National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 1.2017 — March 21, 2017

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NCCN Guidelines Version 1.2017 Panel Members
Gastric Cancer

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NCCN Guidelines Panel Disclosures

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≠ Pathology
Δ Genetics

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

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

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

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017 Updates Gastric Cancer

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Discussion

Updates in Version 1.2017 of the NCCN Guidelines for Gastric Cancer from Version 3.2016 include:

Global Changes

- **"HER2-neu testing" changed to "*HER2* testing."**

GAST-1

- **Workup; Seventh bullet revised, "Endoscopic resection (ER) ~~may contribute to~~ *is essential for the* accurate staging of early-stage cancers (T1a or T1b)"**
- **Footnote "e" is new: "*Microsatellite instability and tumor Epstein-Barr virus status are emerging as potential biomarkers for personalized treatment strategies for gastric cancer, but are not currently recommended for clinical care.*"**

GAST-2

- **Locoregional disease (cM0); Surgically unresectable; Primary treatment recommendations revised:**
  - **"~~Concurrent fluoropyrimidine- or taxane-based~~ Chemoradiation ~~(category 1)~~**
  - **~~Chemotherapy~~ Palliative Management (see GAST-7)."**
- **Locoregional disease (cM0); Non-surgical candidate; Primary treatment recommendation revised: "~~Concurrent fluoropyrimidine- or taxane-based~~ Chemoradiation ~~(category 1)~~ (Definitive)."**

GAST-4

- **Postoperative Management revisions:**
  - **R0 resection; Node negative: "~~Surveillance~~ *Observation until progression, (if received preoperative chemoradiation)*."**
  - **R0 resection; Node positive: "*Observation until progression, (if received preoperative chemoradiation)*" added as an option.**
  - **R1 resection: "Chemotherapy" and "Consider re-resection" added as options.**
- **New footnote "t" added: "*The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.*"**

GAST-5

- **Footnote "u" regarding PET/CT is new: "*In cases of renal insufficiency or allergy to CT contrast.*"**

GAST-6

- **Follow-up/Surveillance revisions:**
  - **"CBC and chemistry profile as *clinically* indicated."**
  - **"*Pelvic CT with contrast as clinically indicated*" added.**

GAST-7

- **Palliative Management for unresectable locally advanced, locally recurrent or metastic disease with good performance status: "Clinical trial" removed as an option.**

Continued

NCCN Guidelines Version 1.2017 Updates
Gastric Cancer

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GAST-B Principles of Pathologic Review and HER2 Testing

1 of 4

- Under Specimen Type: ***"Biopsy"*** added with corresponding recommendations to include in the pathology report.

2 of 4

- Assessment of Treatment response: Revised, "Response of the primary tumor *and lymph node metastases* to previous chemotherapy or radiation therapy should be reported."

3 of 4

- New reference added: "***Bartley AN, Washington MK, Ventura CB, et al. HER2 testing and clinical decision-making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society of Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med 2016;140:1345-63.***"

GAST-F: Principles of Systemic Therapy

1 of 11

- The following bullets were removed:
  - Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.
  - Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.
  - Induction chemotherapy may be appropriate as clinically indicated.

2 of 11

- Perioperative Chemotherapy
  - "*Fluoropyrimidine and oxaliplatin*" added as an option with corresponding footnote, "*The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.*"
- Postoperative Chemotherapy
  - "Capecitabine and oxaliplatin" changed from category 2A to category 1 with corresponding footnote, "*Cisplatin may not be used interchangeably with oxaliplatin in this setting.*"
  - Capecitabine and cisplatin removed as an option.

GAST-F: Principles of Systemic Therapy (continued)

3 of 11 Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- First-Line Therapy; Other Regimens revised:
  - "Fluorouracil and irinotecan" (category ~~1~~ *2A*)
  - "ECF (epirubicin, cisplatin, and fluorouracil) (category ~~1~~ *2B*)"
  - ECF modifications (category ~~1~~*2B*)
- Second-Line Therapy; Preferred Regimens
  - "Fluorouracil and irinotecan *(if not previously used in first-line therapy)*" was added as a category 2A option with the following footnote: "*Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.*" Previously it was listed as a category 2B recommendation under "Other Regimens"
- Second-Line Therapy; Other Regimens
  - "Capecitabine and irinotecan" removed as an option.

4 of 11 Principles of Systemic Therapy—Regimens and Dosing Schedules

- The regimen and dosing schedule pages were updated to reflect the changes on GAST- 2 of 11 and GAST-F 3 of 11.

10 of 11

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

GAST-G Principles of Radiation

1 of 4

- General Guidelines: Second bullet revised, "CT scans, ~~barium swallow,~~ EUS, endoscopy reports..."
- Simulation and Treatment Planning: First bullet revised, "~~Use of~~ CT simulation and ~~3-D~~ *conformal* treatment planning ~~is strongly encouraged~~ *should be used*. Intensity-modulated radiation therapy (IMRT) may be used in clinical settings where reduction in dose to organs at risk (eg, heart, lungs, liver, kidneys, *small bowel*) ~~and critical normal tissues~~ is required, which cannot be achieved by 3-D techniques."

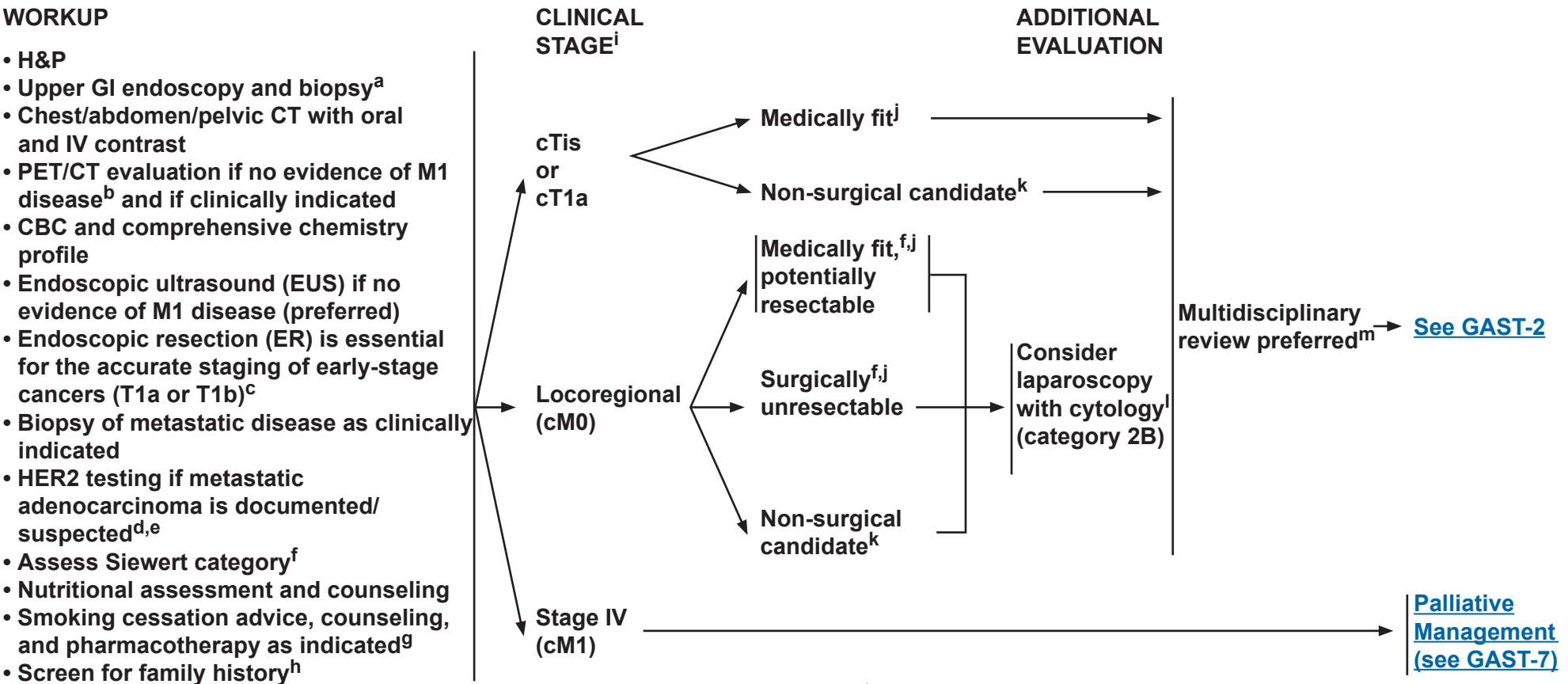
Continued

GAST-G Principles of Radiation
2 of 4

- **Target volume (General Guidelines)**
  - **Bullets under "Preoperative" and "Postoperative" bullets ammended to include "*Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity*."**
  - **"UGI" removed as a diagnostic study.**
- **Proximal One-Third/*Fundus*/Cardia/Esophagogastric Junction Primaries**
  - **"Preoperative and Postoperative" header deleted and bullet revised: "...included. Nodal areas at risk include: perigastric, celiac, *left gastric artery, splenic artery,* splenic hilar, *hepatic artery, and* porta hepatic lymph nodes. ~~Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.~~**
- **Middle One-Third/Body Primaries**
  - **"Preoperative and Postoperative" header deleted and bullet revised: "Nodal areas at risk include: perigastric, ~~suprapancreatic,~~ celiac, *left gastric artery, splenic artery,* splenic hilar, *hepatic artery,* porta hepatic, *suprapyloric, subpyloric* and pancreaticoduodenal lymph nodes.**
- **Distal One-Third/Antrum/Pylorus Primaries**
  - **Preoperative" and "Postoperative" headers deleted and bullet revised:**
    - ◊ ***A 3- to 5-cm margin of*** **~~First and second part of~~ duodenum *or duodenal stump* should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, *left gastric artery*, ~~suprapancreatic,~~ celiac, *hepatic artery,* porta hepatic, *suprapyloric, subpyloric and* pancreaticoduodenal lymph nodes.**
    - ◊ **Bullet deleted and combined with bullet above: "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"**

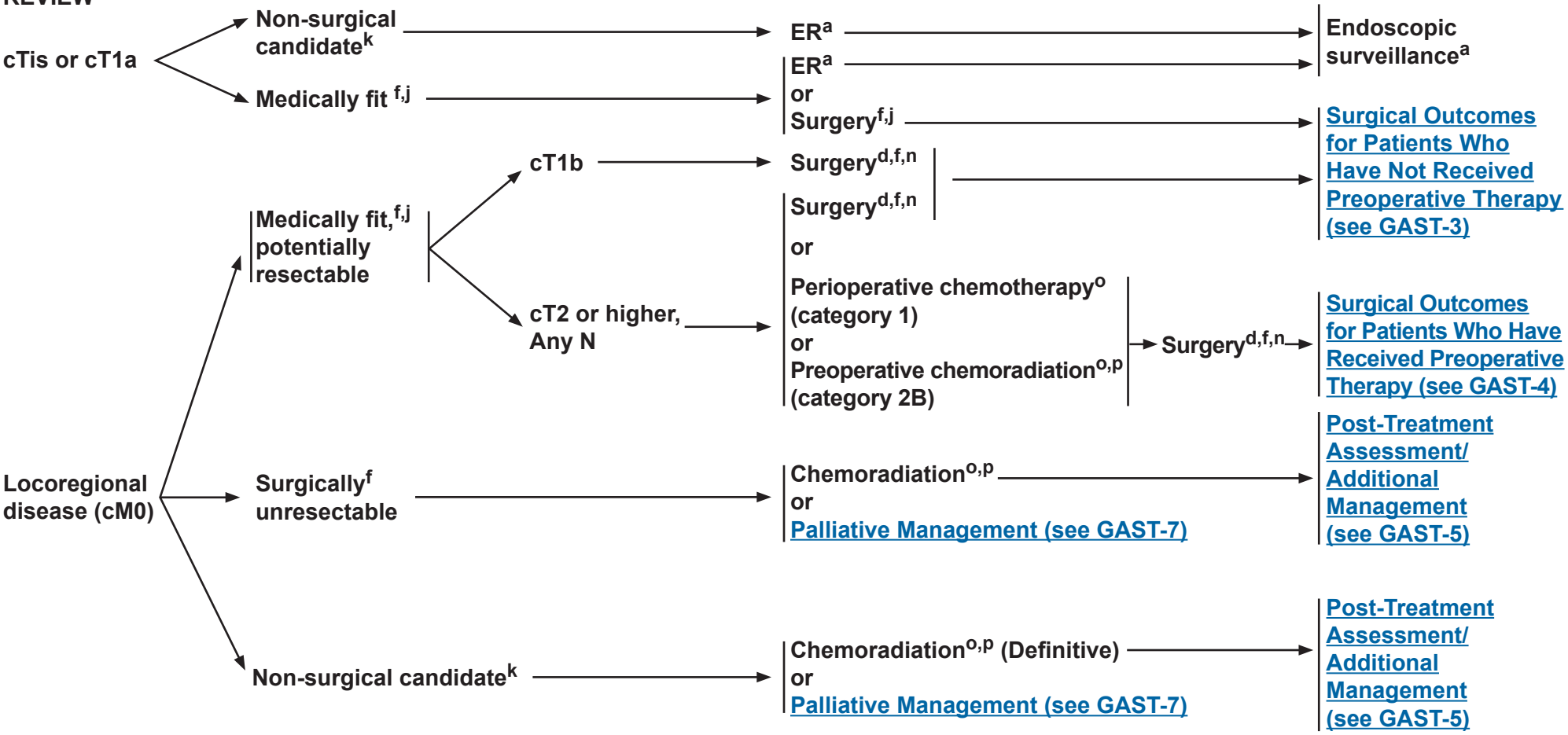
3 of 4

- **Normal Tissue Tolerance Dose-Limits: This section was extesively revised.**
- **Supportive Therapy: Last bullet revised, "Adequate enteral and/or IV hydration ~~is necessary throughout~~ *may be necessary during* chemoradiation and early recover."**



[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[b] May not be appropriate for T1.
[c] EMR may also be therapeutic for early-stage disease/lesions.
[d] See Principles of Pathologic Review and HER2 Testing (GAST-B).
[e] Microsatellite instability and tumor Epstein-Barr virus status are emerging as potential biomarkers for personalized treatment strategies for gastric cancer, but are not currently recommended for clinical care.
[f] See Principles of Surgery (GAST-C).
[g] See NCCN Guidelines for Smoking Cessation.
[h] See Principles of Genetic Risk Assessment for Gastric Cancer (GAST-D). Also see NCCN Guidelines for Colorectal Cancer Screening and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
[i] See Staging (ST-1) for tumor classification.
[j] Medically able to tolerate major surgery.
[k] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[l] Laparoscopy with cytology is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy with cytology is not indicated if a palliative resection is planned. Laparoscopy with cytology is indicated for clinical stage T1b or higher.
[m] See Principles of Multidisciplinary Team Approach (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.



[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[d] See Principles of Pathologic Review and HER2 Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[j] Medically able to tolerate major surgery.
[k] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[n] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).

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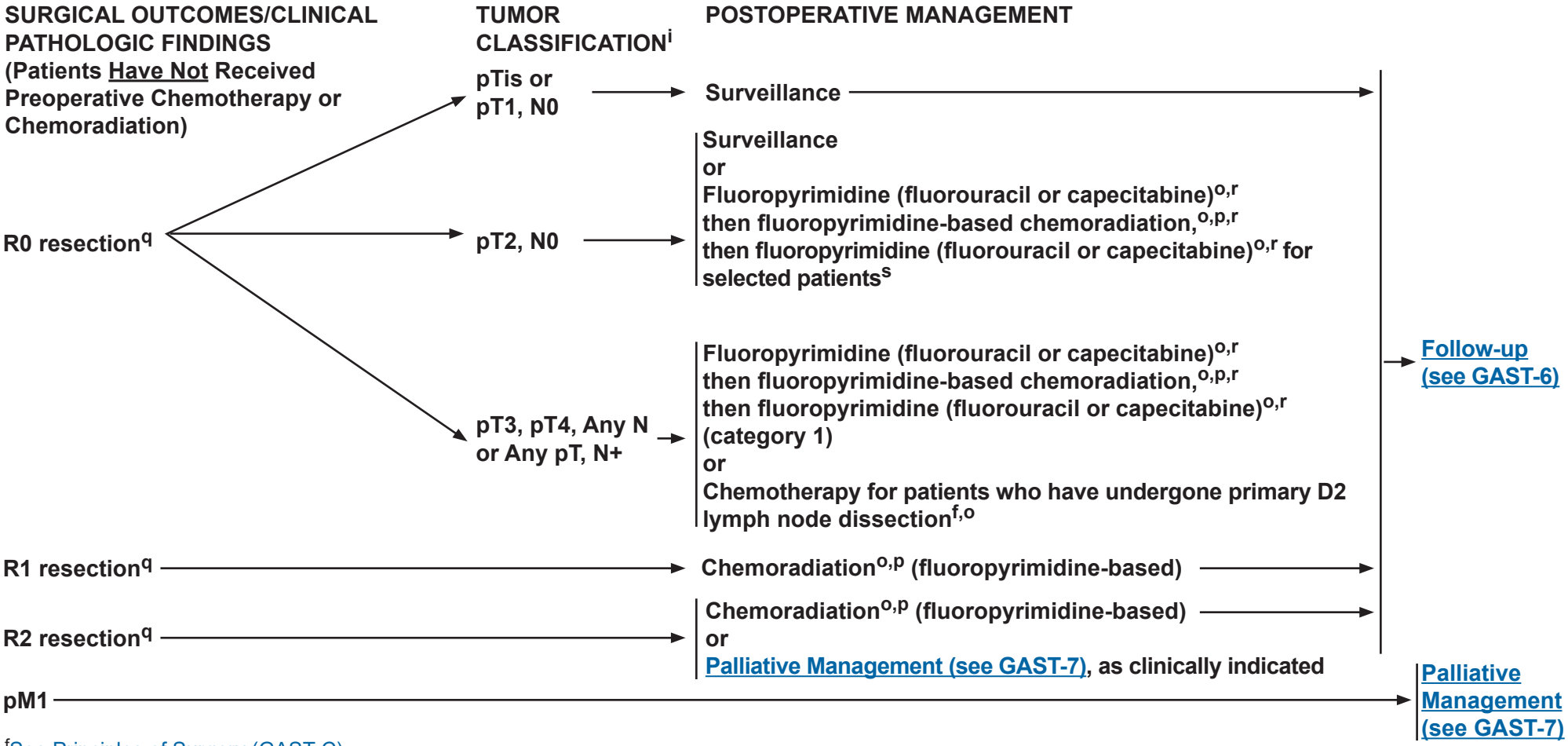

[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[q] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[r] Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333. See Principles of Systemic Therapy (GAST-F).
[s] High-risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or <50 years of age or patients who did not undergo D2 lymph node dissection.

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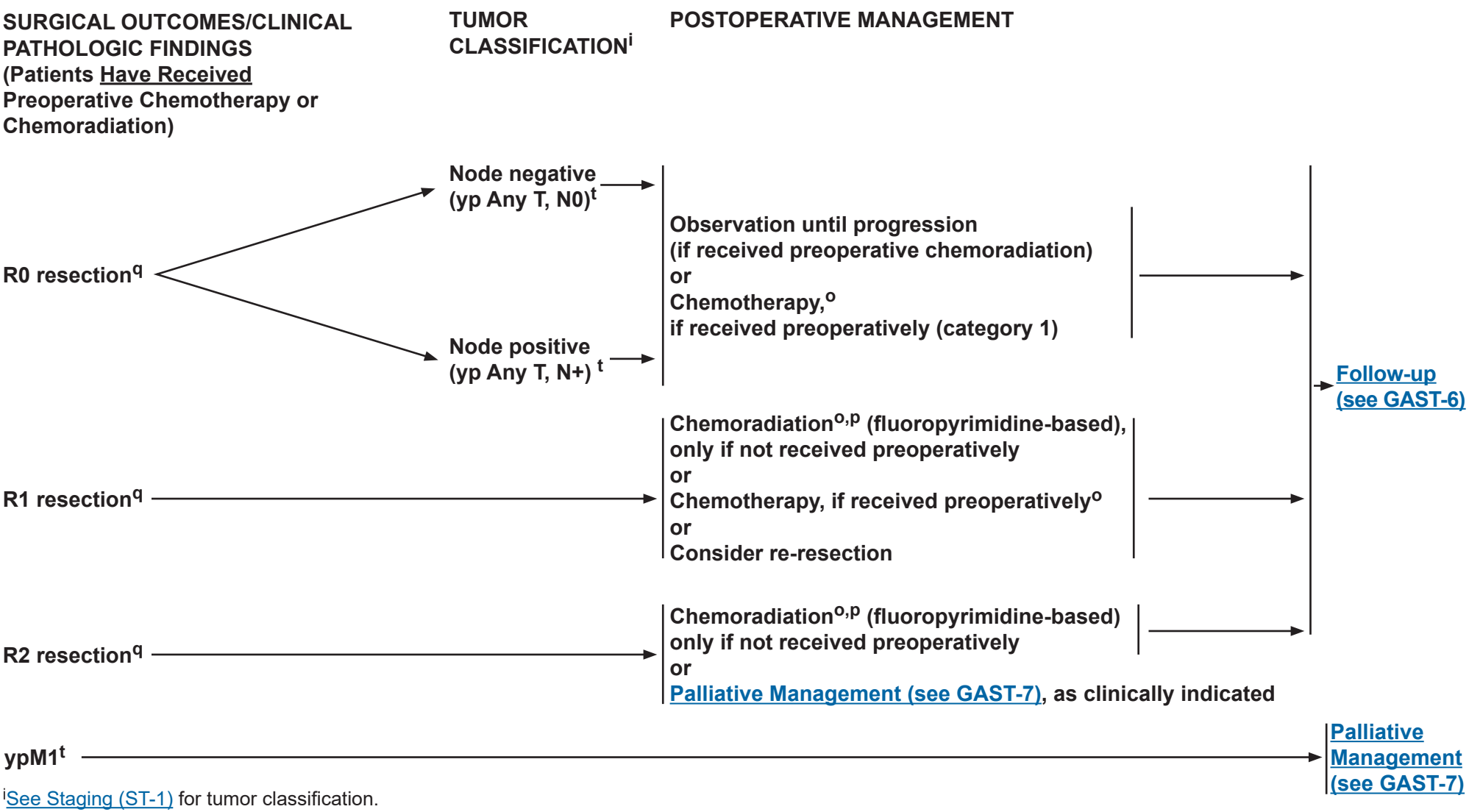

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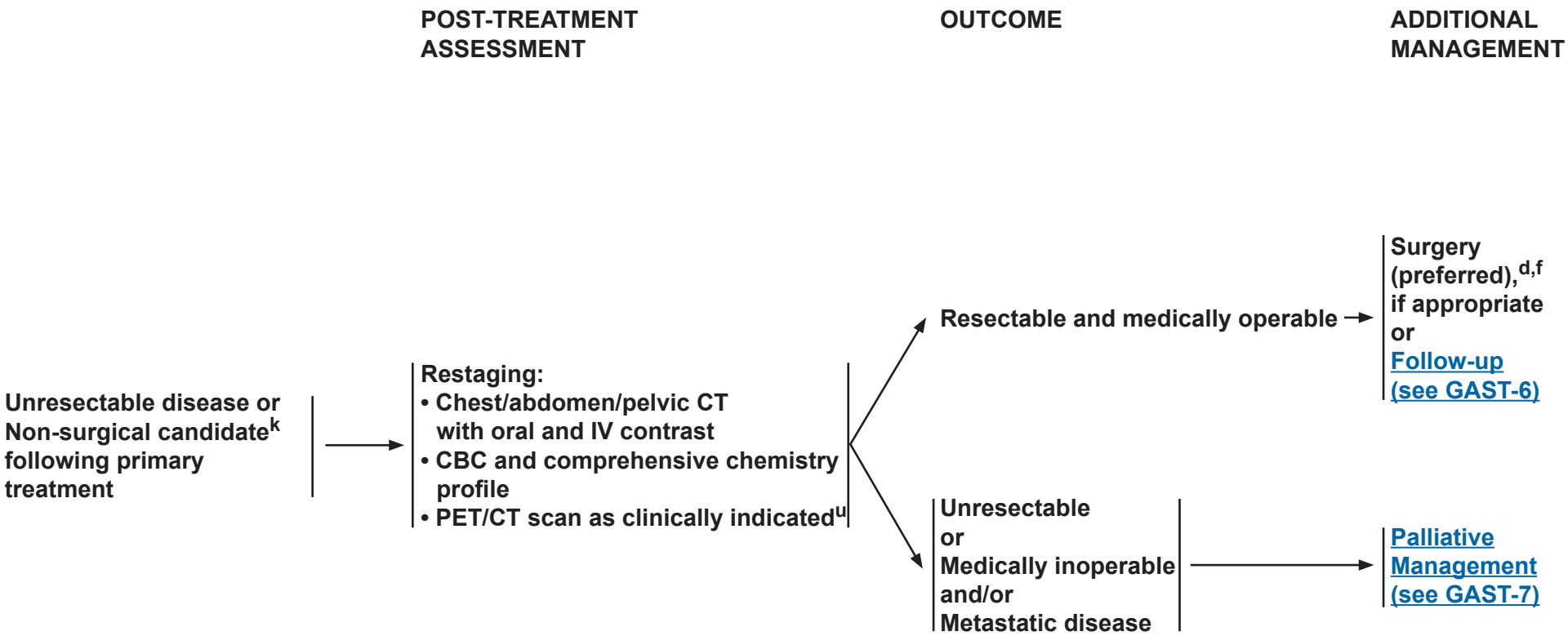

[d] See Principles of Pathologic Review and HER2 Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[k] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[u] In cases of renal insufficiency or allergy to CT contrast.

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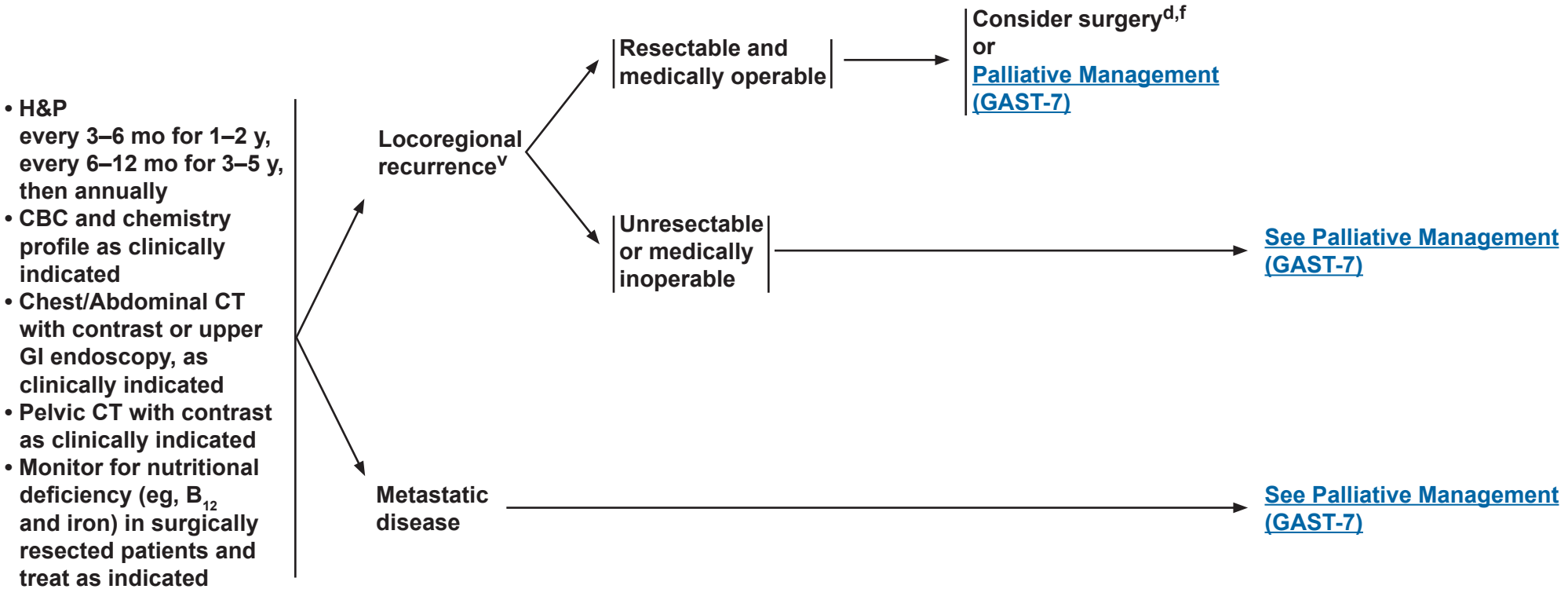
FOLLOW-UP/SURVEILLANCE **RECURRENCE**



[d] See Principles of Pathologic Review and HER2 Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[v] 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.

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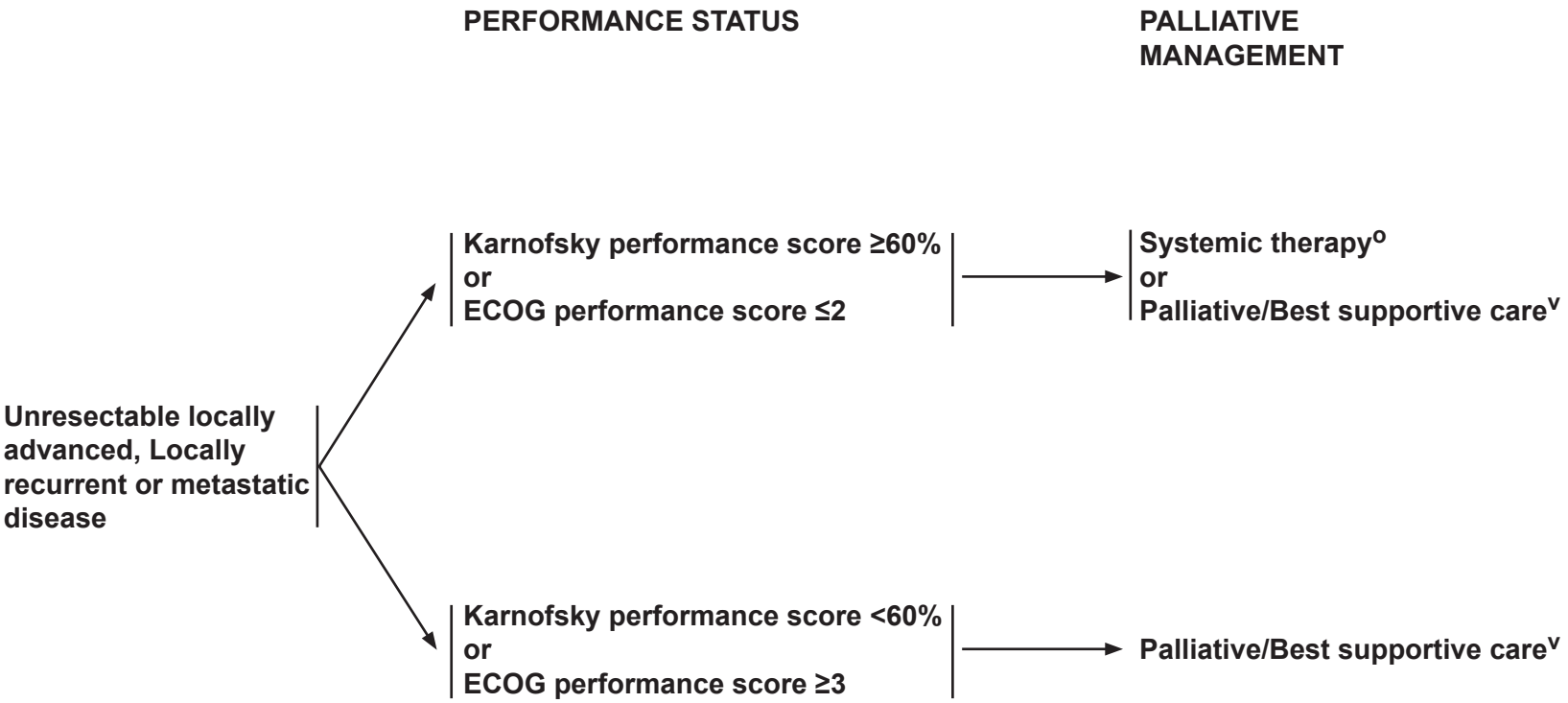

[o]See Principles of Systemic Therapy (GAST-F).
[v]See Principles of Palliative Care/Best Supportive Care (GAST-H).

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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 for 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) or endoscopic submucosal dissection (ESD) can be performed in the evaluation of small lesions. EMR or ESD of focal nodules ≤2 cm can be safely performed to provide a larger specimen that can be better assessed by the pathologist, providing greater information on degree of differentiation, the presence of lymphovascular invasion (LVI), 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

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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

STAGING

- 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-category), 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-category) or the presence of ascites.[6] This is especially important in patients who are being considered for endoscopic resection (EMR or ESD).[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-categories. 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 that correlates with invasion of the subserosa, T3 disease. Loss of the bright line recognized as the serosa is now staged as pT4a, and extension of the mass into surrounding organs such as the liver, pancreas, and spleen is staged as pT4b 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 should be considered to rule out peritoneal spread of disease.

Continued

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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

TREATMENT

- EMR or ESD of early-stage gastric cancer can be considered adequate therapy when the lesion is ≤2 cm in diameter, is shown on histopathology to be well or moderately well differentiated, does not penetrate beyond the superficial submucosa, does not exhibit LVI, and has clear lateral and deep margins. En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in curing *small* early-stage 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 that EMR or ESD should be considered for early-stage gastric cancer lesions ≤2 cm in diameter without associated ulcer formation.[3]
- EMR or ESD of gastric cancers that are poorly differentiated harbor evidence of LVI, invade into the deep submucosa, have positive lateral or deep margins or lymph node metastases, and should be considered to be incomplete. Additional therapy by gastrectomy with lymphadenectomy should be considered.[10]
- EUS performed after chemotherapy or radiation therapy has a reduced ability to accurately determine the post-treatment stage of disease.[11] 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 Palliative Care/Best Supportive Care [GAST-H]).[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

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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.
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Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2 TESTING

Pathologic Review

TABLE 1

Specimen Type	Analysis/Interpretation/Reporting[a]
Biopsy	Include in pathology report: • Invasion, if present • Histologic type[b] • Grade
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 • Lymph node 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 overexpress HER2.[1]
[c]Tumors arising in the proximal stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas.[2]

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2 TESTING

Assessment of Treatment Response

Response of the primary tumor and lymph node metastases to previous chemotherapy or radiation therapy should be reported. Although scoring 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.[3]

TABLE 2

Tumor Regression Score	Description
0 (Complete response)	No cancer cells, including lymph nodes
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).

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2 TESTING

Assessment of Overexpression of HER2 in Gastric Cancer

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or EGJ for whom trastuzumab therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended.[6] The following criteria used in the ToGA trial[7] are recommended:

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

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

Continued

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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2 TESTING
(References)

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PRINCIPLES OF SURGERY

N Category Determination

- 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 preoperative therapy, laparoscopy[1] may be useful in detecting radiographically occult metastatic disease in patients with cT3 and/or cN+ disease seen on preoperative imaging. If laparoscopy with cytology is performed as a separate procedure, peritoneal washings should be performed as well.
- In patients receiving preoperative 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 pM1 disease.[2]

Siewert Classification

- Siewert tumor type should be assessed in all patients with adenocarcinomas involving the esophagogastric junction (EGJ).[3,4]
  - Siewert Type I: adenocarcinoma of the lower esophagus (often associated with Barrett's esophagus) with the center located within 1 cm to 5 cm above the anatomic EGJ.
  - Siewert Type II: true carcinoma of the cardia at the EGJ, with the tumor center within 1 cm above and 2 cm below the EGJ.
  - Siewert Type III: subcardial carcinoma with the tumor center between 2 and 5 cm below EGJ, which infiltrates the EGJ and lower esophagus from below.
- The treatment of Siewert types I and II is as described in the NCCN Guidelines for Esophageal and EGJ Cancers.
- Siewert type III lesions are considered gastric cancers, and thus should be treated as described in the NCCN Guidelines for Gastric Cancer. In some cases additional esophageal resection may be needed in order to obtain adequate margins.[3,5,6]

Criteria of Unresectability for Cure

- Locoregionally advanced
  - Disease infiltration of the root of the mesentery or 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[7] tumors limited to mucosa (T1a) may be candidates for EMR (in experienced centers).[8]
- T1b-T3[9]: 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.
- 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.[10-12]
  - 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, 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.[13] Splenectomy is acceptable when the spleen or the hilum is involved.
- Consider placing feeding 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 is 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.[14]
- Venting gastrostomy and/or feeding tube may be considered.

Continued

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PRINCIPLES OF SURGERY
(References)

[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.
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PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Criteria for Further Risk Evaluation for High-Risk Syndromes:*

- **Referral to cancer genetics professional is recommended for an affected individual with one or more of the following:**
  - **A known mutation in a gastric cancer susceptibility gene within the family**
  - **Gastric cancer in one family member before age 40, or**
  - **Gastric cancer in 2 first-/second-degree relatives with one diagnosis before age 50, or**
  - **Gastric cancer in 3 first-/second-degree relatives independent of age, or**
  - **Gastric cancer and breast cancer in one patient with one diagnosis before age 50, or**
  - **Gastric cancer in one patient and breast cancer in one first-/second-degree relative with one diagnosis before age 50**

Risk Assessment/Genetic Counseling

- **While most gastric cancers are considered sporadic, it is estimated that 5% to 10% have a familial component and 3% to 5% are associated with an inherited cancer predisposition syndrome. Risk assessment and genetic counseling should include:**
  - **Detailed family history**
  - **Detailed medical and surgical history**
  - **Directed examination for related manifestations**
  - **Psychosocial assessment and support**
  - **Risk counseling**
  - **Education support**
  - **Discussion of genetic testing**
  - **Informed consent**

*Adapted and reproduced with permission from Kluijt I, Sijmons RH, Hoogerbrugge N, et al. Familial gastric cancer: guidelines for diagnosis, treatment, and periodic surveillance. Fam Cancer 2012;11:363-369.

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Continued

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Gastric Cancers

- **Hereditary Diffuse Gastric Cancer**
  - **This is an autosomal dominant syndrome characterized by the development of diffuse (signet ring cell) gastric cancers at a young age.[1,2] Truncating mutations in CDH1, the gene encoding the cell adhesion molecular E-cadherin, are found in 30% to 50% of cases.[3] The lifetime risk for gastric cancer by age 80 is estimated to be at 67% for men and 83% for women.[4] Average age at diagnosis of gastric cancer is 37 years. Women with CDH1 mutations are at higher risk of developing lobular carcinoma of the breast. Such patients should be referred to a center with a multidisciplinary team focusing on this condition. The team should include a surgeon specializing in upper gastrointestinal (UGI) cancer surgery, a gastroenterologist, a clinical genetics expert, a nutritionist, and a counselor or psychiatrist.**
  - **Genetic testing for CDH1 mutations should be considered when any of the following criteria are met:****
    - **Two gastric cancer cases in a family, one confirmed diffuse gastric cancer (DGC) diagnosed before age 50 years**
      OR
    - **Three confirmed cases of DGC in first- or second-degree relatives independent of age**
      OR
    - **DGC diagnosed before age 40 years without a family history**
      OR
    - **Personal or family history of DGC and lobular breast cancer, one diagnosed before age 50 years**
- **Lynch Syndrome**
  - **Individuals with Lynch syndrome (LS) have a 1% to 13% risk of developing gastric cancer and the risk is higher in Asian compared to Western kindreds. Gastric cancer is the second most common extracolonic cancer in these patients, after endometrial cancer. Individuals with LS are also at increased risk for other cancers: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**
- **Juvenile Polyposis Syndrome**
  - **Individuals with Juvenile polyposis syndrome (JPS) have a lifetime risk of 21% for developing gastric cancer when involvement of the UGI tract is present, which is primarily seen in SMAD4 mutation carriers. Individuals with JPS are also at increased risk for other cancers: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**
- **Peutz-Jeghers Syndrome**
  - **Individuals with Peutz-Jegers syndrome (PJS) have a 29% risk of developing gastric cancer. Individuals with PJS are also at increased risk for other cancers: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**
- **Familial Adenomatous Polyposis**
  - **Individuals with (FAP), in addition to attenuated FAP (AFAP) have a 1% to 2% lifetime risk for gastric cancer. Individuals with FAP/AFAP are also at increased risk for other cancers: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**

**Adapted and reproduced with permission from Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet 2010;47:436-444.

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Continued

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Surveillance Recommendations

Insufficient evidence exists for surveillance for hereditary cancer syndromes associated with gastric cancer risk, but the following guidelines have been proposed. Each of these cancer syndromes is associated with significant risks for other cancers, some of which are addressed in other NCCN Guidelines.

Syndrome	Gene(s)	Inheritance Pattern	Gastric Surveillance Recommendations
Hereditary diffuse gastric cancer[1-4]	*CDH1*	Autosomal dominant	Prophylactic gastrectomy is recommended between ages 18 and 40 for *CDH1* mutation carriers. A baseline endoscopy with multiple random biopsies is indicated prior to gastrectomy. Intraoperative frozen sections should be performed to verify that the proximal margin contains esophageal squamous mucosa and the distal margin contains duodenal mucosa, to ensure complete removal of gastric tissue. A D2 lymph node dissection is not necessary for prophylactic total gastrectomy. Prophylactic gastrectomy prior to 18 years of age is not recommended, but may be considered for certain patients, especially those with family members diagnosed with gastric cancer before 25 years of age. *CDH1* mutation carriers, who elect not to undergo prophylactic gastrectomy, should be offered surveillance every 6–12 months by upper endoscopy with multiple random biopsies. Women with *CDH1* mutations are at increased risk for breast cancer and should be followed similar to *BRCA1/BRCA2* mutation carriers as outlined in NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
Lynch syndrome (LS)	*EPCAM, MLH1, MSH2, MSH6, PMS2*	Autosomal dominant	Selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum). Given the lower expected risk of gastric cancer in *MSH6* and *PMS2* mutation carriers, gastric cancer screening recommendations are for *MLH1*, *MSH2*, and *EPCAM* mutation carriers at this time. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.

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Continued

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Surveillance Recommendations (continued)

Syndrome	Gene(s)	Inheritance Pattern	Gastric Surveillance Recommendations
Juvenile polyposis syndrome (JPS)	*SMAD4, BMPR1A*	Autosomal dominant	Consider EGD starting around age 15 years and repeat annually if polyps are found and every 2–3 years if no polyps are found. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.
Peutz-Jeghers syndrome (PJS)	*STK11*	Autosomal dominant	Consider EGD starting in late teens and repeating every 2–3 years. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.
Familial adenomatous polyposis (FAP)/ Attenuated FAP (AFAP)	*APC*	Autosomal dominant	There is no clear evidence to support screening for gastric cancer in FAP/AFAP. However, given the increased risk for duodenal cancer in FAP/AFAP, the stomach should be examined at the same time of duodenoscopy. Non-fundic gland polyps in the stomach should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically, but with high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy. A baseline EGD with side-viewing endoscope is recommended at age 25–30 years and repeated based on duodenal polyp status (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for duodenoscopic findings and interval of duodenoscopy). See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.

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PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

Other hereditary cancer predisposition syndromes listed below may also be associated with an increased risk of developing gastric cancer. However, insufficient evidence exists for gastric cancer surveillance in these syndromes.

Syndrome	Gene(s)	Inheritance Pattern
Ataxia- telangiectasia	*ATM*	Autosomal recessive
Bloom syndrome	*BLM/RECQL3*	Autosomal recessive
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*	Autosomal dominant
Li-Fraumeni syndrome	*TP53*	Autosomal dominant
Xeroderma pigmentosum	7 different genes	Autosomal recessive

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Continued

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER
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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

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

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

[1]Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.
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Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.**
- **Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.[1]**
- **Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are 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.**
- **Perioperative chemotherapy,[2,3] or postoperative chemotherapy plus chemoradiation[4] is the preferred approach for localized gastric cancer.**
- **Postoperative chemotherapy is recommended following primary D2 lymph node dissection.[5,6] (See Principles of Surgery [GAST-C])**
- **In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.**

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[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]Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333. (See GAST-F 6 of 11).

[5]Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15:1389-1396.

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Continued

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PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy
(3 cycles preoperative and 3 cycles postoperative):
- **Fluorouracil and cisplatin (category 1)[1]**
- **Fluoropyrimidine and oxaliplatin***
- **ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[2]**
- **ECF modifications (category 2B)[3,4]**
  - **Epirubicin, oxaliplatin, and fluorouracil**
  - **Epirubicin, cisplatin, and capecitabine**
  - **Epirubicin, oxaliplatin, and capecitabine**

Preoperative Chemoradiation
- **Infusional 5-FU can be replaced with capecitabine**
- **Preferred Regimens:**
  - **Paclitaxel and carboplatin (category 1)[5]**
  - **Fluorouracil and cisplatin (category 1)[6,7]**
  - **Fluorouracil† and oxaliplatin (category 1)[8.9]**
- **Other Regimens:**
  - **Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine)[10] (category 2B)**

Postoperative Chemoradiation
- **Fluoropyrimidine (infusional fluorouracil† or capecitabine) before and after fluoropyrimidine-based chemoradiation[11]**

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection)
(See Principles of Surgery [GAST-C])
- **Capecitabine and oxaliplatin** (category 1)[12]**

*The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
**Cisplatin may not be used interchangeably with oxaliplatin in this setting.
†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion (MS-30).

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

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

- **Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and HER2 Testing [GAST-B])**
  - **Combination with fluoropyrimidine and cisplatin (category 1)[13]**
  - **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:**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[14-17] (category 1)**
  - **Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[15,18,19]**
- **Other Regimens:**
  - **Paclitaxel with cisplatin or carboplatin[20-22]**
  - **Docetaxel with cisplatin[23,24]**
  - **Fluoropyrimidine[16,25,26] (fluorouracil† or capecitabine)**
  - **Docetaxel[27,28]**
  - **Paclitaxel[29,30]**
  - **Fluorouracil†,* and irinotecan[31]**
  - **DCF modifications**
    - ◊ **Docetaxel, cisplatin, and fluorouracil†,[32]**
    - ◊ **Docetaxel, oxaliplatin, and fluorouracil[33]**
    - ◊ **Docetaxel, carboplatin, and fluorouracil (category 2B)[34]**
  - **ECF (epirubicin, cisplatin, and fluorouracil)[35]**
  - **ECF modifications (category 2B)[3,4]**
    - ◊ **Epirubicin, oxaliplatin, and fluorouracil**
    - ◊ **Epirubicin, cisplatin, and capecitabine**
    - ◊ **Epirubicin, oxaliplatin, and capecitabine**

Second-Line Therapy

Dependent on prior therapy and PS:

- **Preferred Regimens:**
  - **Ramucirumab and paclitaxel (category 1)[36]**
  - **Docetaxel (category 1)[27,28]**
  - **Paclitaxel (category 1)[29,30,37]**
  - **Irinotecan (category 1)[37-40]**
  - **Ramucirumab (category 1)[41]**
  - **Fluorouracil†,* and irinotecan[38,42,43] (if not previously used in first-line therapy)**

Other Regimens:

- **Irinotecan and cisplatin[18,44]**
- **Docetaxel and irinotecan[45] (category 2B)**

*Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion (MS-30).

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

PERIOPERATIVE CHEMOTHERAPY

Fluorouracil and cisplatin

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

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[18]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[15]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[19]

ECF (epirubicin, cisplatin, and fluorouracil)

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[2]

ECF modifications

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

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

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively[3,4]

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

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

PREOPERATIVE CHEMORADIATION

PREFERRED REGIMENS

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

Fluorouracil and cisplatin
Cisplatin 75–100 mg/m² IV on Days 1 and 29
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4 and 29–32
35-day cycle[6]

Cisplatin 15 mg/m² IV daily on Days 1–5
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for 2 cycles[7]

Fluorouracil and oxaliplatin
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days for 3 cycles with radiation and 3 cycles after radiation[8]

PREFERRED REGIMENS

Capecitabine and cisplatin
Cisplatin 30 mg/m² IV on Day 1
Capecitabine 800 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[46]

Capecitabine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID on Days 1–5 for 5 weeks[47]

OTHER REGIMENS

Paclitaxel and fluoropyrimidine
Paclitaxel 45–50 mg/m² IV on Day 1 weekly
Fluorouracil 300 mg/m² IV continuous infusion daily on Days 1–5
Weekly for 5 weeks[10]

Paclitaxel 45–50 mg/m² IV on Day 1
Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[10]

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

POSTOPERATIVE CHEMORADIATION

Fluorouracil (bolus) and leucovorin (category 1)[11,48]

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

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

With radiation
Fluorouracil 200–250 mg/m² IV continuous infusion over 24 hours daily on Days 1–5 or 1–7
Weekly for 5 weeks[51]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5 or 1–7
Weekly for 5 weeks[52]

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116[11,48] TRIAL[11,48]FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE ABOVE SPECIFIED DOSES OR SCHEDULE OF CYTOTOXIC AGENTS BECAUSE OF CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

- **1 cycle before and 2 cycles after chemoradiation**
  Capecitabine 750–1000 mg/m² PO BID on Days 1–14
  Cycled every 28 days[49]

- **1 cycle before and 2 cycles after chemoradiation**
  Leucovorin 400 mg/m² IV on Days 1 and 15 OR Days 1, 2, 15, and 16
  Fluorouracil 400 mg/m² IV Push on Days 1 and 15 OR Days 1, 2, 15, and 16
  Fluorouracil 600 mg/m² IV continuous infusion over 22 hours daily on Days 1, 2, 15, and 16
  Cycled every 28 days[50]

POSTOPERATIVE CHEMOTHERAPY

(for patients who have undergone primary D2 lymph node dissection)

Capecitabine and oxaliplatin
Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days for 8 cycles[12]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

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

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then
Trastuzumab 6 mg/kg IV every 21 days[13]
or
Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Fluoropyrimidine and cisplatin

Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days[14]

Cisplatin 50 mg/m² IV daily on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days[15,16]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[17]

PREFERRED REGIMENS—continued

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[18]

Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 mg/m² IV on Day 1
Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1
Cycled every 14 days[15]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[19]

OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135–200 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 2
Cycled every 21 days[20]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[21]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[22]

Docetaxel and cisplatin

Docetaxel 70–85 mg/m² IV on Day 1
Cisplatin 70–75 mg/m² IV on Day 1
Cycled every 21 days[23,24]

Fluoropyrimidine

Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[16]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[25]

Capecitabine 1000–1250 mg/m² PO BID on Days 1–14
Cycled every 21 days[26]

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

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

FIRST-LINE THERAPY—continued

OTHER REGIMENS—continued

Taxane

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[27,28]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[29]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[30]

Fluorouracil and irinotecan

Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days [31]

OTHER REGIMENS—continued

DCF modifications

Docetaxel 40 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV on Day 1
Fluorouracil 1000 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cisplatin 40 mg/m² IV on Day 3
Cycled every 14 days[32]

Docetaxel 50 mg/m² IV on Day 1
Oxaliplatin 85 mg/m² IV on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[33]

Docetaxel 75 mg/m² IV on Day 1
Carboplatin AUC 6 IV on Day 2
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1–3
Cycled every 21 days[34]

OTHER REGIMENS—continued

ECF

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[35]

ECF modifications

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Fluorouracil 200 mg/m² IV continuous infusion over 24 hours daily on Days 1–21
Cycled every 21 days[3,4]

Epirubicin 50 mg/m² IV on Day 1
Cisplatin 60 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[3,4]

Epirubicin 50 mg/m² IV on Day 1
Oxaliplatin 130 mg/m² IV on Day 1
Capecitabine 625 mg/m² PO BID on Days 1–21
Cycled every 21 days[3,4]

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

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

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

SECOND-LINE THERAPY

PREFERRED REGIMENS

Ramucirumab and paclitaxel
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m^2 on Days 1, 8, and 15
Cycled every 28 days[36]

Taxane
Docetaxel 75–100 mg/m^2 IV on Day 1
Cycled every 21 days[27,28]

Paclitaxel 135–250 mg/m^2 IV on Day 1
Cycled every 21 days[29]

Paclitaxel 80 mg/m^2 IV on Day 1 weekly
Cycled every 28 days[30]

Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15
Cycled every 28 days[37]

PREFERRED REGIMENS—continued

Irinotecan
Irinotecan 250–350 mg/m^2 IV on Day 1
Cycled every 21 days[39]

Irinotecan 150–180 mg/m^2 IV on Day 1
Cycled every 14 days[37,38]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[40]

Ramucirumab
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[41]

Fluorouracil and irinotecan
Irinotecan 180 mg/m^2 IV on Day 1
Leucovorin 400 mg/m^2 IV on Day 1
Fluorouracil 400 mg/m^2 IV Push on Day 1
Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[38]

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[18,44]

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[45]

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

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY—REFERENCES

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PRINCIPLES OF RADIATION THERAPY

General Guidelines

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, medical oncologists, radiologists, gastroenterologists, and pathologists.
- CT scans, EUS, endoscopy reports, and PET or PET/CT scans, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders prior to simulation.
- All available information from pre-treatment diagnostic studies should be used to determine the target volume.
- In general, Siewert I and II tumors should be managed with radiation therapy guidelines applicable to esophageal and esophagogastric junction (EGJ) cancers. Depending on the clinical situation, Siewert III tumors may be more appropriately managed with radiation therapy guidelines applicable to either esophageal and EGJ or gastric cancers. These recommendations may be modified depending on the location of the bulk of the tumor.
- Image guidance may be used appropriately to enhance clinical targeting.

Simulation and Treatment Planning

- CT simulation and conformal treatment planning should be used. Intensity-modulated radiation therapy (IMRT) may be used in clinical settings where reduction in dose to organs at risk (eg, heart, lungs, liver, kidneys, small bowel) is required, which cannot be achieved by 3-D techniques.
- The patient should be instructed to avoid intake of a heavy meal for 3 hours before simulation and treatment. When clinically appropriate, IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily setup.
- It is optimal to treat patients in the supine position as the setup is generally more stable and reproducible.
- 4D-CT planning or other motion management may be appropriately utilized in select circumstances where organ motion with respiration may be significant.
- Target volumes need to be carefully defined and encompassed while designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion should be taken into account.

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Continued

PRINCIPLES OF RADIATION THERAPY

Target Volume (General Guidelines)

- **Preoperative**[1]
  - **Pre-treatment diagnostic studies (EUS, EGD, PET, 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. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.**
- **Postoperative**[4]
  - **Pre-treatment diagnostic studies (EUS, EGD, PET, 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] **Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.**

Proximal One-Third/Fundus/Cardia/Esophagogastric Junction Primaries

- **With proximal gastric lesions or lesions at the esophagogastric junction (EGJ), a 3- to 5-cm margin of distal esophagus and nodal areas at risk should be included. Nodal areas at risk include: perigastric, celiac, left gastric artery, splenic artery, splenic hilar, hepatic artery, and porta hepatic lymph nodes.**

Middle One-Third/Body Primaries

- **Nodal areas at risk include: perigastric, celiac, left gastric artery, splenic artery, splenic hilar, hepatic artery, porta hepatic, suprapyloric, subpyloric and pancreaticoduodenal lymph nodes.**

Distal One-Third/Antrum/Pylorus Primaries

- **A 3- to 5-cm margin of duodenum or duodenal stump should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, left gastric artery, celiac, hepatic artery, porta hepatic, suprapyloric, subpyloric and pancreaticoduodenal lymph nodes.**

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Continued

PRINCIPLES OF RADIATION THERAPY

Normal Tissue Tolerance Dose-Limits

- Treatment planning is essential to reduce unnecessary dose to organs at risk.
- It is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.

- Lungs[a]
  - V_{20Gy} ≤ 30%
  - Mean ≤ 20 Gy
- Spinal Cord
  - Max ≤ 45 Gy
- Bowel
  - V_{45Gy} <195 cc
- Heart
  - V_{30Gy} ≤ 30% (closer to 20% preferred)
  - Mean < 30 Gy
- Left Kidney, Right Kidney (evaluate each one separately):
  - V_{20Gy} ≤ 33%
  - Mean <18 Gy
- Liver
  - V_{30Gy} ≤ 33 %
  - Mean < 25 Gy

Dose

- 45–50.4 Gy (1.8 Gy/d)
  - Higher doses may be used for positive surgical margins in selected cases as a boost to that area.

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 interruptions.
- During a radiation treatment course, patients should be seen for a 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/d, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomies (J-tube) or nasogastric feeding tubes may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.
- Adequate enteral and/or IV hydration may be necessary during chemoradiation and early recovery.

[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 Member Institutions and others.

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PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE[a]

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

- Acute 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 Treatment
    - The efficacy of endoscopic therapy for bleeding in patients with gastric cancer is not well studied.[2] The limited data suggest that while endoscopic therapies may initially be effective, the rate of recurrent bleeding is very high.[3]
    - Widely available treatment options include injection therapy, mechanical therapy (eg, endoscopic clips), ablative therapy (eg, argon plasma coagulation), or a combination of methods.
  - Interventional Radiology
    - Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful or bleeding occurs.
  - External beam radiation therapy has been shown to effectively manage acute and chronic gastrointestinal bleeding in multiple small series.[4,5]
- Chronic blood loss from gastric cancer
  - Although proton pump inhibitors can be prescribed to reduce bleeding risk from gastric cancer, there are no definite data supporting its use at this time.
  - External beam radiation therapy may be used for chronic blood loss due to gastric cancer.[4,5]

[a] See NCCN Guidelines for Palliative Care.
[b] See Principles of Systemic Therapy (GAST-F).

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Continued

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE[a]

Obstruction

The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet.

- **Alleviate or bypass obstruction**
  - **Endoscopy**
    - **Placement of enteral stent for relief of outlet obstruction,[6] or esophageal stent for EGJ/gastric cardia obstruction (see NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers)**
  - **Surgery**
    - **Gastrojejunostomy[6]**
    - **Gastrectomy in select patients[7]**
  - **External beam radiation therapy**
  - **Chemotherapy[b]**
- **When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy (if endoscopic lumen enhancement is not undertaken or is unsuccessful).[8]**
  - **Percutaneous, endoscopic, surgical, 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.**
- **In patients who cannot take an oral diet, feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or jejunal feeding tubes for patients with mid and distal gastric obstruction can be placed if tumor location permits.**

Pain

- **External beam radiation therapy**
- **Chemotherapy[b]**
- **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.**

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 obstruction is present.**

[a] See NCCN Guidelines for Palliative Care.
[b] See Principles of Systemic Therapy (GAST-F).

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Continued

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE
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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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/03/16

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

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] The proximal lesser curvature, cardia, and the EGJ are the most common sites of gastric cancer in Western countries.[1] Changes in histology and location of upper GI tract tumors have also been observed in some parts of Europe.[2,3] 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. The incidence of gastric cancer is much higher in China than in any other country. In Japan, it remains the most common type of cancer among men. 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 fifth most frequently diagnosed cancer and the third leading cause of death from cancer worldwide.[4] In 2016, an estimated 26,370 people will be diagnosed and 10,730 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 cancer 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]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Gastric Cancer an electronic search of the PubMed database was performed to obtain key literature in Gastric Cancer published between July 2014 and July 2015 using the following search terms: gastric cancer, gastric adenocarcinoma, stomach cancer, imaging, endoscopic treatment, endoscopic resection, ablation, lymph node dissection, and lymphadenectomy. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer reviewed biomedical literature.[12]

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

The PubMed search resulted in 67 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the

Discussion section. Recommendations for which high level evidence is lacking are based on the panel's review of lower level evidence and expert opinion.

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

Hereditary Cancer Predisposition Syndromes Associated with an Increased Risk for Gastric Cancers

While most gastric cancers are considered sporadic, it is estimated that 5% to 10% have a familial component and 3% to 5% are associated with inherited cancer predisposition syndromes. The most common hereditary cancer predisposition syndromes are discussed below. See Principles of Genetic Risk Assessment for Patients with Gastric Cancers in the guidelines for other less common hereditary cancer predisposition syndromes associated with a risk of developing gastric cancer.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by the development of gastric cancers, predominantly the diffuse type, at a young age.[13,14] Germline truncating mutations in the tumor suppressor gene *CDH1* (encoding the cell to cell adhesion protein E cadherin) are found in 30% to 50% of families with HDGC.[15,16] The average age at diagnosis of gastric cancer is 37 years, and the lifetime risk for the development of gastric cancer by the age of 80 years is estimated at 67% for men and 83% for women.[17] Germline *CDH1* mutations are also associated with an increased risk of developing lobular carcinoma of the breast in women.[18]

The safety and efficacy of endoscopic surveillance for patients with HDGC has not been established. On the contrary, available evidence suggests that endoscopy may not adequately detect the precursor lesions in diffuse gastric cancer.[19-21] Prophylactic gastrectomy (without a D2 lymph node dissection) is recommended between ages 18 and 40 years for asymptomatic carriers of germline truncating *CDH1* mutations.[22,23] Prophylactic gastrectomy prior to 18 years of age is not recommended but may be considered for certain patients, especially those with family members diagnosed with gastric cancer before 25 years of age. A baseline endoscopy with multiple random biopsies is indicated prior to gastrectomy. Upper endoscopy with multiple random biopsies should be considered for *CDH1* mutation carriers who elect not to undergo prophylactic gastrectomy. Women with *CDH1* mutations are at increased risk for breast cancer and should be followed similar to *BRCA1/BRCA2* mutation carriers as outlined in the NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian.

Lynch Syndrome

Lynch syndrome (also referred to as hereditary non polyposis colorectal cancer) is an autosomal dominant syndrome characterized by the early onset of colorectal cancer and endometrial cancer as well as a variety of other cancers including gastric cancer.[24] Lynch syndrome arises from germline mutations in any of the four DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6*, and *PMS2*).[25] Recently, deletions of the epithelial cell adhesion molecule (*EPCAM*) gene have been implicated in Lynch syndrome.[26] Gastric cancer is the second most common extracolonic cancer (after endometrial cancer) in patients with Lynch syndrome, and these patients have a 1% to 13% risk of developing gastric cancer, predominantly the intestinal type, occurring at an earlier age than the general population.[27-30]

Selected individuals or families or those of Asian descent may consider esophagogastroduodenoscopy (EGD) with extended duodenoscopy (to

distal duodenum or into the jejunum).[24] Given the lower expected risk of gastric cancer in *MSH6* and *PMS2* mutation carriers, screening recommendations are recommended only for *MLH1*, *MSH2*, and *EPCAM* mutation carriers at this time. See the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal for additional screening recommendations.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant syndrome characterized by the presence of multiple juvenile polyps along the GI tract and is associated with an increased risk of developing GI cancers.[31] JPS arises from a germline mutation in the *SMAD4* or *BMPR1A* genes.[24] The lifetime risk of developing GI cancers in patients with JPS varies from 9% to 50% and varies with the type of mutation.[32] In patients with gastric polyps, JPS carries a lifetime risk of 21% for developing gastric cancer.[32]

EGD may be considered, beginning in the mid-teens and repeated annually if polyps are found and every 2 to 3 years if no polyps are found.[24] See the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal for additional screening recommendations.

Peutz Jeghers Syndrome

Peutz Jeghers syndrome (PJS) is an autosomal dominant syndrome caused by germline mutations in the *STK11/LKB1* tumor suppressor gene.[33,34] Mutations in the *STK11/LKB1* gene have been identified in 30% to 80% of patients.[35] PJS is characterized by mucocutaneous pigmentation and GI polyposis and is associated with an elevated risk of developing GI cancers.[36-40] Individuals with PJS have a 29% lifetime risk of developing gastric cancer.[24,36]

EGD may be considered, beginning in late teens and repeated every 2 to 3 years based on gastric polyp burden.[24] See the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal for additional screening recommendations.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant colorectal cancer syndrome resulting from the germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21.[41,42] FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Upper GI polyps in the stomach, duodenum, and periampullary region are the most common extracolonic manifestations of FAP.[43] The majority (approximately 90%) of gastric polyps is nonadenomatous benign fundic gland polyps, developing in approximately 50% of patients with FAP, whereas gastric adenomatous polyps represent 10% of gastric polyps and can lead to gastric cancer.[43]

There is no clear evidence to support specific screening recommendations for patents with gastric polyps in the setting of FAP. However, given the increased risk of duodenal cancer in FAP, the stomach should be examined at the same time of duodenoscopy. Adenomatous, non fundic gland polyps in the stomach should be managed endoscopically, if possible.[44] Patients with polyps that cannot be removed endoscopically, but with high-grade dysplasia (HGD) or invasive cancer detected on biopsy should be referred for gastrectomy.[44] A baseline EGD with side viewing endoscope is recommended at age 25 to 30 years and is repeated based on duodenal polyp burden. See the NCCN Guidelines for Genetic/Familial High Risk Assessment: Colorectal for additional screening recommendations.

Staging

Two major classifications are currently being used. The Japanese classification is more elaborate and is based on anatomic involvement, particularly the lymph node stations.[45] 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.[46] 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, which 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 will 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.[47] 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.[48] Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, PET/CT, MRI, and laparoscopic staging.[49-51]

EUS is indicated for assessing the depth of tumor invasion.[52] However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.[53] In a more recent large multiinstitutional study that evaluated the use and accuracy of EUS in patients undergoing curative intent resection for gastric adenocarcinoma, the overall accuracy of EUS was 46.2% for T classification and 66.7% for N classification.[54] Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.[55] EUS may be useful for differentiating T3 and T4 tumors and it should be used in combination with other staging modalities.[53,54] EUS is also helpful to identify T1 tumors for potential endoscopic approaches.

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.[56] 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%).[57] Combined PET/CT imaging, on the other hand, has several potential advantages over PET scan alone.[58] 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.[59,60]

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.[61] 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. Cytology testing of peritoneal fluid can help improve laparoscopic staging through identification of occult carcinomatosis.[49] Positive

peritoneal cytology is associated with a poor prognosis in patients with gastric cancer.[62-64] A positive peritoneal cytology is an independent predictor for identifying patients who are at higher risk for recurrence following curative resection.[62] Clearing of cytology positive disease by chemotherapy is associated with a statistically significant improvement in disease specific survival but cures are rare and the role of surgery is uncertain in patients with positive peritoneal cytology.[63] Therefore, positive peritoneal cytology in the absence of visible peritoneal implants should be considered as M1 disease and surgery as initial treatment is not recommended for patients with positive peritoneal cytology. 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.[61] Laparoscopic staging with peritoneal washings for cytology is indicated for clinical stage higher than T1b. The guidelines have included laparoscopic staging with a category 2B recommendation. The panel recommends laparoscopy to evaluate for peritoneal spread when chemoradiation or surgery is considered. Laparoscopy is not indicated if a palliative resection is planned.

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.[65] 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 ER and surgical resection specimens should also include assessment of lymphovascular invasion (LVI), 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.[66]

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.[67] In another study, Becker et al demonstrated that histopathologic grading of tumor regression correlated with survival in patients treated with neoadjuvant chemotherapy.[68] 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).[69] Tumor size, perineural or LVI, 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,[70] 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 Testing Assessment of Treatment Response in the guidelines.

Assessment of HER2 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.[71] The reported rates of *HER2* amplification and HER2 overexpression in patients with gastric cancer range from 12% to 27% and 9% to 23%, respectively.[72-77] HER2 positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[72,75-77] 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; $P = .001$).[77] In the U.S. 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).[76] In the Trastuzumab for Gastric Cancer (ToGA) trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2–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.[78] 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.[74,75,79,80] 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.[76,77,81] 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 ASCO/College of American Pathologists, uniform intense

membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to two major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many gastric cancer patients who could otherwise be candidates for anti HER2 therapy.[82,83] 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).[84,85]

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.[82] In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[83] This modified HER2 scoring system was also used in the ToGA trial.[84]

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.[82,84] A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in situ hybridization techniques. The panel recommends FISH only for patients with 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 Testing Assessment of Treatment Response in the guidelines.

Surgery

Surgery is the primary treatment for patients with 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 pelvis) 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.[86,87] R1 indicates microscopic residual disease (positive margins) and R2 indicates gross (macroscopic) residual disease in the absence of distant metastasis.[88]

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.[89] 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.[90] T4 tumors require en bloc resection of involved structures. Tis or T1a tumors may be candidates for ER 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.[91] 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.[92,93] 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.[94] 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. Retrospective analyses have shown that more extensive lymph node dissection and analysis of 15 or more lymph nodes influences survival in patients with advanced gastric cancer.[95,96] In the SEER data base analysis that included 1377 patients diagnosed with advanced gastric cancer, patients who had more than 15 N2 nodes and more than 20 N3 nodes examined had the best long term survival outcomes.[95] 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.[97] 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 be the right and left cardiac lymph nodes, 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. However, 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.[66,95,98] 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 over D1 lymph node dissection.[99,100] 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 dissection.[99] 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.[100] 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%).[101] More importantly, gastric cancer related death rate was significantly lower in the D2 group compared to the D1 group (37% and 48%, respectively).[101]

Two other studies from Western countries have also reported better outcomes for D2 lymph node dissection when performed according to the recommendations of the Japanese Research Society for Gastric Cancer.[102,103] In an Austrian study, 5 year and 10 year OS rates were 45.7% and 34.3%, respectively.[102] 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%).[103] 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 there may be a benefit in selected patients if the complication rate after a D2 lymph node dissection could be decreased. 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.[99,100,104,105]

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.[104,105] 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.[105] These rates are comparable with 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 gastric cancer (T2b, T3, or T4) reported a postoperative mortality rate of 0.8% in each arm.[106] The final results of this study showed that D2 lymph node dissection with PAND does not improve survival rate, 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.[107] 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. 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 with PAND in patients with node negative disease needs 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.[108-110]

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).[108] 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.

In a randomized phase II trial of D1 vs. D2 lymph node dissection conducted by the Italian Gastric Cancer Study Group in 267 patients with gastric cancer (133 patients allocated to D1 lymph node dissection and 134 patients allocated to D2 lymph node dissection), the morbidity and postoperative mortality rate were not significantly different between the two groups.[109,110] The overall mortality rate was 12% after D1 lymph node dissection vs. 17.9% after D2 lymph node dissection ($P = .183$).

The corresponding postoperative 30 day mortality rates were 3% and 2.2%, respectively (*P* = .722). At the median follow up of 8.8 years, the 5 year OS rates were 66.5% and 64.2% after D1 and D2 lymph node dissections, respectively (*P* = .695).[110] D2 lymph node dissection was associated with a trend towards improved DSS in patients with advanced gastric cancer (pT2 T4) and positive lymph nodes (59% vs. 38% for D1 lymph node dissection; *P* = .055).[110]

Recent meta-analyses have also confirmed that among patients who underwent D2 lymph node dissections, there was a trend toward improved survival and lower gastric cancer related mortality for patients who did not undergo resection of the spleen or pancreas, as well as for patients with T3 or T4 cancers.[111-113]

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.[95,101,104,105] The panel members also acknowledge that the technical aspects of performing a D2 lymph node dissection require a significant degree of training and expertise. Therefore, the guidelines emphasize that D2 lymph node dissection should be performed by experienced surgeons in high volume centers. Prophylactic pancreatectomy and splenectomy is no longer recommended with D2 lymph node dissection.[91,114] 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.[115-117] 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.[118] 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

Endoscopic mucosal resection (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 stage gastric cancer.

EMR represents a major advance in minimally invasive approaches for the management of patients with early stage gastric cancer.[119] Most of the experience with EMR for early stage gastric cancer has been gained by countries with a high incidence of gastric cancer and an active screening program.[120-124] In a series of 124 patients with mucosal early stage gastric cancers less than 2 cm in size, Uedo et al have reported 5 and 10 year survival rates of 84% and 64%, respectively.[121] In another retrospective study of 215 patients with intramucosal gastric cancer, EMR was also comparable to surgery in terms of risk of death and recurrence, and EMR also had significantly shorter hospital stays.[124] A proper selection of patients is essential to improve the clinical outcomes of EMR; endoscopic gross type (depressed lesion), the degree of differentiation, and the depth of invasion were identified as independent predictors of higher complete resection rates.[122]

ESD has also been reported to be a safe and effective procedure for patients with early stage gastric cancer when performed by experienced endoscopists.[125-132] En bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR.[133-138] In a multicenter retrospective study of ER in patients with early stage 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).[133] 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.[134-136] ESD requires greater skills and instrumentation to perform and is also associated with higher rates of bleeding and perforation complications.[138,139]

No randomized studies have compared EMR and ESD for the treatment of patients with early stage gastric cancers. Nevertheless, ER continues to evolve as a promising technology in the diagnosis and treatment of early stage gastric cancers. ER should be performed in 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.[140] 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 or ESD of focal nodules (2.0 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 LVI, and the depth of infiltration, thereby providing accurate staging of the tumor, with the potential of being therapeutic.[141,142]

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.[143,144] This is especially important in patients who are being considered for ER.[145]

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 is confirmed with the use of fine needle aspiration (FNA) biopsy for cytology assessment.[146] 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 the diagnosis of gastric submucosal tumor and for differentiating potentially malignant lesions.[147]

Treatment

Proper patient selection is essential when employing endoscopic or limited wedge gastric resections. The probability of lymph node metastasis in early stage gastric cancer is influenced by the tumor characteristics and increases with increasing tumor size, submucosal invasion, poorly differentiated tumors, and lymphatic and vascular invasion.[148] EMR or ESD can be considered as an adequate therapy for carcinoma in situ (Tis), well or moderately differentiated lesions (2.0 cm or smaller) confined to mucosa (T1a) without evidence of ulceration, lymph node metastases, or LVI and has clear lateral and deep margins.[149]

The Japanese Gastric Cancer guidelines recommend that EMR should be considered for early stage gastric cancer lesions that are 2.0 cm or smaller in diameter without associated ulcer formation.[150] EMR or ESD of poorly differentiated gastric cancers with evidence of LVI, invasion into the deep submucosa, and positive lateral or deep margins or lymph node metastases should be considered incomplete and additional therapy (gastrectomy with lymph node dissection) should be considered.[151]

Endoscopic ablation can be performed for the short term control of bleeding. Endoscopic insertion of self-expanding metal stents (SEMS) is effective for the 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.[152,153]

Long term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic or radiographic assisted placement of feeding gastrostomy (percutaneous endoscopic gastrostomy) in carefully selected patients when the distal stomach is uninvolved by tumor or the placement of a feeding jejunostomy (percutaneous endoscopic jejunostomy).[154]

Surveillance

EUS performed after chemotherapy or RT has a reduced ability to accurately determine the post treatment stage of disease.[155] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease.[156]

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.[157] 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.[158]

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.[159] 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).[160] 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.[161] However, randomized trials are needed to confirm these results in patients from the Western Hemisphere.

External beam RT (45–50.4 Gy) as a single modality has minimal value in patients with locally unresectable gastric cancer and does not improve survival.[162] 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.[163] Patients receiving combined modality treatment had a significantly better median survival (13 months vs. 6 months) and 5 year OS (12% vs. none). In another study by the Gastrointestinal Tumor Study Group, 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.[164] 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.[162]

Intensity modulated RT (IMRT) has the potential to reduce radiation related toxicity by delivering large doses of RT to target tissues. Several retrospective studies have demonstrated the feasibility of IMRT in the treatment of localized and advanced gastric cancer.[165-169] The impact of IMRT and 3D conformal RT needs to be evaluated in randomized clinical trials.

Principles of Radiation Therapy

General Guidelines

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

The panel recommends involvement of a multidisciplinary team, which should include medical, radiation and surgical oncologists, radiologists, gastroenterologists, and pathologists to determine optimal diagnostic, staging, and treatment modalities. All available information from pretreatment diagnostic studies should be used to determine the target

volume. Image guidance may be used appropriately to enhance clinical targeting.

The panel recommends a dose range of 45 to 50.4 Gy delivered in fractions of 1.8 Gy per day. Higher doses may be used as a boost for positive surgical margins in selected patients.

Simulation and Treatment Planning

It is optimal to treat patients in the supine position as the setup is generally more stable and reproducible. The use of an immobilization device is strongly recommended for reproducibility. The panel encourages the use of CT simulation and 3D treatment planning. 4D CT planning or other motion management may be appropriately utilized in select circumstances where organ motion with respiration may be significant. Intravenous and/or oral contrast may be used when appropriate for CT simulation to aid target localization.

IMRT may be used in clinical settings where reduction in dose to organs at risk is required, which cannot be achieved by 3D techniques.[165-169] Target volumes need to be carefully defined and encompassed while designing IMRT. Uncertainties from variations in stomach filling and respiratory motion should be taken into account.

Target Volume

In the preoperative setting, pretreatment diagnostic studies such as EUS, upper GI endoscopy, PET, and CT scans should be used to identify tumor and pertinent nodal groups. In the postoperative setting, in addition to pretreatment diagnostic studies, clip placement should be used to identify the tumor/gastric bed, the anastomosis or stumps, and pertinent nodal groups. Nodal areas at risk include perigastric, suprapancreatic, celiac, hilar, porta hepatic, and pancreaticoduodenal lymph nodes.

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. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity. 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.

Normal Tissue Tolerance and Dose Limits

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

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.

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

Supportive Care

Careful monitoring and management of acute toxicities with aggressive supportive care is essential to avoid treatment interruptions or dose reductions. Antiemetics should be given for prophylaxis when appropriate. Antacid and antidiarrheal medications may be prescribed when needed. If the caloric intake is inadequate, enteral and/or parenteral nutrition should be considered. Feeding jejunostomies may

be placed if clinically indicated. Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery.

Combined Modality 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.[170] 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).[171]

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.[172] 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.[173-177]

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.[175] In a phase III study, Stahl et al compared preoperative chemotherapy (cisplatin, fluorouracil, and leucovorin) with chemoradiation using the same regimen in 119 patients with locally advanced adenocarcinoma of the EGJ.[176] 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 chemoradiation compared with preoperative chemotherapy for patients with EGJ adenocarcinoma. In another 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.[177] R0 resection was

achieved in 65% of patients. Median survival and the actuarial 2 year survival rate were 14.5 months and 35%, respectively.[177]

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 gastric or EGJ.[178,179] 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.[179] No increases in late toxic effects were noted.

The results of the INT-0116 trial have established postoperative chemoradiation therapy as a standard of care in patients with completely resected gastric or EGJ adenocarcinoma who have not received preoperative therapy.[178,179] 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 have been evaluated by other investigators.[180-182] In a pilot study, postoperative chemoradiation with fluorouracil and cisplatin before and after capecitabine (an orally administered fluoropyrimidine that is converted to fluorouracil intracellularly) and concurrent RT was well tolerated in patients with completely resected stage III IV, M0 gastric cancer.[180] Leong et al reported that postoperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) before and after concurrent chemoradiation with infusional fluorouracil was safe and effective in patients with completely resected gastric adenocarcinoma.[181] 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 fluorouracil and RT did not improve survival compared to the INT-0116 regimen in patients who

have undergone curative resection for gastric or EGJ adenocarcinoma.[182]

Although the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric or EGJ adenocarcinoma, 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.[180,181]

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 lymph node 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).[183,184] 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). After median follow-up duration of 7 years, the estimated 5-year OS rates were 73% and 75%, respectively, for postoperative chemotherapy and chemoradiation (P = .484).[184] 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).[183] However, this study demonstrated that postoperative treatment with capecitabine and cisplatin is feasible following a D2 lymph node dissection. The ongoing ARTIST 2 trial is evaluating postoperative chemotherapy versus chemoradiation in patients with node-positive gastric cancer following D2-lymph node dissection. The CRITICS trial comparing perioperative chemotherapy to preoperative chemotherapy and postoperative chemoradiation in patients who had D1 or greater lymph node dissection has not shown benefit for postoperative chemoradiation, however, the results of this trial are available only as an abstract.[185]

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 = .001), whereas there was no significant difference in recurrence rates between the two groups following D2 lymph node dissection.[186]

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.[187] 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 surgery (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% of patients 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 progression-free survival (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 (2 or 3 preoperative cycles and 3 or 4 postoperative cycles) significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[188] 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 lymph node dissection for total gastrectomy were 27.9% in the perioperative chemotherapy group and 30.3% in the surgery only group.[187] In the FNCLCC/FFCD trial, D2 lymph node dissection was recommended and the surgical procedure was decided by the surgeon according to the tumor site and local practice.[188]

Postoperative Chemotherapy

Postoperative chemotherapy following complete resection has not been associated with a significant survival benefit in patients with gastric cancer.[189-194] 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.[189] 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.[195-198]

The 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.[195]

In this study, 1059 patients were randomized to surgery alone or surgery followed by postoperative chemotherapy with S-1. 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.[196] 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 gastric resection with D2 lymph node dissection in patients with stage II IIIB gastric cancer; at least 15 lymph nodes were removed to ensure adequate disease classification.[197,198] In this study, 1035 patients were randomized to surgery alone or surgery followed by postoperative chemotherapy. 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 ($P < .0001$). After a median follow-up of 62.4 months, the estimated 5-year DFS was 68% for patients randomized to receive postoperative chemotherapy compared to 53% for those randomized to surgery alone; the corresponding estimated 5-year OS rates were 78% and 69%, respectively.[198]

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.[178,179,186]

Chemotherapy for Locally Advanced or Metastatic Disease

Chemotherapy can provide palliation of symptoms, improved survival, and quality of life compared to best supportive care in patients with advanced and metastatic disease.[199,200] Chemotherapy regimens including older agents (etoposide, epirubicin, mitomycin, fluorouracil, and cisplatin)[201-209] as well as newer agents (irinotecan, paclitaxel, docetaxel, and pegylated doxorubicin)[210-221] have demonstrated activity in patients with advanced gastric cancer. Capecitabine-based regimens have also been evaluated in several studies for patients with advanced gastric and EGJ cancers.[222-226]

Various fluorouracil-based combination regimens have been evaluated in randomized studies for the treatment of advanced or metastatic gastric cancer.[203-205,207,208] In the pivotal study performed by the North Central Cancer Treatment Group (NCCTG) that evaluated FAM (fluorouracil, doxorubicin with and mitomycin) vs. fluorouracil and doxorubicin vs. fluorouracil alone, combination chemotherapy was associated with higher response rates than fluorouracil alone, although there were no significant survival difference between all 3 arms.[203] Other randomized studies have demonstrated improvements in median survival and quality of life for epirubicin, cisplatin and fluorouracil (ECF) compared to FAMTX (fluorouracil, doxorubicin, and methotrexate) or MCF (mitomycin, cisplatin, and fluorouracil).[205,208] The combination of fluorouracil, leucovorin, and oxaliplatin (FLO) was evaluated as an alternative to cisplatin and fluorouracil in patients with advanced or metastatic gastric cancer.[227-229] A phase III trial conducted by the German Study Group showed that the combination of FLO had a trend toward improved median PFS compared to fluorouracil, leucovorin, and

cisplatin (FLP) (5.8 vs. 3.9 months).[229] 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 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.[224] Patients with histologically confirmed adenocarcinoma, or squamous cell or undifferentiated carcinoma 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) versus the combination of fluorouracil and cisplatin (FP) as first line treatment in patients with previously untreated advanced gastric cancer.[225] Overall response rate (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.[230]

The combination of docetaxel, cisplatin, and fluorouracil (DCF) has also been evaluated in randomized clinical trials for patients with advanced gastric cancer.[231,232] In the randomized multinational phase III study (V325), 445 untreated patients with advanced gastric cancer were randomized to receive either DCF every 3 weeks or cisplatin and fluorouracil (CF).[231] 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; $P = .02$), at a median follow up of 23.4 months; the confirmed ORR was also significantly higher with DCF than CF (37% and 25%, respectively; $P = .01$).[231] The 2-year survival rates for DCF and CF were 18% and 9%, respectively. 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. However, DCF was associated with increased myelosuppression and infectious complications. In the phase III study (V325), grade 3 adverse events occurred in 69% of patients in the DCF arm versus 59% of patients in the CF arm. The most frequent grade 3 or 4 toxicities reported in both treatment arms (DCF vs. CF) were neutropenia (82%

vs. 57% for CF), stomatitis (21% vs. 27% for CF), diarrhea (19% vs. 8%), and lethargy (19% vs. 14%), and complicated neutropenia was more frequent with DCF than CF (29% vs. 12%).

In recent clinical trials, various modifications of the DCF regimen have demonstrated efficacy and improved safety profile in patients with advanced gastric cancer compared to the DCF regimen evaluated in the phase III study (V325).[233-238] In a randomized phase II trial that evaluated the efficacy and tolerability of docetaxel plus oxaliplatin with or without infusional 5-FU or capecitabine in patients with metastatic or locally recurrent gastric adenocarcinoma (including adenocarcinoma of the EGJ), docetaxel, oxaliplatin, and fluorouracil had a better safety profile and was also associated with higher response rate and longer median PFS and OS (47%, 7.7 months and 14.6 months, respectively) compared to docetaxel and oxaliplatin (23%, 4.5 months and 9 months, respectively) and docetaxel, oxaliplatin, and capecitabine (26%, 5.6 months, and 11.3 months, respectively).[237] The frequency of grade 3 or 4 adverse events was lower among patients treated with docetaxel, oxaliplatin, and fluorouracil (25%) compared to those treated with docetaxel and oxaliplatin (37%) or docetaxel, oxaliplatin, and capecitabine (38%). Febrile neutropenia was reported in only 2% of patients treated with docetaxel, oxaliplatin, and fluorouracil (compared to 14% and 9% for docetaxel/oxaliplatin and docetaxel, oxaliplatin, and capecitabine, respectively), which is also much lower than the 16.4% reported with DCF in the V325 trial. Docetaxel, oxaliplatin, and capecitabine was also effective and well tolerated as first-line treatment in patients with metastatic gastric cancer resulting in an ORR of 52.1% with a PFS and OS of 6.9 months and 12.6 months, respectively.[236] In another recent randomized, multicenter, phase II study, a dose-modified DCF regimen (docetaxel 40 mg/m^2 , cisplatin 40 mg/m^2, and fluorouracil 2,000 mg/m^2) was less toxic than parent DCF (even when the parent regimen was given with growth factors) and is also associated with improved efficacy in previously untreated patients with metastatic gastric or EGJ adenocarcinoma.[238] In this study, 85 evaluable patients were randomized to receive dose-modified DCF (n = 54) or the parent DCF regimen (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and fluorouracil 750 mg/m^2 with growth factor support). The DCF arm (n = 31) closed early because of toxicity (71% grade 3 to 4 toxicity within 3 months and 90% grade 3 to 4 toxicity over the course of treatment). In the dose-modified DCF arm, the grade 3 or 4 toxicity rates were 54% within the first 3 months and 76% over the course of treatment. The 6-month PFS rate was 63% for dose-modified DCF and 53% for DCF. Dose-modified DCF was also associated with improved median OS (18.8 months vs. 12.6 months; *P* = .007).

Due to concerns regarding toxicity, the panel does not recommend the doses or the schedule DCF regimen as used in the phase III trial (V325).[231] Dose-modified DCF or other DCF modifications (docetaxel, oxaliplatin or carboplatin and fluorouracil) are included as alternative options for first-line therapy.[234,237,238]

Irinotecan as a single agent or in combination has been explored extensively in single arm and randomized clinical trials.[239-253] The results of a randomized phase III study comparing irinotecan in combination with fluorouracil and folinic acid (IF) to CF in patients with advanced gastric or EGJ adenocarcinoma (337 patients) showed that IF was non inferior to CF for PFS (the estimated probabilities of PFS at 6 and 9 months were 38% and 20% for IF compared to 31% and 12%, respectively, for CF) but not for OS (9 months vs. 8.7 months for CF) and TTP (5 months vs. 4.2 months for CF; *P* = .018).[248] However, IF was associated with a more favorable toxicity profile. Thus, IF can be an alternative option for patients who are unable to tolerate platinum based chemotherapy. In another randomized, multicenter, phase II study,

Moheler et al compared capecitabine combined with irinotecan or cisplatin in metastatic gastric or EGJ adenocarcinoma.[252] 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. A more recent randomized phase III study (A French Intergroup Study) compared fluorouracil, leucovorin, and irinotecan (FOLFIRI) with ECF as first line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[253] In this study, 416 patients (65% of patients had gastric adenocarcinoma and 33% had EGJ adenocarcinoma) were randomized to receive either FOLFIRI or ECF. After a median follow up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECX (5.1 months vs. 4.2 months; *P* = .008).[253] There were no significant differences in median PFS (5.3 months vs. 5.8 months; *P* = .96), median OS (9.5 months vs. 9.7 months; *P* = .95), or response rate (39.2% vs. 37.8%). FOLFIRI was less toxic and better tolerated than ECF. The NCCN Panel felt that FOLFIRI is an acceptable option for first line therapy for patients with advanced gastric cancer.

Irinotecan (single agent or in combination with other cytotoxic agents) has also been evaluated in the second line setting.[254-259] In a randomized phase III study that compared irinotecan with paclitaxel in patients with advanced gastric cancer (223 patients) after failure of fluoropyrimidine based chemotherapy, OS was not significantly different between the two groups.[257] The median OS was 9.5 months and 8.4 months, respectively, for patients treated with paclitaxel and irinotecan (*P* = .38); the median PFS was 3.6 months and 2.3 months, respectively (*P* = .33). Second line chemotherapy with irinotecan, fluorouracil, and leucovorin was active and well tolerated in patients with metastatic gastric cancer with disease progression on docetaxel based chemotherapy.[258] The ORR was 22.8% and stable disease was recorded in 30% of patients. Median PFS and OS were 3.8 months and 6.2 months, respectively. Irinotecan (studied as a single agent or in combination with other cytotoxic agents in phase II and phase III trials) has not produced high level evidence (category 1) 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.[260] 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.[261-263] 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) or CF. CS and CF resulted in similar median OS (8.6 months and 7.9 months, respectively; *P* = .20), but CS was associated with a significantly improved safety profile.[263,264] Additional studies are needed to confirm the activity of S-1 in the United States and Western Hemisphere. S-1 remains an investigational agent in North America.

Targeted Therapies

Trastuzumab and ramucirumab are the 2 targeted therapies approved for the treatment of advanced or metastatic gastric cancer.[84,265,266] A

variety of investigational agents targeting EGFR, MET/hepatocyte growth factor receptors, and immune check point proteins (such as programmed cell death have shown encouraging results in patients with advanced or metastatic gastric cancer.[267-269] However, definite results of ongoing studies are awaited.

Trastuzumab

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in patients with HER2-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[84] In this trial, 594 patients with HER2-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.[84] 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-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.[84] In the post hoc subgroup analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR = .65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR = 1.07).

Ramucirumab

Ramucirumab, a VEGFR 2 antibody, has shown promising results in the treatment of patients with previously treated advanced or metastatic gastric or EGJ cancers in phase III clinical trials.[265,266] An international, randomized, multicenter, placebo controlled, phase III trial (REGARD trial) demonstrated a survival benefit for ramucirumab for patients with advanced gastric or EGJ adenocarcinoma progressing after first line chemotherapy.[265] In this study, 355 patients were randomized to receive ramucirumab (n = 238; 178 patients with gastric cancer; 60 patients with EGJ adenocarcinoma) or placebo (n = 117; 87 patients with gastric cancer; 30 patients with EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). Ramucirumab was associated with higher rates of hypertension than the placebo group (16% vs. 8%), whereas rates of other adverse events were mostly similar between the two groups. In a more recent international phase III randomized trial (RAINBOW trial) that evaluated paclitaxel with or without ramucirumab in patients with metastatic gastric or EGJ adenocarcinoma progressing on first line chemotherapy, the combination of paclitaxel with ramucirumab resulted in significantly higher OS, PFS, and ORR than paclitaxel alone.[266] In this study 665 patients were randomized to ramucirumab plus paclitaxel (n = 330) and paclitaxel alone (n = 335). The median OS was significantly longer for the ramucirumab plus paclitaxel group compared to paclitaxel alone (9.63 months vs. 7.36 months *P* < .0001). The median PFS was 4.4 months and 2.86 months, respectively, for the two treatment groups. The ORR was 28% for ramucirumab plus paclitaxel compared to 16% for paclitaxel alone (*P* = .0001). Neutropenia and hypertension were more common in the

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

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.[93] 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, and upper GI endoscopy with biopsy of the primary tumor. Biopsy to confirm metastatic disease should be done as clinically indicated and is not mandated in all patients, as long as biopsy of the primary tumor has established a diagnosis. A complete blood count (CBC), comprehensive chemistry profile, and CT scan (with oral and IV contrast) of the chest, abdomen, and pelvis should also be performed. EUS and PET/CT evaluation is recommended, if metastatic cancer is not evident. PET/CT scans are also useful for predicting response to preoperative chemotherapy as well as in the evaluation of recurrent gastric cancer.[270-273] 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.[274] PET is also not sensitive to detect peritoneal disease and does not obviate the need for laparoscopy. Additional studies are needed to assess the efficacy of combined PET/CT scan in gastric cancer. HER2 testing is recommended if metastatic disease is documented or suspected. See the section on Principles of Pathology for assessment of HER2 overexpression.

The guidelines also recommend screening for family history of gastric cancers. Referral to a cancer genetics professional is recommended for an individual who meets one or more of the following criteria: [275]

- A known mutation in a gastric cancer susceptibility gene within the family;
- Gastric cancer in one family member before age 40;
- Gastric cancer in two first- or second-degree relatives with one diagnosis before age 50;
- Gastric cancer in three first- or second-degree relatives independent of age;
- Gastric cancer and breast cancer in one patient with one diagnosis before age 50; and
- Gastric cancer in one patient and breast cancer in one first- or second-degree relative with one diagnosis before age 50.

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

- Localized cancer (cTis or cT1a)
- Locoregional cancer (stages I-III or cM0)
- Metastatic cancer (stage IV or cM1)

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
- Surgically unresectable disease in patients medically able to tolerate major surgery
- Non-surgical candidates

Primary Treatment

Medically Fit Patients

ER (EMR or ESD) or surgery is the primary treatment for patients with cTis or cT1a tumors. Surgery with lymph node dissection is the primary treatment for patients with potentially resectable locoregional tumors (cT1b, cT2 or higher, any N). However, for most patients, surgery alone is not sufficient and adjunctive therapy must be considered. The guidelines have included perioperative chemotherapy (3 cycles of preoperative chemotherapy and 3 cycles of postoperative chemotherapy) as a category 1 recommendation for patients with resectable cT2 or higher, any N tumors.[187,188] This strategy is feasible in the institutions where a multidisciplinary approach is already in place for the treatment of patients with localized gastric cancer.

Based on the results of MAGIC trial and FNCLCC/FFCD trial, ECF, ECF modifications, or cisplatin and fluorouracil are included as options for perioperative chemotherapy.[187,188] In the recently reported OEO5 trial that compared 4 cycles of ECX with 2 cycles of cisplatin and fluorouracil as preoperative chemotherapy in 900 patients with esophageal and EGJ adenocarcinoma, there was a trend towards prolonged PFS and DFS with ECX, but this did not translate into an OS benefit.[276] Furthermore, 4 cycles of ECX was also associated with higher toxicity than 2 cycles of CF. However, the majority of the panel members felt that results of the OEO5 trial may not be extrapolated to gastric cancer. In addition, since the inclusion of ECF or its modifications as options for perioperative chemotherapy is based on the results of a well powered phase III trial, the majority of the panel members agreed that these regimens should be included as an option in the guidelines. However, given the unfavorable toxicity profile associated with epirubicin-based chemotherapy, the panel recommends that cisplatin and fluorouracil should be the preferred option for perioperative chemotherapy.

Although preoperative chemoradiation was associated with a survival advantage in two prospective randomized studies, both of these studies were limited by small sample size.[175,176] 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 cT2 or higher, any N tumors.

Concurrent fluoropyrimidine- or taxane-based chemoradiation (category 1) or chemotherapy is recommended for patients with surgically unresectable locoregional cancer after laparoscopic staging.[163,277]

All patients diagnosed with metastatic disease (cM1) after laparoscopic staging should be treated with palliative therapy (systemic therapy, best supportive care, or clinical trial). Systemic therapy 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.

Non-surgical Candidates

ER (EMR or ESD) is recommended for patients with cTis or cT1a tumors. Concurrent fluoropyrimidine- or taxane-based chemoradiation (category 1) or palliative therapy (systemic therapy, best supportive care, or clinical trial) is recommended for patients with cT1b, cT2 or higher, any N tumors.

All patients diagnosed with metastatic disease after laparoscopic staging should be treated with palliative therapy (systemic therapy, best supportive care, or clinical trial).

Posttreatment Assessment and Adjunctive Treatment

Medically fit patients with unresectable disease as well as non-surgical candidates should undergo restaging (including CBC and comprehensive chemistry profile, radiologic imaging, or upper GI endoscopy as clinically indicated) 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 cancer remains unresectable and there is evidence of distant metastatic disease, patients may be offered palliative therapy (systemic therapy, 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.[178,179,183,184]

In patients who have received preoperative therapy, the first results of the ongoing phase III trial (CRITICS study) showed no significant differences in the OS between postoperative chemotherapy and chemoradiation.[185] In this study, 788 patients with stage IB-IVA resectable gastric cancer were randomized to receive either 3 cycles of postoperative chemotherapy (epirubicin, cisplatin or oxaliplatin and capecitabine) or chemoradiation with cisplatin and capecitabine, after adequate surgery (with D1 or greater lymph node dissection). Preoperative chemotherapy (3 cycles of epirubicin, cisplatin or oxaliplatin and capecitabine) were administered for all patients. After a median follow-up of 4.2 years, the 5-year OS rates were 41.3% and 40.9%, respectively (P = .99). The tolerance and rate of completion of postoperative therapy was poor in both treatment arms.

The guidelines recommend postoperative treatment based on pathologic tumor stage, nodal status, surgical margins, and the extent of lymph node dissection.

For Patients Who Have Not Received Preoperative Therapy

No further treatment is necessary for patients with pTis and pT1, 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 fluoropyrimidine-based chemotherapy before and after fluoropyrimidine-based chemoradiation as postoperative treatment for all patients with pT3-T4 tumors and node positive pT1-T2 tumors.[178,179] 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 pT2, 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 pT2, N0 tumors. Postoperative chemoradiation is recommended only for selected patients with pT2, N0 tumors with high risk features (poorly differentiat ed or higher grade cancer, LVI, neural invasion, age younger than 50 years, or patients who did not undergo D2 lymph node dissection) if there is no residual disease at surgical margins (R0 resection).[278]

The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation for patients with completely resected gastric cancer.[178,179] 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.

The panel has included postoperative chemotherapy as an option for patients with pT3-T4 and node positive pT1-T2 tumors following R0 resection and a modified D2 lymph node dissection, based on the results of the CLASSIC trial.[197,198] Postoperative chemotherapy is not recommended for patients with pT3-T4 and node positive pT1-T2 tumors 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.[183,184,186]

For Patients Who Have Received Preoperative Therapy

Postoperative chemotherapy (ECF, ECF modifications, or cisplatin and fluorouracil) is recommended, if given preoperatively for all patients with T2 or higher any N tumors.[187,188] Alternatively, patients with T2, N0 tumors can be observed. Given the unfavorable toxicity profile associated with epirubicin-based chemotherapy, the guidelines recommend that cisplatin and fluorouracil should be the preferred option for perioperative chemotherapy.

Postoperative Chemoradiation Following R1 or R2 Resections

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 surgery alone.[186] 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. Palliative therapy (systemic therapy, best supportive care, or clinical trial) may be offered for patients with macroscopic residual disease, depending on their performance status.

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 to 12 months for 3 to 5 years, and annually thereafter. CBC, chemistry profile, radiologic imaging, or upper GI endoscopy should be done if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B12 and iron deficiency.

Unresectable Locally Advanced, Recurrent or Metastatic Disease

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

The survival benefit of second line chemotherapy compared to best supportive care for patients with metastatic or advanced gastric cancer has been demonstrated in randomized controlled studies.[279-282]

In a randomized comparison between chemotherapy and best supportive care versus best supportive care alone, OS (8 months vs. 5 months, though not statistically significant) and TTP (5 months vs. 2 months) were longer in patients receiving chemotherapy for advanced gastric cancer.[279] 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 alone (20%).

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).[280] 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 care in patients with advanced gastric cancer.[281] However, both studies have limitations and larger studies are now underway.

In a recent open label multicenter, phase III, randomized trial, the addition of docetaxel to active symptom control was associated with a survival benefit for patients with advanced, histologically confirmed adenocarcinoma of the esophagus, EGJ junction, or stomach that had progressed on or within 6 months of treatment with platinum fluoropyrimidine–based combination chemotherapy.[282] In this study, patients (n = 168) with an ECOG PS score of 0 to 2 were randomly assigned to receive docetaxel plus active symptom control or active symptom control alone. After a median follow up of 12 months, the median OS was 5.2 months for patients with docetaxel group compared to 3.6 months for those in the active symptom control group (P = .01). Docetaxel was associated with higher incidence of grade 3/4 neutropenia, infection, and febrile neutropenia. However, disease specific, health related quality-of-life measures also showed benefits for docetaxel in reducing dysphagia and abdominal pain.

First line therapy with two drug chemotherapy regimens is preferred for patients with unresectable locally advanced, recurrent or metastatic disease. Three drug regimens should be reserved for medically fit patients with good performance status and access to frequent toxicity evaluation. Based on the results of the ToGA trial, the guidelines recommend the addition of trastuzumab to first-line chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients with HER2-positive metastatic gastric cancer (a tumor score of IHC 3+ and IHC 2+ with the evidence of HER2 amplification by FISH [HER2:CEP17 ratio ≥2]).[84] 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.

The selection of a second line therapy regimen for patients with unresectable locally advanced, recurrent or metastatic gastric cancer is dependent on prior therapy and performance status. Based on the recent FDA approvals, the guidelines have included ramucirumab, single agent or in combination with paclitaxel (category 1) as options for second line therapy.[265,266] Irinotecan and docetaxel are also included as options for second line therapy.[257,280,282]

Best supportive care is always indicated for patients with unresectable locally advanced, recurrent or metastatic 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 commonly used to assess the performance status in patients with cancer.[283-285] ECOG PS is a 5 point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher scores 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 KPS score of less than 60 or an ECOG performance score of 3 or more should be offered best supportive care only. Best supportive care with or without systemic therapy, or a clinical trial is recommended for patients with better performance status (KPS score of 60 or more or an ECOG PS score of 2 or less). See the Principles of Systemic Therapy section of the guidelines for a list of specific regimens. Some of the systemic therapy regimens and dosing schedules included in the guidelines are based on extrapolations from published studies and institutional preferences that have support only from phase II studies.

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A levoleucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin in all patients, since lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[286-288] Finally, if none of the above options is 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

Acute bleeding is common in patients with gastric cancer and may be secondary to tumor or tumor related phenomenon, or as a consequence of therapy.[289] A multidisciplinary approach is required for the proper diagnosis and management of GI bleeding in patients with cancer. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment. The efficacy of endoscopic therapy for bleeding in patients with gastric cancer is not well studied.[290] Limited available data suggest that while endoscopic therapies may be as effective as initial treatment, the rate of recurrent bleeding is very high.[291] Widely available options for endoscopic therapies include injection therapy, mechanical therapy (eg, endoscopic clip placement), ablative therapy (eg, argon plasma coagulation), or a combination of different modalities.[290] Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful. External beam RT and/or endoscopic treatment has been shown to effectively

manage acute and chronic blood loss due to patients experiencing GI bleeding.[292,293] Proton pump inhibitors can be prescribed to reduce the risk of bleeding from gastric cancer; however, there are no definite data supporting their use at this time.

Obstruction

The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet. Surgery (gastrojejunostomy or gastrectomy in selected patients), external beam RT, chemotherapy, and placement of enteral stent for relief of gastric outlet obstruction, or esophageal stent for EGJ/cardia obstruction are used to alleviate or bypass obstruction. Management of malignant gastric outlet obstruction should be individualized and treatment options should be selected as clinically appropriate. A multimodality interdisciplinary approach is strongly encouraged.

Endoscopic placement of SEMS is a safe and effective, minimally invasive palliative treatment for patients with luminal obstruction due to advanced gastric cancer.[294-297] In a systematic review, patients treated with endoscopic placement of stents were more likely to tolerate oral intake and they also had shorter hospital stays than patients treated with gastrojejunostomy.[298] 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.[94] A recent randomized trial also reported similar findings.[299] However, these results need to be confirmed in a larger cohort of patients. Percutaneous decompressive gastrostomy either by endoscopic or radiologic gastrostomy has also been associated with palliative benefit for patients with gastric outlet obstruction.[300,301]

When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy.[302] 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.[303,304] Feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or a jejunal feeding tube for patients with mild and distal gastric obstruction may be necessary to provide adequate hydration and nutritional support for patients who cannot tolerate an oral diet. 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. Diffuse histology is 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. Referral to cancer genetics professional is recommended for an individual with a genetic predisposition. Multidisciplinary team management is essential for the management of patients with gastric cancer.

ER (EMR or ESD) is the primary treatment option for patients with Tis or T1a tumors. Surgery with lymph node dissection is the primary treatment option for medically fit patients with resectable T1b, T2 or higher, any N tumors. 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 and node-positive T1-T2 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 (systemic therapy, best supportive care, or clinical trial).

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

The NCCN Guidelines for Gastric Cancer provide an evidence and consensus based treatment approach for the management of patients with gastric cancer. The panel encourages patients with gastric cancer to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

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