient's preference. Cervical or cervicothoracic esophageal cancers less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Palliative esophagectomy can be considered for patients with cervical esophageal cancer who develop localized, resectable esophageal recurrence or untreatable stricture after definitive chemoradiation if there is no distant recurrence.[138]

The surgical approach for Siewert Type I and II EGJ tumors are similar to that described above. Siewert Type III tumors are considered as gastric cancers and the surgical approach for these tumors is similar to that described in the NCCN Guidelines for Gastric Cancer.[50,139,140] In some cases, additional esophageal resection may be necessary to obtain adequate surgical margins.

Laparoscopy may be useful in select patients for the detection of radiographically occult metastatic disease, especially in patients with Siewert Type II and III tumors.[141] Positive peritoneal cytology in the absence of overt peritoneal metastases is associated with a poor prognosis in patients with EGJ adenocarcinoma.[142] Patients with advanced tumors, clinical stage T3 tumors, or node-positive tumors should be considered for laparoscopic staging with peritoneal washings.

Patients with Tis or T1a tumors should have an option for endoscopic therapy. Patients with positive deep margins after ER and with tumors in the submucosa (T1b) or deeper may be treated with esophagectomy. Patients with T1-T3 tumors (stage I or II disease) are considered to be

potentially resectable, even in the presence of regional nodal metastases, although patients with bulky, multi-station nodal involvement have poor OS. Selected patients with stage III disease may have resectable tumor as well. T4a tumors with involvement of the pericardium, pleura, or diaphragm may be resectable. EGJ tumors with supraclavicular lymph node involvement, stage IV tumors with distant metastases including non-regional lymph node involvement, and T4b tumors with involvement of the heart, great vessels, trachea, or adjacent organs including liver, pancreas, lung, and spleen are considered unresectable.

Lymph node dissections (or lymphadenectomy) can be performed using the standard or extended (en-bloc) technique. In a retrospective analysis of 29,659 patients diagnosed with invasive esophageal cancer in the SEER database, patients who had more than 12 lymph nodes examined had significant reduction in mortality compared to those who had no lymph node evaluation, and patients who had 30 or more lymph nodes examined had significantly lower mortality than any other groups.[143] The number of lymph nodes removed has also been shown to be an independent predictor of survival after esophagectomy.[144,145] A recent report from the WECC database, which analyzed 4627 patients who had esophagectomy alone, also suggested that greater extent of lymphadenectomy was associated with increased survival for all patients with pN0M0 moderately and poorly differentiated cancers and all node-positive (pN+) cancers.[145] In patients undergoing esophagectomy without preoperative chemoradiation, the guidelines recommend that at least 15 lymph nodes should be removed for adequate nodal staging. The optimum number of nodes to be removed and examined after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.

Endoscopic Therapies

ER (endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD]) and endoscopic ablation (cryoablation, RFA and PDT) are used as effective alternate treatment options for early-stage esophageal and EGJ cancers, with much less treatment-related morbidity than surgical resection.

Although no randomized studies have compared ER and endoscopic ablation procedures with other surgical techniques for GI cancers, retrospective studies have demonstrated that ER and other endoscopic ablation procedures are effective treatment options for selected patients with Barrett's esophagus and early-stage esophageal and EGJ cancers.[146-149] In a SEER database analysis of 1458 patients with T1N0 esophageal cancer treated with surgery or endoscopic therapy (EMR, RFA, cryoablation or PDT), the OS rates were similar after treatment with surgery or endoscopic therapy; however, patients treated with endoscopic therapy had better cancer-specific survival, supporting the use of endoscopic therapy as an effective treatment option for patients with early-stage esophageal and EGJ cancers.[148]

EMR is widely used for the treatment of patients with superficial early SCC of the esophagus in Japan and is gaining acceptance in Western countries for the treatment of Barrett's esophagus and superficial adenocarcinomas.[150-153] Complete Barrett's eradication EMR (CBE-EMR) has been shown to be a highly effective long-term treatment for patients with Barrett's esophagus and HGD.[154-158]

ESD has also been established as a safe and effective procedure for patients with early-stage esophageal and EGJ cancers, resulting in high en-bloc resection rates and lower rates of major complications.[159-162] Retrospective studies have reported significantly better en-bloc

resection and local recurrence rates for ESD than for EMR in patients with early-stage SCC of the esophagus.[163,164]

RFA either alone or in combination with ER is an effective treatment for the complete eradication of residual dysplasia or Barrett's esophagus.[61,146,147,165-168] Endoscopic cryoablation has also been reported to be safe and well-tolerated in patients with Barrett's esophagus and early-stage esophageal cancers.[169,170]

PDT with porfimer sodium or 5-aminolevulinic acid has produced excellent long-term results in patients with Barrett's esophagus and HGD.[171-173] However, more recently, the use of PDT as an endoscopic therapy for esophageal cancers is losing popularity due to long-term consequences.

Principles of Endoscopy

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

Diagnosis

Diagnostic endoscopies are performed to determine the presence and location of esophageal neoplasia and to biopsy any suspicious lesions. The location of the tumor relative to the teeth and EGJ, the degree of obstruction, and the length and the extent of circumferential involvement of the tumor should be carefully recorded to assist with treatment planning. Esophageal tumor length, as assessed by preoperative endoscopy, has been identified as an independent predictor of long-term survival in patients with adenocarcinoma of the esophagus.[174] The 5-year survival rate was significantly higher for patients with a tumor length of 2 cm or less (78% vs. 29% for those with a tumor length of more than 2 cm).

Multiple biopsies (6–8), using standard size endoscopy forceps, should be performed to provide sufficient material for histologic interpretation.[175] High-resolution endoscopy and narrow-band imaging may enhance visualization during endoscopy, with improved detection of lesions in Barrett's and non-Barrett's esophagus and stomach.[176,177]

ER of focal nodules should be performed in the setting of early-stage disease to provide accurate depth of invasion, degree of differentiation and the presence of vascular and/or lymphatic invasion.[178-180] The depth of tumor invasion, evidence of lymphovascular invasion (LVI) and status of resection margins have been identified as the strongest predictors of OS.[181-183] ER may be potentially therapeutic when a lesion ≤2 cm in diameter is fully removed with clear lateral and deep margins and histopathologic assessment demonstrates well or moderate differentiation, invasion no deeper than the superficial submucosa and no LVI.[181,184,185]

ER should be considered in the treatment of Barrett's esophagus associated with HGD and patches of squamous cell dysplasia, specifically focusing on areas on nodularity or ulceration. Pathologists should be asked to provide an assessment of the depth of tumor infiltration into the lamina propria, muscularis mucosa and submucosa, invasion of vascular structures, and nerves and the presence of tumor or dysplastic cells at the lateral and deep margins.

Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment.

Staging

EUS performed prior to any treatment provides evidence of depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and occasionally signs of distant spread, such as lesions in surrounding organs (M).[179,186,187] ER should be performed for small nodular lesions (≤2 cm) as it provides more accurate depth of invasion than EUS.[188,189] A decision to proceed with further treatment such as ablation, resection or to consider the ER completely therapeutic would depend upon the final pathologic assessment of the ER specimen.

Mediastinal and perigastric lymph nodes are readily identified by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well circumscribed, and rounded structures in these areas indicates the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but also is confirmed with the use of FNA biopsy for cytology assessment.[190] The combined use of EUS and FNA (EUS-FNA) has a greater accuracy than EUS alone in the evaluation of lymph node metastasis, especially celiac lymph nodes.[191,192] In a study that compared the performance characteristics of CT, EUS, and EUS-FNA for preoperative nodal staging in 125 patients with esophageal cancer, EUS-FNA was more sensitive than CT (83% vs. 29%) and more accurate than CT (87% vs. 51%) or EUS (87% vs. 74%) for nodal staging.[193] Direct surgical resection was contraindicated in 77% of evaluable patients due to advanced locoregional/metastatic disease.

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

Treatment

Tis or HGD, well to moderately differentiated lesions pathologically confined to the lamina propria or muscularis mucosa (pT1a) or the superficial submucosa (pT1b) without evidence of LVI or lymph node metastases can be treated with full ER.[182,194-198]

Small flat lesions (≤ 2cm) of Tis or HGD and Barrett's esophagus associated with HGD should be treated by ER as it provides more accurate histologic assessment of the lesion.[188] Larger flat lesions (> 2 cm) can be treated effectively by ER, but this is associated with greater risk of complications.[166,199] Such lesions can be effectively treated by ablation alone, but there are very limited data for the treatment of SCC with ablation alone.[61,146,147,166]

The goal of ER and/or ablation is the complete removal or eradication of early-stage disease (pTis, pT1a, selected superficial pT1b without LVI) and Barrett’s esophagus. Endoscopic therapy is considered “preferred” for patients with early-stage cancer (well or moderately differentiated Tis and T1a, ≤2 cm), because the risk of harboring lymph node metastases, local or distant recurrence and death from esophageal cancer is low following endoscopic therapy.[195,196] However, a thorough and detailed discussion regarding the comparative risk of

esophagectomy vs. potential for concurrent nodal disease should be undertaken, preferably between patient and surgeon, especially in cases with larger tumors, or deeper invasion.

Surveillance

Endoscopic surveillance following definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes and multiple biopsies of any visualized abnormalities. Patients who have received therapeutic ER should have endoscopic surveillance and mucosal ablation (as clinically indicated) approximately every 3 months for the first year and then less frequently in the second year.

Assessment with endoscopy with biopsy and brushings should be done 6 weeks after completion of preoperative therapy, in patients whom avoidance of surgery is being considered. Strictures should be biopsied to rule out neoplastic cause. EUS performed in conjunction with endoscopy exams has a high sensitivity for recurrent disease.[200] EUS-FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging.

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

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% to 10%.[201-203] 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.[204] However, in the RTOG 85-01 trial, all patients in the RT alone arm who received 64 Gy at 2 Gy per day with conventional techniques died of cancer by 3 years.[205] Therefore, the panel recommends that RT alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy.

Alternative RT techniques, such as hypoxic cell sensitizers and hyperfractionation, have not resulted in a clear survival advantage. Experience with intraoperative RT as an alternative to external beam RT is limited.[206] Intensity modulated RT (IMRT) is currently being investigated.[207-210] Retrospective studies comparing three dimensional (3D) conformal vs. IMRT for patients with esophageal cancer have generally shown superior dose conformity and homogeneity with IMRT and reduction of RT dose to the lungs and heart.[208,209]

In the adjuvant setting, randomized trials have not shown a survival advantage for preoperative or postoperative RT alone.[211-213] A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with preoperative RT.[214]

Brachytherapy alone is a palliative modality and results in a local control rate of 25% to 35% and in a median survival of approximately 5 months. In the randomized trial, Sur et al reported no significant

difference in local control or survival with high-dose brachytherapy compared with external beam RT.[215] In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 combined modality regimen (fluorouracil and cisplatin with 50 Gy of external beam RT) followed by an intraluminal boost.[216] The local failure rate was 27%, and acute toxicity rates were 58% (grade 3), 26% (grade 4), and 8% (grade 5). The cumulative incidence of fistula was 18% per year, and the crude incidence was 14%. Therefore, the additional benefit of adding intraluminal brachytherapy to RT or combined modality therapy, although reasonable, remains unclear.

Principles of Radiation Therapy

General Guidelines

RT (definitive, preoperative, postoperative, or palliative) can be an integral part of treatment for esophageal and EGJ cancers. In general, Siewert I and II tumors should be managed with RT guidelines applicable to esophageal and EGJ cancers. Depending on the clinical situation, Siewert III tumors may be more appropriately managed with RT guidelines applicable to either esophageal and EGJ cancers or gastric cancer. These recommendations may be modified depending on the location of the bulk of the tumor.

The panel recommends involvement of a multidisciplinary team, which should include medical, radiation and surgical oncologists, radiologists, gastroenterologists, and pathologists to determine optimal diagnostic, staging, and treatment modalities. All available information from pre-treatment diagnostic studies should be used to determine the target volume. Image guidance may be used appropriately to enhance clinical targeting.

A dose range of 41.4 to 50.4 Gy (delivered in fractions of 1.8–2 Gy per day) is recommended for preoperative RT. Patients who are not candidates for surgery due to the presence of comorbidities or other risk factors should receive RT doses of 50 to 50.4 Gy because the lower dose may not be adequate. The recommended dose ranges for postoperative and definitive RT are 45 to 50.4 Gy and 50 to 50.4 Gy, respectively. For definitive therapy, higher doses (60–66) may be appropriate for tumors of the cervical esophagus, especially when surgery is not planned.[217] However there is no evidence from randomized trials to support the additional benefit of this higher dose range.[218]

Simulation and Treatment Planning

It is optimal to treat patients in the supine position as the setup is generally more stable and reproducible. The use of an immobilization device is strongly recommended for reproducibility. The panel encourages the use of CT simulation and 3D treatment planning. When 4D-CT planning or other motion management techniques are used, margins may be modified to account for observed motion and may also be reduced if justified. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid target localization.

IMRT may be used in clinical settings where dose reduction to organs at risk cannot be achieved by 3D techniques.[208,209] Target volumes need to be carefully defined and encompassed while designing IMRT. Uncertainties from variations in stomach filling and respiratory motion should be taken into account. In designing IMRT for organs at risk such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses. In addition, the uninvolved stomach that may be used for future reconstruction should also be spared from high doses.

Target Volume

The gross tumor volume (GTV) should include the primary tumor and involved regional lymph nodes as identified by pre-treatment diagnostic studies such as CT scan, barium swallow, EUS, and PET/CT scans.

The clinical target volume (CTV) should include the areas at risk for microscopic disease and elective nodal regions (such as celiac axis nodal regions, supraclavicular nodes, cervical nodes and para-esophageal lymph nodes). Elective treatment of nodal regions depends upon the location of the primary tumor in the esophagus and EGJ.

The planning target volume (PTV) should include the tumor plus a cephalad and caudal margin of 5 cm, and a radial margin of 1.5 to 2 cm.

Normal Tissue Tolerance and Dose-limits

Treatment planning is essential to reduce unnecessary RT doses to organs at risk (such as the liver, kidneys, spinal cord, heart, especially the left ventricle, and lungs) and to limit the volume of organs at risk receiving high RT doses (< 30 Gy to 60% of liver; < 20 Gy to at least 60% of one kidney; <45 Gy to the spinal cord; <40 Gy to 30% of the heart) and effort should be made to keep the left ventricle doses to a minimum.

Lung dose may require particular attention, especially in the preoperatively treated patient. Normal lung (more than 2 cm outside the target volume) should not receive more than 40 Gy. As a general guideline, the proportion of total lung receiving ≥ 20 Gy should be limited to 25% and the proportion of total lung receiving ≥5 Gy should be limited to 50%, to reduce the incidence of postoperative pulmonary complications). Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients treated with concurrent chemoradiation. Optimal criteria for DVH parameters are actively being developed in NCCN Member Institutions.

These guidelines may be exceeded as needed to achieve other important planning goals, and as further information becomes available.

Supportive Care

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

Combined Modality Therapy

Combined modality therapy has been employed for the treatment of esophageal and EGJ cancers because of the poor OS rates in patients who have been treated with resection alone.[219]

Definitive Chemoradiation Therapy

Concurrent chemoradiation therapy versus RT, each without resection, was studied in the only randomized trial (RTOG 85-01) designed to deliver adequate doses of systemic chemotherapy with concurrent RT.[205,220] In this trial, patients with SCC or adenocarcinoma with clinical stage T1-3, N0-1, M0 received 4 cycles of fluorouracil and cisplatin.[205,220] RT (50 Gy at 2 Gy/d) was given concurrently with day 1 of chemotherapy. The control arm was RT alone (64 Gy). Patients who

were randomly assigned to receive combined modality therapy showed a significant improvement in both median survival (14 vs. 9 months) and 5-year OS (27% vs. none) with projected 8-year and 10-year survival rates of 22% and 20%, respectively. The incidence of local failure as the first site of failure (defined as local persistence plus recurrence) was also lower in the combined modality arm (47% vs. 65%).

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

The results of these two studies established definitive chemoradiation with fluorouracil and cisplatin using the RT dose of 50.4 Gy as the standard of care for patients with SCC or adenocarcinoma of the esophagus.

Recent reports have also confirmed the efficacy of definitive chemoradiation in patients with locally advanced esophageal cancer.[27,221-223] Definitive chemoradiation with docetaxel and cisplatin resulted in high ORR in patients with SCC (98%; 71% complete response). At the median follow-up of 18 months, the median OS time was 23 months.[221] The rate of locoregional progression-free survival (PFS), PFS and 3-year OS rates were 60%, 29%, and 37%, respectively. Definitive chemoradiation with carboplatin and paclitaxel was also well tolerated resulting in superior OS, disease-specific survival, durable locoregional control, and palliation in about half of the patients with unresectable esophageal cancer.[27,222] In a recent randomized phase III trial, 267 patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to definitive chemoradiation with either FOLFOX 4 (fluorouracil, leucovorin, and oxaliplatin) or fluorouracil and cisplatin.[223] The majority of patients had SCC. The median follow-up was 25.3 months. The median PFS was 9.7 months in the FOLFOX group and 9.4 months in the fluorouracil and cisplatin group (P = .64).[223] Although definitive chemoradiation with FOLFOX was not associated with a PFS benefit compared to chemoradiation with fluorouracil and cisplatin, the investigators suggest that FOLFOX might be a more convenient option for patients with localized esophageal cancer who may not be candidates for surgery.

Preoperative Chemoradiation Therapy

Preoperative chemoradiation followed by surgery is the most common approach for patients with resectable esophageal cancer, although this approach remains investigational.[224] The results of two meta-analyses have shown that preoperative chemoradiation therapy plus surgery significantly reduced 3-year mortality and locoregional recurrence, and preoperative chemoradiation therapy also downstaged the tumor when compared with surgery alone.[225,226] Another recent meta-analysis (1854 patients,12 randomized trials comparing preoperative chemoradiation vs. surgery alone) showed a significant survival benefit for preoperative chemoradiation in patients with resectable adenocarcinoma of the esophagus.[227] Swisher et al also reported that preoperative chemoradiation was associated with increased pCR (28% vs. 4%) and 3-year OS (48% vs. 29%) compared with preoperative chemotherapy in

patients with locally advanced esophageal cancer.[228] In a retrospective analysis of 363 patients with adenocarcinoma of the lower esophagus, the OS after preoperative chemoradiation was significantly shorter for patients with Barrett's esophagus compared to those without Barrett's esophagus (32 months vs. 51 months, respectively).[229]

However, randomized trials comparing surgery alone with preoperative chemoradiation followed by surgery in patients with clinically resectable cancer have shown conflicting results.[115,230-236] Results from the multicenter phase III randomized trial (CROSS study), the largest trial in its class, showed that preoperative chemoradiation with carboplatin and paclitaxel significantly improved OS and DFS compared to surgery alone in patients with resectable (T2-3, N0-1, M0) esophageal or EGJ cancers (368 patients;75% had adenocarcinoma and 23% had SCC).[115] R0 resection rate was higher in the chemoradiation arm compared to the surgery alone arm (92% and 69%, respectively). Median survival was 49 months in the chemoradiation arm compared to 24 months in the surgery alone arm. The 1-, 2-,3-, and 5-year survival rates were 82%, 67%, 58%, and 47%, respectively, in the chemoradiation arm compared to 70%, 50%, 44%, and 34%, respectively, in the surgery alone arm. The rate of pCR was higher for patients with SCC than for those with adenocarcinoma (49% and 23%, respectively; $P = .008$), but the histologic type was not a prognostic factor for survival. After a minimum follow-up of 24 months, the overall rate of recurrence rate was 35% in the chemoradiation arm compared to 58% in the surgery arm. Preoperative chemoradiation significantly reduced locoregional recurrence from 34% to 14% ($P < .001$) and peritoneal carcinomatosis from 14% to 4% ($P < .001$).[237]

In contrast to the results of the CROSS study, the results of another phase III randomized controlled study (FFCD 9901) showed that preoperative chemoradiation therapy with cisplatin and fluorouracil did not improve the rate of R0 resection and OS but enhanced postoperative mortality rate for patients with localized stage I or II esophageal cancer compared with surgery alone.[236] After a median follow-up of 93.6 months, the rate of R0 resection was 93.8% for chemoradiation vs. 92.1% for surgery alone (P = .749). The 3-year OS rates were 47.5% and 53.0% respectively ($P = .94$) and the postoperative mortality rate was 11.1% for chemoradiation compared to 3.4% for surgery alone ($P = .049$).

The effect of adding surgery to chemoradiation therapy in patients with locally advanced SCC of the esophagus has been evaluated in randomized trials.[238,239] Stahl et al randomized 172 patients to either induction chemotherapy followed by chemoradiation therapy and surgery or induction chemotherapy followed by chemoradiation therapy.[238] The 2-year PFS rate was better in the surgery group (64.3%) than in the chemoradiation group (40.7%). However, there was no difference in OS between the two groups. The surgery group had significantly higher treatment-related mortality than the chemoradiation therapy group (12.8% vs. 3.5%, respectively). Long-term results with a median follow-up of 10 years also showed no clear difference in survival between the two groups.[240] The Stahl trial was prematurely terminated due to lack of accrual. Bedenne et al (FFCD 9102 trial) also showed that adding surgery to chemoradiation provides no benefit compared with treatment with additional chemoradiation, especially in patients with locally advanced SCC of the esophagus who experience response to initial chemoradiation therapy.[239] However, this trial suffers from suboptimal design and low number of patients.

The CALGB 9781 trial was a prospective randomized intergroup trial that evaluated trimodality therapy vs. surgery alone for the treatment of patients with stage I-III esophageal cancer.[241] The study fell short of its accrual goals with only 56 patients enrolled. Patients were randomized

to undergo either surgery alone or receive concurrent chemoradiation therapy with cisplatin and fluorouracil. Median follow-up was 6 years. An intent-to-treat analysis showed a median survival of 4.5 years vs.1.8 years, favoring trimodality therapy. Patients receiving trimodality therapy also had a significantly better 5-year survival rate (39% vs.16%). Although the accrual rate was low, the observed difference in survival was significant and this study showed that trimodality therapy might be an appropriate standard of care for patients with localized esophageal cancer.

In a recent phase II randomized study, preoperative chemoradiation with cisplatin and fluorouracil did not show any survival benefit over preoperative chemotherapy in patients (n = 75) with resectable adenocarcinoma of the esophagus and EGJ.[242] The median PFS was 26 and 14 months for chemotherapy and chemoradiation, respectively (*P* = .37). The corresponding median OS was 32 months and 30 months, respectively (*P* = .83). However, the pathologic response rate (31% vs. 8%; *P* = .01) and R1 resection rate (0% vs. 11%; *P* = .04) favored chemoradiation therapy.

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Sequential preoperative chemotherapy followed by chemoradiation has also been evaluated in clinical studies for patients with locally advanced esophageal and EGJ cancers.[243-251]

In a phase III study, Stahl et al compared preoperative chemotherapy (cisplatin, fluorouracil, and leucovorin) with chemoradiation therapy using the same regimen in 119 patients with locally advanced EGJ adenocarcinoma.[247] Patients with locally advanced adenocarcinoma of the lower esophagus or EGJ were randomized to chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiation followed by surgery (arm B). Patients in arm B had a significantly higher probability of achieving pCR (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection. Preoperative chemoradiation therapy improved 3-year survival rate from 27.7% to 47.4%. Although the study was closed prematurely due to low accrual and statistical significance was not achieved, there was a trend towards survival advantage for preoperative chemoradiation compared with preoperative chemotherapy in patients with EGJ adenocarcinoma.

In a phase II study, preoperative chemotherapy with irinotecan and cisplatin followed by concurrent chemoradiation with the same regimen resulted in moderate response rates in patients with resectable, locally advanced gastric and EGJ adenocarcinoma.[248] R0 resection was achieved in 65% of patients. Median survival and the actuarial 2-year survival rate were 14.5 months and 35%, respectively.[248] In another multicenter phase II trial (SAKK 75/02), preoperative induction chemotherapy with docetaxel and cisplatin followed by chemoradiation with the same regimen was effective in patients with SCC or adenocarcinoma of the esophagus (66 patients; 57 underwent surgery). R0 resection was achieved in 52 patients. Median OS and EFS were 36.5 months and 22.8 months, respectively.[249]

In a phase II trial that evaluated preoperative induction chemotherapy followed by chemoradiation with irinotecan and cisplatin prior to surgery for esophageal and EGJ cancers, the rate of pCR (16%) was relatively low and the rates of R0 resection (69%), PFS and OS were either comparable or inferior to those observed in phase II trials that have evaluated preoperative chemoradiation.[250] With a median follow-up of 65 months, the median PFS and OS were 15.2 months and 31.7 months, respectively. The results of another phase II randomized trial also showed that the use of induction chemotherapy (oxaliplatin plus fluorouracil) before preoperative chemoradiation with the same regimen

resulted in a non-significant increase in the rate of pCR and did not prolong OS in patients with esophageal cancer.[251]

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

Postoperative Chemoradiation Therapy

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[252] In this trial 556 patients (20% of patients had EGJ adenocarcinoma) with resected adenocarcinoma of the stomach or EGJ (stage IB-IV, M0 according to 1988 AJCC staging criteria) were randomly assigned to surgery plus postoperative chemoradiation (n=281; bolus fluorouracil and leucovorin before and after concurrent chemoradiation with 5-fluorouracil and leucovorin) or surgery alone (n=275). The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%); only 31% of the patients had T1-T2 tumors and 14% of patients had node-negative tumors. Surgery was not part of the trial protocol, but resection of all detectable disease was required for participation in the trial. Patients were eligible for the study only after recovery from surgery. Postoperative chemoradiation (offered to all patients with tumors T1 or higher, with or without lymph node metastases) significantly improved OS and RFS. Median OS in the surgery-only group was 27 months and was 36 months in the chemoradiation group (P = .005). The chemoradiation group had better 3-year OS (50% vs. 41%) and RFS rates (48% vs.31%) than the surgery-only group. There was also a significant decrease in local failure as the first site of failure (19% vs. 29%) in the chemoradiation group. With more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric or EGJ adenocarcinoma treated with postoperative chemoradiation. No increases in late toxic effects were noted.[253]

The results of the INT-0116 trial have established postoperative chemoradiation therapy as a standard of care in patients with completely resected gastric or EGJ adenocarcinoma who have not received preoperative therapy. However, the regimen used in this trial (bolus fluorouracil and leucovorin before and after chemoradiation with the same combination) was associated with high rates of grade 3 or 4 hematologic and GI toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group only 64%, of patients completed treatment and 17% discontinued treatment due to toxicity. Three patients died as a result of chemoradiation-related toxic effects, including pulmonary fibrosis, cardiac event, and myelosuppression.

Although the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric or EGJ adenocarcinoma, the recommended doses or schedule of chemotherapy agents as used in the INT-0116 trial are no longer used due to concerns regarding toxicity. In retrospective analyses, the addition of postoperative chemoradiation has been associated with survival benefit in patients with lymph node–positive locoregional esophageal cancer.[254,255] Data from a more recent retrospective analysis also showed that postoperative chemoradiation according to the Intergroup-0116 protocol resulted in improved DFS after curative resection in patients (n = 211) with EGJ adenocarcinomas and positive lymph nodes, who did not receive neoadjuvant chemotherapy.[256] The 3-year DFS rate after postoperative chemoradiation was 37% compared to 24% after surgery alone.

Alternative postoperative chemoradiation regimens have been evaluated by other investigators.[257,258] In a phase II non-randomized trial that evaluated postoperative concurrent chemoradiation with cisplatin and fluorouracil in patients with poor-prognosis esophageal and EGJ adenocarcinoma, the projected rates of 4-year OS, freedom from recurrence, distant metastatic control, and locoregional control were 51%, 50%, 56%, and 86%, respectively, for patients with node-positive tumors (T3 or T4), which are better than the historical outcomes with surgery alone.[257] In the randomized Intergroup trial (CALGB 80101), postoperative chemoradiation with ECF before and after fluorouracil and RT did not improve survival compared to the INT-0116 regimen in patients who have undergone curative resection for gastric or EGJ adenocarcinoma.[258]

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

Chemotherapy

Preoperative Chemotherapy

Chemotherapy alone has been investigated in the preoperative setting. The RTOG 8911 (Intergroup 0113) trial randomized patients with potentially resectable esophageal cancer of both histologic types to either receive preoperative chemotherapy (fluorouracil plus cisplatin) or undergo surgery alone. The preliminary results of this study did not show any survival benefit between the two groups.[259] 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.[260] Although preoperative chemotherapy decreased the incidence of R1 resection (4% compared with 15% in the surgery only group), there was no improvement in OS between the two groups.

In the MRC OEO2 trial conducted by the Medical Research Council, 802 patients with potentially resectable esophageal cancer were randomly assigned to either 2 cycles of preoperative fluorouracil (1000 mg/m^2 per day by continuous infusion for 4 days) and cisplatin (80 mg/m^2 on day 1) repeated every 21 days followed by surgery, or surgery alone.[261] 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 months vs.13.3 months). Long-term follow-up confirmed that preoperative chemotherapy improves survival in patients with resectable esophageal cancer.[262] At a median follow-up of 6 years, DFS and OS were significantly longer for the preoperative chemotherapy group. The difference in survival favoring the preoperative chemotherapy group (23% vs.17% for surgery) was consistent in patients with SCC and adenocarcinoma.[262]

Long-term results of another randomized trial also showed that preoperative chemotherapy with a combination of etoposide and cisplatin significantly improved OS and DFS in patients (n = 169) with SCC of the esophagus.[263] Median OS was 16 months for patients assigned to preoperative chemotherapy followed by surgery compared to 12 months for those who underwent surgery alone. The 5-year survival rates were 26% and 17%, respectively.

An individual, patient, data-based meta-analysis showed a small but significant OS and DFS benefit favoring preoperative chemotherapy over surgery alone.[264] The results of an updated meta-analysis, which

included 1981 patients from 9 randomized trials comparing preoperative chemotherapy vs. surgery alone, showed a survival benefit for preoperative chemotherapy in patients with resectable adenocarcinoma of the esophagus.[227]

Perioperative Chemotherapy

The British Medical Research Council performed the first well-powered phase III trial (MAGIC trial) that evaluated perioperative chemotherapy for patients with resectable gastroesophageal cancer.[116] In this trial, 503 patients were randomized to receive either surgery alone or perioperative chemotherapy (preoperative and postoperative chemotherapy) with ECF and surgery. Patients were randomized prior to surgical intervention. The majority (74%) of the patients had stomach cancer, whereas a small group of patients had adenocarcinoma of the lower esophagus (14%) and EGJ (11%). The majority of patients had T2 or higher tumors (12% had T1 tumors, 32% had T2 tumors, and 56% had T3-T4 tumors), and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5%, respectively). Perioperative chemotherapy significantly improved PFS ($P < .001$) and OS ($P = .009$). The 5-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

In a more recent FNCLCC/FFCD trial (n = 224; 75% of patients had adenocarcinoma of the lower esophagus or EGJ and 25% had gastric cancer), Ychou et al reported that perioperative chemotherapy with fluorouracil and cisplatin significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[265] At the median follow-up of 5.7 years, the 5-year OS rate was 38% for patients in the surgery plus perioperative chemotherapy group and 24% for patients in the surgery only group ($P = .02$). The corresponding 5-year DFS rates were 34% and 19%, respectively. This trial was prematurely terminated due to low accrual.

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

Chemotherapy for Locally Advanced or Metastatic Cancer

Cisplatin is one of the most active agents, with a single-agent response rate consistently in the range of 20% or greater.[266] Several other agents including irinotecan,[267-269] docetaxel,[270,271] paclitaxel[272,273] and etoposide[274] have also shown single agent activity in patients with advanced or metastatic esophageal cancer. Cisplatin plus fluorouracil is the most investigated and most commonly used regimen for patients with esophageal cancer, resulting in response rates of 20% to 50%.

Cisplatin plus paclitaxel or docetaxel, with or without fluorouracil, has also demonstrated activity in patients with locally advanced EGJ or metastatic esophageal cancers.[275-280] In a randomized multinational phase III study (V325), 445 untreated patients were randomized to receive either DCF (every 3 weeks) or the combination of cisplatin and fluorouracil (CF).[279] The majority of patients had advanced gastric cancer and 19% to 25% of patients had EGJ cancer. At a median follow-up of 13.6 months, time to progression was significantly longer with DCF compared with CF (5.6 months vs. 3.7 months; $P < .001$). The median OS was significantly longer for DCF compared with CF (9.2 months vs. 8.6 months; $P = .02$), at a median follow-up time of 23.4 months; the overall confirmed response rate was also significantly higher with DCF than CF (37% and 25%, respectively; $P = .01$).[279] Various modifications of the DCF regimen with the intent to improve

tolerability are being evaluated in clinical trials for patients with advanced esophagogastric cancer.[281-285]

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

Irinotecan-based combination regimens have also been evaluated in prospective studies as first-line therapy for patients with advanced or metastatic esophageal or EGJ cancers.[287-293] The results of a randomized phase III study (n = 337) showed that irinotecan in combination with fluorouracil and folinic acid (IF) was non-inferior to cisplatin in combination with infusional fluorouracil (CF) in terms of PFS (the estimated probabilities of PFS at 6 and 9 months were 38% and 20% for IF compared to 31% and 12%, respectively for CF) but not for OS (9 months vs. 8.7 months for CF) and time to treatment progression (5 months vs. 4.2 months for CF; P = .018).[288] IF was associated with a more favorable toxicity profile. In a phase II study that evaluated irinotecan in combination with fluorouracil and folinic acid (AIO regimen) in patients with locally advanced or metastatic esophageal cancer (adenocarcinoma or SCC), partial response was achieved in 33% of evaluable patients (n=19); 38% had stable disease and 8% had progressive disease.[289] Median survival was 20 months and 10 months, respectively, for patients with adenocarcinoma and SCC. A more recent randomized phase III study (A French Intergroup Study) compared fluorouracil, leucovorin, and irinotecan (FOLFIRI) with ECF as first-line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[293] In this study, 416 patients (65% of patients had gastric adenocarcinoma and 33% had EGJ adenocarcinoma) were randomized to receive either FOLFIRI or ECF. After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECX (5.1 months vs. 4.2 months; *P* = .008).[293] There were no significant differences in median PFS (5.3 months vs. 5.8 months; *P* = .96), median OS (9.5 months *vs.* 9.7 months; *P* = .95), or response rate (39.2% *vs* 37.8%). FOLFIRI was less toxic and better tolerated than ECF. The NCCN panel felt that FOLFIRI is an acceptable option for first-line therapy for patients with advanced or metastatic EGJ adenocarcinoma.

Irinotecan in combination with fluorouracil or docetaxel or capecitabine has also demonstrated activity in patients with advanced or metastatic esophagogastric cancer that had progressed on platinum-based chemotherapy.[290,294,295]

Combination chemotherapy regimens containing oxaliplatin,[296,297] carboplatin,[298] mitomycin[299] and gemcitabine[300,301] have also been evaluated in patients with advanced or metastatic esophageal cancer. A phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin, and oxaliplatin (FLO) was associated with significantly less toxicity and showed a trend towards

improved median PFS (5.8 vs. 3.9 months) compared to fluorouracil, leucovorin, and cisplatin (FLP) in patients with metastatic esophagogastric cancer.[297] However, no significant differences were seen in median OS (10.7 vs. 8.8 months, respectively) between the FLO and FLP regimens. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), and PFS (6.0 vs. 3.1 months), and an improved OS (13.9 vs. 7.2 months) compared with FLP, respectively. The combination of carboplatin and paclitaxel was moderately active with a response rate of 43% in patients with advanced esophageal cancer.[298] However, 52% of patients had neutropenia (grade 3-4). In a prospective randomized study, the combination of mitomycin, cisplatin, and fluorouracil (protracted intravenous infusion) was equally efficient to ECF (protracted intravenous infusion) for patients with advanced esophagogastric cancer, but the quality of life was superior with the ECF regimen.[299]

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.[302] 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.[303] Adequately powered phase III studies are lacking.

Targeted Therapies

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-neu-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[73] In this trial, 594 patients with HER2-neu-positive (3+ on IHC or FISH positive [HER2:CEP17 ≥2]), locally advanced, recurrent, or metastatic gastric and EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone.[73] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 months and 17 months, respectively, in the two groups. There was a significant improvement in the median OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone in patients with *HER2*-neu overexpression or amplification (13.8 vs.11 months, respectively; *P* = .046). This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with HER2-neu-positive advanced or metastatic gastric and EGJ adenocarcinoma.

However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3 + or IHC 2+ and FISH positive. There was no significant survival benefit for patients whose tumors were IHC 0 or 1+ and FISH positive.[73] In the post-hoc subgroup analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; hazard ratio [HR] = .65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR = 1.07).

Ramucirumab, a VEGFR-2 antibody, has shown promising results in the treatment of patients with previously treated advanced or metastatic gastric or EGJ cancers in phase III clinical trials.[304,305] An international, randomized, multicenter, placebo-controlled, phase III trial (REGARD trial) demonstrated a survival benefit for ramucirumab for patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[304] In this study, 355 patients were randomized to receive ramucirumab (n=238; 178 patients with gastric cancer; 60

patients with EGJ adenocarcinoma) or placebo (n=117; 87 patients with gastric cancer; 30 patients with EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). Ramucirumab was associated with higher rates of hypertension than the placebo group (16% vs. 8%), whereas rates of other adverse events were mostly similar between the two groups. In a more recent international phase III randomized trial (RAINBOW trial) that evaluated paclitaxel with or without ramucirumab in patients with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy, the combination of paclitaxel with ramucirumab resulted in significantly higher OS, PFS, and ORR than paclitaxel alone.[305] In this study 665 patients were randomized to ramucirumab plus paclitaxel (n =330) and paclitaxel alone (n = 335). The median OS was significantly longer for ramucirumab plus paclitaxel group compared to paclitaxel alone (9.63 months vs. 7.36 months *P* < .0001). The median PFS was 4.4 months and 2.86 months, respectively, for the two treatment groups. The ORR was 28% for ramucirumab plus paclitaxel compared to 16% for paclitaxel alone (*P* = .0001). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel.

Based on the results of these two studies, ramucirumab either as a single agent or in combination with paclitaxel was recently approved by the FDA for the treatment for patients with advanced EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy.

Other investigational agents targeting EGFR and MET/hepatocyte growth factor receptors have shown encouraging results in patients with advanced or metastatic esophageal and EGJ cancers.[306-308] Results of ongoing studies are awaited.

Treatment Guidelines

The management of patients with esophageal and EGJ cancers requires the expertise of several disciplines, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines are also desirable. Geneticists should be engaged when appropriate. Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of any discipline taking care of patients with esophagogastric cancer. Optimally at each meeting, the panel encourages participation of all relevant disciplines. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient. See *Principles of Multidisciplinary Team Approach for Esophagogastric Cancers* in the guidelines.

Workup

Newly diagnosed patients should undergo a complete history, physical examination, complete blood count (CBC) and chemistry profile, biopsy (to confirm histologic classification and metastatic cancer) and endoscopy with biopsy of the entire upper GI tract. If the cancer is located at or above the carina, bronchoscopy (including biopsy of any abnormality and cytology of the washings) should be performed. For patients in whom the upper GI tract cannot be visualized, a double contrast barium study of the upper GI tract is optional. CT scan (with oral and IV contrast) of the chest and abdomen should also be performed. ER is essential for the accurate staging of early-stage cancers.[178,179,180] Pelvic CT should be obtained when clinically indicated. EUS and PET/CT evaluation is recommended if metastatic cancer is not evident. HER2-neu testing is

recommended if metastatic disease is documented or suspected. See *Principles of Pathology* for assessment of *HER2-neu* overexpression. The guidelines recommended assessment of Siewert tumor type as part of initial workup in all patients with EGJ adenocarcinoma.[50,51] The guidelines also recommend screening for family history of esophageal or EGJ cancers. Referral to cancer genetics professional is recommended for an individual with a known high-risk syndrome associated with esophageal and EGJ cancers.

PET/CT scans are useful for the initial staging and evaluation of patients after chemoradiation prior to surgery for the detection of distant lymphatic and hematogenous metastases.[309-311] PET/CT scan has been shown to improve lymph node staging and the detection of stage IV esophageal cancer.[312] It has also been shown to be an independent predictor of OS in patients with non-metastatic esophageal cancer.[313] In addition, a recent study reported that combined PET/CT scans are more accurate than EUS-FNA and CT scan for predicting nodal status and complete response after neoadjuvant therapy in patients with esophageal cancer.[314] 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. A recent retrospective analysis involving patients with biopsy-proven esophageal cancer identified in a prospectively held database showed that the addition of PET/CT to standard staging led to changes in the multidisciplinary recommendations in 38.2% patients, improving the patient selection for radical treatment.[315]

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

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

Additional Evaluation

In patients with apparent locoregional cancer, additional evaluations may be warranted to assess their medical condition and feasibility of resection, especially for patients with celiac-positive disease. These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. Nasoduodenal or jejunostomy tube should be considered for preoperative nutritional support. PEG is not recommended. In patients with adenocarcinoma of the esophagus or EGJ, laparoscopic staging of the peritoneal cavity should be considered (optional) if there is no evidence of metastatic disease (M1).[141] 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 patients when colon interposition is planned.

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

- Medically fit patients
- Non-surgical candidates able to tolerate chemotherapy or chemoradiation
- Non-surgical candidates unable to tolerate chemotherapy or chemoradiation

Management of Locoregional Cancer in Medically Fit Patients

Primary Treatment for Squamous Cell Carcinoma

ER (EMR or ESD) with or without ablation (to completely eliminate multifocal dysplasia) is the preferred primary treatment option for patients with Tis or T1a tumors (less than or equal to 2 cm, and well or

moderately differentiated carcinoma). Ablation alone is an appropriate primary treatment option for patients with Tis tumors.

Available evidence (although very limited) indicates that ablation following ER may be effective for the complete removal or eradiation of early-stage SCC of the esophagus.[146,316] Ablation may not be needed if the lesions are completely excised. Esophagectomy is indicated for patients with extensive carcinoma in situ (Tis) or superficial T1a tumors, especially nodular disease that is not adequately controlled by ER with or without ablation.[181] Esophagectomy is the recommended primary treatment option for patients with T1b, N0 tumors.[181]

Primary treatment options for patients with T1b, N+ tumors and those with locally advanced resectable tumors (T2-T4a, any regional N) include preoperative chemoradiation (for non-cervical esophagus),[238,239] definitive chemoradiation (recommended for cervical esophagus)[218,220,317] or esophagectomy (for non-cervical esophagus).

Definitive chemoradiation is also the preferred treatment for patients with T4b (unresectable) tumors and occasionally can facilitate surgical resection in selected patients.[222] Chemotherapy can be considered only in the setting of invasion of trachea, great vessels, or heart.

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

Primary Treatment for Adenocarcinoma

Primary treatment options for patients with Tis, T1a or T1b, N0 tumors are similar to those described above for patients with SCC. ER (EMR or ESD) followed by ablation is the primary treatment for patients with superficial T1b tumors. Esophagectomy is indicated for nodular disease that is not adequately controlled by ER with or without ablation.[181]

Primary treatment options for patients with T1b, N+ and those with locally advanced resectable tumors (T2-T4a, any regional N) include preoperative chemoradiation (preferred),[115] definitive chemoradiation (only for patients who decline surgery),[218,220,223] perioperative chemotherapy,[116] or esophagectomy (for patients with low-risk and well-differentiated lesions less than 2 cm in size).

Definitive chemoradiation is the preferred treatment for patients with unresectable T4b tumors and occasionally can facilitate surgical resection in selected patients.[222]

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

Additional Treatment (SCC and Adenocarcinoma)

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

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

chemoradiation, patients with no evidence of disease can be observed and those with persistent local disease can be treated with palliative esophagectomy or palliative therapy.

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

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

Postoperative Treatment

Postoperative treatment is based on the surgical margins, nodal status, and histology. The efficacy of postoperative treatment has not been established in randomized trials for patients with esophageal cancer. Available evidence for the use of postoperative chemoradiation (only for patients who have not received preoperative therapy) and perioperative chemotherapy for patients with adenocarcinoma of the distal esophagus or EGJ comes from prospective randomized clinical trials involving patients with gastric cancer that have included patients with adenocarcinoma of the distal esophagus or EGJ.[116,252]

For Patients with SCC Who Have Not Received Preoperative Therapy

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

For Patients with Adenocarcinoma Who Have Not Received Preoperative Therapy

No further treatment is necessary for patients with Tis and T1, N0 tumors, if there is no residual disease at surgical margins (R0 resection). Based on the results of the INT-0116 trial, the panel has included postoperative fluoropyrimidine-based chemoradiation for all patients with T3-T4a tumors and node positive T1-T2 tumors.[252,253] Given the lack of evidence from randomized clinical trials showing any survival benefit for postoperative chemoradiation for patients with T2, N0 tumors, postoperative chemoradiation is recommended (category 2B) only for selected patients with high-risk features (poorly differentiated or higher grade cancer, LVI, neural invasion, or age younger than 50 years) if there is no residual disease at surgical margins (R0 resection).[318] Alternatively, patients with node-negative T2-T4a tumors can also be observed.

The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer.[252,253] However, the panel does not recommend the doses or the schedule of chemotherapy agents as used in the INT-0116 trial due to concerns regarding toxicity. Instead, the panel recommends the use of fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation.

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

For Patients with SCC Who Have Received Preoperative Therapy

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

For Patients with Adenocarcinoma Who Have Received Preoperative Therapy

Postoperative chemotherapy (category 1), if received preoperatively, is recommended for all patients (irrespective of the nodal status) if there is no residual disease at surgical margins (R0 resection).[116] Observation is an option for patients who have not received preoperative chemotherapy. Alternatively, patients with node-positive adenocarcinoma could be treated with chemoradiation (category 2B), if not received preoperatively. However, this approach has not been evaluated in prospective studies.

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

Management of Locoregional Cancer in Non-surgical Candidates

ER (EMR or ESD) with or without ablation (to completely eliminate residual dysplasia or Barrett's epithelium) is recommended for patients with Tis, T1a or T1b, N0 tumors. Ablation may not be needed if all the lesions are completely excised. Ablation alone may be an appropriate option for patients with Tis tumors.

Fluoropyrimidine-based or taxane-based definitive chemoradiation is the preferred treatment option for technically resectable locally advanced cancer (T2-T4a, any regional N) in non-surgical candidates who are able to tolerate chemotherapy or chemoradiation. Alternatively, these patients can also be treated with chemotherapy or RT or best supportive care.

Palliative RT or best supportive care are the appropriate options for non-surgical candidates who are unable to tolerate chemotherapy or chemoradiation.

Surveillance

All patients should be followed systematically. However, the surveillance strategies after successful local therapy of esophageal and EGJ cancers remain controversial since very limited prospective data is available on effective surveillance strategies.

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

The stage-specific recommendations for surveillance included in the NCCN Guidelines are based on the available evidence from retrospective studies[237,319-323] and the expertise of the panel members.

Stage (0-I): Tis, T1a and T1b

Early stage esophageal cancers are associated with a heterogenous pattern of relapse.[149,324-329] Recommendations for surveillance vary according to the depth of tumor invasion and the treatment modality. Evidence-based guidelines have not been established for all stages of completely treated early stage esophageal cancer. The recommendations outlined in the guidelines are based on available evidence from clinical trials and current practice.

Endoscopic surveillance with upper GI endoscopy (EGD) is recommended for patients with Tis, T1a and T1b tumors, after completion of endoscopic therapy. In patients with T1b tumors treated with esophagectomy, endoscopic surveillance with EGD should be done as clinically indicated based on the symptoms and radiographic findings. Routine imaging studies are not recommended for patients with Tis and T1a tumors.

See "*Principles of Surveillance for Esophageal and EGJ cancers"* in the guidelines for stage-specific recommendations.

Stage (II-III): T2-T4, N0-N+, T4b

Locoregional recurrences are common after bimodality therapy. Therefore, EGD is a valuable surveillance tool following bimodality therapy. In patients treated with bimodality therapy, the majority of recurrences (95%) occur within 24 months. Thus, surveillance for at least 24 months is recommended following bimodality therapy.[322]

EGD for surveillance is not recommended after trimodality therapy since locoregional recurrences are uncommon following trimodality therapy.[237,320,321]

The risk and rate of recurrence following trimodality therapy have been correlated with surgical pathology stage. In patients treated with trimodality therapy, the majority of recurrences (90%) occur within 36 months of surgery. Therefore, surveillance for at least 36 months is recommended following trimodality therapy.

See "*Principles of Surveillance for Esophageal and EGJ cancers"* in the guidelines for stage-specific recommendations.

Management of Metastatic, or Recurrent Cancer

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

When recurrence develops after chemoradiation therapy with no prior esophagectomy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option. When patients experience another recurrence after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described for locally advanced or metastatic cancer. Palliative therapy is recommended for medically unfit patients and those who develop an unresectable or metastatic recurrence.

Phase III trials for locally advanced or metastatic esophageal cancer have not been performed for many years. The survival benefit of second-line chemotherapy compared to best supportive care has been

demonstrated in a small cohort of patients with lower esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma trials.[330,331]

In a randomized phase III study, second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n = 40).[330] The study was closed prematurely due to poor accrual. Median survival was 4 months in the irinotecan arm compared to 2.4 months in the best supportive care only arm. In a recent open-label, multicenter, phase III, randomized trial, the addition of docetaxel to active symptom control was associated with a survival benefit for patients with advanced, histologically confirmed adenocarcinoma of the esophagus, EGJ junction, or stomach that had progressed on or within 6 months of treatment with combination chemotherapy with platinum and fluoropyrimidine.[331] In this study, patients (n = 168) with an ECOG PS score of 0-2 were randomly assigned to receive docetaxel plus active symptom control or active symptom control alone. After a median follow-up of 12 months, the median OS was 5.2 months for patients with the docetaxel group compared to 3.6 months for those in the active symptom control group (*P* = .01). Docetaxel was associated with higher incidence of grade 3-4 neutropenia, infection, and febrile neutropenia. However, disease-specific, health-related quality of life measures also showed benefits for docetaxel in reducing dysphagia and abdominal pain.

Docetaxel and irinotecan are included as options for second-line therapy for patients with locally advanced or metastatic disease. Other regimens included in the guidelines for patients with locally advanced or metastatic disease are derived from the gastric adenocarcinoma phase III trials that have included patients with lower esophageal and/or EGJ cancer.

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

Based on the results of the ToGA trial, the guidelines recommend the addition of trastuzumab to first-line chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients with HER2-overexpressing adenocarcinoma (a tumor score of IHC 3+ and IHC 2+ with the evidence of *HER2* amplification by FISH [HER2:CEP17 ratio ≥2]).[73] Trastuzumab is not recommended for patients with a tumor score of IHC 0 or 1+. The use of trastuzumab in combination with an anthracycline is not recommended. Based on the recent FDA approvals, the guidelines have included ramucirumab single agent or in combination with paclitaxel as options for second-line therapy in patients with advanced or metastatic esophageal or EGJ adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma).[304,305]

Best supportive care is always indicated for patients with locally advanced, metastatic, or recurrent disease. The decision to offer best supportive care alone or with chemotherapy is dependent on the patient's performance status. The Karnofsky Performance Status Scale (KPS)[332,333] and the ECOG Performance Status Scale (ECOG PS)[334] are the two commonly used scales to assess the performance status in patients with cancer.

KPS is an ordered scale with 11 levels (0 to 100) and the general functioning and survival of a patient is assessed based on his or her health status (http://www.hospicepatients.org/karnofsky.html).[332,333] Low Karnofsky scores are associated with poor survival and serious illnesses. ECOG PS is a 5-point scale (0–4) based on the level of symptom interference with normal activity.[334] Patients with higher levels are considered to have poor performance status. (http://www.ecog.org/general/perf_stat.html). Patients with a KPS score ≤60 or an ECOG PS score ≥3 should probably be offered best supportive care only. Patients with better performance status (KPS score ≥60 or an ECOG PS score ≤2) may be offered chemotherapy along with best supportive care. Further treatment after two sequential regimens depends on the patient's performance status and availability of clinical trials.

See the *Principles of Systemic Therapy* section of the guidelines for a list of specific regimens. Some of the chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published studies and institutional preferences that have support only from phase II studies.

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. Levoleucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin for all doses in all patients, since lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[335-337] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. A modest increase in fluorouracil dose (in the range of 10%) may be considered for patients who can tolerate this without grade II or higher toxicity.

Best Supportive Care

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

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Assessing the severity of the disease and swallowing impairment is essential to initiate appropriate interventions for long-term palliation of dysphagia in patients with esophageal cancer. Available palliative methods for the management of dysphagia include endoscopic lumen restoration or enhancement, placement of permanent or temporary self-expanding metal stents (SEMS), RT, brachytherapy, chemotherapy, or surgery.

Long term palliation of dysphagia can be achieved with endoscopic ablation or endoscopic and radiographic assisted insertion of expandable metal or plastic stents.[338,339] Temporary placement of SEMS with concurrent RT was found to be beneficial for increasing survival rates compared with permanent stent placement.[340] SEMS is the preferred treatment for patients with tracheoesophageal fistula and those who are not candidates for chemoradiation or those who failed to achieve adequate palliation with such therapy.[341] Membrane-covered stents have significantly better palliation than conventional bare metal

stents because of decreased rate of tumor ingrowth, which in turn is associated with lower rates of endoscopic reintervention for dysphagia.[339]

Although various treatment options are available for the management of dysphagia, optimal treatment is still debated. Treatment options for the management of dysphagia should be individualized. A multimodality interdisciplinary approach is strongly encouraged.

For patients with complete esophageal obstruction, the guidelines recommend endoscopic lumen restoration, external beam RT, chemotherapy, or surgery. Surgical or radiologic placement of jejunostomy or gastronomy tubes may be necessary to provide adequate hydration and nutrition, if endoscopic lumen restoration is not undertaken or is unsuccessful. Brachytherapy may be considered instead of RT, if lumen can be restored using appropriate applicators during the delivery of brachytherapy to decrease excessive dose on mucosal surfaces. Single-dose brachytherapy was associated with fewer complications and better long-term relief of dysphagia compared with metal stents.[342] Brachytherapy should only be performed by practitioners experienced with the delivery of esophageal brachytherapy.

For patients with severe esophageal obstruction (those able to swallow liquids only), the options include endoscopic lumen enhancement (wire-guided or balloon dilation), endoscopy, or fluoroscopy-guided placement of covered expandable metal stents or other measure described above. While there are data suggesting that a lower migration and re-obstruction rate with the larger diameter covered expandable metal stents, there may be a higher risk of stent-related complications.[343] Caution should be exercised when dilating malignant strictures, as this may be associated with an increased risk of perforation.[344]

Pain

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

Bleeding

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

Nausea and Vomiting

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

Summary

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

Tobacco and alcohol abuse are major risk factors for SCC of the esophagus. Barrett's esophagus, obesity, and GERD seem to be the major risk factors for development of adenocarcinoma of the esophagus or EGJ. In addition, some hereditary cancer predisposition syndromes are also associated with an increased risk of developing esophageal and EGJ cancers. Referral to cancer genetics professional is recommended for an individual with a genetic predisposition.

ER (with or without ablation) is recommended for patients with Tis, T1a, or superficial T1b tumors. Esophagectomy is the preferred primary treatment option for medically fit patients with T1b, N0 tumors. For medically fit patients with locally advanced resectable tumors (T1b, N+, T2 or higher, any N), primary treatment options include preoperative chemoradiation, definitive chemoradiation, preoperative chemotherapy (only for adenocarcinoma), or esophagectomy.

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

All patients with residual disease at surgical margins (R1 and R2 resections) may be treated with fluoropyrimidine-based chemoradiation. Fluoropyrimidine-based or taxane-based concurrent chemoradiation is recommended for patients with unresectable disease and for those with technically resectable disease who decline surgery and for non-surgical candidates able to tolerate chemotherapy.

Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal and EGJ cancers. Trastuzumab plus chemotherapy is recommended as first-line therapy for patients with HER2-positive advanced or metastatic adenocarcinoma. Ramucirumab single agent or in combination with paclitaxel is included as an option for second-line therapy for patients with advanced or metastatic adenocarcinoma. Best supportive care is an integral part of treatment, especially in patients with locally advanced or metastatic disease.

The NCCN Guidelines for Esophageal and EGJ Cancers provide an evidence- and consensus-based treatment approach. The panel encourages patients to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

References

1. Brown LM, Devesa SS, Chow W-H. Incidence of Adenocarcinoma of the Esophagus Among White Americans by Sex, Stage, and Age. J. Natl. Cancer Inst. 2008;100:1184-1187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18695138.

2. Trivers KF, Sabatino SA, Stewart SL. Trends in esophageal cancer incidence by histology, United States, 1998-2003. Int J Cancer 2008;123:1422-1428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18546259.

3. Bosetti C, Levi F, Ferlay J, et al. Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer 2008;122:1118-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17990321.

4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21296855.

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015:Epub ahead of print. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

6. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. Int J Epidemiol 2001;30:1415-1425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11821356.

7. Pickens A, Orringer MB. Geographical distribution and racial disparity in esophageal cancer. Ann Thorac Surg 2003;76:S1367-1369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14530066.

8. Siewert JR, Katja O. Are squamous and adenocarcinomas of the esophagus the same disease? Seminars in radiation oncology 2007;17:38-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17185196.

9. Siewert JR, Stein HJ, Feith M, et al. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11524589.

10. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000;85:340-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10652424.

11. Engel LS, Chow W-H, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1404-1413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13130116.

12. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007;165:1424-1433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17420181.

13. Gammon M, Schoenberg J, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J. Natl. Cancer Inst. 1997;89:1277-1284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9293918.

14. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium. Journal of the National Cancer Institute 2010;102:1344-1353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20716718.

15. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7742727.

16. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1998;90:150-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9450576.

17. Morris Brown L, Swanson CA, Gridley G, et al. Adenocarcinoma of the Esophagus: Role of Obesity and Diet. J. Natl. Cancer Inst. 1995;87:104-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7707381.

18. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883-890. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10375336.

19. Chow WH, Finkle WD, McLaughlin JK, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 1995;274:474-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7629956.

20. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10080844.

21. Cossentino MJ, Wong RK. Barrett's esophagus and risk of esophageal adenocarcinoma. Semin Gastrointest Dis 2003;14:128-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14653412.

22. Cameron AJ, Romero Y. Symptomatic gastro-oesophageal reflux as a risk factor for oesophageal adenocarcinoma. Gut 2000;46:754-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10807883.

23. Sharma P. Clinical practice. Barrett's esophagus. N Engl J Med 2009;361:2548-2556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20032324.

24. Gopal DV, Lieberman DA, Magaret N, et al. Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. Dig Dis Sci 2003;48:1537-1541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12924649.

25. Anandasabapathy S, Jhamb J, Davila M, et al. Clinical and endoscopic factors predict higher pathologic grades of Barrett dysplasia. Cancer 2007;109:668-674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17211862.

26. Das A, Thomas S, Zablotska LB, et al. Association of esophageal adenocarcinoma with other subsequent primary cancers. J Clin Gastroenterol 2006;40:405-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721221.

27. Ruppert BN, Watkins JM, Shirai K, et al. Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol 2010;33:346-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19841574.

28. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008:1-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559331.

29. Ellis A, Field JK, Field EA, et al. Tylosis associated with carcinoma of the oesophagus and oral leukoplakia in a large Liverpool family--a review of six generations. Eur J Cancer B Oral Oncol 1994;30B:102-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8032299.

30. Stevens HP, Kelsell DP, Bryant SP, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Literature survey and proposed updated classification of the keratodermas. Arch Dermatol 1996;132:640-651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8651714.

31. Risk JM, Field EA, Field JK, et al. Tylosis oesophageal cancer mapped. Nat Genet 1994;8:319-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7534553.

32. Kelsell DP, Risk JM, Leigh IM, et al. Close mapping of the focal non-epidermolytic palmoplantar keratoderma (PPK) locus associated with oesophageal cancer (TOC). Hum Mol Genet 1996;5:857-860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8776604.

33. Risk JM, Evans KE, Jones J, et al. Characterization of a 500 kb region on 17q25 and the exclusion of candidate genes as the familial Tylosis Oesophageal Cancer (TOC) locus. Oncogene 2002;21:6395-6402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12214281.

34. Langan JE, Cole CG, Huckle EJ, et al. Novel microsatellite markers and single nucleotide polymorphisms refine the tylosis with oesophageal cancer (TOC) minimal region on 17q25 to 42.5 kb: sequencing does not identify the causative gene. Hum Genet 2004;114:534-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15007728.

35. Romero Y, Cameron AJ, Locke GR, 3rd, et al. Familial aggregation of gastroesophageal reflux in patients with Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 1997;113:1449-1456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9352846.

36. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut 2002;51:323-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12171951.

37. Verbeek RE, Spittuler LF, Peute A, et al. Familial Clustering of Barrett's Esophagus and Esophageal Adenocarcinoma in a European Cohort. Clin Gastroenterol Hepatol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24480679.

38. Sun X, Elston R, Barnholtz-Sloan J, et al. A segregation analysis of Barrett's esophagus and associated adenocarcinomas. Cancer Epidemiol Biomarkers Prev 2010;19:666-674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20200424.

39. Orloff M, Peterson C, He X, et al. Germline mutations in MSR1, ASCC1, and CTHRC1 in patients with Barrett esophagus and esophageal adenocarcinoma. JAMA 2011;306:410-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21791690.

40. Ek WE, Levine DM, D'Amato M, et al. Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux. J Natl Cancer Inst 2013;105:1711-1718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24168968.

41. Ellis NA, German J. Molecular genetics of Bloom's syndrome. Hum Mol Genet 1996;5 Spec No:1457-1463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8875252.

42. German J. Bloom's syndrome. XX. The first 100 cancers. Cancer Genet Cytogenet 1997;93:100-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9062585.

43. de Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia. Mutat Res 2009;668:11-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19061902.

44. Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. Haematologica 2008;93:511-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322251.

45. van Zeeburg HJT, Snijders PJF, Wu T, et al. Clinical and molecular characteristics of squamous cell carcinomas from Fanconi anemia patients. J Natl Cancer Inst 2008;100:1649-1653. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19001603.

46. Oostra AB, Nieuwint AW, Joenje H, de Winter JP. Diagnosis of fanconi anemia: chromosomal breakage analysis. Anemia 2012;2012:238731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22693659.

47. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual (ed 7). New York, NY: Springer; 2010.

48. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. Dis Esophagus 2009;22:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19196264.

49. Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality Assessment of Esophageal Cancer: Preoperative Staging and Monitoring of Response to Therapy. Radiographics 2009;29:403-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19325056.

50. Siewert JR. Carcinoma of the cardia: carcinoma of the gastroesophageal junction classification, pathology, and extent of resection. Dis Esophagus 1996;9:173-182. Available at:

51. Siewert JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. Ann Surg 2000;232:353-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10973385.

52. Prasad GA, Bansal A, Sharma P, Wang KK. Predictors of progression in Barrett's esophagus: current knowledge and future directions. Am J Gastroenterol 2010;105:1490-1502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20104216.

53. Sharma P, Dent J, Armstrong D, et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. Gastroenterology 2006;131:1392-1399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17101315.

54. Chennat J, Waxman I. Endoscopic treatment of Barrett's esophagus: From metaplasia to intramucosal carcinoma. World J Gastroenterol 2010;16:3780-3785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20698040.

55. Nealis TB, Washington K, Keswani RN. Endoscopic therapy of esophageal premalignancy and early malignancy. J Natl Compr Canc Netw 2011;9:890-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21900219.

56. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014;63:7-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24165758.

57. Komanduri S, Swanson G, Keefer L, Jakate S. Use of a new jumbo forceps improves tissue acquisition of Barrett's esophagus surveillance biopsies. Gastrointest Endosc 2009;70:1072-1078 e1071. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19595312.

58. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103:1049-1057. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21680910.

59. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365:1375-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21995385.

60. Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2008;103:788-797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18341497.

61. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med

2009;360:2277-2288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474425.

62. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24668102.

63. Hechtman JF, Polydorides AD. HER2/neu gene amplification and protein overexpression in gastric and gastroesophageal junction adenocarcinoma: a review of histopathology, diagnostic testing, and clinical implications. Arch Pathol Lab Med 2012;136:691-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22646280.

64. Dreilich M, Wanders A, Brattstrom D, et al. HER-2 overexpression (3+) in patients with squamous cell esophageal carcinoma correlates with poorer survival. Dis Esophagus 2006;19:224-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16866851.

65. Reichelt U, Duesedau P, Tsourlakis MC, et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol 2007;20:120-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17143264.

66. Schoppmann SF, Jesch B, Friedrich J, et al. Expression of Her-2 in carcinomas of the esophagus. Am J Surg Pathol 2010;34:1868-1873. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21107094.

67. Moelans CB, van Diest PJ, Milne ANA, Offerhaus GJA. Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. Patholog Res Int 2011;2011:674182-674182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21188213.

68. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 2008;19:1523-1529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18441328.

69. Tanner M, Hollmen M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol 2005;16:273-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668283.

70. Bang Y, Chung H, Xu J, et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract 4556. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4556.

71. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008;52:797-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18422971.

72. Ruschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 2010;457:299-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20665045.

73. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20728210.

74. Barros-Silva JD, Leitao D, Afonso L, et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 2009;100:487-493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19156142.

75. Ancona E, Ruol A, Santi S, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell

carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer 2001;91:2165-2174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11391598.

76. Rohatgi PR, Swisher SG, Correa AM, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. Cancer 2005;104:1349-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16130133.

77. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg 2005;242:684-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16244542.

78. Brucher BL, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. Cancer 2006;106:2119-2127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16607651.

79. Langer R, Ott K, Feith M, et al. Prognostic significance of histopathological tumor regression after neoadjuvant chemotherapy in esophageal adenocarcinomas. Mod Pathol 2009;22:1555-1563. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19801967.

80. Meredith KL, Weber JM, Turaga KK, et al. Pathologic response after neoadjuvant therapy is the major determinant of survival in patients with esophageal cancer. Ann Surg Oncol 2010;17:1159-1167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20140529.

81. Lorenzen S, Thuss-Patience P, Al-Batran SE, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. Ann Oncol 2013;24:2068-2073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23592699.

82. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer 2005;103:1347-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15719440.

83. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680-2686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8194005.

84. Wu TT, Chirieac LR, Abraham SC, et al. Excellent interobserver agreement on grading the extent of residual carcinoma after preoperative chemoradiation in esophageal and esophagogastric junction carcinoma: a reliable predictor for patient outcome. Am J Surg Pathol 2007;31:58-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17197919.

85. Swisher SG, Erasmus J, Maish M, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. Cancer 2004;101:1776-1785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15386332.

86. Westerterp M, Omloo JMT, Sloof GW, et al. Monitoring of response to pre-operative chemoradiation in combination with hyperthermia in oesophageal cancer by FDG-PET. Int J Hyperthermia 2006;22:149-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16754598.

87. Bruzzi JF, Swisher SG, Truong MT, et al. Detection of interval distant metastases: clinical utility of integrated CT-PET imaging in patients with esophageal carcinoma after neoadjuvant therapy. Cancer 2007;109:125-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17146785.

88. Konski AA, Cheng JD, Goldberg M, et al. Correlation of molecular response as measured by 18-FDG positron emission tomography with outcome after chemoradiotherapy in patients with esophageal carcinoma. Int J Radiat Oncol Biol Phys 2007;69:358-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17532577.

89. Higuchi I, Yasuda T, Yano M, et al. Lack of fludeoxyglucose F 18 uptake in posttreatment positron emission tomography as a significant predictor of survival after subsequent surgery in multimodality treatment for patients with locally advanced esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg 2008;136:205-212, 212 e201-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18603077.

90. McLoughlin JM, Melis M, Siegel EM, et al. Are patients with esophageal cancer who become PET negative after neoadjuvant chemoradiation free of cancer? J Am Coll Surg 2008;206:879-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18471715.

91. Cerfolio RJ, Bryant AS, Talati AA, et al. Change in maximum standardized uptake value on repeat positron emission tomography after chemoradiotherapy in patients with esophageal cancer identifies complete responders. J Thorac Cardiovasc Surg 2009;137:605-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19258075.

92. Smith JW, Moreira J, Abood G, et al. The influence of (18)flourodeoxyglucose positron emission tomography on the management of gastroesophageal junction carcinoma. Am J Surg 2009;197:308-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245906.

93. Schmidt M, Bollschweiler E, Dietlein M, et al. Mean and maximum standardized uptake values in [18F]FDG-PET for assessment of histopathological response in oesophageal squamous cell carcinoma or adenocarcinoma after radiochemotherapy. Eur J Nucl Med Mol Imaging 2009;36:735-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19096843.

94. Vallbohmer D, Holscher AH, Dietlein M, et al. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg 2009;250:888-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19953708.

95. Monjazeb AM, Riedlinger G, Aklilu M, et al. Outcomes of patients with esophageal cancer staged with [(1)F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol 2010;28:4714-4721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20876421.

96. Brucher BL, Weber W, Bauer M, et al. Neoadjuvant therapy of esophageal squamous cell carcinoma: response evaluation by positron emission tomography. Ann Surg 2001;233:300-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11224616.

97. Flamen P, Van Cutsem E, Lerut A, et al. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 2002;13:361-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11996465.

98. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003;21:428-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12560430.

99. Kroep JR, Van Groeningen CJ, Cuesta MA, et al. Positron emission tomography using 2-deoxy-2-[18F]-fluoro-D-glucose for response monitoring in locally advanced gastroesophageal cancer; a comparison of different analytical methods. Mol Imaging Biol 2003;5:337-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14630513.

100. Wieder HA, Brucher BLDM, Zimmermann F, et al. Time course of tumor metabolic activity during chemoradiotherapy of esophageal

squamous cell carcinoma and response to treatment. J Clin Oncol 2004;22:900-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990646.

101. Song SY, Kim JH, Ryu JS, et al. FDG-PET in the prediction of pathologic response after neoadjuvant chemoradiotherapy in locally advanced, resectable esophageal cancer. Int J Radiat Oncol Biol Phys 2005;63:1053-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15964705.

102. Duong CP, Hicks RJ, Weih L, et al. FDG-PET status following chemoradiotherapy provides high management impact and powerful prognostic stratification in oesophageal cancer. Eur J Nucl Med Mol Imaging 2006;33:770-778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16550384.

103. Gillham CM, Lucey JA, Keogan M, et al. (18)FDG uptake during induction chemoradiation for oesophageal cancer fails to predict histomorphological tumour response. Br J Cancer 2006;95:1174-1179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17024121.

104. Levine EA, Farmer MR, Clark P, et al. Predictive value of 18-fluoro-deoxy-glucose-positron emission tomography (18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg 2006;243:472-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16552197.

105. Kim MK, Ryu J-S, Kim S-B, et al. Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer 2007;43:1385-1391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17512192.

106. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007;8:797-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17693134.

107. Smithers BM, Couper GC, Thomas JM, et al. Positron emission tomography and pathological evidence of response to neoadjuvant therapy in adenocarcinoma of the esophagus. Dis Esophagus 2008;21:151-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18269651.

108. Klaeser B, Nitzsche E, Schuller JC, et al. Limited predictive value of FDG-PET for response assessment in the preoperative treatment of esophageal cancer: results of a prospective multi-center trial (SAKK 75/02). Onkologie 2009;32:724-730. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20016233.

109. Malik V, Lucey JA, Duffy GJ, et al. Early repeated 18F-FDG PET scans during neoadjuvant chemoradiation fail to predict histopathologic response or survival benefit in adenocarcinoma of the esophagus. J Nucl Med 2010;51:1863-1869. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21078796.

110. van Heijl M, Omloo JM, van Berge Henegouwen MI, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. Ann Surg 2011;253:56-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21233607.

111. Piessen G, Petyt G, Duhamel A, et al. Ineffectiveness of (1)(8)F-fluorodeoxyglucose positron emission tomography in the evaluation of tumor response after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg 2013;258:66-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23470576.

112. Erasmus JJ, Munden RF, Truong MT, et al. Preoperative chemo-radiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. J

Thorac Oncol 2006;1:478-486. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409902.

113. Piessen G, Messager M, Mirabel X, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. Ann Surg 2013;258:793-799; discussion 799-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24096755.

114. Murphy CC, Correa AM, Ajani JA, et al. Surgery is an essential component of multimodality therapy for patients with locally advanced esophageal adenocarcinoma. J Gastrointest Surg 2013;17:1359-1369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23715646.

115. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22646630.

116. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16822992.

117. Aloia TA, Harpole DH, Reed CE, et al. Tumor marker expression is predictive of survival in patients with esophageal cancer. Ann Thorac Surg 2001;72:859-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11565671.

118. Luthra R, Wu TT, Luthra MG, et al. Gene expression profiling of localized esophageal carcinomas: association with pathologic response to preoperative chemoradiation. J Clin Oncol 2006;24:259-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16344314.

119. McManus DT, Olaru A, Meltzer SJ. Biomarkers of esophageal adenocarcinoma and Barrett's esophagus. Cancer Res 2004;64:1561-1569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14996709.

120. Ng T, Vezeridis MP. Advances in the surgical treatment of esophageal cancer. Journal of Surgical Oncology 2010;101:725-729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20512949

121. Visbal AL, Allen MS, Miller DL, et al. Ivor Lewis esophagogastrectomy for esophageal cancer. Ann Thorac Surg 2001;71:1803-1808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11426751.

122. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. Br J Surg 1976;63:259-262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1276657.

123. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246:363-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17717440.

124. Hulscher JBF, van Sandick JW, de Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002;347:1662-1669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12444180.

125. Chang AC, Ji H, Birkmeyer NJ, et al. Outcomes after transhiatal and transthoracic esophagectomy for cancer. Ann Thorac Surg 2008;85:424-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18222237.

126. Forshaw MJ, Gossage JA, Ockrim J, et al. Left thoracoabdominal esophagogastrectomy: still a valid operation for carcinoma of the distal esophagus and esophagogastric junction. Diseases of the Esophagus 2006;19:340-345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16984529

127. Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;238:486-494; discussion 494-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14530720.

128. Zingg U, McQuinn A, DiValentino D, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. Ann Thorac Surg 2009;87:911-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19231418.

129. Perry Y, Fernando HC, Buenaventura PO, et al. Minimally invasive esophagectomy in the elderly. JSLS 2002;6:299-304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12500826.

130. Decker G, Coosemans W, De Leyn P, et al. Minimally invasive esophagectomy for cancer. Eur J Cardiothorac Surg 2009;35:13-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18952454.

131. Levy RM, Wizorek J, Shende M, Luketich JD. Laparoscopic and thoracoscopic esophagectomy. Adv Surg 2010;44:101-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20919517.

132. Walther B, Johansson J, Johnsson F, et al. Cervical or thoracic anastomosis after esophageal resection and gastric tube reconstruction: a prospective randomized trial comparing sutured neck anastomosis with stapled intrathoracic anastomosis. Ann Surg 2003;238:803-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14631217.

133. Urschel JD, Blewett CJ, Bennett WF, et al. Handsewn or stapled esophagogastric anastomoses after esophagectomy for cancer: meta-analysis of randomized controlled trials. Dis Esophagus 2001;14:212-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11869322.

134. Klink CD, Binnebosel M, Schneider M, et al. Operative outcome of colon interposition in the treatment of esophageal cancer: a 20-year experience. Surgery 2010;147:491-496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20004440.

135. Steyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 2006;24:4277-4284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16963730.

136. Krasna MJ, Reed CE, Jaklitsch MT, et al. Thoracoscopic staging of esophageal cancer: a prospective, multiinstitutional trial. Cancer and Leukemia Group B Thoracic Surgeons. Ann Thorac Surg 1995;60:1337-1340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8526623.

137. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-1137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11948273.

138. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg 2002;123:175-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11782772.

139. Rusch VW. Are cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several? Semin Oncol 2004;31:444-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297937.

140. Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophagogastric junction. Scand J Surg 2006;95:260-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17249275.

141. de Graaf GW, Ayantunde AA, Parsons SL, et al. The role of staging laparoscopy in oesophagogastric cancers. Eur J Surg Oncol 2007;33:988-992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17344017.

142. Nath J, Moorthy K, Taniere P, et al. Peritoneal lavage cytology in patients with oesophagogastric adenocarcinoma. Br J Surg 2008;95:721-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18412292.

143. Groth SS, Virnig BA, Whitson BA, et al. Determination of the minimum number of lymph nodes to examine to maximize survival in patients with esophageal carcinoma: data from the Surveillance Epidemiology and End Results database. J Thorac Cardiovasc Surg 2010;139:612-620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19709685.

144. Peyre CG, Hagen JA, DeMeester SR, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg 2008;248:979-985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19092342.

145. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. Annals of Surgery 2010;251:46-50 Available at: http://www.ncbi.nlm.nih.gov/pubmed/20032718.

146. Bergman JJGHM, Zhang Y-M, He S, et al. Outcomes from a prospective trial of endoscopic radiofrequency ablation of early squamous cell neoplasia of the esophagus. Gastrointest Endosc 2011;74:1181-1190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21839994.

147. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology 2011;141:460-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21679712.

148. Berry MF, Zeyer-Brunner J, Castleberry AW, et al. Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. J Thorac Oncol 2013;8:796-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24614244.

149. Pech O, May A, Manner H, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology 2014;146:652-660 Available at: http://www.ncbi.nlm.nih.gov/pubmed/24269290.

150. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118:670-677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10734018.

151. Fujita H, Sueyoshi S, Yamana H, et al. Optimum treatment strategy for superficial esophageal cancer: endoscopic mucosal resection versus radical esophagectomy. World J Surg 2001;25:424-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11344392.

152. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol 2005;23:4490-4498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16002839.

153. Conio M, Repici A, Cestari R, et al. Endoscopic mucosal resection for high-grade dysplasia and intramucosal carcinoma in Barrett's esophagus: an Italian experience. World J Gastroenterol 2005;11:6650-6655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16425359.

154. Seewald S, Akaraviputh T, Seitz U, et al. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. Gastrointest Endosc 2003;57:854-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12776032.

155. Larghi A, Lightdale CJ, Ross AS, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. Endoscopy 2007;39:1086-1091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17701854.

156. Lopes CV, Hela M, Pesenti C, et al. Circumferential endoscopic resection of Barrett's esophagus with high-grade dysplasia or early

adenocarcinoma. Surg Endosc 2007;21:820-824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17294308.

157. Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. Gastrointest Endosc 2008;68:35-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18355819.

158. Chennat J, Konda VJ, Ross AS, et al. Complete Barrett's eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma--an American single-center experience. Am J Gastroenterol 2009;104:2684-2692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19690526.

159. Repici A, Hassan C, Carlino A, et al. Endoscopic submucosal dissection in patients with early esophageal squamous cell carcinoma: results from a prospective Western series. Gastrointest Endosc 2010;71:715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20363414.

160. Ono S, Fujishiro M, Koike K. Endoscopic submucosal dissection for superficial esophageal neoplasms. World J Gastrointest Endosc 2012;4:162-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22624067.

161. Higuchi K, Tanabe S, Azuma M, et al. A phase II study of endoscopic submucosal dissection for superficial esophageal neoplasms (KDOG 0901). Gastrointest Endosc 2013;78:704-710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23680178.

162. Omae M, Fujisaki J, Horiuchi Y, et al. Safety, efficacy, and long-term outcomes for endoscopic submucosal dissection of early esophagogastric junction cancer. Gastric Cancer 2013;16:147-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22692465.

163. Takahashi H, Arimura Y, Masao H, et al. Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). Gastrointest Endosc 2010;72:255-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20541198.

164. Teoh AY, Chiu PW, Yu Ngo DK, et al. Outcomes of endoscopic submucosal dissection versus endoscopic mucosal resection in management of superficial squamous esophageal neoplasms outside Japan. J Clin Gastroenterol 2010;44:e190-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20844363.

165. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. Clin Gastroenterol Hepatol 2010;8:23-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19602454.

166. van Vilsteren FGI, Pouw RE, Seewald S, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut 2011;60:765-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21209124.

167. Alvarez Herrero L, van Vilsteren FGI, Pouw RE, et al. Endoscopic radiofrequency ablation combined with endoscopic resection for early neoplasia in Barrett's esophagus longer than 10 cm. Gastrointest Endosc 2011;73:682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21292262.

168. Neuhaus H, Terheggen G, Rutz EM, et al. Endoscopic submucosal dissection plus radiofrequency ablation of neoplastic Barrett's esophagus. Endoscopy 2012;44:1105-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22968641.

169. Dumot JA, Vargo JJ, 2nd, Falk GW, et al. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc 2009;70:635-644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19559428.

170. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010;71:680-685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20363409.

171. Overholt BF, Lightdale CJ, Wang KK, et al. Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial. Gastrointest Endosc 2005;62:488-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16185958.

172. Pech O, Gossner L, May A, et al. Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. Gastrointest Endosc 2005;62:24-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15990815.

173. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007;66:460-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17643436.

174. Gaur P, Sepesi B, Hofstetter WL, et al. Endoscopic esophageal tumor length: A prognostic factor for patients with esophageal cancer. Cancer 2011;117:63-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20803613.

175. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982;82:228-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7054024.

176. Anagnostopoulos GK, Yao K, Kaye P, et al. Novel endoscopic observation in Barrett's oesophagus using high resolution magnification endoscopy and narrow band imaging. Aliment Pharmacol Ther 2007;26:501-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17635385.

177. Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Endoscopy 2010;42:351-359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20200809.

178. Maish MS, DeMeester SR. Endoscopic mucosal resection as a staging technique to determine the depth of invasion of esophageal adenocarcinoma. Ann Thorac Surg 2004;78:1777-1782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15511474.

179. Larghi A, Lightdale CJ, Memeo L, et al. EUS followed by EMR for staging of high-grade dysplasia and early cancer in Barrett's esophagus. Gastrointest Endosc 2005;62:16-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15990814.

180. Thomas T, Singh R, Ragunath K. Trimodal imaging-assisted endoscopic mucosal resection of early Barrett's neoplasia. Surg Endosc 2009;23:1609-1613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19296171.

181. Pennathur A, Farkas A, Krasinskas AM, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg 2009;87:1048-1054; discussion 1054-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19324126.

182. Leggett CL, Lewis JT, Wu TT, et al. Clinical and Histological Determinants of Mortality for Patients with Barrett's Esophagus-related T1 Esophageal Adenocarcinoma. Clin Gastroenterol Hepatol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25151255.

183. Merkow RP, Bilimoria KY, Keswani RN, et al. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. J Natl Cancer Inst 2014;106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25031273.

184. Westerterp M, Koppert LB, Buskens CJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch 2005;446:497-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15838647.

185. Ancona E, Rampado S, Cassaro M, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol 2008;15:3278-3288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18726651.

186. Barbour AP, Rizk NP, Gerdes H, et al. Endoscopic ultrasound predicts outcomes for patients with adenocarcinoma of the gastroesophageal junction. J Am Coll Surg 2007;205:593-601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17903735.

187. Choi J, Kim SG, Kim JS, et al. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 2010;24:1380-1386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20033712.

188. Thosani N, Singh H, Kapadia A, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc 2012;75:242-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22115605.

189. Hofstetter WL. The Esophageal Cancer Study Group. Surgery Alone or Preoperative Therapy in cT2N0 Esophageal Cancer?A multi-institutional study on staging deficiencies, treatment patterns, and outcomes in cT2N0 esophageal cancer [abstract]. Presented at American Association for Thoracic Surgery (Annual Meeting) 2014. Available at: http://aats.org/annualmeeting/Program-Books/2014/27.cgi.

190. Keswani RN, Early DS, Edmundowicz SA, et al. Routine positron emission tomography does not alter nodal staging in patients undergoing EUS-guided FNA for esophageal cancer. Gastrointest Endosc 2009;69:1210-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19012886.

191. Bergman JJ. The endoscopic diagnosis and staging of oesophageal adenocarcinoma. Best Pract Res Clin Gastroenterol 2006;20:843-866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16997165.

192. Vazquez-Sequeiros E, Norton ID, Clain JE, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc 2001;53:751-757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11375583.

193. Vazquez-Sequeiros E, Wiersema MJ, Clain JE, et al. Impact of lymph node staging on therapy of esophageal carcinoma. Gastroenterology 2003;125:1626-1635. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14724814.

194. Cen P, Hofstetter WL, Correa AM, et al. Lymphovascular invasion as a tool to further subclassify T1b esophageal adenocarcinoma. Cancer 2008;112:1020-1027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18205187.

195. Alvarez Herrero L, Pouw RE, van Vilsteren FG, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy 2010;42:1030-1036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20960392.

196. Leers JM, DeMeester SR, Oezcelik A, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg 2011;253:271-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21119508.

197. Lee L, Ronellenfitsch U, Hofstetter WL, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple

scoring system. J Am Coll Surg 2013;217:191-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23659947.

198. Nentwich MF, von Loga K, Reeh M, et al. Depth of submucosal tumor infiltration and its relevance in lymphatic metastasis formation for T1b squamous cell and adenocarcinomas of the esophagus. J Gastrointest Surg 2014;18:242-249; discussion 249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24091912.

199. Chadwick G, Groene O, Markar SR, et al. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. Gastrointest Endosc 2014;79:718-731 e713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24462170.

200. Lightdale CJ, Botet JF, Kelsen DP, et al. Diagnosis of recurrent upper gastrointestinal cancer at the surgical anastomosis by endoscopic ultrasound. Gastrointest Endosc 1989;35:407-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2676688.

201. Newaishy GA, Read GA, Duncan W, Kerr GR. Results of radical radiotherapy of squamous cell carcinoma of the oesophagus. Clin Radiol 1982;33:347-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7075142.

202. Okawa T, Kita M, Tanaka M, Ikeda M. Results of radiotherapy for inoperable locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 1989;17:49-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2745207.

203. Sun DR. Ten-year follow-up of esophageal cancer treated by radical radiation therapy: analysis of 869 patients. Int J Radiat Oncol Biol Phys 1989;16:329-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2921133.

204. Shi XH, Yao W, Liu T. Late course accelerated fractionation in radiotherapy of esophageal carcinoma. Radiother Oncol 1999;51:21-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10386713.

205. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-1598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1584260.

206. Hosokawa M, Shirato H, Ohara M, et al. Intraoperative radiation therapy to the upper mediastinum and nerve-sparing three-field lymphadenectomy followed by external beam radiotherapy for patients with thoracic esophageal carcinoma. Cancer 1999;86:6-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10391557.

207. Nutting CM, Bedford JL, Cosgrove VP, et al. Intensity-modulated radiotherapy reduces lung irradiation in patients with carcinoma of the oesophagus. Front Radiat Ther Oncol 2002;37:128-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11764654.

208. Fu W-H, Wang L-H, Zhou Z-M, et al. Comparison of conformal and intensity-modulated techniques for simultaneous integrated boost radiotherapy of upper esophageal carcinoma. World J Gastroenterol 2004;10:1098-1102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15069706.

209. Chandra A, Guerrero TM, Liu HH, et al. Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol 2005;77:247-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16298001.

210. Mayo CS, Urie MM, Fitzgerald TJ, et al. Hybrid IMRT for treatment of cancers of the lung and esophagus. Int J Radiat Oncol Biol Phys 2008;71:1408-1418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18262730.

211. Wang M, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of

esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys 1989;16:325-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2646253.

212. Teniere P, Hay JM, Fingerhut A, Fagniez PL. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. Surg Gynecol Obstet 1991;173:123-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1925862.

213. Arnott SJ, Duncan W, Kerr GR, et al. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol 1992;24:108-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1496141.

214. Arnott SJ, Duncan W, Gignoux M, et al. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data (Oesophageal Cancer Collaborative Group). Int J Radiat Oncol Biol Phys 1998;41:579-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9635705.

215. Sur RK, Donde B, Levin VC, Mannell A. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. Int J Radiat Oncol Biol Phys 1998;40:447-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9457834.

216. Gaspar LE, Qian C, Kocha WI, et al. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. Int J Radiat Oncol Biol Phys 1997;37:593-599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9112458.

217. Wang S, Liao Z, Chen Y, et al. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. J Thorac Oncol 2006;1:252-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409865.

218. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11870157.

219. Kleinberg L, Forastiere AA. Chemoradiation in the management of esophageal cancer. J Clin Oncol 2007;25:4110-4117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17827461.

220. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235156.

221. Li QQ, Liu MZ, Hu YH, et al. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. Dis Esophagus 2010;23:253-259. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19732130.

222. Meerten EV, van Rij C, Tesselaar ME, et al. Definitive concurrent chemoradiation (CRT) with weekly paclitaxel and carboplatin for patients (pts) with irresectable esophageal cancer: A phase II study [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract e14508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/e14508.

223. Conroy T, Galais M-P, Raoul J-L, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24556041.

224. Iyer R, Wilkinson N, Demmy T, Javle M. Controversies in the multimodality management of locally advanced esophageal cancer: evidence-based review of surgery alone and combined-modality

therapy. Ann Surg Oncol 2004;11:665-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197012.

225. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185:538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12781882.

226. Fiorica F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. Gut 2004;53:925-930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15194636.

227. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21684205.

228. Swisher SG, Hofstetter W, Komaki R, et al. Improved long-term outcome with chemoradiotherapy strategies in esophageal cancer. Ann Thorac Surg 2010;90:892-898; discussion 898-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20732514.

229. Cen P, Correa AM, Le JH, et al. Adenocarcinoma of the lower esophagus with Barrett's esophagus or without Barrett's esophagus: differences in patients' survival after preoperative chemoradiation. Diseases of the Esophagus 2009;22:32-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19021684.

230. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8672151.

231. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9219702.

232. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305-313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11208820.

233. Bains MS, Stojadinovic A, Minsky B, et al. A phase II trial of preoperative combined-modality therapy for localized esophageal carcinoma: initial results. J Thorac Cardiovasc Surg 2002;124:270-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12167786.

234. Kaklamanos IG, Walker GR, Ferry K, et al. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. Ann Surg Oncol 2003;10:754-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12900366.

235. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659-668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16129366.

236. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416-2422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24982463.

237. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 2014;32:385-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24419108.

238. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell

carcinoma of the esophagus. J Clin Oncol 2005;23:2310-2317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15800321.

239. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160-1168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17401004.

240. Stahl M, Wilke H, Lehmann N, et al. Long-term results of a phase III study investigating chemoradiation with and without surgery in locally advanced squamous cell carcinoma (LA-SCC) of the esophagus [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 4530. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4530.

241. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18309943.

242. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 2011;47:354-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21084184.

243. Ajani JA, Komaki R, Putnam JB, et al. A three-step strategy of induction chemotherapy then chemoradiation followed by surgery in patients with potentially resectable carcinoma of the esophagus or gastroesophageal junction. Cancer 2001;92:279-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11466680.

244. Swisher SG, Ajani JA, Komaki R, et al. Long-term outcome of phase II trial evaluating chemotherapy, chemoradiotherapy, and surgery for locoregionally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 2003;57:120-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12909224.

245. Ajani JA, Walsh G, Komaki R, et al. Preoperative induction of CPT-11 and cisplatin chemotherapy followed by chemoradiotherapy in patients with locoregional carcinoma of the esophagus or gastroesophageal junction. Cancer 2004;100:2347-2354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15160337.

246. Henry LR, Goldberg M, Scott W, et al. Induction cisplatin and paclitaxel followed by combination chemoradiotherapy with 5-fluorouracil, cisplatin, and paclitaxel before resection in localized esophageal cancer: a phase II report. Ann Surg Oncol 2006;13:214-220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418887.

247. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009;27:851-856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139439.

248. Rivera F, Galan M, Tabernero J, et al. Phase II trial of preoperative irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for resectable locally advanced gastric and esophagogastric junction adenocarcinoma. Int J Radiat Oncol Biol Phys 2009;75:1430-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19540072.

249. Ruhstaller T, Widmer L, Schuller JC, et al. Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02). Ann Oncol 2009;20:1522-1528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19465425.

250. Ilson DH, Minsky BD, Ku GY, et al. Phase 2 trial of induction and concurrent chemoradiotherapy with weekly irinotecan and cisplatin followed by surgery for esophageal cancer. Cancer 2012;118:2820-2827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21990000.

251. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 2013;24:2844-2849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23975663.

252. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11547741.

253. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22585691.

254. Bedard EL, Inculet RI, Malthaner RA, et al. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. Cancer 2001;91:2423-2430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11413534.

255. Rice TW, Adelstein DJ, Chidel MA, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. J Thorac Cardiovasc Surg 2003;126:1590-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14666038.

256. Kofoed SC, Muhic A, Baeksgaard L, et al. Survival after adjuvant chemoradiotherapy or surgery alone in resectable adenocarcinoma at the gastro-esophageal junction. Scand J Surg 2012;101:26-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22414465.

257. Adelstein DJ, Rice TW, Rybicki LA, et al. Mature results from a phase II trial of postoperative concurrent chemoradiotherapy for poor prognosis cancer of the esophagus and gastroesophageal junction. J Thorac Oncol 2009;4:1264-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19668013.

258. Fuchs CS, Tepper JE, Niedzwiecki D, et al. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101[abstract]. J Clin Oncol 2011;29 (Suppl 15):Abstract 4003. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/4003.

259. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979-1984. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9869669.

260. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol 2007;25:3719-3725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17704421.

261. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12049861.

262. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062-5067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19770374.

263. Boonstra JJ, Kok TC, Wijnhoven BP, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer 2011;11:181-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21595951.

264. Thirion PG, Michiels S, Le Maitre A, et al. Individual patient data-based meta-analysis assessing pre-operative chemotherapy in

resectable oesophageal carcinoma [abstract]. J Clin Oncol 2007;25(Suppl 18):Abstract 4512. Available at: http://meeting.jco.org/cgi/content/abstract/25/18_suppl/4512.

265. Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21444866.

266. Leichman L, Berry BT. Experience with cisplatin in treatment regimens for esophageal cancer. Semin Oncol 1991;18:64-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2003229.

267. Muhr-Wilkenshoff F, Hinkelbein W, Ohnesorge I, et al. A pilot study of irinotecan (CPT-11) as single-agent therapy in patients with locally advanced or metastatic esophageal carcinoma. Int J Colorectal Dis 2003;18:330-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12774248.

268. Enzinger PC, Kulke MH, Clark JW, et al. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. Dig Dis Sci 2005;50:2218-2223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16416165.

269. Burkart C, Bokemeyer C, Klump B, et al. A phase II trial of weekly irinotecan in cisplatin-refractory esophageal cancer. Anticancer Res 2007;27:2845-2848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17695458.

270. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 2004;15:955-959. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15151954.

271. Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007;24:407-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17917090.

272. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994;86:1086-1091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7912736.

273. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898-902. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17351256.

274. Harstrick A, Bokemeyer C, Preusser P, et al. Phase II study of single-agent etoposide in patients with metastatic squamous-cell carcinoma of the esophagus. Cancer Chemother Pharmacol 1992;29:321-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1537080.

275. Ilson DH, Ajani J, Bhalla K, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998;16:1826-1834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9586897.

276. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998;78:511-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9716036.

277. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 2000;6:316-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11079171.

278. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal

adenocarcinoma. J Clin Oncol 2005;23:5660-5667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110025.

279. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17075117.

280. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer Chemother Pharmacol 2010;66:31-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19763571.

281. Al-Batran S-E, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19:1882-1887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18669868.

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

283. Overman MJ, Kazmi SM, Jhamb J, et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010;116:1446-1453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20108336.

284. Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. Br J Cancer 2010;102:475-481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20068567.

285. Stein A, Arnold D, Thuss-Patience PC, et al. Docetaxel, oxaliplatin and capecitabine (TEX regimen) in patients with metastatic gastric or gastro-esophageal cancer: Results of a multicenter phase I/II study. Acta Oncol 2014;53:392-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24024696.

286. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18172173.

287. Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15685830.

288. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008;19:1450-1457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18558665.

289. Wolff K, Wein A, Reulbach U, et al. Weekly high-dose 5-fluorouracil as a 24-h infusion and sodium folinic acid (AIO regimen) plus irinotecan in patients with locally advanced nonresectable and metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus: a phase II trial. Anticancer Drugs 2009;20:165-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125117.

290. Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. Ann Oncol 2009;20:1242-1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19429872.

291. Lustberg MB, Bekaii-Saab T, Young D, et al. Phase II randomized study of two regimens of sequentially administered mitomycin C and irinotecan in patients with unresectable esophageal and

gastroesophageal adenocarcinoma. J Thorac Oncol 2010;5:713-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20354452.

292. Moehler M, Kanzler S, Geissler M, et al. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2010;21:71-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19605504.

293. Guimbaud R, Louvet C, Ries P, et al. Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014;32:3520-3526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25287828.

294. Assersohn L, Brown G, Cunningham D, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol 2004;15:64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14679122.

295. Leary A, Assersohn L, Cunningham D, et al. A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol 2009;64:455-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19104814.

296. Mauer AM, Kraut EH, Krauss SA, et al. Phase II trial of oxaliplatin, leucovorin and fluorouracil in patients with advanced carcinoma of the esophagus. Ann Oncol 2005;16:1320-1325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15919687.

297. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18349393.

298. El-Rayes BF, Shields A, Zalupski M, et al. A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 2004;15:960-965. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15151955.

299. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002;20:1996-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11956258.

300. Urba SG, Chansky K, VanVeldhuizen PJ, et al. Gemcitabine and cisplatin for patients with metastatic or recurrent esophageal carcinoma: a Southwest Oncology Group Study. Invest New Drugs 2004;22:91-97. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14707499.

301. Millar J, Scullin P, Morrison A, et al. Phase II study of gemcitabine and cisplatin in locally advanced/metastatic oesophageal cancer. Br J Cancer 2005;93:1112-1116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16278660.

302. Homs MY, v d Gaast A, Siersema PD, et al. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. Cochrane Database Syst Rev 2006:CD004063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17054195.

303. Shah MA, Schwartz GK. Treatment of metastatic esophagus and gastric cancer. Semin Oncol 2004;31:574-587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297948.

304. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24094768.

305. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25240821.

306. Ramos-Suzarte M, Lorenzo-Luaces P, Lazo NG, et al. Treatment of malignant, non-resectable, epithelial origin esophageal tumours with the humanized anti-epidermal growth factor antibody nimotuzumab combined with radiation therapy and chemotherapy. Cancer Biol Ther 2012;13:600-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22555809.

307. Liang J, E M, Wu G, et al. Nimotuzumab combined with radiotherapy for esophageal cancer: preliminary study of a Phase II clinical trial. Onco Targets Ther 2013;6:1589-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24235844.

308. Iveson T, Donehower RC, Davidenko I, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. The Lancet Oncology 2014;15:1007-1018. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1470204514700233.

309. van Westreenen HL, Westerterp M, Bossuyt PMM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 2004;22:3805-3812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15365078.

310. Rosenbaum S, Stergar H, Antoch G, et al. Staging and follow-up of gastrointestinal tumors with PET/CT. Abdominal Imaging 2006;31:25-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16333707.

311. Munden RF, Macapinlac HA, Erasmus JJ. Esophageal cancer: the role of integrated CT-PET in initial staging and response assessment after preoperative therapy. J Thorac Imaging 2006;21:137-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16770230.

312. Flamen P, Lerut A, Van Cutsem E, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18:3202-3210. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10986052.

313. Flamen P, Lerut T, Haustermans K, et al. Position of positron emission tomography and other imaging diagnostic modalities in esophageal cancer. Q J Nucl Med Mol Imaging 2004;48:96-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15243407.

314. Cerfolio RJ, Bryant AS, Ohja B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1232-1241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15942562.

315. Blencowe NS, Whistance RN, Strong S, et al. Evaluating the role of fluorodeoxyglucose positron emission tomography-computed tomography in multi-disciplinary team recommendations for oesophago-gastric cancer. Br J Cancer 2013;109:1445-1450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23963146.

316. van Vilsteren FG, Alvarez Herrero L, Pouw RE, et al. Radiofrequency ablation for the endoscopic eradication of esophageal squamous high grade intraepithelial neoplasia and mucosal squamous cell carcinoma. Endoscopy 2011;43:282-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21455869.

317. Burmeister BH, Dickie G, Smithers BM, et al. Thirty-four patients with carcinoma of the cervical esophagus treated with chemoradiation therapy. Arch Otolaryngol Head Neck Surg 2000;126:205-208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10680872.

318. Du C, Zhou Y, Huang K, et al. Defining a high-risk subgroup of pathological T2N0 gastric cancer by prognostic risk stratification for adjuvant therapy. J Gastrointest Surg 2011;15:2153-2158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21938559.

319. Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol 2013;8:1558-1562. Available at: http://www.hubmed.org/display.cgi?uids=24389438.

320. Sudo K, Taketa T, Correa AM, et al. Locoregional failure rate after preoperative chemoradiation of esophageal adenocarcinoma and the outcomes of salvage strategies. J Clin Oncol 2013;31:4306-4310. Available at: http://www.hubmed.org/display.cgi?uids=24145339.

321. Dorth JA, Pura JA, Palta M, et al. Patterns of recurrence after trimodality therapy for esophageal cancer. Cancer 2014;120:2099-2105. Available at: http://www.hubmed.org/display.cgi?uids=24711267.

322. Sudo K, Xiao L, Wadhwa R, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol 2014;32:3400-3405. Available at: http://www.hubmed.org/display.cgi?uids=25225435.

323. Taketa T, Sudo K, Correa AM, et al. Post-chemoradiation surgical pathology stage can customize the surveillance strategy in patients with esophageal adenocarcinoma. J Natl Compr Canc Netw 2014;12:1139-1144. Available at: http://www.hubmed.org/display.cgi?uids=25099446.

324. Katada C, Muto M, Manabe T, et al. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 2005;61:219-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15729229.

325. Haidry RJ, Butt MA, Dunn J, et al. Radiofrequency ablation for early oesophageal squamous neoplasia: outcomes form United Kingdom registry. World J Gastroenterol 2013;19:6011-6019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24106401.

326. Perry KA, Walker JP, Salazar M, et al. Endoscopic management of high-grade dysplasia and intramucosal carcinoma: experience in a large academic medical center. Surg Endosc 2014;28:777-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24122245.

327. Yasuda K, Choi SE, Nishioka NS, et al. Incidence and predictors of adenocarcinoma following endoscopic ablation of Barrett's esophagus. Dig Dis Sci 2014;59:1560-1566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24395382.

328. Pasricha S, Bulsiewicz WJ, Hathorn KE, et al. Durability and predictors of successful radiofrequency ablation for Barrett's esophagus. Clin Gastroenterol Hepatol 2014;12:1840-1847 e1841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24815329.

329. Manner H, Rabenstein T, Pech O, et al. Ablation of residual Barrett's epithelium after endoscopic resection: a randomized long-term follow-up study of argon plasma coagulation vs. surveillance (APE study). Endoscopy 2014;46:6-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24353120.

330. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the

Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47:2306-2314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21742485.

331. Ford HER, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014;15:78-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24332238.

332. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York Columbia University Press; 1949:199-205.

333. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187-193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6699671.

334. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7165009.

335. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. Cancer 1989;63:1026-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2465076.

336. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol 1996;14:2274-2279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8708717.

337. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. Lancet 2000;355:1588-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10821362.

338. Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gastrointest Endosc 1995;42:507-512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8674919.

339. Vakil N, Morris AI, Marcon N, et al. A prospective, randomized, controlled trial of covered expandable metal stents in the palliation of malignant esophageal obstruction at the gastroesophageal junction. Am J Gastroenterol 2001;96:1791-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11419831.

340. Shin JH, Song HY, Kim JH, et al. Comparison of temporary and permanent stent placement with concurrent radiation therapy in patients with esophageal carcinoma. J Vasc Interv Radiol 2005;16:67-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15640412.

341. Ross WA, Alkassab F, Lynch PM, et al. Evolving role of self-expanding metal stents in the treatment of malignant dysphagia and fistulas. Gastrointest Endosc 2007;65:70-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17185082.

342. Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet 2004;364:1497-1504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15500894.

343. Verschuur EM, Steyerberg EW, Kuipers EJ, Siersema PD. Effect of stent size on complications and recurrent dysphagia in patients with esophageal or gastric cardia cancer. Gastrointest Endosc

2007;65:592-601. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17383456.

344. Fan Y, Song HY, Kim JH, et al. Evaluation of the incidence of esophageal complications associated with balloon dilation and their management in patients with malignant esophageal strictures. AJR Am J Roentgenol 2012;198:213-218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22194500.