National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

(Including cancer in the proximal 5cm of the stomach)

Version 2.2013

NCCN.org

Continue

NCCN Guidelines Version 2.2013 Panel Members
Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

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

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

Stephen Besh, MD †
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

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

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

Crystal Denlinger, MD †
Fox Chase Cancer Center

Marwan G. Fakih, MD †
City of Hope Comprehensive Cancer Center

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

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

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

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

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

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

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

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

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

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

Kenneth Meredith, MD ¶
Moffitt 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

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

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

Walter J. Scott, MD ¶
Fox Chase Cancer Center

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

Thomas K. Varghese, Jr, MD ¶
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Graham Warren, MD, PhD §
Roswell Park Cancer Institute

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

Christopher Willett, MD §
Duke Cancer Institute

Cameron D. Wright, MD ¶
Massachusetts General Hospital

NCCN
Lauren Gallagher, RPh, PhD
Nicole McMillian, MS
Hema Sundar, PhD

Continue

NCCN Guidelines Panel Disclosures

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

NCCN Guidelines Version 2.2013 Panel Members
Gastric Cancer

NCCN Guidelines Index
Gastric Cancer 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

Crystal 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

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 Willett, MD §
Duke Cancer Institute

Principles of Surgery

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

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

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

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

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

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

Principles of Best Supportive Care
Hans Gerdes, MD ¤ Þ
Memorial Sloan-Kettering Cancer Center

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

Mary F. Mulcahy, MD ‡
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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013 Table of Contents
Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

NCCN Gastric Cancer Guidelines Panel Members
NCCN Gastric Cancer Guidelines Sub-Committee Members
Summary of the Guidelines Updates
Workup and Evaluation (GAST-1)
Postlaparoscopy Staging and Treatment (GAST-2)
Surgical Outcomes For Patients Who Have Not Received Preoperative Therapy (GAST-3)
Surgical Outcomes For Patients Who Have Received Preoperative Therapy (GAST-4)
Post Treatment Assessment/Adjunctive Treatment (GAST-5)
Follow-up, Recurrence (GAST-6)
Palliative Therapy (GAST-7)
Principles of Endoscopic Staging and Therapy (GAST-A)
Principles of Pathologic Review and HER2-neu Testing (GAST-B)
Principles of Multidisciplinary Team Approach (GAST-C)
Principles of Surgery (GAST-D)
Principles of Systemic Therapy (GAST-E)
Principles of Radiation Therapy (GAST-F)
Principles of Best Supportive Care (GAST-G)
Staging (ST-1)

Clinical Trials: The 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

The NCCN Guidelines® for Gastric Cancer includes cancer in the proximal 5cm of the stomach.

NCCN Guidelines Version 2.2013 Updates Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

The 2.2013 version of the NCCN Guidelines for Gastric Cancer represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

Updates in version 1.2013 of the NCCN Guidelines for Gastric Cancer from version 2.2012 include:

GAST-1

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

GAST-2

- **The page was revised for clarity.**

GAST-3--Patients Have Not Received Preoperative Chemotherapy or Chemoradiation

- **R0 resection; T3, T4, Any N or Any T, N+: For Postoperative Treatment, the recommendation was revised as follows, "~~Capecitabine + oxaliplatin or cisplatin~~ Chemotherapy for patients who have undergone primary D2 lymph node dissection". The regimens are listed in the "Principles of Systemic Therapy" (GAST-E).**
- **R2 resection: For Postoperative Treatment, the recommendations "Chemotherapy or Best supportive care" changed to "Palliative Therapy (see GAST-7), as clinically indicated". A similar change was also made on GAST-4.**
- **Footnote p: The following sentence was added, "5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy (GAST-E)."**

GAST-4--Patients Received Preoperative Chemotherapy or Chemoradiation

- **R0 resection: The recommendation "(ECF or its modifications, or fluorouracil and cisplatin) if received preoperatively..." changed to "Chemotherapy, if received preoperatively..." The regimens are listed in the "Principles of Systemic Therapy" (GAST-E).**

GAST-5:

- **Post Treatment Assessment: The recommendations in this section were revised.**

GAST-6 and GAST-7:

- **The Follow-up and Recurrence algorithms were revised for clarity.**
- **Footnote "t" is new to the algorithm: "Review if surgery is appropriate for patients with isolated local recurrences. Surgery should be considered as an option for locoregional recurrence in medically fit patients". (for GAST-6 only)**

Continued

NCCN Guidelines Version 2.2013 Updates Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

GAST- A: Principles of Endoscopic Staging and Therapy

1 of 4

- Diagnosis
  - Second bullet: "Multiple (8-10) biopsies..." changed to "...(6-8) biopsies".
  - The third bullet is new to the algorithm: "Endoscopic mucosal resection (EMR) can be performed in the evaluation of small lesions. EMR of focal nodules ≤ 3 cm can be safely performed to provide a larger specimen which can be better assessed by the pathologist, providing greater information on degree of differentiation, the presence of lymphovascular invasion and the depth of infiltration, thereby providing accurate T-staging. Such excisional biopsies have the potential of being therapeutic."

2 of 4

- Staging
  - Third bullet: The following sentence was added: "Furthermore, an attempt should be made to identify the presence of ascites and FNA considered to rule out peritoneal spread of disease".

3 of 4

- Treatment
  - The first bullet is new to the page: "EMR of early gastric cancer can be considered adequate therapy when the lesion is less than 1.5 cm in diameter, is shown on histopathology to be well or moderately well differentiated, does not penetrate beyond the superficial submucosa, and does not exhibit lymphovascular invasion. En-bloc excision of small gastric lesions by endoscopic submucosal dissection (ESD) has been shown to be more effective than EMR in curing early gastric cancer, but requires greater skills and instrumentation to perform and has a significant risk of complications including perforation. Japanese Gastric Cancer guidelines recommend EMR should be considered for early gastric cancer lesions ≤ 3 cm in diameter without associated ulcer formation. EMR or ESD treatments of gastric lesions that are poorly differentiated, harbor evidence of lymphovascular invasion, have lymph node metastases, or invade into the deep submucosa, should be considered to be incomplete, and additional therapy by gastrectomy with lymphadenectomy should be considered."

GAST-B 3 of 4: Principles of Pathologic Review and HER2-neu Testing

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

GAST-D: Principles of Surgery

- This page was revised extensively, including:
  - N Staging: The following bullet was added, "In patients receiving pre-operative therapy, a baseline laparascopy along with peritoneal washings should be considered.
  - Resectable tumors: Under Definition of D1 and D2 lymph node dissections: The second bullet was revised as follows, "D2 dissection is a D1 plus ~~the anterior leaf of the transverse mesocolon and~~ all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery".

Continued

GAST-E Principles of Systemic Therapy

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

1 of 13:

- **Third bullet was revised: Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Ninth bullet: The following statement was added, "Perioperative chemotherapy is an alternative, but less preferred option.**
- **The following bullets are new to the algorithm:**
  - **Postoperative chemotherapy is recommended following primary D2 lymph node dissection. (See Principles of Surgery [GAST-D]).**
  - **Induction chemotherapy may be appropriate as clinically indicated.**

Footnote 5: The following sentence was added to the cited Intergroup 0116 trial "5-FU/Leucovorin as described in this reference is no longer recommended. See GAST-E 6 of 13."

2 of 13:

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

3 of 13:

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

4 of 13:

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

Continued

NCCN Guidelines Version 2.2013 Updates Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

GAST-E: Principles of Systemic Therapy---continued
6 of 13

- **Postoperative chemoradiation (including eg junction): The following changes were made:**
  - **The regimen for the Intergroup 0116 trial was added, with the corresponding statement: "The panel acknowledges that the intergroup 0116 trial formed the basis for postoperative adjuvant chemoradiation strategy. However, the panel does not recommend the above specified doses or schedule of cytotoxic agents because of concerns regarding toxicity. The panel recommends one of the following modifications instead:**
    - **1 cycle before and 2 cycles after chemoradiation**
      Capecitabine 750-1000 mg/m^2 PO BID on Days 1-14
      Cycled every 28 days
    - **1 cycle before and 2 cycles after chemoradiation**
      Leucovorin 400 mg/m^2 IV on Days 1 and 15 or Days 1, 2, 15, and 16
      Fluorouracil 400 mg/m^2 IVP on Days 1 and 15 or Days 1, 2, 15, and 16
      Fluorouracil 1200 mg/m^2 IV continuous infusion
      over 24 hours daily on Days 1, 2, 15, and 16
      Cycled every 28 days"

GAST-F: Principles of Radiation Therapy

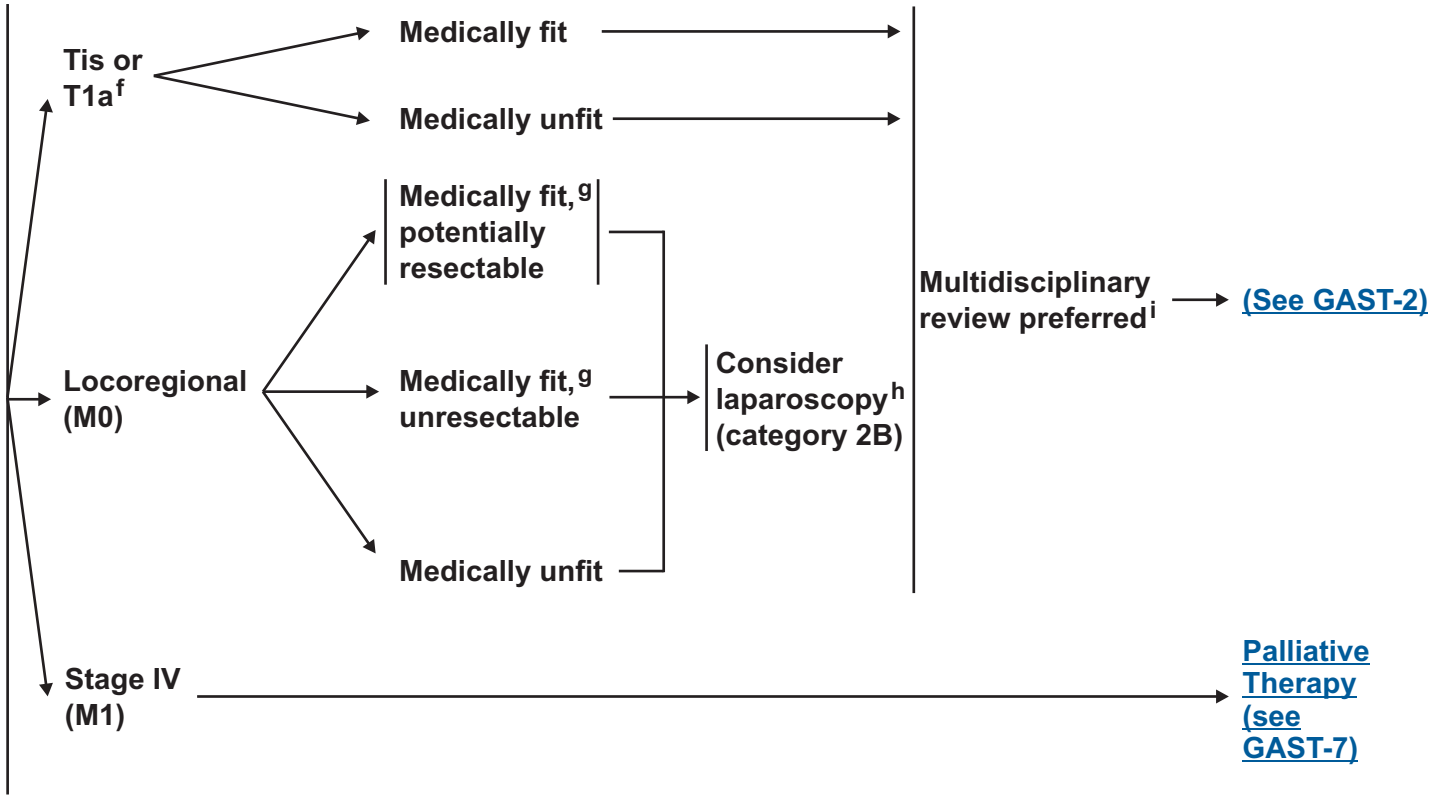
- **General Guidelines: The following bullet was added, "In general, Siewert I and II tumors should be managed with radiation guidelines applicable to esophageal cancers. Depending on the clinical situation, Siewert III tumors, may be more appropriately managed with radiation guidelines applicable to either esophageal or gastric cancers. These recommendations may be modified depending on where the bulk of the tumor is located."**
- **Simulation and Treatment Planning: The seventh bullet was revised, "Intensity modulated radiation therapy (IMRT) ~~may be~~ is appropriate in selected cases to reduce dose to normal structures..."**

NCCN Guidelines Version 2.2013
Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion

WORKUP

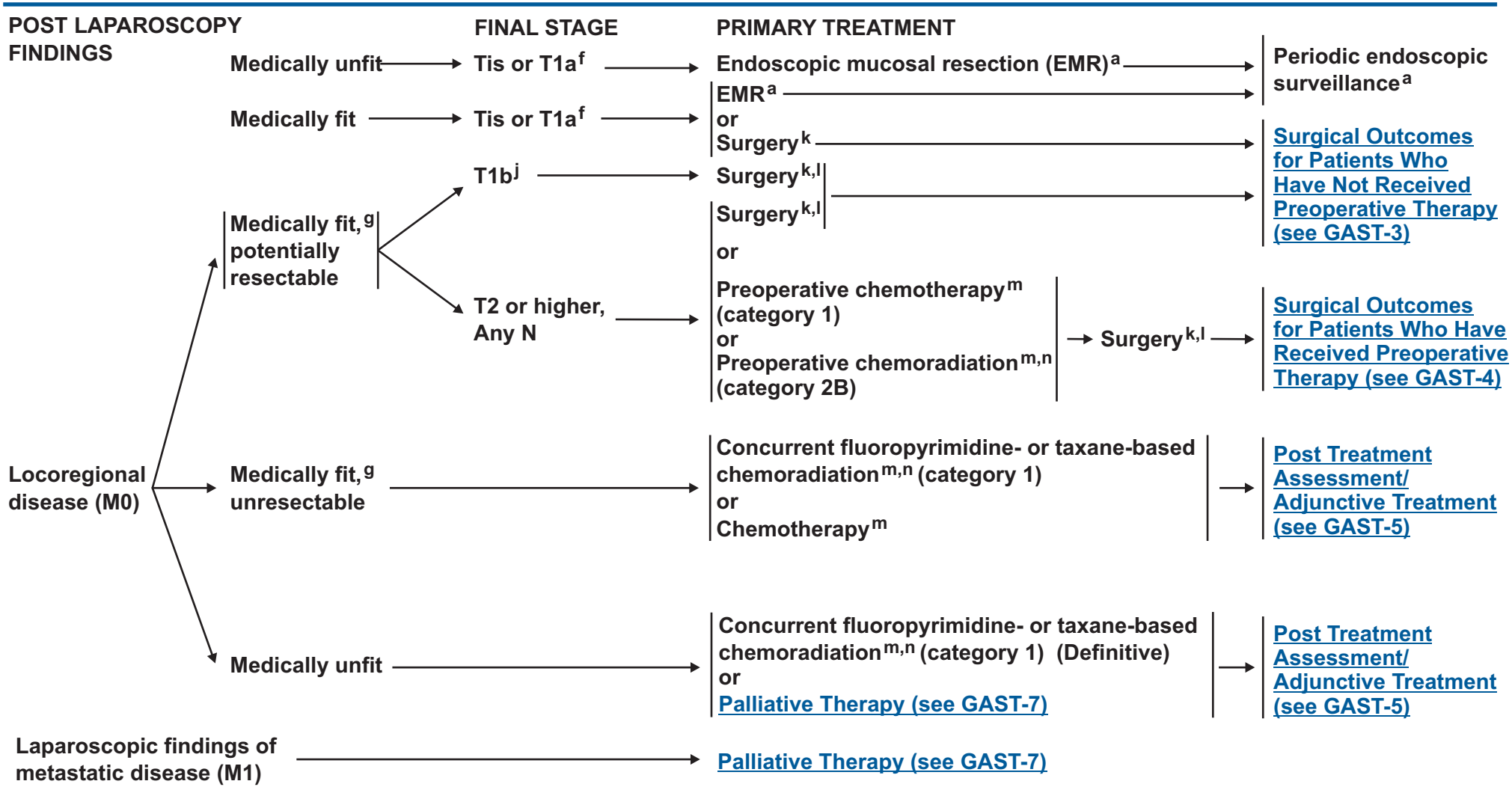
- H&P
- Upper GI endoscopy and biopsy[a]
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT as clinically indicated
- PET-CT evaluation if no evidence of M1 disease[b]
- CBC and chemistry profile
- Endoscopic ultrasound (EUS) if no evidence of M1 disease (preferred).
- Endoscopic mucosal resection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



[a] See Principles of Endoscopic Surgery and Therapy (GAST-A).
[b] May not be appropriate for T1 patients.
[c] EMR may also be therapeutic for early stage disease/lesions.
[d] See Principles of Pathologic Review and HER2-neu Testing (GAST-B).
[e] Smoking cessation guidelines are available from the Public Health Service at: www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf or http://guideline.gov/content.aspx?id=12520

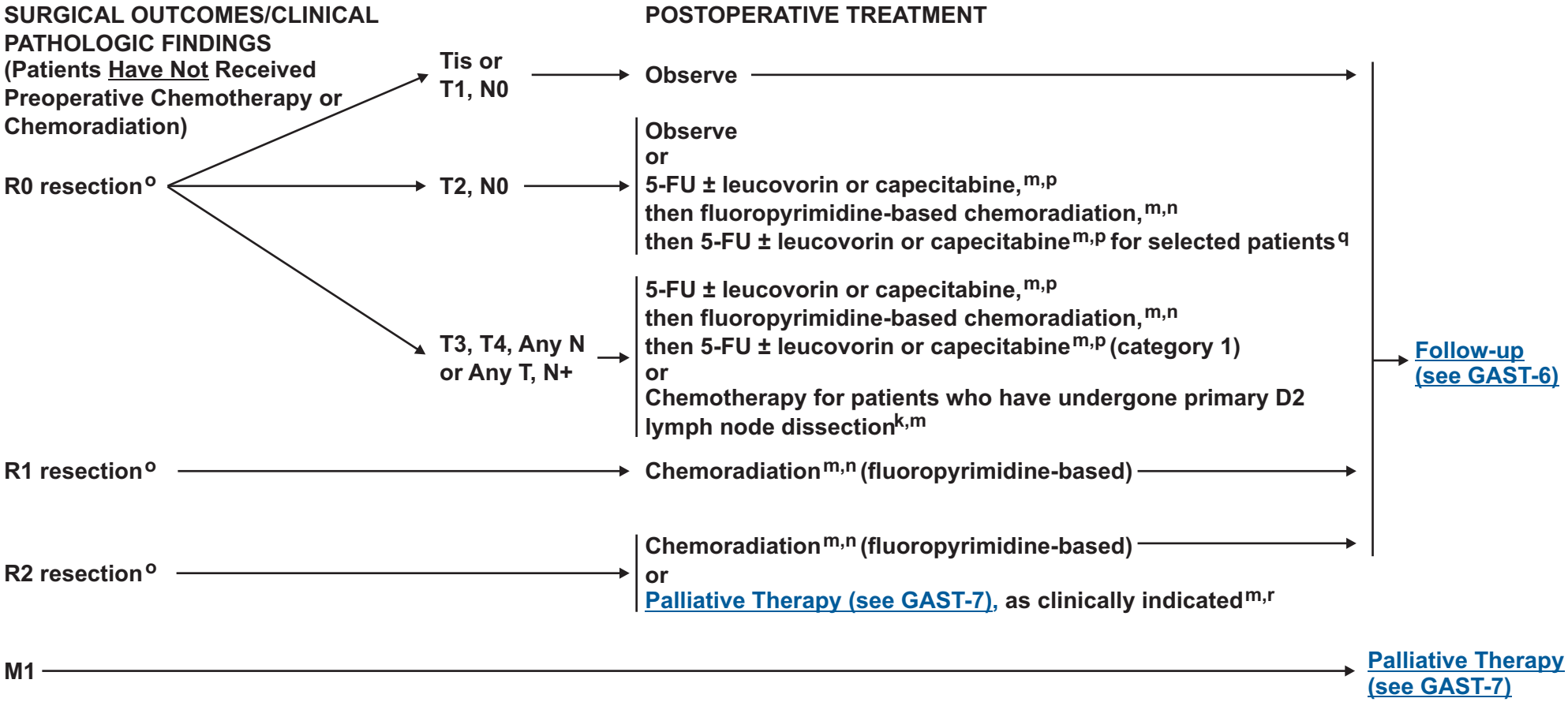
[f] Tis or T1a: Defined as carcinoma in situ (Tis) or invasion of mucosa without submucosal invasion (T1a).
[g] Medically able to tolerate major abdominal surgery.
[h] Laparoscopy is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy is not indicated if a palliative resection is planned.
[i] See Principles of Multidisciplinary Team Approach (GAST-C).

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.



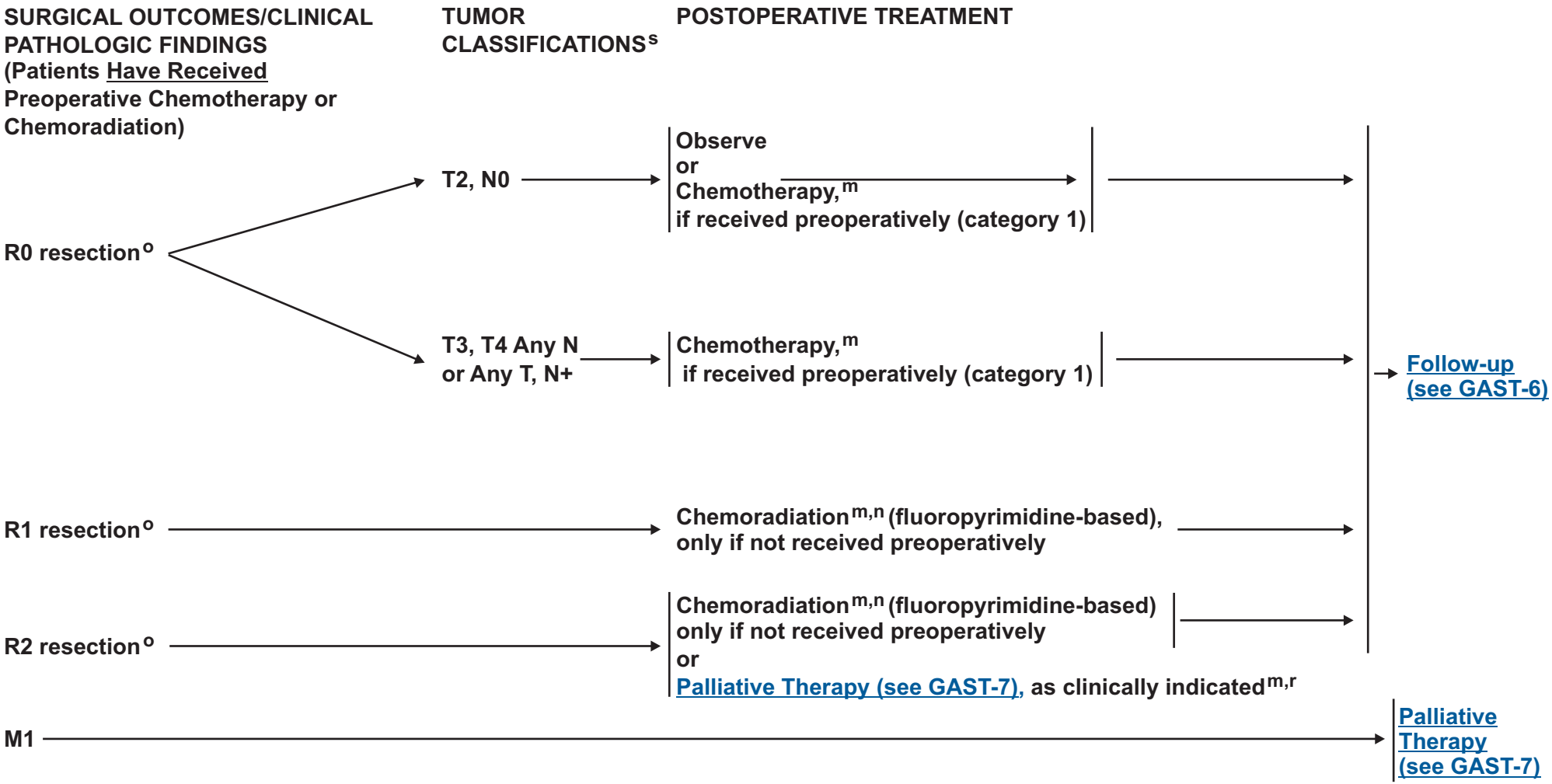
[a] See Principles of Endoscopic Surgery and Therapy (GAST-A).
[f] Tis or T1a: Defined as carcinoma in situ (Tis) or invasion of mucosa without submucosal invasion (T1a).
[g] Medically able to tolerate major abdominal surgery.
[i] See Principles of Multidisciplinary Team Approach (GAST-C).
[j] T1b: Tumors invading the submucosa.
[k] See Principles of Surgery (GAST-D).
[l] Surgery as primary therapy is appropriate for ≥ T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[m] See Principles of Systemic Therapy (GAST-E).
[n] See Principles of Radiation Therapy (GAST-F).

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.



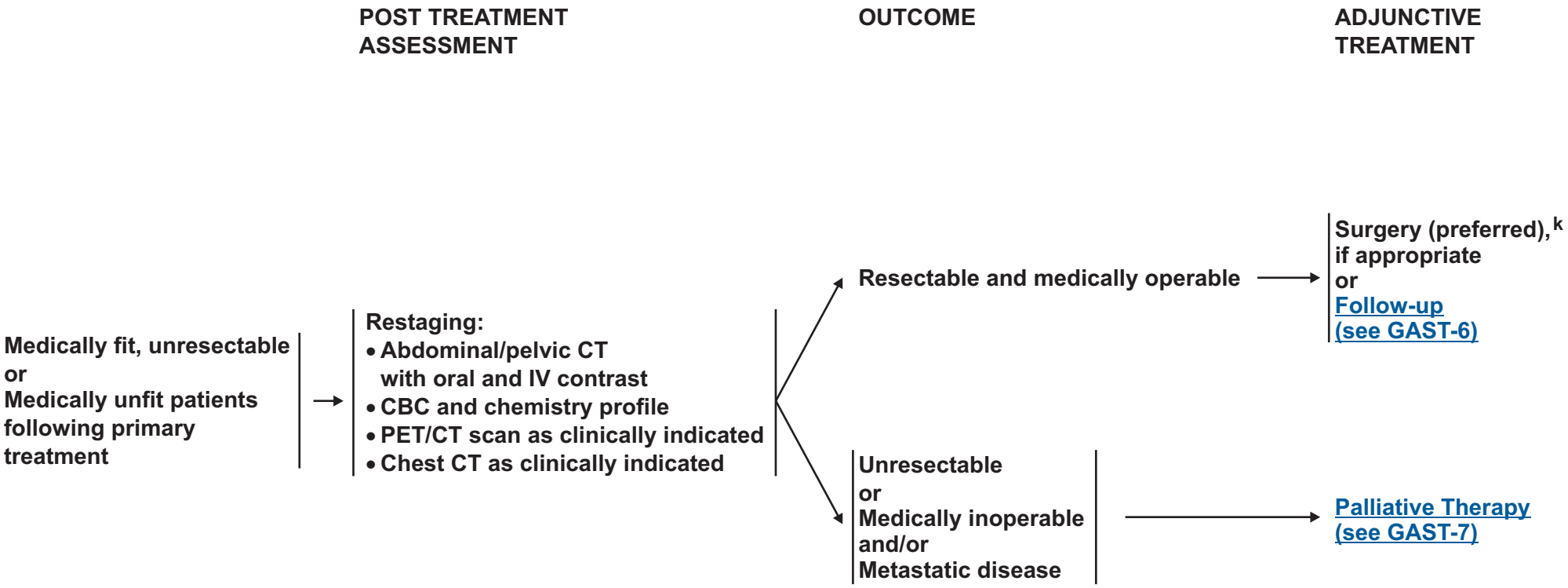
[k] See Principles of Surgery (GAST-D).
[m] See Principles of Systemic Therapy (GAST-E).
[n] See Principles of Radiation Therapy (GAST-F).
[o] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[p] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730. 5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy (GAST-E).
[q] High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age.
[r] See Principles of Best Supportive Care (GAST-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.



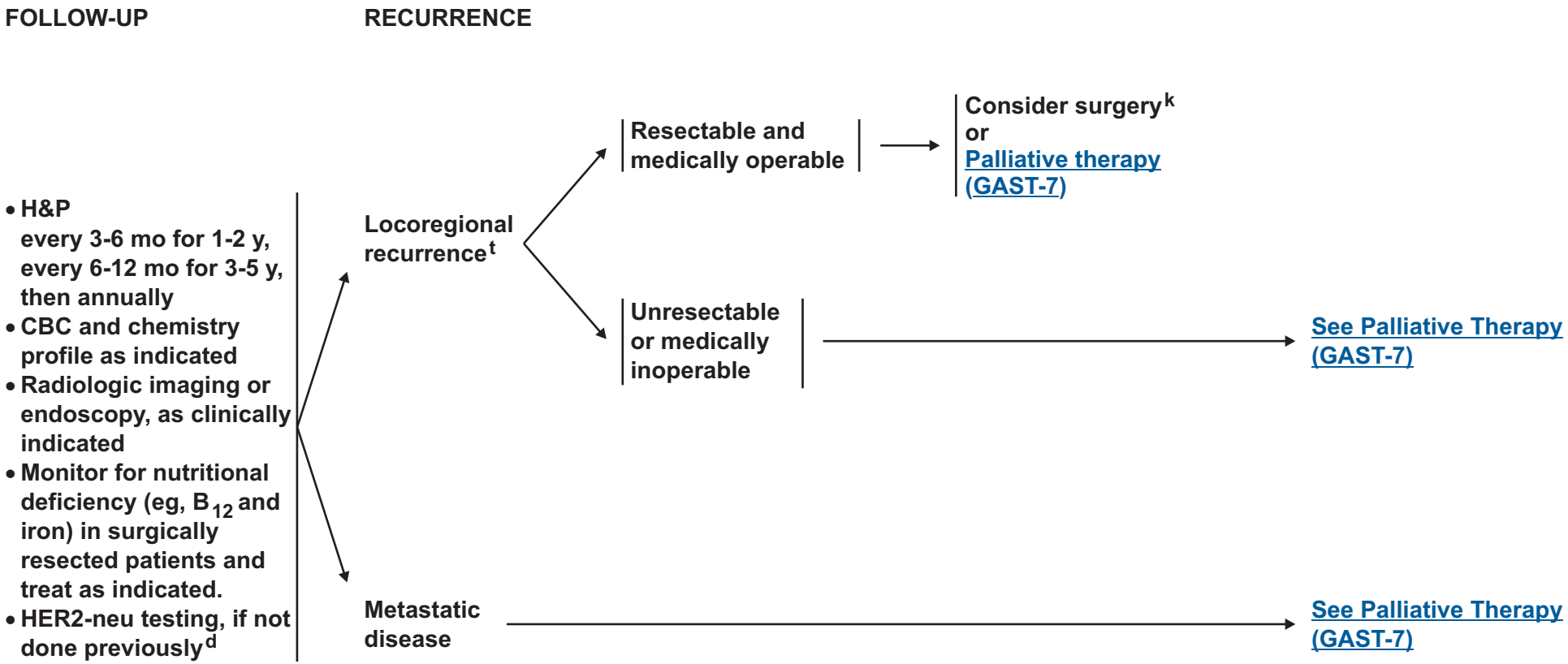
[m] See Principles of Systemic Therapy (GAST-E).
[n] See Principles of Radiation Therapy (GAST-F).
[o] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[r] See Principles of Best Supportive Care (GAST-G).
[s] See Staging (ST-1).

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.



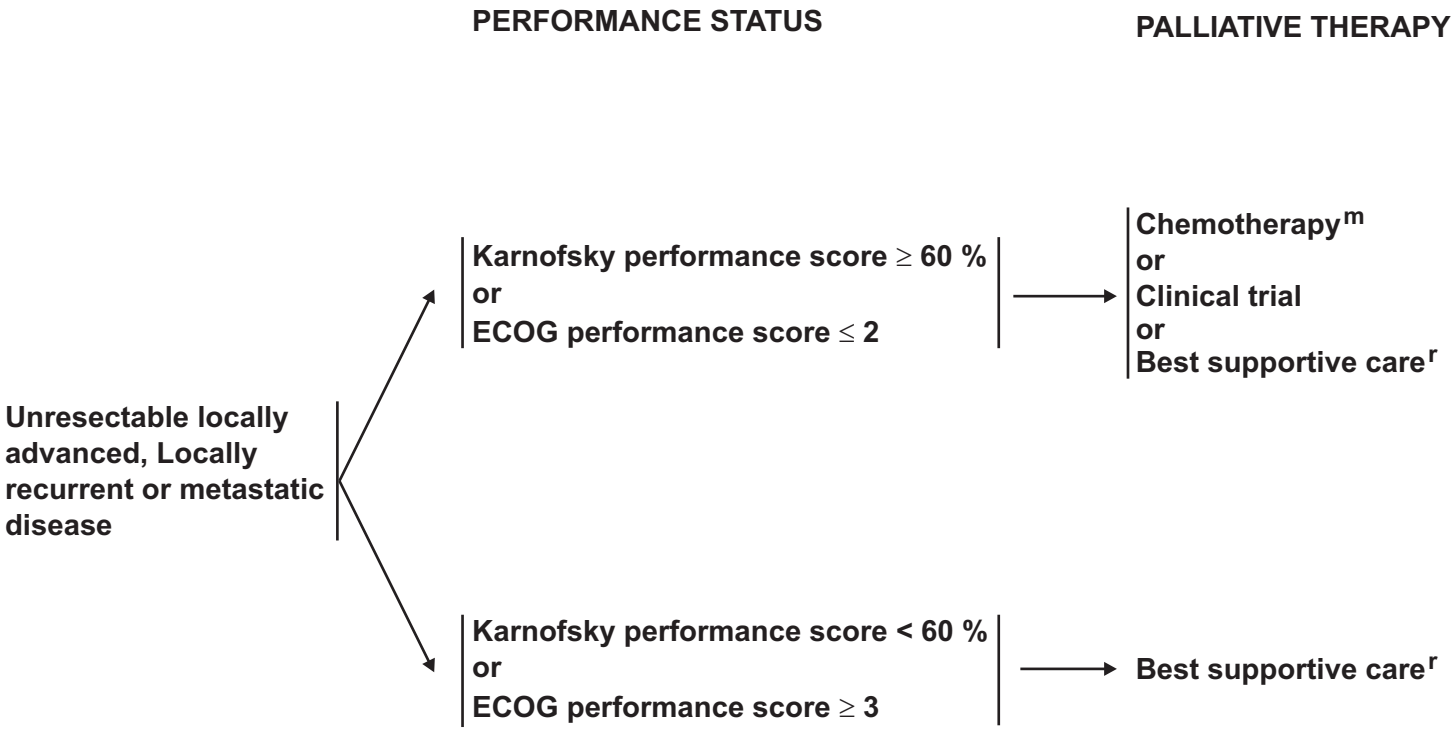
[k] See Principles of Surgery (GAST-D).

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.



[d] See Principles of Pathologic Review and HER2-neuTesting (GAST-B).
[k] See Principles of Surgery (GAST-D).
[t] Review if surgery is appropriate for patients with isolated local recurrences. Surgery should be considered as an option for locoregional recurrence in medically fit patients.

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.



[m] See Principles of Systemic Therapy (GAST-E).
[r] See Principles of Best Supportive Care (GAST-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.

PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Endoscopy has become an important tool in the diagnosis, staging, treatment and palliation of patients with gastric cancer. Although some endoscopy procedures can be performed without anesthesia, most are performed with conscious sedation administered by the endoscopist or assisting nurse or deeper anesthesia (monitored anesthesia care) provided by the endoscopist and 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 neoplastic disease and to biopsy any suspicious lesion. Thus, an adequate endoscopic exam addresses both of these components. The location of the tumor in the stomach (cardia, fundus, body, antrum, and pylorus) and relative to the esophagogastric junction (EGJ) for proximal tumors should be carefully recorded to assist with treatment planning and follow up examinations.**
- **Multiple (6-8) biopsies using standard size endoscopy forceps should be performed to provide adequate sized material for histologic interpretation, especially in the setting of an ulcerated lesion.[1,2] Larger forceps may improve the yield.**
- **Endoscopic mucosal resection (EMR) can be performed in the evaluation of small lesions. EMR of focal nodules $\leq$ 3 cm can be safely performed to provide a larger specimen which can be better assessed by the pathologist, providing greater information on degree of differentiation, the presence of lymphovascular invasion and the depth of infiltration, thereby providing accurate T-staging.[3] Such excisional biopsies have the potential of being therapeutic.[4]**
- **Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming the presence of cancer when biopsies are not diagnostic.**

Continued

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 ENDOSCOPIC STAGING AND THERAPY

STAGING

- Endoscopic ultrasound (EUS) performed prior to any treatment is important in the initial clinical staging of gastric cancer.[5] Careful attention to ultrasound images, provides evidence of depth of tumor invasion (T-stage), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N-assessment), and occasionally signs of distant spread, such as lesions in surrounding organs (M-stage) or the presence of ascites.[6] This is especially important in patients who are being considered for EMR.[7]
- Hypoechoic (dark) expansion of the gastric wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal stomach wall corresponding with greater depths of tumor penetration, correlating with higher T-stages. A dark expansion of layers 1-3 correspond with infiltration of the superficial and deep mucosa plus the submucosal, T1 disease. A dark expansion of layers 1-4, correlates with penetration into the muscularis propria, T2 disease, and expansion beyond the muscularis propria resulting in an irregular outer border correlates with invasion of the subserosa, T3 disease. Loss of the bright line recognized as the serosa is now staged as T4a, and extension of the mass into surrounding organs such as the liver, pancreas, spleen is staged T4b disease.
- Perigastric lymph nodes are readily seen by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well circumscribed, rounded structures around the stomach correlates with the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but also may be confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[8] FNA of suspicious lymph nodes should be performed if it can be achieved without traversing an area of primary tumor or major blood vessels, and if it will impact on treatment decisions. Furthermore, an attempt should be made to identify the presence of ascites and FNA considered to rule out peritoneal spread of disease.

Continued

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 ENDOSCOPIC STAGING AND THERAPY

TREATMENT

- EMR of early gastric cancer can be considered adequate therapy when the lesion is less than 1.5 cm in diameter, is shown on histopathology to be well or moderately well differentiated, does not penetrate beyond the superficial submucosa, and does not exhibit lymphovascular invasion. En-bloc excision of small gastric lesions by endoscopic submucosal dissection (ESD) has been shown to be more effective than EMR in curing early gastric cancer, but requires greater skills and instrumentation to perform and has a significant risk of complications including perforation.[9] Japanese Gastric Cancer guidelines recommend EMR should be considered for early gastric cancer lesions $\leq$ 3 cm in diameter without associated ulcer formation.[3] EMR or ESD treatments of gastric lesions that are poorly differentiated, harbor evidence of lymphovascular invasion, have lymph node metastases, or invade into the deep submucosa, should be considered to be incomplete, and additional therapy by gastrectomy with lymphadenectomy should be considered.[10]
- EUS exams performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the post-treatment stage of disease.[10] Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease but still provide useful information.[12]
- Endoscopic tumor ablation can be performed for the short-term control of bleeding. Endoscopic insertion of expandable metal stents is effective in long-term relief of tumor obstruction at the EGJ or the gastric outlet, though surgical gastrojejunostomy may be more efficacious for those with longer-term survival (see Principles of Best Supportive Care [GAST-G]).[13,14]
- Long-term palliation of anorexia, dysphagia or malnutrition may be achieved with endoscopic or radiographic assisted placement of feeding gastrostomy (PEG) in carefully selected cases where the distal stomach is uninvolved by tumor, or the placement of a feeding jejunostomy (PEJ).[15]

POST-TREATMENT SURVEILLANCE

- Endoscopic surveillance following definitive treatment of gastric cancer requires careful attention to detail for mucosal surface changes, and multiple (4-6) biopsies of any visualized abnormalities. Strictures should be biopsied to rule-out neoplastic cause. EUS performed in conjunction with endoscopy exams has a high sensitivity for recurrent disease.[16] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

Continued

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 ENDOSCOPIC STAGING AND THERAPY (REFERENCES)

[1]Hatfield AR, Slavin G, Segal AW, Levi AJ. Importance of the site of endoscopic gastric biopsy in ulcerating lesions of the stomach. Gut. 1975;16:884-886.
[2]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.
[3]Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14:113-23.
[4]Akiyama M, Ota M, Nakajima H, Yamagata K, Munakata A. Endoscopic mucosal resection of gastric neoplasms using a ligating device. Gastrointest Endosc. 1997;45:182-186.
[5]Botet JF, Lightdale CJ, Zauber AG, et al. Endoscopic ultrasound in the pre-operative staging of gastric cancer: A comparative study with dynamic CT. Radiology. 1991;181:426-432.
[6]Bentrem D, Gerdes H, Tang L, Brennan M, Coit D. Clinical correlation of endoscopic ultrasonography with pathologic stage and outcome in patients undergoing curative resection for gastric cancer. Ann Surg Oncol. 2007;14:1853-1859.
[7]Okada K, Fujisaki J, Kasuga A, et al., Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. Surg Endosc. 2010, 1279-1284.
[8]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.
[9]Yahagi N, Fujishiro M, Kakushima N, et al. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Digestive Endoscopy. 2004;16:34-38.
[10]Ahn JY, Jung HY, Choi KD. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications Gastrointest Endosc 2011;74:485-93.
[11]Park SR, Lee JS, Kim CG, et al. Endoscopic ultrasound and computed tomography in restaging and predicting prognosis after neoadjuvant chemotherapy in patients with locally advanced gastric cancer. Cancer 2008;112:2368-2376.
[12]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.
[13]Schmidt C, Gerdes H, Hawkins W, et al. A prospective observational study examining quality of life in patients with malignant gastric outlet obstruction. Am J Surg. 2009;198:92-99.
[14]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.
[15]Shike M, Latkany L, Gerdes H, Bloch AS. Direct percutaneous endoscopic jejunostomies for enteral feeding. Gastrointest Endosc. 1996;44:536-540.
[16]Lightdale CJ, Botet JF, Kelsen DP, Turnbull AD, Brennan MF. Diagnosis of recurrent upper gastrointestinal cancer at the surgical anastomosis by endoscopic ultrasound. Gastrointest Endosc. 1989;35:407-412.

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

Pathologic Review

TABLE 1

Specimen Type	Analysis/Interpretation/Reporting[a]
Endoscopic mucosal resection	Include in pathology report: • Invasion, if present • Histologic type[b] • Grade • Depth of tumor invasion • Vascular invasion • Status of mucosal and deep margins
Gastrectomy, without prior chemoradiation	For pathology report, include all elements as for endoscopic mucosal resection plus • Location of tumor midpoint in relationship to EGJ[c] • Whether tumor crosses EGJ • LN status and number of lymph nodes recovered
Gastrectomy, with prior chemoradiation	Tumor site should be thoroughly sampled 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]Subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy, as intestinal type cancers may be more likely to overrexpress HER2-neu.[1]
[c]Tumors arising in the proximal stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[2]

Continued

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

Assessment of treatment response

Response of the primary tumor to previous chemotherapy or radiation therapy should be reported. Although grading systems for tumor response in gastric cancer have not been uniformly adopted, in general, three-category systems provide good reproducibility among pathologists. The following system developed for rectal carcinoma is reported to provide good interobserver agreement, but other systems may also be used. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

TABLE 2

Tumor Regression Grade	Description
0 (Complete response)	No cancer cells
1 (Moderate response)	Single cells or small groups of cancer cells
2 (Minimal response)	Residual cancer outgrown by fibrosis
3 (Poor response)	Minimum or no treatment effect; extensive residual cancer cells

Number of lymph nodes retrieved

- **While there is no universally accepted minimum number of lymph nodes necessary for accurate staging of gastric cancer, retrieval of at least 15 lymph nodes is recommended to avoid stage migration.[4,5]**

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).

Continued

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

Assessment of Overexpression of HER2-neu in Gastric Cancer

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended. The following criteria used in the ToGA trial[6] are recommended:

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

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

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

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

Continued

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

[1]Hofmann M, Stoss O, Shi D, Buttner R, van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: Results from a validation study. Histopathology. 2008;52:797-805.
[2]Edge SE, Byrd DR, Carducci MA, Compton CC. AJCC TNM Staging Manual. 7th ed. New York, NY: Springer 2009.
[3]Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology. 2005;47:141-146.
[4]Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. Cancer. 2000 Feb 15;88(4):921-932.
[5]Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. Journal of Clinical Oncology. 2005 Oct 1;23(28):7114-7124.
[6]Bang Y-J, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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(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 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, Thompson JN, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.
[2] Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Jr., Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281(17):1623-1627.
[3] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730.

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

N Staging

- Determine extent of disease by CT scan (chest, abdomen, and pelvic) ± EUS (if no metastatic disease seen on CT)
- In patients being considered for surgical resection without pre-operative therapy, laparoscopy[1] may be useful in detecting radiographically occult metastatic disease in patients with T3 and/or N+ disease seen on preoperative imaging. If laparoscopy is performed as a separate procedure, peritoneal washings should be performed as well.
- In patients receiving pre-operative therapy, a baseline laparoscopy along with peritoneal washings should be considered.
- Positive peritoneal cytology (performed in the absence of visible peritoneal implants), is associated with poor prognosis and is defined as M1 disease.[2]

Criteria of unresectability for cure

- Locoregionally advanced
  - Level N3 (hepatoduodenal and root of mesentery) or N4 (para-aortic) lymph node highly suspicious on imaging or confirmed by biopsy
  - Invasion or encasement of major vascular structures (excluding the splenic vessels)
- Distant metastasis or peritoneal seeding (including positive peritoneal cytology)

Resectable tumors

- Tis or T1[3] tumors limited to mucosa (T1a) may be candidates for endoscopic mucosal resection (in experienced centers)[4]
- T1b-T3[5]: Adequate gastric resection to achieve negative microscopic margins (typically ≥ 4 cm from gross tumor).
  - Distal gastrectomy
  - Subtotal gastrectomy
  - Total gastrectomy
- T4 tumors require en bloc resection of involved structures

Resectable tumors---continued

- Gastric resection should include the regional lymphatics-- perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining at least 15 or greater lymph nodes[6,7,8]
  - Definition of D1 and D2 lymph node dissections
    - D1 dissection entails gastrectomy and the resection of both the greater and lesser omenta (which would include the lymph nodes along right and left cardiac, along lesser and greater curvature, suprapyloric along the right gastric artery, and infrapyloric area);
    - D2 dissection is a D1 plus all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery.
- Routine or prophylactic splenectomy is not required.[9] Splenectomy is acceptable when the spleen or the hilum is involved.
- Consider placing feeding jejunostomy tube in select patients (especially if postoperative chemoradiation appears a likely recommendation)

Palliative procedures

- Gastric resections should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease.
- Lymph node dissection not required
- In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) is preferable to endoluminal stenting in patients with gastric outlet obstruction. [10]
- Venting gastrostomy and/or jejunostomy tube may be considered

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]Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. Am J Surg. 2006;191:134-138.
[2]Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol 2010;17:3173-3180.
[3]Soetikno R, Kaltenbac T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005;23:4490-4498.
[4]Ono H, Kondo H, Gotoda T, Shirao K, et al,. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-229.
[5]Ito H, Clancy TE, Osteen RT, Swanson RS, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg. 2004;199:880-886.
[6]Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-449.
[7]Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. Ann Surg Oncol. 2007;14:317-328.
[8]Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. Ann Surg. 2000;232:362-571.
[9]Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg. 2006;93:559-563.
[10]Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18-27.

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

- **Chemotherapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status, medical comorbidities, toxicity profile, and HER2-neu expression (for adenocarcinoma only).**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without a compromise of efficacy.**
- **Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.**
- **Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.**
- **Infusional fluorouracil and capecitabine may be used interchangeably (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.[1]**
- **Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.**
- **Preoperative chemoradiation is the preferred approach for localized EGJ adenocarcinoma.[2] Perioperative chemotherapy[3,4] is an alternative but less preferred option.**
- **Perioperative chemotherapy,[3,4] or postoperative chemotherapy plus chemoradiation[5] is the preferred approach for localized gastric cancer.**
- **Postoperative chemotherapy is recommended following primary D2 lymph node dissection. (See Principles of Surgery [GAST-D]).**
- **Induction chemotherapy may be appropriate as clinically indicated.**
- **Upon completion of chemotherapy, patients should be assessed for response and monitored for any long-term complications.**
- **Please refer to the Principles of Radiation Therapy for the radiation therapy administration details (GAST-F).**

[1] 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.
[2] 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.
[3] 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.
[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] 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. 5-FU/Leucovorin as described in this reference is no longer recommended. See GAST-E 6 of 13.

Continue

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

Preoperative Chemoradiation (EGJ and gastric cardia):

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

Perioperative Chemotherapy (including EGJ adenocarcinoma)
(3 cycles preoperative and 3 cycles postoperative):

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

Postoperative Chemoradiation (including EGJ):

- **Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation[14-19]**

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection) (See Principles of Surgery [GAST-D])

- **Capecitabine and oxaliplatin[20]**
- **Capecitabine and cisplatin[21]**

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

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

Continue

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

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

- **Trastuzumab can be added to chemotherapy for HER2-neu overexpressing adenocarcinoma [See Principles of Pathologic Review and HER2-neu Testing (GAST-B)]**
  - **Combination with cisplatin and fluoropyrimidine (category 1 for first-line therapy)[22]**
  - **Combination with other chemotherapy agents (category 2B)**
  - **Trastuzumab is not recommended for use with anthracyclines**

First-Line Therapy

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

- **Preferred Regimens:**
  - **DCF (docetaxel, cisplatin and fluorouracil†) (category 1)[23-26]**
  - **DCF modifications**
    - **Docetaxel, oxaliplatin and fluorouracil†,[27,28]**
    - **Docetaxel, carboplatin and fluorouracil (category 2B)[29]**
  - **ECF (epirubicin, cisplatin and fluorouracil) (category 1)[30,31]**
  - **ECF modifications (category 1)[31]**
    - **Epirubicin, oxaliplatin and fluorouracil**
    - **Epirubicin, cisplatin and capecitabine**
    - **Epirubicin, oxaliplatin and capecitabine**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin (category 1)[32-35]**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[33,36,37]**
  - **Fluorouracil† and irinotecan[38-40]**
- **Other Regimens:**
  - **Paclitaxel with cisplatin or carboplatin[41-43]**
  - **Docetaxel with cisplatin[26,44,45]**
  - **Docetaxel and irinotecan (category 2B)[46]**
  - **Fluoropyrimidine (fluorouracil† or capecitabine)[39,47,48]**
  - **Docetaxel[49]**
  - **Paclitaxel[50,51]**

Second-Line Therapy

Dependent on prior therapy and performance status (PS):

- **Preferred Regimens:**
  - **Docetaxel (category 2B)[49]**
  - **Paclitaxel (category 2B)[50-52]**
  - **Irinotecan (category 2B)[52-55]**
- **Other Regimens:**
  - **Irinotecan and cisplatin[36,56]**
  - **Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine) (category 2B)[39,57,58]**
  - **Docetaxel and Irinotecan(category 2B)[46]**

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

- **Mitomycin and irinotecan[59-61]**
- **Mitomycin and fluorouracil†,[62]**
- **Etoposide[63,64]**

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

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

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.

Continue

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

PREOPERATIVE CHEMORADIATION (EG JUNCTION AND GASTRIC CARDIA)

PREFERRED REGIMENS

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

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

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

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

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

PREFERRED REGIMENS

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

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

OTHER REGIMENS

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

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

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

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

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

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

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

Continue

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--REGIMENS AND DOSING SCHEDULES††

PERIOPERATIVE CHEMOTHERAPY (INCLUDING EG JUNCTION)

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

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

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

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

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

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

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.

Continue

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--REGIMENS AND DOSING SCHEDULES††

POSTOPERATIVE CHEMORADIATION (INCLUDING EG JUNCTION)

5-FU (bolus) and leucovorin (category 1)[14]

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

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

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[14] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE ABOVE SPECIFIED DOSES OR SCHEDULE OF CYTOTOXIC AGENTS BECAUSE OF CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

- 1 cycle before and 2 cycles after chemoradiation
  Capecitabine 750-1000 mg/m^2 PO BID on Days 1-14
  Cycled every 28 days [15,16]

- 1 cycle before and 2 cycles after chemoradiation
  Leucovorin 400 mg/m^2 IV on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 400 mg/m^2 IVP on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1, 2, 15, and 16
  Cycled every 28 days[17]

With radiation
Fluorouracil 200-250 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 or 1-7
Weekly for 5 weeks[18]

With radiation
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5 or 1-7
Weekly for 5 weeks[19]

POSTOPERATIVE CHEMOTHERAPY

Capecitabine and oxaliplatin
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days for 8 cycles[20]

Capecitabine and Cisplatin
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Cisplatin 60 mg/m^2 IV on Day 1
Cycled every 21 days for 6 cycles[21]

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

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

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.

Continue

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

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

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

Trastuzumab 8 mg/kg IV loading dose
on Day 1 of Cycle 1, then
Trastuzumab 6 mg/kg IV every 21 days[22]
or
Trastuzumab 6 mg/kg IV loading dose on
Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

DCF (docetaxel, cisplatin, and fluorouracil)

Docetaxel 75 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 1
Fluorouracil 1000 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-5
Cycled every 28 days [23]

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

Docetaxel 60 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Fluorouracil 750 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-4
Cycled every 21 days [25]

Docetaxel 75-85 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 1
Fluorouracil 300 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-14
Cycled every 21 days[26]

PREFERRED REGIMENS---continued

DCF modifications

Docetaxel 50 mg/m^2 IV on Day 1
Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 200 mg/m^2 IV on Day 1
Fluorouracil 2600 mg/m^2 IV continuous infusion
over 24 hours daily on Day 1
Cycled every 14 days[27]

Docetaxel 50 mg/m^2 IV on Day 1
Oxaliplatin 85 mg/m^2 IV on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[28]

Docetaxel 75 mg/m^2 IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-3
Cycled every 21 days [29]

ECF

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-21
Cycled every 21 days[30,31]

ECF modifications

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Fluorouracil 200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-21
Cycled every 21 days[31]

PREFERRED REGIMENS---continued

ECF modifications--continued

Epirubicin 50 mg/m^2 IV on Day 1
Cisplatin 60 mg/m^2 IV on Day 1
Capecitabine 625 mg/m2 PO BID on Days 1-21
Cycled every 21 days[31]

Epirubicin 50 mg/m^2 IV on Day 1
Oxaliplatin 130 mg/m^2 IV on Day 1
Capecitabine 625 mg/m^2 PO BID on Days 1-21
Cycled every 21 days[31]

Fluoropyrimidine and cisplatin

Cisplatin 75-100 mg/m^2 IV on Day 1
Fluorouracil 750-1000 mg/m^2 IV continuous
infusion over 24 hours daily on Days 1-4
Cycled every 28 days[32]

Cisplatin 50 mg/m^2 IV daily on Day 1
Leucovorin 200 mg/m^2 IV on Day 1
Fluorouracil 2000 mg/m^2 IV continuous infusion
over 24 hours daily on Day 1
Cycled every 14 days [33,34]

Cisplatin 80 mg/m^2 IV daily on Day 1
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Cycled every 21 days[35]

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.

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

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--REGIMENS AND DOSING SCHEDULES††

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

FIRST-LINE THERAPY---continued

PREFERRED REGIMENS

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[36]

Oxaliplatin 85 mg/m^2 IV on Day 1
Leucovorin 200 mg/m^2 IV on Day 1
Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[33]

Capecitabine 1000 mg/m^2 PO BID on Days 1-14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days[37]

Fluorouracil and irinotecan

Irinotecan 80 mg/m^2 IV on Day 1
Leucovorin 500 mg/m^2 IV on Day 1
Fluorouracil 2000 mg/m^2 IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 1 week off treatment [38]

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

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

OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135-200 mg/m^2 IV on Day 1
Cisplatin 75 mg/m^2 IV on Day 2
Cycled every 21 days[41]

Paclitaxel 90 mg/m^2 IV on Day 1
Cisplatin 50 mg/m^2 IV on Day 1
Cycled every 14 days[42]

Paclitaxel 200 mg/m^2 IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[43]

Docetaxel and cisplatin

Docetaxel 70-85 mg/m^2 IV on Day 1
Cisplatin 70-75 mg/m^2 IV on Day 1
Cycled every 21 days[26,44,45]

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[46]

OTHER REGIMENS--continued

Fluoropyrimidine

Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[39]

Fluorouracil 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5
Cycled every 28 days[47]

Capecitabine 1000-1250 mg/m^2 PO BID on Days 1-14
Cycled every 21 days[48]

Taxane

Docetaxel 75-100 mg/m^2 IV on Day 1
Cycled every 21 days[49]

Paclitaxel 135-250 mg/m^2 IV on Day 1
Cycled every 21 days[50]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[51]

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

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

Continue

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--REGIMENS AND DOSING SCHEDULES††

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

Trastuzumab (with chemotherapy)
Trastuzumab 8 mg/kg IV loading dose
on Day 1 of Cycle 1, then
Trastuzumab 6 mg/kg IV every 21 days[22]
or
Trastuzumab 6 mg/kg IV loading dose on
Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Taxane
Docetaxel 75-100 mg/m^2 IV on Day 1
Cycled every 21 days[49]

Paclitaxel 135-250 mg/m^2 IV on Day 1
Cycled every 21 days[50]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[51]

Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15
Cycled every 28 days[52]

Irinotecan
Irinotecan 250-350 mg/m^2 IV on Day 1
Cycled every 21 days[53]

Irinotecan 150-180 mg/m^2 IV on Day 1
Cycled every 14 days[52,54,55]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[54]

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[36,56]

Irinotecan and fluoropyrimidine
Irinotecan 250 mg/m^2 IV on Day 1
Capecitabine 1000 mg/m^2 PO BID
on Days 1-14
Cycled every 21 days[57]

Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IVP on Day 1
Fluorouracil 600-1200 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1 and 2
Cycled every 14 days[39,58]

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[46]

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

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

Continue

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--REGIMENS AND DOSING SCHEDULES††

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

Mitomycin and irinotecan
Mitomycin 6 mg/m^2 IV on Day 1
Irinotecan 125 mg/m^2 IV on Days 2 and 9
Cycled every 28 days[59]

Irinotecan 150 mg/m^2 IV on Days 1 and 15
Mitomycin 8 mg/m^2 IV on Day 1
Cycled every 28 days[60]

Irinotecan 125 mg/m^2 Day 1
Mitomycin 5 mg/m^2 IV on Day 1
Cycled every 14 days[61]

Mitomycin, leucovorin, and fluorouracil
Mitomycin 10 mg/m^2 IV on Days 1 and 22
Leucovorin 500 mg/m^2 IV on Day 1
Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[62]

Etoposide
Etoposide 90-120 mg/m^2 IV on Days 1-3
Cycled every 28 days[63,64]

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

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

Continue

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--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 M-P, Raoul JL, et al. Phase III randomized trial of definitive chemoradiotherapy (CRT) with FOLFOX or cisplatin and fluorouracil in esophageal cancer (EC): Final results of the PRODIGE 5/ACCORD 17 trial. ASCO Meeting Abstracts 2012;30:LBA4003.
[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] 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.
[7] 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.
[8] 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. .
[9] 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.
[10] Hihara J, Yoshida K, Hamai Y, et al. Phase I study of docetaxel (TXT) and 5-fluorouracil (5-FU) with concurrent radiotherapy in patients with advanced esophageal cancer. Anticancer Res 2007;27:2597-2603.
[11] 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.
[12] 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.
[13] 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.
[14] 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.
[15] 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.
[16] Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010 Mar;11:241-248.
[17] 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.
[18] 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.
[19] 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.
[20] Bang Y-J, Kim Y-W, Yang H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. The Lancet 2012;379:315-321.
[21] Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-273.
[22] 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.
[23] 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.
[24] Shah MA, Shibata S, Stoller RG, et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE) [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 4014.
[25] Ozal G, Dogan M, Akbulut H, et al. The safety and efficacy of modified-dose docetaxel, cisplatin, and 5-fluorouracil (mDCF) combination in the front-line treatment of advanced gastric cancer. [abstract]. Presented at the 2010 Gastrointestinal Cancers Symposium Abstract 113.
[26] Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007;25:3217-3223.

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.

Continue

PRINCIPLES OF SYSTEMIC THERAPY--REFERENCES

[27] Al-Batran SE, 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.
[28] 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.
[29] 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] [abstract]. Presented at the 2008 Gastrointestinal Cancers Symposium 2008. Abstract 38.
[30] 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.
[31] Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
[32] 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.
[33] 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.
[34] 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.
[35] 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.
[36] 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.
[37] 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.
[38] 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.
[39] Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 1999;35:1343-1347.
[40] 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.
[41] 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. .
[42] 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.
[43] 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.
[44] 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.
[45] 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.
[46] Burtness B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal
[47] 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.
[48] 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.
[49] 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.
[50] 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.
[51] 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.

Continue

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--REFERENCES

[52] Ueda S, Hironaka S, Yasui H, et al. Randomized phase III study of irinotecan (CPT-11) versus weekly paclitaxel (wPTX) for advanced gastric cancer (AGC) refractory to combination chemotherapy (CT) of fluoropyrimidine plus platinum (FP): WJOG4007 trial. ASCO Meeting Abstracts 2012;30:4002.

[53] 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.

[54] 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.

[55] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.

[56] Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004;18:22-25.

[57] 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.

[58] Di Lauro L, Fattoruso SI, Giacinti L, et al. Second-line chemotherapy with FOLFIRI in patients with metastatic gastric cancer (MGC) not previously treated with fluoropyrimidines [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 4549.

[59] 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.

[60] Giuliani F, Molica S, Maiello E, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol

[61] Bamias A, Papamichael D, Syrigos K, Pavlidis N. Phase II study of irinotecan and mitomycin C in 5-fluorouracil-pretreated patients with advanced colorectal and gastric cancer. J Chemother 2003;15:275-281. .

[62] Hofheinz RD, Hartung G, Samel S, et al. High-dose 5-fluorouracil / folinic acid in combination with three-weekly mitomycin C in the treatment of advanced gastric cancer. A phase II study. Onkologie 2002;25:255-260.

[63] Taal BG, Teller FG, ten Bokkel Huinink WW, et al. Etoposide, leucovorin, 5-fluorouracil (ELF) combination chemotherapy for advanced gastric cancer: experience with two treatment schedules incorporating intravenous or oral etoposide. Ann Oncol 1994;5:90-92.

[64] Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000;18:2648-2657.

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 RADIATION THERAPY

General Guidelines

- Prior to simulation, pertinent radiographs, procedure notes and pathology reports should be reviewed by a multidisciplinary team including surgical, radiation, medical oncologists, gastroenterologists, radiologists and pathologists. This will allow an informed determination of treatment volume and field borders prior to simulation.
- In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal cancers. Depending on the clinical situation, Siewert III tumors, may be more appropriately managed with radiation therapy guidelines applicable to either esophageal or gastric cancers. These recommendations may be modified depending on where the bulk of the tumor is located.

Simulation and Treatment Planning

- Use of CT simulation and 3D treatment planning is strongly encouraged.
- The patient should be instructed to avoid intake of a heavy meal for 3 hours before simulation and treatment. When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily set-up.
- All patients should be simulated and treated in the supine position.
- Although AP/PA fields can be weighted anteriorly to keep the spinal cord dose at acceptable levels using only parallel-opposed techniques, a 4-field technique (AP/PA and opposed laterals), if feasible, can spare spinal cord with improved dose homogeneity. Patients with a stomach that is sufficiently anterior to allow treatment via laterals to the target volume and draining lymph nodes with 1.5-2 cm margin while sparing spinal cord may have more liberal use of lateral beams with multiple-field techniques. The uncertainties arising from variations in stomach filling and respiratory motion should also be taken into consideration.
- With the wide availability of 3D treatment-planning systems, it may be possible to target more accurately the high-risk volume and to use unconventional field arrangements to produce superior dose distributions. To accomplish this without marginal misses, it will be necessary to both carefully define and encompass the various target volumes because the use of oblique or non-coplanar beams could exclude target volumes that would be included in AP/PA fields or multiple-field techniques.
- Intensity modulated radiation therapy (IMRT) is appropriate in selected cases to reduce dose to normal structures such as heart, lungs, kidneys and liver. As discussed above, target volumes need to be carefully defined and encompassed while designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion need to be taken into account. For structures such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses.

Continued

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 RADIATION THERAPY

Target Volume (General Guidelines)

- **Preoperative**[1]
  - **Pre-treatment diagnostic studies (EUS, UGI, EGD, and CT scans) should be used to identify the tumor and pertinent nodal groups.[2,3] The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.**
- **Postoperative**[4]
  - **Pre-treatment diagnostic studies (EUS, UGI, EGD, and CT scans) and clip placement should be used to identify the tumor/gastric bed, the anastomosis or stumps, and pertinent nodal groups.[2,3] Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach. The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.[5]**

Proximal one-third/Cardia/Esophagogastric Junction Primaries

- **Preoperative and Postoperative**
  - **With proximal gastric lesions or lesions at the EG junction, a 3- to 5-cm margin of distal esophagus, medial left hemidiaphragm and adjacent pancreatic body should be included. Nodal areas at risk include: adjacent paraesophageal, perigastric, suprapancreatic, and celiac lymph nodes.**

Middle one-third/Body Primaries

- **Preoperative and Postoperative**
  - **Body of pancreas should be included. Nodal areas at risk include: perigastric, suprapancreatic, celiac, splenic hilar, porta hepatic, and pancreaticoduodenal lymph nodes.**

Distal one-third/Antrum/Pylorus Primaries

- **Preoperative**
  - **Head of pancreas, 1st and 2nd part of duodenum should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.**
- **Postoperative**
  - **Head of pancreas, a 3- to 5-cm margin of duodenal stump should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.**

Blocking

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

Dose

- **45-50.4 Gy (1.8 Gy/day)**

[a] Lung Dose Volume Histogram (DVH) parameters as predictors of pulmonary complications in gastric/esophagogastric junction cancer patients treated with concurrent chemoradiotherapy should be strongly considered, though consensus on optimal criteria has not yet emerged. Every effort should be made to keep the lung volume and doses to a minimum. Treating physicians should be aware that the DVH reduction algorithm is hardly the only risk factor for pulmonary complications. DVH parameters as predictors of pulmonary complications in gastric/esophagogastric junction cancer patients are an area of active development among the NCCN institutions and others.

Continued

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 RADIATION THERAPY

Supportive Therapy

- Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks.
- During 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, and antacid and antidiarrheal medications may be prescribed when needed.
- If estimated caloric intake is < 1500 kcal/day, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomies (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.
- B_{12}, iron, and calcium level should be closely monitored, especially for postoperative patients. Monthly B_{12} shots may be needed because of loss of intrinsic factor. Iron absorption is reduced without gastric acid. Oral supplementation, given with acid such as orange juice, can often maintain adequate levels. Calcium supplementation should also be encouraged.
- Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery.

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

[1]Ajani AJ, 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. JCO 2006;24:3953-3958.
[2]Willett CG, Gunderson LL. Stomach, in: Perez and Brady's principles and practice of radiation oncology, 5th ed. Lippincott Williams & Wilkins, 2007;1318-1335.
[3]Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. Int J Radiat Oncol Biol Phys 2002;52:283-293.
[4]Macdonald JS, Smalley S, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725-730, 2001.
[5]Tepper JE, Gunderson LE, Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol 2002;12(2):187-195.

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 BEST SUPPORTIVE CARE

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 gastric cancer, interventions undertaken to relieve major symptoms may result in 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 gastric cancer patient is encouraged.

Bleeding

- Bleeding is common in patients with gastric cancer and may directly arise from the tumor, or as a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment.[1]
  - Endoscopic hemostatic interventions appropriate to the findings should be carried out
  - Interventional radiology angiographic embolization techniques may be useful in those situations where endoscopy is not helpful
  - External beam radiation therapy[2]
- Chronic blood loss from gastric cancer
  - External beam radiation therapy[2]

Obstruction

- Endoscopic relief of obstruction
  - Balloon dilation
  - Placement of enteral stent for relief of outlet obstruction,[3] or esophageal stent for EGJ/cardia obstruction (see NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers)
- Surgery
  - Gastrojejunal bypass[3]
  - Gastrectomy in select patients[4]
- Establish enteral access for purposes of hydration and nutrition if endoscopic lumen enhancement is not undertaken or is unsuccessful
  - Feeding percutaneous endoscopic gastrostomy for patients with EGJ/cardia obstruction if tumor location permits
  - Endoscopic or surgical placement of jejunal feeding tube for patients with mid and distal gastric obstruction
- Venting gastrostomy (if endoscopic lumen enhancement is not undertaken or is unsuccessful)
  - Percutaneous endoscopic or interventional radiology gastrostomy tube placement can be placed for gastric decompression if tumor location permits
  - Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.
- External beam radiation therapy
- Chemotherapy[a]

[a] See Principles of Systemic Therapy (GAST-E)

Continued

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 BEST SUPPORTIVE CARE

Pain

- External beam radiation therapy[2]
- Chemotherapy[a]
- 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 gastric stent placement should be treated with endoscopic removal of the stent once uncontrollable nature of pain is established.

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.

[a] See Principles of Systemic Therapy (GAST-E)

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 BEST SUPPORTIVE CARE
(References)

[1]Imbesi JJ, Kurtz RC. A multidisciplinary approach to gastrointestinal bleeding in cancer patients. J Support Oncol. 2005;3(2):101-110.
[2]Kim MM, Rana V, Janjan NA, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol. 2008;47(3):421-427.
[3]Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol. 2007;7:18.
[4]Lim S, Muhs BE, Marcus SG, Newman E, Berman RS, Hiotis SP. Results following resection for stage IV gastric cancer; are better outcomes observed in selected patient subgroups? J Surg Oncol. 2007;95(2):118-122.

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 Staging Classification for Carcinoma of the Stomach
(7th ed., 2010)

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
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 penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures**,***
T4 Tumor invades serosa (visceral peritoneum) or adjacent structures**,***
T4a Tumor invades serosa (visceral peritoneum)
T4b Tumor invades adjacent structures

Regional Lymph Nodes (N)
NX Regional lymph node(s) 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
N3a Metastasis in 7 - 15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

* Note: A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4.

**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

§A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Continued

Table 1 - Continued

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Carcinoma of the Stomach

(7th ed., 2010)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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 and 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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview MS-2
Staging MS-2
Principles of Pathology MS-4
- Biopsy MS-4
- Assessment of Treatment Response MS-4
- Assessment of HER2-neu Overexpression MS-5

Surgery MS-6
- Principles of Surgery MS-6
- Lymph Node Dissection MS-7
- Laparoscopic Resection MS-9

Endoscopic Therapies MS-10
- Principles of Endoscopy MS-10

Radiation Therapy MS-12
- Principles of Radiation Therapy MS-13

Combined Modality Treatment: Concurrent Chemotherapy and Radiation Therapy MS-14
- Preoperative Chemoradiation Therapy MS-14
- Preoperative Sequential Chemotherapy and Chemoradiation Therapy MS-14
- Postoperative Chemoradiation Therapy MS-15

Chemotherapy MS-16
- Perioperative Chemotherapy MS-16
- Postoperative Chemotherapy MS-17
- Chemotherapy for Locally Advanced or Metastatic Disease MS-18

Targeted Therapies MS-20
Treatment Guidelines MS-21
- Workup MS-21
- Primary Treatment MS-22
- Posttreatment Assessment and Adjunctive Treatment MS-23
- Postoperative Treatment MS-23
- Follow-up MS-24
- Locally Advanced, Metastatic or Recurrent Disease MS-24
- Leucovorin Shortage MS-25
- Best Supportive Care MS-25

Summary MS-26
References MS-28

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] Changes in histology and location of upper GI tract tumors have also been observed in some parts of Europe.[2,3] In Western countries, the most common sites of gastric cancer are the proximal lesser curvature, cardia, and the EGJ.[1] It is possible that in the coming decades these changing trends will also occur in South America and Asia.

Gastric cancer is rampant in many countries around the world. In Japan, it remains the most common type of cancer among men. The incidence of gastric cancer is much higher in China than in any other country. The incidence of gastric cancer, however, has been declining globally since World War II and it is one of the least common cancers in North America. By some estimates, it is the fourth most common cancer worldwide.[4] In 2013, an estimated 21,600 people will be diagnosed and 10,990 people will eventually die of their disease in the United States.[5] In developed countries, the incidence of gastric cancer originating from the cardia follows the distribution of esophageal cancer.[6-8] Non-cardia gastric adenocarcinoma shows marked geographic variation with countries such as Japan, Korea, China, Taiwan, Costa Rica, Peru, Brazil, Chile and the former Soviet Union.[9] In contrast to the incidence trends in the West, non-proximal tumors continue to predominate in Japan and other parts of the world.[10] The etiology of this shift remains elusive and may be multifactorial.

Gastric cancer is often diagnosed at an advanced stage. In Japan (and in a limited fashion in Korea) where screening is performed widely, early detection is often possible. In other parts of the world, it continues to pose a major challenge for health care professionals. Environmental risk factors include Helicobacter pylori (H. pylori) infection, smoking, high salt intake, and other dietary factors. In a recent meta-analysis, there was no appreciable association between moderate alcohol drinking and gastric cancer risk, however, there was a positive association with heavy alcohol drinking, particularly for non-cardia gastric cancers.[11] Patients with a family history of non-hereditary gastric cancer have a higher risk of developing gastric cancer. In a limited number of patients (1% to 3%), its diagnosis is associated with inherited syndromes. E-cadherin mutations occur in approximately 25% of families with an autosomal dominant, hereditary form of diffuse gastric cancer.[12] Genetic counseling is recommended and consideration should be given to prophylactic gastrectomy in young, asymptomatic carriers of germ-line truncating *CDH1* mutations who belong to families with highly penetrant hereditary diffuse gastric cancer.[13]

Staging

Two major classifications are currently used. The Japanese classification is more elaborate and is based on anatomic involvement, particularly the lymph node stations.[14] The other staging system developed jointly by the AJCC and the Union for International Cancer Control (UICC), is the system used in countries in the Western Hemisphere.[15] A minimum of 15 examined lymph nodes is recommended for adequate staging. The 7th Edition of the AJCC Staging Manual does not include the proximal 5 cm of the stomach and this has created debates, confusion and disagreements. In addition, the new classification suffers from a number of other drawbacks, as it is based on primary surgery and is not reliable when considering clinical baseline staging or after preoperative therapy.

Clinical baseline stage provides useful information for the development of an initial treatment strategy. Approximately 50% of patients will present with advanced disease at diagnosis and have a poor outcome. Other measures of poor outcome include poor performance status, presence of metastases, and alkaline phosphatase level of 100 U/L or more.[16] In patients with localized resectable disease, outcome depends on the surgical stage of the disease. Nearly 70% to 80% of patients have involvement of the regional lymph nodes. The number of positive lymph nodes has a profound influence on survival.[17]

Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, PET /CT, MRI and laparoscopic staging.[18-20]

CT scan is routinely used for preoperative staging. It has an overall accuracy of 43% to 82% for T staging. PET/CT has a low detection rate because of the low tracer accumulation in diffuse and mucinous tumor types which are frequent in gastric cancer.[21] It has a significantly lower sensitivity compared to CT in the detection of local lymph node involvement (56% vs.78%), although it has an improved specificity (92% vs. 62%).[22] Combined PET/CT imaging, on the other hand, has several potential advantages over PET scan alone.[23] PET/CT has a significantly higher accuracy in preoperative staging (68%) than PET (47%) or CT (53%) alone. Recent reports have confirmed that PET alone is not an adequate diagnostic procedure in the detection and preoperative staging of gastric cancer but it could be helpful when used in conjunction with CT.[24,25]

EUS is indicated for assessing the depth of tumor invasion.[26] The accuracy of EUS for T-staging ranges from 65% to 92% and 50% to 95% for N staging and is operator dependent. Distant lymph node evaluation by EUS is suboptimal given the limited depth and visualization of the transducer.[27]

Laparoscopic staging can detect occult metastases. In a study conducted by Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a period of 10 years.[28] Distant metastatic disease (M1) was detected in 31% of the patients. Limitations of laparoscopic staging include two-dimensional evaluation and limited use in the identification of hepatic metastases and perigastric lymph nodes. In patients being considered for surgical resection without preoperative therapy, laparoscopy may be useful for the detection of radiographically occult metastatic disease in patients with T3 and/or N+ tumors identified on preoperative imaging. In patients receiving preoperative therapy, laparoscopy along with cytology of peritoneal washings is recommended.[28] The guidelines have included laparoscopic staging with a category 2B recommendation.

Cytogenetic analysis of peritoneal fluid can help improve staging through identification of occult carcinomatosis.[18] Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer. A positive peritoneal cytology is an independent predictor for identifying patients who are at higher risk for recurrence following curative resection.[29] Laparoscopic lavage cytology is also very useful to identify the subset of patients with M1 disease who are unlikely to benefit from resection alone.[30] A recent report suggests that clearing of cytology-positive disease by chemotherapy is associated with a statistically significant improvement in disease-specific-survival but cures are rare.[31] Therefore, positive peritoneal cytology in the absence of visible peritoneal implants should be considered as M1 disease. The panel recommends that patients with advanced tumors, T3 or N1

disease should be considered for laparoscopic staging with peritoneal washings for cytology.

Principles of Pathology

Biopsy

A specific diagnosis of gastric adenocarcinoma should be established for staging and treatment purposes. In the revised AJCC staging system, tumors arising in the proximal stomach and crossing the EGJ are classified as esophageal carcinomas.[32] 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 endoscopic mucosal resection (EMR) and surgical resection specimens should also include assessment of lymphovascular invasion, depth of tumor invasion, and the status of mucosal and deep margins. The pathology report of the surgical resection specimen should also document the location of the tumor midpoint in relationship to the EGJ, lymph node status and the number of lymph nodes recovered. In the case of gastrectomy with prior chemoradiation and without grossly obvious residual tumor, the tumor site should be thoroughly sampled to detect microscopic residual disease.

While there is no universally accepted minimum number of lymph nodes necessary for accurate staging of gastric cancer, retrieval of at least 15 lymph nodes is recommended to stage nodal status more accurately. Data from a SEER database show that the number of lymph nodes examined correlated with overall survival (OS) after gastrectomy. A trend for superior survival based on more lymph nodes examined was confirmed across all stage subgroups.[33]

Assessment of Treatment Response

The type of pathologic response and histologic tumor regression after neoadjuvant therapy has been shown to be a predictor of survival in patients with gastric adenocarcinoma. Lowy et al reported that clinical response to neoadjuvant chemotherapy was the only important predictor of OS in patients who underwent curative resection for gastric cancer.[34] In another study, Becker et al demonstrated that histopathologic grading of tumor regression correlated with survival in patients treated with neoadjuvant chemotherapy.[35] Median survival was significantly better for patients with less than 10% of the residual tumor compared to those patients with 10% to 50% or greater than 50% of the residual tumor. In a recent report, Mansour et al reported that the 3-year disease-specific survival was significantly higher for patients with more than 50% pathologic response to neoadjuvant chemotherapy compared to those with less than 50% (69% and 44% respectively).[36] Tumor size, perineural or lymphovascular invasion, and the nodal status have been shown to be stronger predictors of survival.

Although grading systems for tumor response in patients with gastric cancer have not been uniformly adopted, in general, a 3-tiered classification system provides good reproducibility among pathologists. The grading system developed by Ryan et al for rectal carcinoma is reported to provide good interobserver agreement,[37] but other systems may also be used. Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor. See the “Principles of Pathologic Review and HER2-neu Testing-Assessment of Treatment Response-Table 2” in the guidelines.

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.[38] The reported rates of *HER2* amplification and HER2 overexpression in patients with gastric cancer range from 12% to 27% and 9% to 23% respectively.[39-44] HER2-positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[39,42-44] HER2-positivity is reported in ≤ 20% of Western patients with metastatic gastric cancer with significantly higher rates of HER2-positivity in patients with intestinal histology (33% vs. 8% for diffuse/mixed histology; P = .001).[44] In the US population, the reported HER2-positive rate is 12% and is more often identified in the intestinal subtype rather than the diffuse subtype (19% and 6% respectively).[43] In the Trastuzumab for Gastric Cancer (ToGA) trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2-neu-positive advanced gastric cancer, HER2-neu-positivity rates were 33%, 21%, 32% and 6% respectively in patients with EGJ adenocarcinoma, gastric adenocarcinoma, intestinal and diffuse cancer or mixed type cancer.[45] Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

However, unlike in breast cancer, the prognostic significance of HER2 status in patients with gastric cancer remains unclear with some studies suggesting that HER2-positivity is associated with poor prognosis[41,42,46,47] and others have shown that it is not an independent prognostic factor of patient outcome, except in a very small subgroup of patients with intestinal histology.[43,44,48] While further studies are needed to assess the prognostic significance of HER2-positivity, the most important clinical application of HER2 status in patients with gastric cancer concerns the management of patients with advanced or metastatic disease.

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

According to the HER2 scoring system for breast cancer proposed by the American Society of Clinical Oncology/College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for *HER2* overexpression. However, due to two major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many gastric cancer patients who could otherwise be candidates for anti-HER2 therapy.[49,50] 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).[51,52]

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.[49] In a subsequent

validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[50] This modified HER2 scoring system was also used in the ToGA trial.[51]

HER2 testing is now recommended for all patients with metastatic disease 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).[49,51] A score of 0 or 1+ is considered to be negative for *HER2* expression. A score 2+ is considered equivocal and should be confirmed with FISH or other in-situ hybridization techniques. The panel recommends FISH only for patients with a score of IHC 2+, although some institutions routinely perform both IHC and FISH on all patients. See the "Principles of Pathologic Review and HER2-neu Testing-Assessment of Treatment Response -Table 3" in the guidelines.

Surgery

Surgery is the primary treatment for early stage gastric cancer. Complete resection with adequate margins (4 cm or greater) is widely considered as a standard goal, whereas the type of resection (subtotal vs. total gastrectomy) along with extent of lymph node dissection remains a subject of controversy.

Principles of Surgery

Clinical staging using CT scan (chest, abdomen and pelvic) with or without EUS should be performed before surgery to assess the extent of the disease. The primary goal of surgery is to accomplish a complete resection with negative margins (R0 resection). Only 50% of patients will end up with an R0 resection of their primary.[53,54] R1 indicates microscopic residual disease (positive margins) and R2 indicates gross (macroscopic) residual disease in the absence of distant metastasis.[55]

Subtotal gastrectomy is the preferred approach for distal gastric cancers. This procedure has a similar surgical outcome compared to total gastrectomy although with significantly fewer complications.[56] Proximal gastrectomy and total gastrectomy are both indicated for proximal gastric cancers and are typically associated with postoperative nutritional impairment.

Adequate gastric resection (distal, subtotal or total gastrectomy) to achieve negative microscopic margins (4 cm or greater from the gross tumor) is preferred for resectable T1b-T3 tumors.[57] T4 tumors require en bloc resection of involved structures. Tis or T1b tumors may be candidates for EMR in experienced centers.

Routine or prophylactic splenectomy should be avoided if possible. In a randomized clinical study, postoperative mortality and morbidity rates were slightly higher in patients who underwent total gastrectomy combined with splenectomy, and marginally better survival, but there were no statistically significant differences between the groups.[58] The results of this study do not support the use of prophylactic splenectomy to remove macroscopically negative lymph nodes near the spleen in patients undergoing total gastrectomy for proximal gastric cancer. Placement of a jejunostomy feeding tube may be considered for selected patients who will be receiving postoperative chemoradiation.

Carcinomas are considered unresectable if there is evidence of peritoneal involvement (including positive peritoneal cytology), distant metastases, or locally advanced disease (N3 or N4 lymph node involvement highly suspicious on imaging or confirmed by biopsy; invasion or encasement of major vascular structures, excluding the splenic vessels). Limited gastric resection, even with positive margins is acceptable for unresectable tumors for palliation of symptomatic bleeding.

Gastric resections should be reserved for the palliation of symptoms (obstruction or uncontrollable bleeding) in patients with incurable disease.[59] Lymph node dissection is not required. Gastric bypass with gastrojejunostomy (open or laparoscopic) is preferable to endoluminal stenting in symptomatic patients, if they are fit for surgery and have a reasonable prognosis due to lower rate of recurrent symptoms.[60] Placement of venting gastrotomy and/or a feeding jejunostomy tube may be considered.

Lymph Node Dissection

Gastric resection should include lymph node dissection (or lymphadenectomy) which involves the removal of regional lymph nodes. A recent retrospective analysis has shown that more extensive lymph node dissection and analysis influences survival in patients with advanced gastric cancer. This analysis included 1377 patients diagnosed with advanced gastric cancer in the SEER database. Patients who had more than 15 N2 nodes and more than 20 N3 nodes examined had the best long-term survival outcomes.[61] However, the extent of lymph node dissection remains controversial. The Japanese Research Society for the Study of Gastric Cancer has established guidelines for pathologic examination and evaluation of lymph node stations that surround the stomach.[62] The perigastric lymph node stations along the lesser curvature (stations 1, 3, and 5) and greater curvature (stations 2, 4, and 6) of the stomach are grouped together as N1. The nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), and splenic artery (stations 10 and 11) are grouped together as N2. More distant nodes, including para-aortic (N3 and N4), are regarded as distant metastases.

Lymph node dissection may be classified as D0, D1 or D2 depending on the extent of lymph nodes removed at the time of gastrectomy. D0 refers to incomplete resection of N1 lymph nodes. D1 involves gastrectomy and the removal of the involved proximal or distal part of the stomach or the entire stomach (distal or total resection), including the greater and lesser omental lymph nodes (which would include the lymph nodes along the right and left cardiac, along lesser and greater curvature, and suprapyloric along the right gastric artery and infra pyloric area). D2 involves D1 plus the removal of all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery. The technical aspects of performing a D2 lymph node dissection require a significant degree of training and expertise.

Gastrectomy with D2 lymph node dissection is the standard treatment for curable gastric cancer in eastern Asia. In Western countries, extended lymph node dissection of distant lymph nodes contributes to accurate staging of the disease but its contribution to the prolongation of survival is unclear and much of the survival benefit associated with an extensive lymph node dissection may be due to the effect of stage migration.[33,61,63] In the West, D2 lymph node dissection is considered a recommended but not a required procedure. However, there is uniform consensus that removal of an adequate number of nodes (15 or greater) is beneficial for staging purposes.

Initial results from two large randomized trials performed in Western countries failed to demonstrate a significant survival benefit for D2 lymph node dissection over D1 dissection.[64,65] In the Dutch Gastric Cancer Group Trial, 711 patients who underwent surgical resection with curative intent were randomized to undergo either a D1 or D2 lymph node dissections.[64] Both the postoperative morbidity (25% vs. 43%, $P < .001$) and mortality (4% vs. 10%, $P = .004$) were higher for patients who underwent D2 lymph node dissection, with no difference in OS (30% vs. 35%, $P = .53$) between the two groups. In a subset analysis, patients

with N2 cancer undergoing a D2 lymph node dissection showed a trend towards improved survival. Unfortunately, N2 cancer can only be detected after microscopic examination of the surgical specimen. After a median follow-up of 15 years, D2 lymph node dissection was associated with lower local (12% vs. 22%) regional recurrence (13% vs. 19%) and gastric-cancer-related death rates (37% vs. 48%) than D1 lymph node dissection. D2 lymph node dissection was also associated with significantly higher postoperative mortality, morbidity, and reoperation rates. The British Cooperative trial conducted by the Medical Research Council also failed to demonstrate a survival benefit for D2 over D1 lymph node dissection.[65] The 5-year OS rates were 35% and 33% respectively, for D1 and D2 lymph node dissections. In addition, the D2 lymph node dissection was associated with increased postoperative morbidity and mortality.

Long-term follow-up data from the Dutch Gastric Cancer Group trial have confirmed a survival benefit for D2 lymph node dissection. The 15-year OS rates were 21% and 29% respectively for the D1 and D2 group (P = .34). D2 lymph node dissection was also associated with lower rates of local (12% vs. 22%) and regional recurrence (13% vs.19%).[66] More importantly, gastric cancer-related death rate was significantly lower in the D2 group compared to the D1 group (37% and 48% respectively).[66]

Two other studies from Western countries have also reported better outcomes for D2 lymph node dissection when performed according to the recommendations of Japanese Research Society for Gastric Cancer.[67,68] In an Austrian study, 5-year and 10-year OS rates were 45.7% and 34.3% respectively.[67] For patients who underwent curative surgery, 5-year and 10-year survival rates were 57.7% and 44.3% respectively, which are comparable to those reported in Japanese trials. Postoperative mortality rates for R0, R1/R2 and palliative resections were 4.9%, 9% and 13.4% respectively. Sierra and colleagues from a single institution in Spain reported longer 5-year survival rates in the D2 group (50.6%) than in the D1 group (41.4%).[68] No significant differences were seen in morbidity (48.2% and 53.5% respectively for D1 and D2). Operative mortality rate was 2.3% for D1 and 0% for D2 lymph node dissection. Pancreatectomy, hepatic wedge resection or partial colectomy was performed only for macroscopic invasion.

Investigators have long been arguing that if the complication rate after a D2 lymph node dissection could be decreased then there may be a benefit in selected patients. Although pancreatectomy and splenectomy have been widely performed with D2 lymph node dissection in Japan, both of these procedures have been shown to increase postoperative mortality and morbidity.[64,65,69,70]

In a prospective randomized phase II study conducted by the Italian Gastric Cancer Study Group, pancreas-preserving D2 lymph node dissection was associated with a survival benefit and lower complication rate.[69,70] Pancreatectomy was performed only when T4 tumor involvement was suspected. Postoperative complications were higher after D2 gastrectomy (16.3% vs.10.5% after D1), but the difference was not statistically significant (P < .29). Postoperative mortality rates were 0% and 1.3% respectively. The 5-year OS rate among all eligible patients was 55%. The overall 5-year morbidity rate was 20.9% and a postoperative in-hospital mortality rate was 3.1% for D2 lymph node dissection without pancreatectomy.[69] These rates are comparable to the rates for D1 lymph node dissections in the Dutch and United Kingdom trial.

In a randomized controlled trial (JCOG9501), Japanese investigators comparing D2 lymph node dissection alone with D2 lymph node

dissection with para-aortic nodal dissection (PAND) in patients undergoing gastrectomy for curable (T2b, T3 or T4) gastric cancer reported a postoperative mortality rate of 0.8% in each arm.[71] The final results of this study showed that D2 lymph node dissection with PAND does not improve survival rate in curable gastric cancer, compared to D2 lymph node dissection alone. The 5-year OS rates were 70.3% and 69.2% respectively. There were also no significant differences in the relapse-free survival (RFS) rates between the two groups.[72] In a post hoc subgroup analysis, among patients with pathologically negative nodes, the survival rates were better for patients who underwent D2 lymph node dissection plus PAND than those who were assigned to D2 lymph node dissection alone, whereas in patients with metastatic nodes, the survival rates were worse for those assigned to D2 lymph node dissection plus PAND. However, the investigators of this study caution that these results from post hoc analysis could be false positive due to multiple testing and the survival benefit of D2 lymph node dissection plus PAND in node-negative patients need to be clarified in further studies. The investigators concluded that D2 lymph node dissection plus PAND should not be used to treat patients with curable gastric cancer (T2b, T3 or T4).

Recent reports from Western countries also suggest that D2 lymph node dissection is associated with lower postoperative complications and a trend toward improved OS when performed in high-volume centers that have sufficient experience with the operation and postoperative management.[73,74] In an analysis involving patients from the Intergroup 0116 trial, Enzinger and colleagues assessed the impact of hospital volume on the outcome of patients who underwent lymph node dissection (54% underwent D0 lymph node dissection and 46% underwent D1 or D2 lymph node dissection).[73] High-volume centers did not have any effect on OS or disease-free survival (DFS) for patients who underwent D0 lymph node dissection. However, there was a trend toward improved OS among patients who underwent D1 or D2 lymph node dissection at moderate to high volume cancer centers. Deguili et al from the Italian Gastric Cancer Study Group also reported that a modified D2 lymph node dissection (without pancreatectomy and splenectomy) is associated with low mortality and reasonable survival times when performed in institutions that have sufficient experience with the operation and postoperative management.[74] A recent meta-analysis also confirmed that among patients who underwent D2 lymph node dissections, there was a trend toward improved survival for patients who did not undergo resection of the spleen or pancreas, as well as for patients with T3 or T4 cancers.[75]

The guidelines recommend gastrectomy with D1 or a modified D2 lymph node dissection, with a goal of examining at least 15 if not more lymph nodes, for patients with localized resectable cancer.[61,66,69,70] The panel members also acknowledge that the technical aspects of performing a D2 dissection require a significant degree of training and expertise. Therefore, the guidelines emphasize that D2 dissection should be performed by experienced surgeons in high volume centers. Prophylactic pancreatectomy and splenectomy is no longer recommended with D2 lymph node dissection.[58,76] The NCCN Guidelines recommend splenectomy only when spleen or hilum is involved.

Laparoscopic Resection

Laparoscopic resection is an emerging surgical approach that offers important advantages (less blood loss, reduced postoperative pain, accelerated recovery, early return to normal bowel function and reduced hospital stay) when compared with open surgical procedures for patients with gastric cancer.[77] A prospective randomized study

conducted by Hulscher and colleagues compared early and 5-year clinical outcomes of laparoscopic and open subtotal gastrectomy in 59 patients with distal gastric cancer.[78] Operative mortality rates (3.3% vs. 6.7% respectively), 5-year OS (58.9% vs. 55.7% respectively) and DFS rates (57.3% vs. 54.8% respectively) were better for the laparoscopic group, though not significant. However, the role of this approach in the treatment of gastric cancer requires further investigation in larger randomized clinical trials.

Endoscopic Therapies

EMR and endoscopic submucosal dissection (ESD) have been used as alternatives to surgery for the treatment of patients with early stage gastric cancer. The applicability of these techniques in the United States is limited because of the low incidence of early gastric cancer.

EMR represents a major advance in minimally invasive approaches for the management of patients with upper GI tract cancers.[79] Most of the experience with EMR for early gastric cancer has been gained by countries with a high incidence of gastric cancer and an active screening program.[80] En-bloc excision by ESD has been shown to be more effective than EMR in curing early gastric cancer.[81] In a multicenter retrospective study of endoscopic resection in patients with early gastric cancer, the 3-year cumulative residual-free or recurrence-free rate in the ESD group (97.6%) was significantly higher than that in the EMR group (98% and 93% respectively).[82] The complete resection rates were significantly better for ESD for lesions more than 5 mm in diameter whereas the rates were not different between EMR and ESD for lesions less than 5 mm in diameter regardless of location.[83-86] ESD requires greater skills and instrumentation to perform and is also associated with higher rates of bleeding and perforation complications.

No randomized studies have compared EMR with other surgical techniques for GI tract cancers. Nevertheless, EMR continues to evolve as a promising technology in the diagnosis and treatment of early gastric cancers. Since long-term follow-up and survival data are lacking, the routine use of endoscopic techniques is not recommended outside a clinical trial and should be limited to medical centers with extensive experience.

Principles of Endoscopy

Endoscopy has become an important tool in the diagnosis, staging, treatment and palliation of patients with gastric 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 for aspiration during endoscopy may require general anesthesia.

Diagnosis

Diagnostic endoscopies are performed to determine the presence and location of a gastric cancer and to biopsy any suspicious lesions. Multiple biopsies (6-8), using standard size endoscopy forceps should be performed to provide sufficient material for histologic interpretation, especially in the setting of an ulcerated lesion.[87] Larger forceps may improve the yield. Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming persistent disease following treatment.

For proximal tumors, the location of tumor in the stomach (cardia, fundus, body, antrum, and pylorus) relative to the EGJ should be carefully recorded to assist with treatment planning and follow-up. EMR of focal nodules (1.5 cm or smaller) can be safely performed in the setting of early stage disease to provide greater information on the degree of differentiation, the presence of lymphovascular invasion and

the depth of infiltration, thereby providing accurate staging of the tumor, with the potential of being therapeutic.[88,89]

Staging

EUS provides accurate initial clinical staging of locoregional gastric cancer. EUS performed prior to any treatment provides evidence of depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and occasionally signs of distant spread, such as lesions in surrounding organs (M) or the presence of ascites.[90,91] This is especially important in patients who are being considered for endoscopic resection.[92]

Perigastric lymph nodes are readily identified by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well circumscribed, rounded structures in these areas indicates the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but also confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[93] FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. Furthermore, an attempt should be made to identify the presence of ascites and FNA should be considered to rule out the peritoneal spread of disease. The combined use of EUS and FNA is an accurate method for diagnosis of gastric submucosal tumor and for differentiating potentially malignant lesions.[94]

Treatment

Proper patient selection is essential when employing endoscopic or limited wedge gastric resections. The probability of lymph node metastasis in early gastric cancer is influenced by the tumor characteristics and increases with increasing tumor size, submucosal invasion, poorly differentiated tumors, and lymphatic and vascular invasion.[95] EMR can be considered as an adequate therapy for carcinoma in situ (Tis), well or moderately differentiated lesions (less than 1.5 cm in diameter) confined to mucosa (T1a) without evidence of ulceration, lymph node metastases or lymphovascular invasion.[96]

En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR for patients with early stage gastric cancer, but requires greater skills and instrumentation to perform and has a significant risk of complications including perforation. Japanese Gastric Cancer guidelines recommend that EMR should be considered for early gastric cancer lesions that are 3 cm or less in diameter without associated ulcer formation.[97] EMR or ESD of poorly differentiated gastric lesions with evidence of lymph node metastases, invasion into the deep submucosa or lymphovascular invasion should be considered incomplete and additional therapy (gastrectomy with lymph node dissection) should be considered.[98]

Endoscopic tumor ablation can be performed for the short-term control of bleeding. Endoscopic insertion of expandable metal stents is effective in long-term relief of tumor obstruction at the EGJ or the gastric outlet, though surgical gastrojejunostomy may be more efficacious for those with longer-term survival.[99,100]

Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic or radiographic-assisted placement of feeding gastrostomy (percutaneous endoscopic gastrostomy, PEG) in carefully selected cases where the distal stomach is uninvolved by tumor, or the placement of a feeding jejunostomy (percutaneous endoscopic jejunostomy, PEJ).[101]

Surveillance

EUS performed after chemotherapy or RT has a reduced ability to accurately determine the post-treatment stage of disease.[102] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease.[103]

Endoscopic surveillance following definitive treatment of gastric cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS performed in conjunction with endoscopy exams has a high sensitivity for recurrent disease. [104] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

Radiation Therapy

Radiation therapy (RT) has been assessed in randomized trials in both the preoperative and postoperative setting in patients with resectable gastric cancer. Smalley and colleagues have reviewed clinical and anatomic issues related to RT and offer detailed recommendations for the application of RT for the management of patients with resected gastric cancer.[105]

Two randomized trials have compared surgery alone to surgery plus RT in patients with gastric cancer. In the first trial conducted by the British Stomach Cancer Group, 432 patients were randomized to undergo surgery alone or surgery followed by RT or chemotherapy.[106] At 5-year follow-up, no survival benefit was seen for patients receiving postoperative RT or chemotherapy compared with those who underwent surgery alone. But there was a significant reduction in locoregional recurrence with the addition of RT to surgery (27% with surgery vs. 10% for surgery plus RT and 19% for surgery plus chemotherapy). In the second trial Zhang and colleagues randomized 370 patients to preoperative RT or surgery alone. There was a significant improvement in survival with preoperative RT (30% vs. 20%, P = .0094).[107] Resection rates were also higher in the preoperative RT arm (89.5%) compared to surgery alone (79%), suggesting that preoperative RT improves local control and survival.

The results from a recent systematic review and meta-analysis showed a statistically significant 5-year survival benefit with the addition of RT in patients with resectable gastric cancer.[108] However, randomized trials are needed to confirm these results in patients from the Western Hemisphere.

External-beam RT (45 to 50.4 Gy) as a single modality has minimal value in patients with locally unresectable gastric cancer and does not improve survival.[109] However, when used concurrently with fluorouracil, external-beam RT improves survival. Moertel and colleagues assessed fluorouracil plus RT compared with RT alone in the treatment of locally unresectable gastric cancer.[110] Patients receiving combined modality treatment had a significantly better median survival (13 vs. 6 months) and 5-year OS (12% vs. none). In another study by the Gastrointestinal Tumor Study Group (GITSG), 90 patients with locally advanced gastric cancer were randomized to receive either combination chemotherapy with fluorouracil and methyl-CCNU (lomustine) or split-course RT with a concurrent bolus fluorouracil followed by maintenance with fluorouracil and lomustine.[111] In the first 12 months mortality was higher in the combined modality group. At 3 years the survival curve reached a plateau in the combined modality arm, but tumor-related deaths continued to occur in the chemotherapy alone arm, suggesting that a small fraction of patients can be cured with combined modality treatment. In most of the randomized trials, combined modality treatment showed advantage over RT alone in relatively few patients with unresectable cancer, as reviewed by Hazard and colleagues.[109]

Intensity modulated RT (IMRT) has great potential to reduce radiation-related toxicity by delivering large doses of radiation to target tissues.[112] The use of this technique in gastric cancer remains investigational and the impact of new conformal radiotherapy technologies needs to be assessed in randomized clinical trials.

Principles of Radiation Therapy

RT (preoperative, postoperative or palliative) can be an integral part of treatment for gastric cancer. All patients should be simulated and treated in the supine position. The panel encourages the use of CT simulation and 3D treatment planning. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid target localization. Use of an immobilization device is strongly recommended for reproducibility.

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. 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.

Pretreatment diagnostic studies such as EUS, upper GI endoscopy and CT scans should be used to identify tumor and pertinent nodal groups. The relative risk of nodal metastases at a specific location is dependent on the location of the primary tumor and the extent of invasion of the gastric wall. It may be possible to accurately target high-risk areas and to produce superior dose distributions with the use of 3-D treatment planning systems and unconventional field arrangements. To accomplish this, it is necessary to carefully define and encompass various target volumes.

The panel recommends a dose range of 45 to 50.4 Gy delivered in fractions of 1.8 Gy per day. Every effort should be made to reduce unnecessary radiation doses to vital organs such as liver, kidneys, spinal cord, heart (especially the left ventricle) and lungs. Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients with gastric and EGJ cancers treated with concurrent chemoradiation, though optimal criteria have not yet emerged. Optimal criteria for DVH parameters are being actively developed at NCCN Member Institutions.

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

Close patient monitoring and aggressive supportive care are essential during radiation treatment. Management of acute toxicities is necessary to avoid treatment interruptions or dose reductions. Antiemetics should be given for prophylaxis when appropriate. Antacid and antidiarrheal

medications may be prescribed when needed. If the caloric intake is inadequate, enteral and/or parenteral nutrition should be considered. Oral and/or intravenous hydration is often necessary throughout chemoradiation and early recovery. Feeding jejunostomies may be placed if clinically indicated. It is essential to monitor levels of B_{12}, iron and calcium in postoperative patients. Oral supplementation is recommended to maintain adequate levels.

Combined Modality Treatment: Concurrent Chemotherapy and Radiation Therapy

Preoperative Chemoradiation Therapy

In a pilot study, Lowy and colleagues assessed the feasibility of preoperative chemoradiation (45 Gy of external beam RT with concurrent continuous infusion of fluorouracil) followed by surgery and intraoperative RT (IORT) (10 Gy) in the treatment of patients with potentially resectable gastric cancer.[113] Significant pathologic responses were seen in 63% of patients and complete pathologic response was seen in 11% of patients who received preoperative chemoradiation. Eighty three percent of patients who received chemoradiation therapy underwent D2 lymph node dissection. In a prospective, randomized trial, preoperative chemoradiation with fluorouracil and cisplatin followed by surgery was superior to surgery alone in patients with resectable adenocarcinoma of the esophagus (74 patients) and gastric cardia (39 patients); the median survival was 16 months and 11 months respectively, for patients assigned to multimodal therapy and surgery alone (P = .01).[114]

The value of preoperative chemoradiation therapy for patients with resectable gastric cancer remains uncertain and is the subject of an ongoing international prospective phase III randomized trial.[115] The regimens listed in the guidelines are derived from the phase III trials that have included patients with adenocarcinoma of the esophagus and/or EGJ.

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Recent studies have also shown that sequential preoperative induction chemotherapy followed by chemoradiation yields a substantial pathologic response that results in durable survival time.[116-120]

In the RTOG 9904 study, preoperative induction chemotherapy with fluorouracil and cisplatin followed by concurrent chemoradiation with infusional fluorouracil and paclitaxel resulted in a pathologic complete response rate of 26% of patients with localized gastric adenocarcinoma. D2 lymph node dissection and R0 resection were achieved in 50% and 77% of patients respectively.[118]

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.[120] R0 resection was achieved in 65% of patients. Median survival and the actuarial 2-year survival rate were 14.5 months and 35% respectively.[120]

In a recent 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 adenocarcinoma of the EGJ.[119] Patients with locally advanced adenocarcinoma of the lower esophagus or EGJ were randomized between two treatment groups: chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiation followed by surgery (arm B). Patients in arm B had a significantly higher probability of achieving pathologic complete response (15.6% vs. 2.0%)

or tumor-free lymph nodes (64% vs. 38%) at resection. Preoperative chemoradiation improved 3-year survival rate from 28% to 47%. Although the study was closed prematurely due to low accrual and statistical significance was not achieved, there was a trend towards survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy for patients with EGJ adenocarcinoma.

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

Postoperative Chemoradiation Therapy

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effect of surgery plus postoperative chemoradiation on the survival of patients with resectable adenocarcinoma of the stomach or EGJ.[121] In this trial 556 patients with completely resected gastric cancer or EGJ adenocarcinoma (stage IB-IV, M0) were randomized to surgery alone (n=275) or surgery plus postoperative chemoradiation (n=281; bolus fluorouracil and leucovorin before and after concurrent chemoradiation with fluorouracil and leucovorin). The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%); only 31% of the patients had T1-T2 tumors and 14% of patients had node-negative tumors. Surgery was not part of the trial protocol but resection of all detectable disease was required for participation in the trial. Patients were eligible for the study only after recovery from surgery. Postoperative chemoradiation (offered to all patients with tumors T1 or higher, with or without lymph node metastases) significantly improved OS and RFS. Median OS in the surgery-only group was 27 months and was 36 months in the chemoradiation group (P = .005). The chemoradiation group had better 3-year OS (50% vs. 41%) and RFS rates (48% vs.31%) than the surgery only group. There was also a significant decrease in local failure as the first site of failure (19% vs. 29%) in the chemoradiation group. With more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric cancer or EGJ adenocarcinoma treated with postoperative chemoradiation. No increases in late toxic effects were noted.[122]

The results of the INT-0116 trial have established postoperative chemoradiation therapy as a standard of care in patients with completely resected gastric cancer who have not received preoperative therapy. However, the regimen used in this trial (bolus fluorouracil and leucovorin before and after chemoradiation with the same combination) was associated with high rates of grade 3 or 4 hematologic and GI toxicities (54% and 33% respectively). Among the 281 patients assigned to the chemoradiation group only 64% of patients completed treatment and 17% discontinued treatment due to toxicity. Three patients (1%) died as a result of chemoradiation-related toxic effects including pulmonary fibrosis, cardiac event and myelosuppression).

Alternative postoperative chemoradiation regimens containing infusional fluorouracil or capecitabine have been evaluated by other investigators.[123-125] In a pilot study, postoperative chemoradiation with fluorouracil and cisplatin before and after capecitabine and concurrent RT was well tolerated in patients with completely resected stage III-IV, M0 gastric cancer.[123] Leong et al reported that postoperative chemotherapy with epirubicin, cisplatin, and 5-FU (ECF) before and after concurrent chemoradiation with infusional fluorouracil was safe and effective in patients with completely resected gastric adenocarcinoma.[124] At a median follow-up of 36 months, the estimated 3-year OS rate was 62%. The 3-year DFS and OS rates were 82.7% and 83.4%, respectively. In the randomized Intergroup trial (CALGB 80101), postoperative chemoradiation with ECF before and after 5-FU and RT did not improve survival compared to the INT-0116 regimen in

patients who have undergone curative resection for gastric or EGJ adenocarcinoma.[125] The ECF regimen, however, had a favorable toxicity profile compared to bolus fluorouracil and leucovorin which was associated with more GI toxicities (15% vs. 7% for ECF) and neutropenia (33% vs. 19% for ECF).

Although the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer, the recommend doses or the schedule of chemotherapy agents as used in the INT-0116 trial are no longer used due to concerns regarding toxicity. Instead, regimens containing infusional fluorouracil or capecitabine are used for patients with completely resected gastric cancer.[123,124,126]

While the results of the INT-0116 trial demonstrated a significant survival benefit for postoperative chemoradiation (after curative surgery with (D0 or D1 lymph node dissection) in patients with T3-T4, N0 and any T, node positive tumors, the effectiveness of this approach in patients with T2, N0 tumors remains unclear because of the smaller number of such patients enrolled in this trial. This trial was also not sufficiently powered to evaluate the role of postoperative chemoradiation when a D2 lymph node dissection is performed. In the INT-0116 trial, D2 lymph node dissection was not commonly performed and patients were not excluded on the basis of the extent of lymph node dissection. D0, D1 and D2 dissections were performed in 54%, 36% and 10% of patients respectively.

The results of the recently completed phase III trial (ARTIST trial) showed that postoperative chemoradiation with capecitabine and cisplatin did not significantly reduce recurrence after D2 lymph node dissection in patients with curatively resected gastric cancer (n = 458; stage IB-IV, M0).[127] Patients with T2a, N0 tumors, microscopically positive resection margin, involvement of M1 lymph node or distant metastases and those who had undergone gastrectomy with D1 lymph node dissection were excluded from this study. At a median follow-up of 53 months, the estimated 3-year DFS rates were 78% and 74% respectively for postoperative chemoradiation and chemotherapy P = .0862). In the subgroup analysis of patients with positive pathologic lymph nodes, postoperative chemoradiation was associated with a statistically significant prolongation of 3-year DFS compared to chemotherapy alone (77.5% and 72%, respectively; P =.0365).[127] However, this study demonstrated that postoperative treatment with capecitabine and cisplatin is feasible following a D2 lymph node dissection.

In a recent retrospective analysis that compared the outcome of patients treated with surgery alone and patients treated with postoperative fluoropyrimidine-based chemoradiation in several Dutch phase I/II studies, postoperative chemoradiation was associated with significantly lower recurrence rates after D1 lymph node dissection (2% for those who underwent D1 lymph node dissection followed by postoperative chemoradiation compared to 8% for patients who underwent D1 lymph node dissection alone; p = 0.001) whereas there was no significant difference in recurrence rates between the two groups following D2 lymph node dissection.[128]

Chemotherapy

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.[129] In this trial, 503 patients were randomized to receive either perioperative chemotherapy [preoperative and postoperative chemotherapy with

ECF] and surgery or surgery alone. Patients were randomized prior to surgical intervention (74% of patients had gastric cancer; 69% in the surgery plus chemotherapy group and 66% in the surgery only group had undergone R0 resection). The majority of patients had T2 or higher tumors (12% had T1 tumors, 32% of patients had T2 tumors and 56% of patients had T3-T4 tumors) and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5% respectively). Perioperative chemotherapy significantly improved PFS (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.[130] The 5-year OS rate was 38% for patients in the surgery plus perioperative chemotherapy group and 24% in the surgery only group (P = .02). The corresponding 5-year DFS rates were 34% and 19% respectively. This trial was prematurely terminated even after allowing gastric cancer patients due to the lack of accrual.

The results of these two studies established perioperative chemotherapy as another alternative option for patients with resectable gastric cancer who have undergone curative surgery with limited lymph node dissection (D0 or D1). However, these studies were not powered to evaluate the role of preoperative or postoperative treatment when a D2 lymph node dissection is performed. In the MAGIC trial, the extent of lymph node dissection was determined by the surgeon's discretion; the reported rates of D2 dissection were 28% in the perioperative chemotherapy group and 30% in the surgery only group.[129] In the FNCLCC/FFCD trial, D2 dissection was recommended and the surgical procedure was decided by the surgeon according to the tumor site and local practice.[130]

Postoperative Chemotherapy

Postoperative chemotherapy following complete resection has not been associated with a significant survival benefit in patients with gastric cancer.[131-136] In the randomized trial conducted by Japan Clinical Oncology Group (JCOG 8801), curative surgery alone was associated with very good survival rates in patients with T1 cancer.[131] However, two recent large Asian randomized phase III studies (ACTS GC trial and CLASSIC trial) have documented survival benefit for postoperative chemotherapy after curative D2 lymph node dissection in patients with gastric cancer.[137,138]

ACTS GC trial in Japan evaluated the efficacy of postoperative chemotherapy with a novel oral fluoropyrimidine S-1 (combination of tegafur [prodrug of fluorouracil; 5-chloro-2,4-dihydropyridine] and oxonic acid) in patients with stage II (excluding T1) or stage III gastric cancer who underwent R0 gastric resection with D2 lymph node dissection. In this study, 1059 patients were randomized to surgery alone or surgery followed by postoperative chemotherapy with S-1.[137] The 3-year OS rate was 80.1% and 70.1% respectively, for S-1 group and surgery alone. Hazard ratio for death in the S-1 group was 0.68. The 5-year follow-up data also confirmed these findings.[139] This is the first time postoperative chemotherapy has been shown to be beneficial after D2 resection in the Japanese patient population. S-1 remains an investigational agent in North America.

The CLASSIC trial (conducted in South Korea, China and Taiwan) evaluated postoperative chemotherapy with capecitabine and oxaliplatin after curative D2 gastrectomy in patients with stage II-IIIB gastric cancer; at least 15 lymph nodes were removed to ensure adequate disease classification.[138] In this study, 1035 patients were randomized to surgery alone or surgery followed by postoperative chemotherapy.[138] The planned interim analysis of this trial (after a median follow-up of 34.2 months) showed that postoperative chemotherapy with capecitabine and oxaliplatin significantly improved DFS compared to surgery alone for all disease stages (II, IIIA and IIIB). The 3-year DFS rates were 74% and 59% respectively (P < .0001). The lack of difference in OS is most likely due to inadequate length of follow-up but the OS is expected to become significant.

The results of these two studies support the use of postoperative chemotherapy after curative surgery with D2 lymph node dissection in patients with resectable gastric cancer. However, it should be noted that the benefit of this approach following a D1 or D0 lymph node dissection has not been documented in randomized clinical trials. Thus postoperative chemoradiation remains an effective treatment of choice for this group of patients.[121,128]

Chemotherapy for Locally Advanced or Metastatic Disease

Chemotherapy can provide palliation, improved survival and improved quality of life compared to best supportive care in patients with advanced and metastatic disease.[140,141] Chemotherapy regimens including older agents (mitomycin, fluorouracil, cisplatin, and etoposide)[142-144] as well as newer agents (irinotecan, oral etoposide, paclitaxel, docetaxel and pegylated doxorubicin)[145-158] have demonstrated activity in patients with advanced gastric cancer.

In the early 1980s, FAM (fluorouracil, doxorubicin, and mitomycin) was considered the gold standard for patients with advanced gastric cancer.[159] The pivotal study performed by the North Central Cancer Treatment Group (NCCTG) comparing FAM to fluorouracil alone and fluorouracil plus doxorubicin showed no significant survival difference between all 3 arms.[160] Higher response rates were observed in patients who received combination chemotherapy vs. fluorouracil alone. Several randomized studies have compared various fluorouracil-based combination regimens (FAM vs. FAMTX [fluorouracil, adriamycin, and methotrexate],[161] FAMTX vs. ECF [epirubicin, cisplatin, and fluorouracil],[162] FAMTX vs. ELF [etoposide, leucovorin, and fluorouracil] vs. fluorouracil plus cisplatin,[163] and ECF vs. MCF [mitomycin, cisplatin, fluorouracil][164]) ECF demonstrated improvements in median survival and quality of life when compared to FAMTX or MCF regimens.

The combination of fluorouracil, leucovorin and oxaliplatin has been evaluated as an alternative to cisplatin and fluorouracil in patients with advanced or metastatic gastric cancer.[165,166] Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) had a trend toward improved median PFS compared to fluorouracil, leucovorin and cisplatin (FLP) (5.8 vs. 3.9 months).[167] However, there were no significant differences in median OS (10.7 vs. 8.8 months, respectively) between the two groups. FLO was associated with significantly less toxicity than FLP. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), PFS (6.0 vs. 3.1 months), and an improved OS (13.9 vs. 7.2 months) compared with FLP.

The combination of docetaxel, cisplatin and fluorouracil (DCF) was evaluated in a randomized multinational phase III study (V325). In this trial, 445 untreated patients with advanced gastric cancer were

randomized to receive either DCF every 3 weeks or cisplatin and fluorouracil (CF).[168] 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 (TTP) 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 = 0.02), at a median follow-up of 23.4 months; the confirmed overall response rate (ORR) was also significantly higher with DCF than CF ((37% and 25%, respectively; P = .01).[168] In 2006, based on the results of this study, the FDA approved the DCF regimen for the treatment of patients with advanced gastric cancer, including EGJ cancers, in patients who have not received prior chemotherapy.

In a subsequent randomized phase II trial of the Swiss Group for Clinical Cancer Research, a trend towards better ORR was observed in patients with advanced gastric cancer treated with DCF compared to those who received ECF or docetaxel plus cisplatin.[169] However, DCF was associated with increased myelosuppression and infectious complications.

Various modifications of the DCF regimen to improve tolerability are being evaluated in clinical trials for patients with advanced gastric cancer.[170-173] In a recent randomized phase II trial, treatment with docetaxel, oxaliplatin and fluorouracil had a better safety profile and was also associated with improved TTP, RR and median OS (7.7 months, 47% and 15 months respectively) compared to docetaxel and oxaliplatin (4.5 months, 23% and 9 months respectively) and docetaxel, oxaliplatin and capecitabine (5.6 months, 26% and 11 months respectively) in patients with advanced gastric cancer.[172]

Capecitabine is an orally administered fluoropyrimidine that is converted to fluorouracil intracellularly. Several studies have evaluated capecitabine, as a single agent or in combination regimens, in patients with advanced gastric and EGJ cancers.[174-177] Two phase III trials (REAL-2 and ML 17032) have compared the efficacy and safety of capecitabine-based combinations and fluorouracil-based combinations in patients with advanced gastric cancer.[178,179]

The REAL-2 (with 30% of patients having an esophageal cancer) trial was a randomized multicenter phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in 1003 patients with advanced esophagogastric cancer.[178] Patients with histologically confirmed adenocarcinoma, squamous or undifferentiated cancer of the esophagus, EGJ or stomach were randomized to receive one of the four epirubicin-based regimens (ECF, epirubicin, oxaliplatin, 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 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.

ML 17032, another phase III randomized trial, evaluated the combination of capecitabine and cisplatin (XP) vs. the combination of fluorouracil and cisplatin (FP) as first-line treatment in patients with previously untreated advanced gastric cancer.[179] ORR (41% vs. 29%) and OS (10.5 months vs. 9.3 months) were superior for patients who received the XP regimen. No difference in median PFS was seen for

both regimens (5.6 months for XP and 5.0 months for FP). The results of this study suggest that capecitabine is as effective as fluorouracil in the treatment of patients with advanced gastroesophageal cancers.

A meta-analysis of the REAL-2 and ML17032 trials suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared with the 664 patients treated with fluorouracil-based combinations although no significant difference in PFS between treatment groups was seen.[180]

Irinotecan as a single agent or in combination has been explored extensively in single arm and randomized clinical trials.[181-195] The results of a randomized phase III study comparing irinotecan in combination with fluorouracil and folinic acid to cisplatin combined with infusional fluorouracil in patients with advanced adenocarcinoma of the stomach or EGJ showed non-inferiority for PFS but not for OS and improved tolerance of the irinotecan containing regimen. Thus, it can be an alternative when platinum-based therapy cannot be delivered.[190] In another randomized multicenter phase II study, Moheler et al. compared capecitabine combined with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or EGJ.[194] There were no significant differences in ORR (37.7% and 42.0% respectively), and median PFS (4.2 months and 4.8 months respectively), although there was a trend towards better median OS in the irinotecan arm (10.2 vs. 7.9 months). The results of this study need to be validated further in larger studies.

Irinotecan has also been evaluated in the second-line setting.[176,196-198] Second-line chemotherapy with irinotecan, fluorouracil and leucovorin (FOLFIRI) was active and well tolerated in patients with metastatic gastric cancer not previously treated with fluoropyrimidines.[197] Irinotecan (studied in combination with other cytotoxic agents in phase II and phase III trials) has not produced category 1 evidence for prolongation of survival in patients with advanced gastric cancer; therefore, its use is preferred in the second line or third line setting.

The novel oral fluoropyrimidine S-1 has shown promise in advanced gastric cancer, both as a single agent and in combination with cisplatin in early phase studies. In a randomized phase III trial (SPIRITS trial), 298 patients with advanced gastric cancer were randomized to S-1 plus cisplatin and S-1 alone. Median OS (13 months vs.11 months respectively) and PFS (6.0 months vs. 4 months respectively) were significantly longer for the combination of S-1 and cisplatin compared with S-1 alone.[199] The combination of S-1 and cisplatin in patients with untreated advanced gastric and EGJ adenocarcinoma was shown to be safe and active in multicenter phase II/III trials conducted in the United States.[200,201,202] In the phase III randomized trial (First Line Advanced Gastric Cancer Study [FLAGS]), 1053 patients with advanced gastric or EGJ adenocarcinoma were randomized to either cisplatin and S-1 (CS) with CF. CS and CF resulted in similar median OS (8.6 months and 7.9 months respectively; p = 0.20), but cisplatin and S-1 was associated with a significantly improved safety profile.[202] In a subset analysis, CS produced statistically superior OS for patients with diffuse type histology. Additional studies are needed to confirm the activity of S-1 in the US and western hemisphere. S-1 remains an investigational agent in North America.

Targeted Therapies

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in patients with HER2-neu-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[51] 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 trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone.[51] 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.[51] In the post-hoc sub group analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR = .65) compared to those with whose tumors were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR = 1.07).

Ongoing trials are evaluating the efficacy and safety of EGFR inhibitors (erlotinib[203] and cetuximab[204-208]) and VEGFR inhibitors (bevacizumab,[209-211] and sorafenib[212]) in combination with chemotherapy in patients with advanced gastric and EGJ adenocarcinoma.

Treatment Guidelines

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

Workup

Newly diagnosed patients should undergo a complete history, physical examination, biopsy (to confirm metastatic cancer) and endoscopy with biopsy of the entire upper GI tract. A complete blood cell count (CBC), chemistry profile and CT scan (with oral and IV contrast) of the chest and abdomen should also be performed. Pelvic CT should be obtained as clinically indicated. EUS and PET/CT evaluation is recommended, if metastatic cancer is not evident. HER2-neu testing is recommended if metastatic disease is documented or suspected. See the section on “Principles of Pathology”, for assessment of *HER2-neu* overexpression.

PET/CT scans are useful for predicting response to preoperative chemotherapy as well as in the evaluation of recurrent gastric cancer.[213-216] They may also be useful in demonstrating occult metastatic disease, although there may be false positive results.

Therefore, histologic confirmation of occult PET-avid metastasis is recommended.[217] Additional studies are needed to assess the efficacy of combined PET/CT scan in gastric cancer.

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

- Localized (Tis or T1a) cancer
- Locoregional cancer (stages I-III or M0)
- Metastatic cancer (stage IV or M1)

Patients with apparent locoregional cancer are further classified into the following groups:

- Medically fit patients (who are able to tolerate major abdominal surgery) with potentially resectable disease
- Medically fit patients with unresectable disease
- Medically unfit patients

Primary Treatment

Medically Fit Patients

EMR or surgery is the primary treatment option for patients with Tis or T1a tumors whereas surgery with lymph node dissection is the primary treatment option for patients with potentially resectable locoregional tumors (T1b, T2 or higher, any N tumors). However, for most patients, surgery alone is not sufficient and adjunctive therapy must be considered. The guidelines have included perioperative chemotherapy with a category 1 recommendation for patients with resectable T2 or higher, any N tumors.[129,130] This strategy is feasible in the institutions where a multidisciplinary approach is already in place for the treatment of patients with localized gastric cancer. Although preoperative chemoradiation was associated with a survival advantage in two prospective randomized studies, both of these studies were limited by small sample size.[114,118,119] Since the efficacy of preoperative chemoradiation has not been proven in large prospective randomized trials, the panel has included preoperative chemoradiation (fluoropyrimidine- or taxane-based) as an alternate option with a category 2B recommendation for patients with resectable T2 or higher, any N tumors.

Concurrent fluoropyrimidine- or taxane-based chemoradiation or chemotherapy is recommended (category 1) for patients with unresectable locoregional cancer.[110,218]

All patients diagnosed with metastatic disease after laparoscopic staging should be treated with palliative therapy (chemotherapy, best supportive care or clinical trial). Chemotherapy with any one of the regimens used for patients with metastatic or locally advanced cancer may be offered to this group of patients depending on their performance status.

See the “Principles of Systemic Therapy” section of the guidelines for a list of specific regimens.

Medically Unfit Patients

EMR is the preferred option for patients with Tis or T1a tumors whereas concurrent fluoropyrimidine- or taxane-based chemoradiation (category 1) is recommended for patients with T1b, T2 or higher, any N tumors.

All patients diagnosed with metastatic disease after laparoscopic staging should be treated with palliative therapy as described above for medically fit patients.

Posttreatment Assessment and Adjunctive Treatment

Medically fit patients with unresectable disease as well as medically unfit patients should undergo restaging (including CBC and chemistry profile, CT scan [with oral and IV contrast] of the chest and abdomen, pelvic CT as clinically indicated, and PET/CT or PET scan) after completion of primary treatment. If the cancer has become resectable and medically operable, surgery is the preferred treatment. Alternatively, these patients can also be observed. If the disease remains unresectable and there is evidence of distant metastatic disease, patients may be offered palliative therapy (chemotherapy, best supportive care, or clinical trial) depending on their performance status.

Postoperative Treatment

The benefit of postoperative chemoradiation following complete resection (R0) has been established in randomized studies only in patients who have not received any preoperative therapy.[121,127] The guidelines recommend postoperative treatment based on tumor stage, nodal status and the extent of lymph node dissection.

For Patients 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 chemoradiation for all patients with T3-T4 tumors and node positive T1-T2 tumors. Given the relatively good prognosis combined with the lack of evidence from randomized clinical trials showing any survival benefit for postoperative chemoradiation for patients with T2, N0 tumors, some of the panel members felt that chemoradiation is not necessary for this group of patients. Therefore, observation is included as an option for patients with T2, N0 tumors.

Postoperative chemoradiation is recommended only for selected patients with T2, N0 tumors with high risk features (poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or age younger than 50 years), if there is no residual disease at surgical margins (R0 resection).[219]

The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer.[121,122] 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.

Based on the interim results of the CLASSIC trial, the panel has included postoperative chemotherapy as an option for patients with T3-T4 tumors and node-positive T1-T2 tumors following R0 resection and a modified D2 lymph node dissection.[138] Postoperative chemotherapy is not recommended for undergoing less than a D2 lymph node dissection. The panel emphasizes that postoperative chemoradiation is the preferred option (category 1) for this group of patients.[127]

For Patients Who Have Received Preoperative Therapy

Postoperative chemotherapy (category 1) with ECF or its modifications is recommended, if given preoperatively for all patients with T2 or higher any N tumors.[129] Alternatively patients with T2, N0 tumors can be observed. The value of postoperative chemoradiation in patients who have received preoperative therapy is currently being evaluated in a phase III trail (CRITICS study).[220]

Postoperative Chemoradiation Following R1 or R2 Resections

In the absence of distant metastases, fluoropyrimidine-based chemoradiation is recommended for patients with microscopic (R1 resection) or macroscopic residual disease (R2 resection), only if not received preoperatively. Although this approach has not been evaluated in a prospective study, given the significantly worse prognosis associated with margin positive resections, the panel members feel that this could be a reasonable treatment option especially in patients who have not received preoperative chemoradiation. Data from a recent retrospective analysis suggest that postoperative chemoradiation may be associated with a significant improvement in 2-year OS (66% vs. 29%; P =.002) and a significant decrease in the local recurrence rate (6% vs. 26%; P = .02) after an R1 resection as compared with the surgery alone.[128] Palliative chemotherapy or best supportive care, based on the performance status, may be offered for patients with macroscopic residual disease.

Follow-up

All patients should be followed up systematically. Follow-up should include a complete history and physical examination every 3 to 6 months for 1 to 2 years, every 6 to12 months for 3 to 5 years and annually thereafter. CBC, chemistry profile, imaging studies or endoscopy should be done if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B_{12} and iron deficiency.

Locally Advanced, Metastatic or Recurrent Disease

Palliative therapy (chemotherapy, or clinical trial or best supportive care) is recommended for patients with locally advanced, metastatic or recurrent gastric cancer. Surgery should be considered as an option for locoregional recurrence in medically fit patients.

Best supportive care is always indicated for patients with locally advanced, metastatic or recurrent gastric cancer. The decision to offer best supportive care alone or with chemotherapy is dependent on the patient's performance status. The ECOG Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are the two commonly used scales to assess the performance status in patients with cancer.[221-223] ECOG PS is a 5-point scale (0-4) based on the level of symptom interference with normal activity. Patients with higher levels are considered to have poor performance status (http://www.ecog.org/general/perf_stat.html). KPS is an ordered scale with 11 levels (0 to 100) and the general functioning and survival of a patient is assessed based on his or her health status (activity, work and self-care). Low Karnofsky scores are associated with poor survival and serious illnesses (http://www.hospicepatients.org/karnofsky.html). Patients with a Karnofsky performance score of 60 or less or an ECOG performance score of 3 or more should probably be offered best supportive care only. Patients with better performance status (KPS score of 60 or more or an ECOG PS score of 2 or less) may be offered best supportive care with or without chemotherapy, or a clinical trial.

The survival benefit of second line chemotherapy compared to best supportive care has been demonstrated in a small cohort of patients with metastatic or advanced gastric cancer.[224-227] In a randomized comparison between chemotherapy and best supportive care vs. best supportive care alone for advanced gastric cancer, OS (8 months vs. 5 months, though not statistically significant) and TTP (5 months vs. 2 months) were longer in patients receiving chemotherapy.[224] More patients in the chemotherapy group (45%) had an improved or prolonged high quality of life for a minimum of 4 months compared to those who received only best supportive care (20%). A recent meta-analysis of randomized trials that compared chemotherapy and

supportive care in patients with advanced gastric cancer also showed that chemotherapy increased the one year survival rate and improved the quality of life.[225] In another 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).[226] 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 another larger randomized trial (n = 193), second-line chemotherapy with irinotecan or docetaxel significantly improved OS (5.1 months vs. 3.8 months) compared to best supportive in patients with advanced gastric cancer.[227] However, both studies have limitations and larger studies are now underway.

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

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

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A levo-leucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin in all patients, since lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[228-230] 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, reduce, and relieve suffering, and improve the quality of life for patients and their caregivers, regardless of disease stage. In patients with unresectable or locally advanced cancer, palliative interventions undertaken to relieve major symptoms may result in prolongation of life.

Bleeding

Bleeding is common in patients with gastric cancer and may be secondary to tumor or tumor related phenomenon, or as a consequence of therapy. A multidisciplinary approach is required for the proper diagnosis and management of GI bleeding in patients with cancer.[231] Patients with acute severe bleeding (hematemesis or

melena) should undergo prompt endoscopic assessment. Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful. External beam RT and/or endoscopic treatment may be indicated in patients experiencing bleeding.[232]

Obstruction

Surgery (gastrojejunostomy or gastrectomy in selected patients), venting gastrostomy, external beam RT, chemotherapy and endoscopic palliative procedures such as balloon dilation, placement of enteral stent for relief of gastric outlet obstruction or esophageal stent for EGJ/cardia obstruction are used to alleviate symptoms of obstruction. The optimal palliative treatment for patients with malignant gastric outlet obstruction needs to be determined in large randomized clinical trials. Treatment options for the management of obstruction should be individualized. A multimodality interdisciplinary approach is strongly encouraged.

Endoscopic placement of self-expanding metal stents (SEMS) is a safe and effective minimally invasive palliative treatment for patients with luminal obstruction due to advanced gastric cancer.[233-235] In a systematic review, patients treated with endoscopic placement of stents were more likely to tolerate oral intake and they also had shorter hospital stay than patients treated with gastrojejunostomy.[236] The results of a systematic review suggest that stent placement may be associated with more favorable results in patients with a relatively short life expectancy, whereas gastrojejunostomy is preferable in patients with a more prolonged prognosis.[60] A recent randomized trial also reported similar findings.[237] However, these results need to be confirmed in a larger cohort of patients. Percutaneous decompressive gastrostomy either by endoscopic or radiologic gastrostomy have also been beneficial for patients with gastric outlet obstruction.[238,239]

If endoscopic lumen restoration is not undertaken or successful, percutaneous endoscopic or interventional radiology gastrostomy tube placement for gastric decompression may be performed, if tumor location permits. Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.[240,241] Endoscopic or surgical placement of a jejunal feeding tube may be necessary to provide adequate hydration and nutritional support for patients with mild and distal gastric obstruction. Nutritional counseling may also be valuable.

Pain

Pain control may be achieved with the use of RT and pain medications. If the patient is experiencing tumor related pain, then pain should be assessed and treated according to the NCCN Guidelines for Adult Cancer Pain. Severe uncontrolled pain following gastric stent placement should be treated emergently with endoscopic removal of the stent once the uncontrollable nature of pain is established.

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

Gastric cancer is rampant in several countries around the world. In the past 15 years, the incidence of proximal gastric cancer has increased in Western countries compared to non-proximal gastric cancer, which is more prevalent in Japan and other parts of the world. Diffuse histology is also more common now than the intestinal type of histology. H. pylori infection, smoking, and high salt intake are the risk factors for gastric

cancer. Few gastric cancers are associated with inherited gastric cancer predisposition syndromes.

Several advances have been made in the treatment approaches, imaging techniques and staging procedures. Multidisciplinary team management is essential for the management of patients with gastric cancer.

EMR is an appropriate primary treatment option for patients with Tis or T1a tumors whereas surgery with lymph node dissection is the primary treatment option for medically fit patients with resectable T1b, T2 or higher, any N tumors. In the West, surgery alone is an insufficient therapy for most patients. Perioperative chemotherapy is recommended (category 1) following R0 resection for patients with resectable T1b, T2 or higher, any N tumors. Preoperative chemoradiation may also be considered for these patients (category 2B). For patients who have not received preoperative therapy, postoperative chemoradiation is recommended following R0 resection for all patients with T3-T4 tumors and node positive T1-T2 tumors, and for selected patients with T2, N0 tumors with high risk features. Postoperative chemotherapy is included as an option following R0 resection and D2 lymph node dissection in patients with T3, T4, any N tumors.

Fluoropyrimidine-based postoperative chemoradiation is recommended for all patients with residual disease at surgical margins. Patients with unresectable and/or distant metastatic disease may be offered palliative therapy (chemotherapy, best supportive care or clinical trial).

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

Best supportive care is an integral part of treatment, especially in patients with metastatic and advanced gastric cancer. Patients with good performance status can be treated with chemotherapy or best supportive care, whereas best supportive care alone is the appropriate treatment for patients with poor performance status. Assessment of severity of the disease and related symptoms is essential to initiate appropriate palliative interventions that will prevent and relieve suffering and improve quality of life for patients and their caregivers. Treatment options used for palliation of symptoms in patients with advanced gastric cancer include endoscopic placement of SEMS, surgery, chemotherapy or RT.

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

References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1995976.

2. Johnston BJ, Reed PI. Changing pattern of oesophageal cancer in a general hospital in the UK. Eur J Cancer Prev 1991;1:23-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1842678.

3. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer 1990;62:440-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2206952.

4. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-2150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682732.

5. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23335087.

6. Crew KD, Neugut AI. Epidemiology of upper gastrointestinal malignancies. Semin Oncol 2004;31:450-464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297938.

7. Kubo A, Corley DA. Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. Cancer 2002;95:2096-2102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12412162.

8. Powell J, McConkey CC, Gillison EW, Spychal RT. Continuing rising trend in oesophageal adenocarcinoma. Int J Cancer 2002;102:422-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12402314.

9. 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.

10. Parkin DM, Muir CS. Cancer incidence in five continents. comparability and quality of data. IARC Sci Publ 1992:45-173. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1284606.

11. Tramacere I, Negri E, Pelucchi C, et al. A meta-analysis on alcohol drinking and gastric cancer risk. Annals of Oncology 2012;23:28-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21536659.

12. Fitzgerald RC, Caldas C. Clinical implications of E-cadherin associated hereditary diffuse gastric cancer. Gut 2004;53:775-778. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15138199.

13. Huntsman DG, Carneiro F, Lewis FR, et al. Early gastric cancer in young, asymptomatic carriers of germ-line E-cadherin mutations. N Engl J Med 2001;344:1904-1909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11419427.

14. Japanese Research Society for Gastric cancer. The general rules for the gastric cancer study in surgery and pathology (ed 12): Tokyo: Kanahara Shuppan; 1993.

15. Roder JD, Bottcher K, Busch R, et al. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. Cancer 1998;82:621-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9477092.

16. Chau I, Norman AR, Cunningham D, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004;22:2395-2403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197201.

17. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. Ann Surg 2000;232:362-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10973386.

18. Abdalla EK, Pisters PWT. Staging and preoperative evaluation of upper gastrointestinal malignancies. Semin Oncol 2004;31:513-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297943.

19. Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. J Clin Oncol 2007;25:2107-2116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17513817.

20. Weber WA, Ott K. Imaging of esophageal and gastric cancer. Semin Oncol 2004;31:530-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15297944.

21. Stahl A, Ott K, Weber WA, et al. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging 2003;30:288-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12552348.

22. Chen J, Cheong J-H, Yun MJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer 2005;103:2383-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15856477.

23. Rosenbaum SJ, Stergar H, Antoch G, et al. Staging and follow-up of gastrointestinal tumors with PET/CT. Abdom Imaging 2006;31:25-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16333707.

24. Dassen AE, Lips DJ, Hoekstra CJ, et al. FDG-PET has no definite role in preoperative imaging in gastric cancer. Eur J Surg Oncol 2009;35:449-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19147324.

25. Lim JS, Yun MJ, Kim M-J, et al. CT and PET in stomach cancer: preoperative staging and monitoring of response to therapy. Radiographics 2006;26:143-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418249.

26. Matsumoto Y, Yanai H, Tokiyama H, et al. Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer. J Gastroenterol 2000;35:326-331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10832666.

27. Tsendsuren T, Jun S-M, Mian X-H. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. World J Gastroenterol 2006;12:43-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16440415.

28. Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. Am J Surg 2006;191:134-138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16399124.

29. Bentrem D, Wilton A, Mazumdar M, et al. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. Ann Surg Oncol 2005;12:347-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15915368.

30. Burke EC, Karpeh MS, Conlon KC, Brennan MF. Peritoneal lavage cytology in gastric cancer: an independent predictor of outcome. Ann Surg Oncol 1998;5:411-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9718170.

31. Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol 2010;17:3173-3180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20585870.

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

33. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005;23:7114-7124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16192595.

34. Lowy AM, Mansfield PF, Leach SD, et al. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Ann Surg 1999;229:303-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10077040.

35. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 2003;98:1521-1530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14508841.

36. Mansour JC, Tang L, Shah M, et al. Does graded histologic response after neoadjuvant chemotherapy predict survival for completely resected gastric cancer? Ann Surg Oncol 2007;14:3412-3418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17909917.

37. Ryan R, Gibbons D, Hyland JM, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005;47:141-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16045774.

38. 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.

39. 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.

40. Yan B, Yau EX, Bte Omar SS, et al. A study of HER2 gene amplification and protein expression in gastric cancer. J Clin Pathol 2010;63:839-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696687.

41. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. Int J Cancer 2012;130:2845-2856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21780108.

42. Gomez-Martin C, Garralda E, Echarri MJ, et al. HER2/neu testing for anti-HER2-based therapies in patients with unresectable and/or metastatic gastric cancer. J Clin Pathol 2012;65:751-757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22569536.

43. Kunz PL, Mojtahed A, Fisher GA, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. Appl Immunohistochem Mol Morphol 2012;20:13-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21617522.

44. Janjigian YY, Werner D, Pauligk C, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. Ann Oncol 2012;23:2656-2662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22689179.

45. 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.

46. 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.

47. Jorgensen JT, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. J Cancer 2012;3:137-144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22481979.

48. Grabsch H, Sivakumar S, Gray S, et al. HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. Cell Oncol 2010;32:57-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20208134.

49. 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.

50. 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.

51. 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.

52. 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.

53. Ajani JA, Mayer RJ, Ota DM, et al. Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. J Natl Cancer Inst 1993;85:1839-1844. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8230264.

54. Leichman L, Silberman H, Leichman CG, et al. Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: a University of Southern California pilot program. J Clin Oncol 1992;10:1933-1942. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1453207.

55. Hermanek P, Wittekind C. Residual tumor (R) classification and prognosis. Semin Surg Oncol 1994;10:12-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8115781.

56. Bozzetti F, Marubini E, Bonfanti G, et al. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. Ann Surg 1999;230:170-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10450730.

57. Ito H, Clancy TE, Osteen RT, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg 2004;199:880-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15555971.

58. Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg 2006;93:559-563. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16607678.

59. Lim S, Muhs BE, Marcus SG, et al. Results following resection for stage IV gastric cancer; are better outcomes observed in selected patient subgroups? J Surg Oncol 2007;95:118-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17262741.

60. Jeurnink SM, van Eijck CHJ, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17559659.

61. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. Ann Surg Oncol

2007;14:317-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17094022.

62. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. Jpn J Surg 1981;11:127-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7300058.

63. Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. Gastric Cancer 2012;15 Suppl 1:S70-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22895615.

64. Hartgrink HH, van de Velde CJH, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22:2069-2077. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15082726.

65. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999;79:1522-1530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10188901.

66. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20409751.

67. Jatzko GR, Lisborg PH, Denk H, et al. A 10-year experience with Japanese-type radical lymph node dissection for gastric cancer outside of Japan. Cancer 1995;76:1302-1312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8620402.

68. Sierra A, Regueira FM, Hernandez-Lizoain JL, et al. Role of the extended lymphadenectomy in gastric cancer surgery: experience in a single institution. Ann Surg Oncol 2003;10:219-226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12679305.

69. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004;30:303-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15028313.

70. Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer 2004;90:1727-1732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15150592.

71. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501. J Clin Oncol 2004;22:2767-2773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15199090.

72. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008;359:453-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18669424.

73. Enzinger PC, Benedetti JK, Meyerhardt JA, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. Ann Surg 2007;245:426-434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17435550.

74. Degiuli M, Sasako M, Ponti A. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. Br J Surg 2010;97:643-649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20186890.

75. Seevaratnam R, Bocicariu A, Cardoso R, et al. A meta-analysis of D1 versus D2 lymph node dissection. Gastric Cancer 2012 15 Suppl 1:S60-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22138927.

76. Csendes A, Burdiles P, Rojas J, et al. A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. Surgery 2002;131:401-407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11935130.

77. Reyes CD, Weber KJ, Gagner M, Divino CM. Laparoscopic vs open gastrectomy. A retrospective review. Surg Endosc 2001;15:928-931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11605108.

78. Huscher CGS, Mingoli A, Sgarzini G, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. Ann Surg 2005;241:232-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15650632.

79. 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.

80. Bonenkamp JJ, van de Velde CJ, Kampschoer GH, et al. Comparison of factors influencing the prognosis of Japanese, German, and Dutch gastric cancer patients. World J Surg 1993;17:410-414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8337889.

81. Yahagi N, Fujishiro M, Kakushima N, et al. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Digestive Endoscopy 2004;16:34-38. Available at:

82. Oda I, Saito D, Tada M, et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 2006;9:262-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17235627.

83. Cao Y, Liao C, Tan A, et al. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. Endoscopy 2009;41:751-757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19693750.

84. Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. J Gastroenterol Hepatol 2009;24:1102-1106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19383079.

85. Nakamoto S, Sakai Y, Kasanuki J, et al. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. Endoscopy 2009;41:746-750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19681023.

86. Watanabe T, Kume K, Taip M, et al. Gastric mucosal cancer smaller than 7mm can be treated with conventional endoscopic mucosal resection as effectively as with endoscopic submucosal dissection. Hepatogastroenterology 2010;57:668-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20698247.

87. Hatfield AR, Slavin G, Segal AW, Levi AJ. Importance of the site of endoscopic gastric biopsy in ulcerating lesions of the stomach. Gut 1975;16:884-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1193417.

88. Akiyama M, Ota M, Nakajima H, et al. Endoscopic mucosal resection of gastric neoplasms using a ligating device. Gastrointest Endosc 1997;45:182-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9041007.

89. Hull MJ, Mino-Kenudson M, Nishioka NS, et al. Endoscopic mucosal resection: an improved diagnostic procedure for early gastroesophageal epithelial neoplasms. Am J Surg Pathol 2006;30:114-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16330950.

90. Botet JF, Lightdale CJ, Zauber AG, et al. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. Radiology 1991;181:426-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1924784.

91. Bentrem D, Gerdes H, Tang L, et al. Clinical correlation of endoscopic ultrasonography with pathologic stage and outcome in patients undergoing curative resection for gastric cancer. Ann Surg Oncol 2007;14:1853-1859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17357856.

92. Okada K, Fujisaki J, Kasuga A, et al. Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. Surg Endosc 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20734082.

93. 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.

94. Mekky MA, Yamao K, Sawaki A, et al. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. Gastrointest Endosc 2010;71:913-919. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20226456.

95. Hyung WJ, Cheong JH, Kim J, et al. Application of minimally invasive treatment for early gastric cancer. J Surg Oncol 2004;85:181-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14991872.

96. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11156645.

97. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21573742.

98. Ahn JY, Jung HY, Choi KD, et al. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. Gastrointest Endosc 2011;74:485-493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21741645.

99. Schmidt C, Gerdes H, Hawkins W, et al. A prospective observational study examining quality of life in patients with malignant gastric outlet obstruction. Am J Surg 2009;198:92-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19482259.

100. 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.

101. Shike M, Latkany L, Gerdes H, Bloch AS. Direct percutaneous endoscopic jejunostomies for enteral feeding. Gastrointest Endosc 1996;44:536-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8934158.

102. Park SR, Lee JS, Kim CG, et al. Endoscopic ultrasound and computed tomography in restaging and predicting prognosis after neoadjuvant chemotherapy in patients with locally advanced gastric cancer. Cancer 2008;112:2368-2376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18404697.

103. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19387328.

104. 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.

105. Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. Int J Radiat Oncol Biol Phys 2002;52:283-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11872272.

106. Hallissey MT, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 1994;343:1309-1312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7910321.

107. Zhang ZX, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)--report on 370 patients. Int J Radiat Oncol Biol Phys 1998;42:929-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9869212.

108. Valentini V, Cellini F, Minsky BD, et al. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. Radiother Oncol 2009;92:176-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19586672.

109. Hazard L, O'Connor J, Scaife C. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol 2006;12:1511-1520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16570342.

110. Moertel CG, Childs DS, Reitemeier RJ, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 1969;2:865-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4186452.

111. Schein PS. A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. Cancer 1982;49:1771-1777. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6176313.

112. Milano MT, Garofalo MC, Chmura SJ, et al. Intensity-modulated radiation therapy in the treatment of gastric cancer: early clinical outcome and dosimetric comparison with conventional techniques. Br J Radiol 2006;79:497-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16714752.

113. Lowy AM, Feig BW, Janjan N, et al. A pilot study of preoperative chemoradiotherapy for resectable gastric cancer. Ann Surg Oncol 2001;8:519-524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11456051.

114. 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.

115. Leong T, Smithers M, Michael M, et al. TOPGEAR: An international randomized phase III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer (AGITG/TROG/EORTC/NCIC CTG) [abstract]. J Clin Oncol 2012;30 (suppl):Abstract TPS4141. Available at: http://abstract.asco.org/AbstView_114_99024.html.

116. Ajani JA, Mansfield PF, Crane CH, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol 2005;23:1237-1244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718321.

117. Ajani JA, Mansfield PF, Janjan N, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol 2004;22:2774-2780. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15254045.

118. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921048.

119. 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.

120. 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.

121. 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.

122. 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. Journal of Clinical Oncology 2012;30:2327-2333. Available at: http://jco.ascopubs.org/content/30/19/2327.abstract.

123. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16489675.

124. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20472363.

125. 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.

126. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17704423.

127. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22184384.

128. Dikken JL, Jansen EP, Cats A, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol 2010;28:2430-2436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20368551.

129. 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.

130. 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.

131. Nakajima T, Nashimoto A, Kitamura M, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. Lancet 1999;354:273-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10440302.

132. Nashimoto A, Nakajima T, Furukawa H, et al. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol 2003;21:2282-2287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12805327.

133. Bouche O, Ychou M, Burtin P, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol 2005;16:1488-1497. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15939717.

134. De Vita F, Giuliani F, Orditura M, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol 2007;18:1354-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17525087.

135. Di Costanzo F, Gasperoni S, Manzione L, et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst 2008;100:388-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18334706.

136. Kulig J, Kolodziejczyk P, Sierzega M, et al. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial. Oncology 2010;78:54-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20215786.

137. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-1820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17978289.

138. Bang Y-J, Kim Y-W, Yang H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. The Lancet 2012;379:315-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22226517.

139. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387-4393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010012.

140. Glimelius B, Hoffman K, Haglund U, et al. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 1994;5:189-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8186165.

141. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995;71:587-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7533517.

142. Hartmann JT, Quietzsch D, Daikeler T, et al. Mitomycin C continuous infusion as salvage chemotherapy in pretreated patients with advanced gastric cancer. Anticancer Drugs 1999;10:729-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10573205.

143. Hofheinz RD, Hartung G, Samel S, et al. High-dose 5-fluorouracil / folinic acid in combination with three-weekly mitomycin C in the treatment of advanced gastric cancer. A phase II study. Onkologie 2002;25:255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12119460.

144. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506170.

145. Bugat R. Irinotecan in the treatment of gastric cancer. Ann Oncol 2003;14 Suppl 2:ii37-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12810456.

146. Ajani JA, Mansfield PF, Dumas P. Oral etoposide for patients with metastatic gastric adenocarcinoma. Cancer J Sci Am 1999;5:112-114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10198733.

147. Taal BG, Teller FG, ten Bokkel Huinink WW, et al. Etoposide, leucovorin, 5-fluorouracil (ELF) combination chemotherapy for advanced gastric cancer: experience with two treatment schedules incorporating intravenous or oral etoposide. Ann Oncol 1994;5:90-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8172800.

148. Einzig AI, Lipsitz S, Wiernik PH, Benson AB, 3rd. Phase II trial of taxol in patients with adenocarcinoma of the upper gastrointestinal tract (UGIT). The Eastern Cooperative Oncology group (ECOG) results. Invest New Drugs 1995;13:223-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8729950.

149. Ajani JA, Fairweather J, Dumas P, et al. Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am 1998;4:269-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9689986.

150. Ohtsu A, Boku N, Tamura F, et al. An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol 1998;21:416-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9708646.

151. Kim YH, Shin SW, Kim BS, et al. Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. Cancer 1999;85:295-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10023695.

152. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12576922.

153. Sulkes A, Smyth J, Sessa C, et al. Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. Br J Cancer 1994;70:380-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7914428.

154. Einzig AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol 1996;13:87-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9013471.

155. Roth AD, Maibach R, Martinelli G, et al. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 2000;11:301-306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10811496.

156. Bang YJ, Kang WK, Kang YK, et al. Docetaxel 75 mg/m(2) is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. Jpn J Clin Oncol 2002;32:248-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12324575.

157. 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.

158. Cascinu S, Galizia E, Labianca R, et al. Pegylated liposomal doxorubicin, 5-fluorouracil and cisplatin versus mitomycin-C, 5-fluorouracil and cisplatin for advanced gastric cancer: a randomized phase II trial. Cancer Chemother Pharmacol 2011;68:37-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20821330.

159. MacDonald JS, Schein PS, Woolley PV, et al. 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med 1980;93:533-536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7436184.

160. Cullinan SA, Moertel CG, Fleming TR, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. JAMA 1985;253:2061-2067. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2579257.

161. Wils JA, Klein HO, Wagener DJ, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin--a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 1991;9:827-831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2016625.

162. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8996151.

163. Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000;18:2648-2657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10894863.

164. 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.

165. Louvet C, Andre T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002;20:4543-4548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12454110.

166. Al-Batran S-E, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004;22:658-663. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14966088.

167. 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.

168. 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.

169. Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007;25:3217-3223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664469.

170. Al-Batran SE, 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.

171. Shah MA, Shibata S, Stoller RG, et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth factor support (GCSF) in metastatic gastroesophageal adenocarcinoma (GE) [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 4014. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/4014.

172. Van Cutsem E, Boni C, Tabernero J, et al. Randomized phase II study (GATE study) of docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer [abstract]. J Clin Oncol 2011;29 (Suppl 15):Abstract 4018. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/4018.

173. Inal A, Kaplan MA, Kucukoner M, Isikdogan A. Docetaxel and cisplatin plus fluorouracil compared with modified docetaxel, cisplatin, and 5-fluorouracil as first-line therapy for advanced gastric cancer: aretrospective analysis of single institution. Neoplasma 2012;59:233-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22248282.

174. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15319239.

175. Park YH, Lee JL, Ryoo BY, et al. Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. Cancer Chemother Pharmacol 2008;61:623-629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17522863.

176. 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.

177. Luo HY, Xu RH, Wang F, et al. Phase II trial of XELOX as first-line treatment for patients with advanced gastric cancer. Chemotherapy 2010;56:94-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20357440.

178. 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.

179. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19153121.

180. Okines AFC, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced

oesophago-gastric cancer. Ann Oncol 2009;20:1529-1534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474114.

181. 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.

182. Boku N, Ohtsu A, Shimada Y, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 1999;17:319-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458249.

183. Ajani JA, Baker J, Pisters PWT, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. Cancer 2002;94:641-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11857295.

184. Bamias A, Papamichael D, Syrigos K, Pavlidis N. Phase II study of irinotecan and mitomycin C in 5-fluorouracil-pretreated patients with advanced colorectal and gastric cancer. J Chemother 2003;15:275-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12868555.

185. Moehler M, Haas U, Siebler J, et al. Weekly treatment with irinotecan, folinic acid and infusional 5-fluorouracil (ILF) in patients with advanced gastric cancer. Anticancer Drugs 2003;14:645-650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14501387.

186. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15514373.

187. Pozzo C, Barone C, Szanto J, et al. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. Ann Oncol 2004;15:1773-1781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15550582.

188. Moehler M, Eimermacher A, Siebler J, et al. Randomised phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. Br J Cancer 2005;92:2122-2128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15942629.

189. Beretta E, Di Bartolomeo M, Buzzoni R, et al. Irinotecan, fluorouracil and folinic acid (FOLFIRI) as effective treatment combination for patients with advanced gastric cancer in poor clinical condition. Tumori 2006;92:379-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17168428.

190. 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.

191. Brell JM, Krishnamurthi SS, Javle M, et al. A multi-center phase II study of oxaliplatin, irinotecan, and capecitabine in advanced gastric/gastroesophageal junction carcinoma. Cancer Chemother Pharmacol 2009;63:851-857. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18670776.

192. Enzinger PC, Ryan DP, Clark JW, et al. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. Ann Oncol 2009;20:475-480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139178.

193. 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.

194. 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.

195. Samalin E, Afchain P, Thezenas S, et al. Efficacy of irinotecan in combination with 5-fluorouracil (FOLFIRI) for metastatic gastric or gastroesophageal junction adenocarcinomas (MGA) treatment. Clin Res Hepatol Gastroenterol 2011;35:48-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21634054.

196. Giuliani F, Molica S, Maiello E, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol 2005;28:581-585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16317268.

197. Di Lauro L, Fattoruso SI, Giacinti L, et al. Second-line chemotherapy with FOLFIRI in patients with metastatic gastric cancer (MGC) not previously treated with fluoropyrimidines [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 4549. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4549.

198. Hawkes E, Okines AF, Papamichael D, et al. Docetaxel and irinotecan as second-line therapy for advanced oesophagogastric cancer. Eur J Cancer 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21269822.

199. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9:215-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18282805.

200. Ajani JA, Lee F-C, Singh DA, et al. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006;24:663-667. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16446338.

201. Lenz H-J, Lee F-C, Haller DG, et al. Extended safety and efficacy data on S-1 plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study. Cancer 2007;109:33-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17133415.

202. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010;28:1547-1553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20159816.

203. Dragovich T, McCoy S, Fenoglio-Preiser CM, et al. Phase II Trial of Erlotinib in Gastroesophageal Junction and Gastric Adenocarcinomas: SWOG 0127. J Clin Oncol 2006;24:4922-4927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17050876.

204. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol 2007;18:510-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17164226.

205. Pinto C, Di Fabio F, Barone C, et al. Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer 2009;101:1261-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19773760.

206. Kim C, Lee J-L, Ryu M-H, et al. A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer.

Invest New Drugs 2011;29:366-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19997960.

207. Lordick F, Luber B, Lorenzen S, et al. Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer 2010;102:500-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20068568.

208. Woll E, Greil R, Eisterer W, et al. Oxaliplatin, irinotecan and cetuximab in advanced gastric cancer. A multicenter phase II trial (Gastric-2) of the Arbeitsgemeinschaft Medikamentose Tumortherapie (AGMT). Anticancer Res 2011;31:4439-4443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22199312.

209. Shah MA, Jhawer M, Ilson DH, et al. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. J Clin Oncol 2011;29:868-874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21189380.

210. El-Rayes BF, Zalupski M, Bekai-Saab T, et al. A phase II study of bevacizumab, oxaliplatin, and docetaxel in locally advanced and metastatic gastric and gastroesophageal junction cancers. Ann Oncol 2010;21:1999-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20332133.

211. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29:3968-3976. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844504.

212. Sun W, Powell M, O'Dwyer PJ, et al. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol 2010;28:2947-2951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458043.

213. Jadvar H, Tatlidil R, Garcia AA, Conti PS. Evaluation of recurrent gastric malignancy with [F-18]-FDG positron emission tomography. Clin Radiol 2003;58:215-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12639527.

214. Ott K, Fink U, Becker K, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. J Clin Oncol 2003;21:4604-4610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14673049.

215. Ott K, Herrmann K, Lordick F, et al. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. Clin Cancer Res 2008;14:2012-2018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18381939.

216. Vallbohmer D, Holscher AH, Schneider PM, et al. [18F]-fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemotherapy in gastric cancer. J Surg Oncol 2010;102:135-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20648583.

217. Tian J, Chen L, Wei B, et al. The value of vesicant 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) in gastric malignancies. Nucl Med Commun 2004;25:825-831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15266178.

218. The concept of locally advanced gastric cancer. Effect of treatment on outcome. The Gastrointestinal Tumor Study Group. Cancer 1990;66:2324-2330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1700927.

219. 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.

220. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011;11:329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21810227.

221. 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.

222. 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.

223. 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.

224. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997;8:163-168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9093725.

225. Casaretto L, Sousa PLR, Mari JJ. Chemotherapy versus support cancer treatment in advanced gastric cancer: a meta-analysis. Braz J Med Biol Res 2006;39:431-440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16612465.

226. 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.

227. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase iii trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22412140.

228. Comparison of flourouracil 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.

229. 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.

230. 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.

231. Imbesi JJ, Kurtz RC. A multidisciplinary approach to gastrointestinal bleeding in cancer patients. J Support Oncol 2005;3:101-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15796441.

232. Kim MM, Rana V, Janjan NA, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol 2008;47:421-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17899453.

233. Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metallic stents: the treatment of choice? Gastrointest Endosc 2004;60:1010-1017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15605026.

234. Lindsay JO, Andreyev HJN, Vlavianos P, Westaby D. Self-expanding metal stents for the palliation of malignant gastroduodenal obstruction in patients unsuitable for surgical bypass. Aliment Pharmacol Ther 2004;19:901-905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15080851.

235. Kim TO, Kang DH, Kim GH, et al. Self-expandable metallic stents for palliation of patients with malignant gastric outlet obstruction caused by stomach cancer. World J Gastroenterol 2007;13:916-920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17352023.

236. Ly J, O'Grady G, Mittal A, et al. A systematic review of methods to palliate malignant gastric outlet obstruction. Surg Endosc 2010;24:290-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19551436.

237. Jeurnink SM, Steyerberg EW, van Hooft JE, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc 2010;71:490-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20003966.

238. Wollman B, D'Agostino HB. Percutaneous radiologic and endoscopic gastrostomy: a 3-year institutional analysis of procedure performance. AJR Am J Roentgenol 1997;169:1551-1553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9393163.

239. Silas AM, Pearce LF, Lestina LS, et al. Percutaneous radiologic gastrostomy versus percutaneous endoscopic gastrostomy: a comparison of indications, complications and outcomes in 370 patients. Eur J Radiol 2005;56:84-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16168268.

240. Lee MJ, Saini S, Brink JA, et al. Malignant small bowel obstruction and ascites: not a contraindication to percutaneous gastrostomy. Clin Radiol 1991;44:332-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1836988.

241. Ryan JM, Hahn PF, Mueller PR. Performing radiologic gastrostomy or gastrojejunostomy in patients with malignant ascites. AJR Am J Roentgenol 1998;171:1003-1006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9762985.