National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Gastric Cancer

## NCCN Evidence Blocks™

Version 1.2019 — April 16, 2019

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**Clinical Trials:** NCCN believes that the best management for any patient with cancer 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/clinicians.aspx.

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

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference

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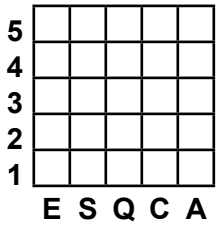
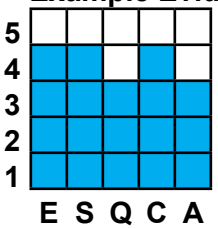
## NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS




**E = Efficacy of Regimen/Agent**
**S = Safety of Regimen/Agent**
**Q = Quality of Evidence**
**C = Consistency of Evidence**
**A = Affordability of Regimen/Agent**

**Example Evidence Block**




**E = 4**
**S = 4**
**Q = 3**
**C = 4**
**A = 3**

### Efficacy of Regimen/Agent

| | |
|---|---|
| **5** | **Highly effective:** Cure likely and often provides long-term survival advantage |
| **4** | **Very effective:** Cure unlikely but sometimes provides long-term survival advantage |
| **3** | **Moderately effective:** Modest impact on survival, but often provides control of disease |
| **2** | **Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease |
| **1** | **Palliative:** Provides symptomatic benefit only |

### Safety of Regimen/Agent

| | |
|---|---|
| **5** | **Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs) |
| **4** | **Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs |
| **3** | **Mildly toxic:** Mild toxicity that interferes with ADLs |
| **2** | **Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent |
| **1** | **Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe |

**Note: For significant chronic or long-term toxicities, score decreased by 1**

### Quality of Evidence

| | |
|---|---|
| **5** | **High quality:** Multiple well-designed randomized trials and/or meta-analyses |
| **4** | **Good quality:** One or more well-designed randomized trials |
| **3** | **Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) |
| **2** | **Low quality:** Case reports or extensive clinical experience |
| **1** | **Poor quality:** Little or no evidence |

### Consistency of Evidence

| | |
|---|---|
| **5** | **Highly consistent:** Multiple trials with similar outcomes |
| **4** | **Mainly consistent:** Multiple trials with some variability in outcome |
| **3** | **May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome |
| **2** | **Inconsistent:** Meaningful differences in direction of outcome between quality trials |
| **1** | **Anecdotal evidence only:** Evidence in humans based upon anecdotal experience |

### Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

| | |
|---|---|
| **5** | **Very inexpensive** |
| **4** | **Inexpensive** |
| **3** | **Moderately expensive** |
| **2** | **Expensive** |
| **1** | **Very expensive** |

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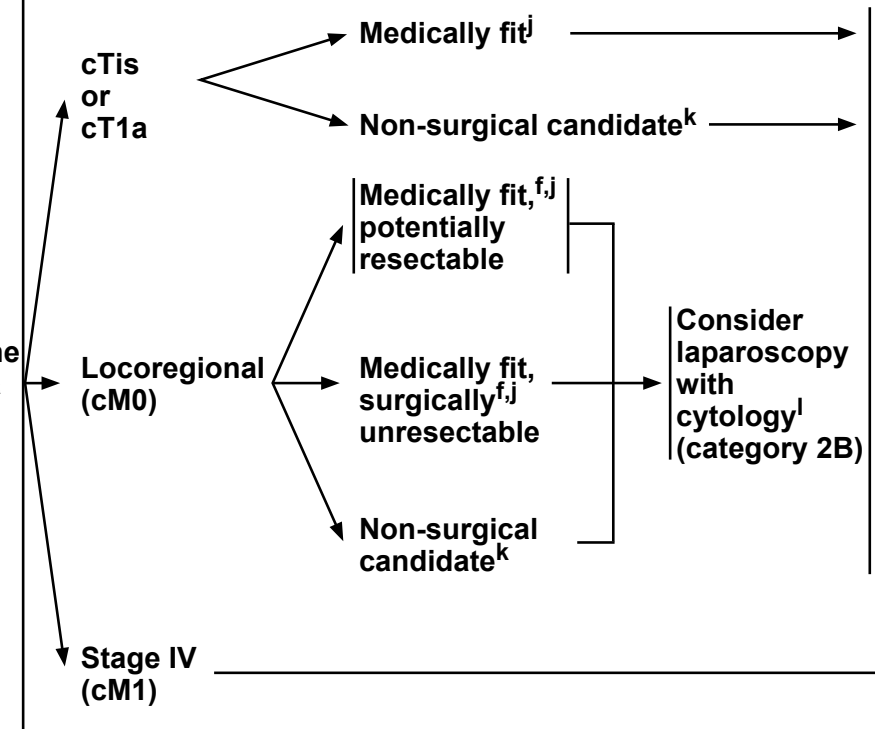
**WORKUP**

- H&P
- Upper GI endoscopy and biopsy[a]
- Chest/abdomen/pelvic CT with oral and IV contrast
- FDG-PET/CT evaluation (skull base to mid-thigh) if no evidence of M1 disease[b] and if clinically indicated
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS) if early stage disease suspected or if early versus locally advanced disease needs to be determined (preferred)
- Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b)[c]
- Biopsy of metastatic disease as clinically indicated
- MSI-H/dMMR testing if metastatic disease is documented/suspected[d]
- HER2 and PD-L1 testing if metastatic adenocarcinoma is documented/ suspected[d,e]
- Assess Siewert category[f]
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated[g]
- Screen for family history[h]

**CLINICAL STAGE[i]**




**ADDITIONAL EVALUATION**

Multidisciplinary review preferred[m] → See GAST-2

Palliative Management (see GAST-9)

[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 Biomarker Testing (GAST-B).
[e] Tumor Epstein-Barr virus status is emerging as a potential biomarker for personalized treatment strategies for gastric cancer, but is 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).

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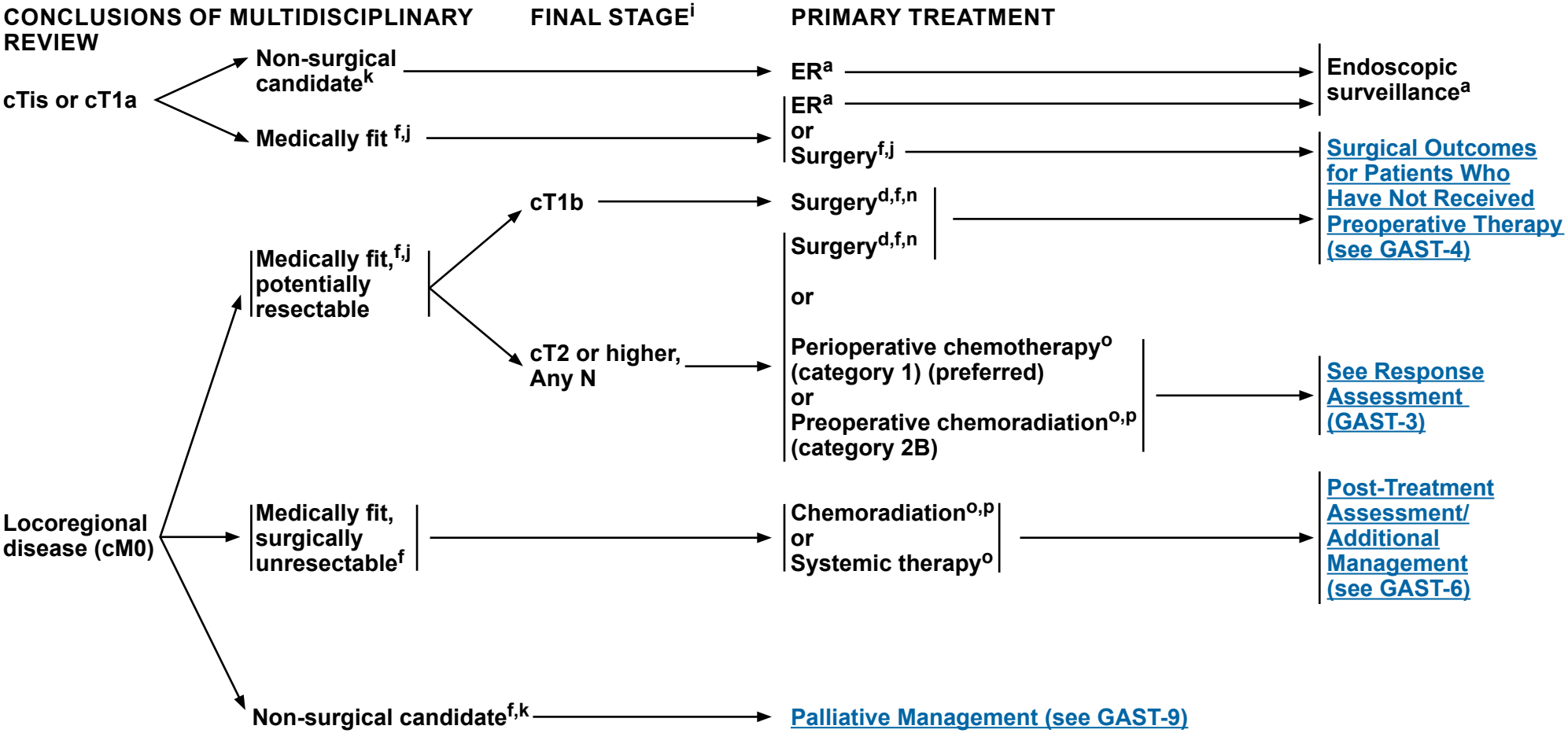


[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[j] Medically able to tolerate major surgery.
[k] Medically unable to tolerate 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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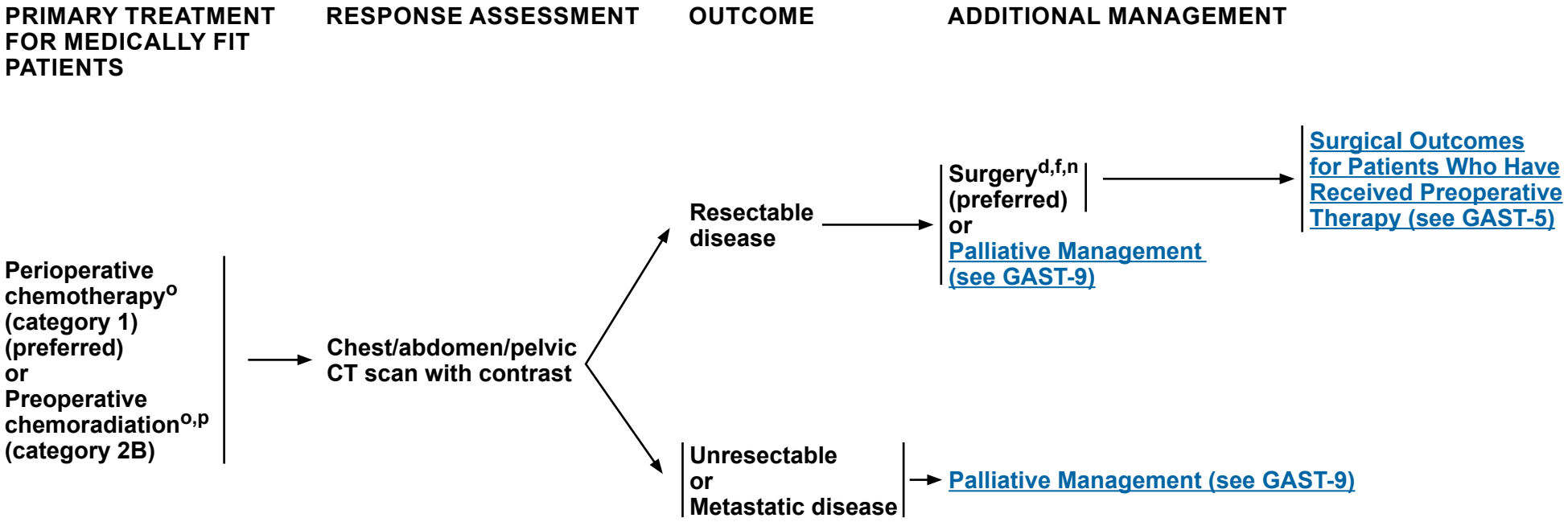


[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[n] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).

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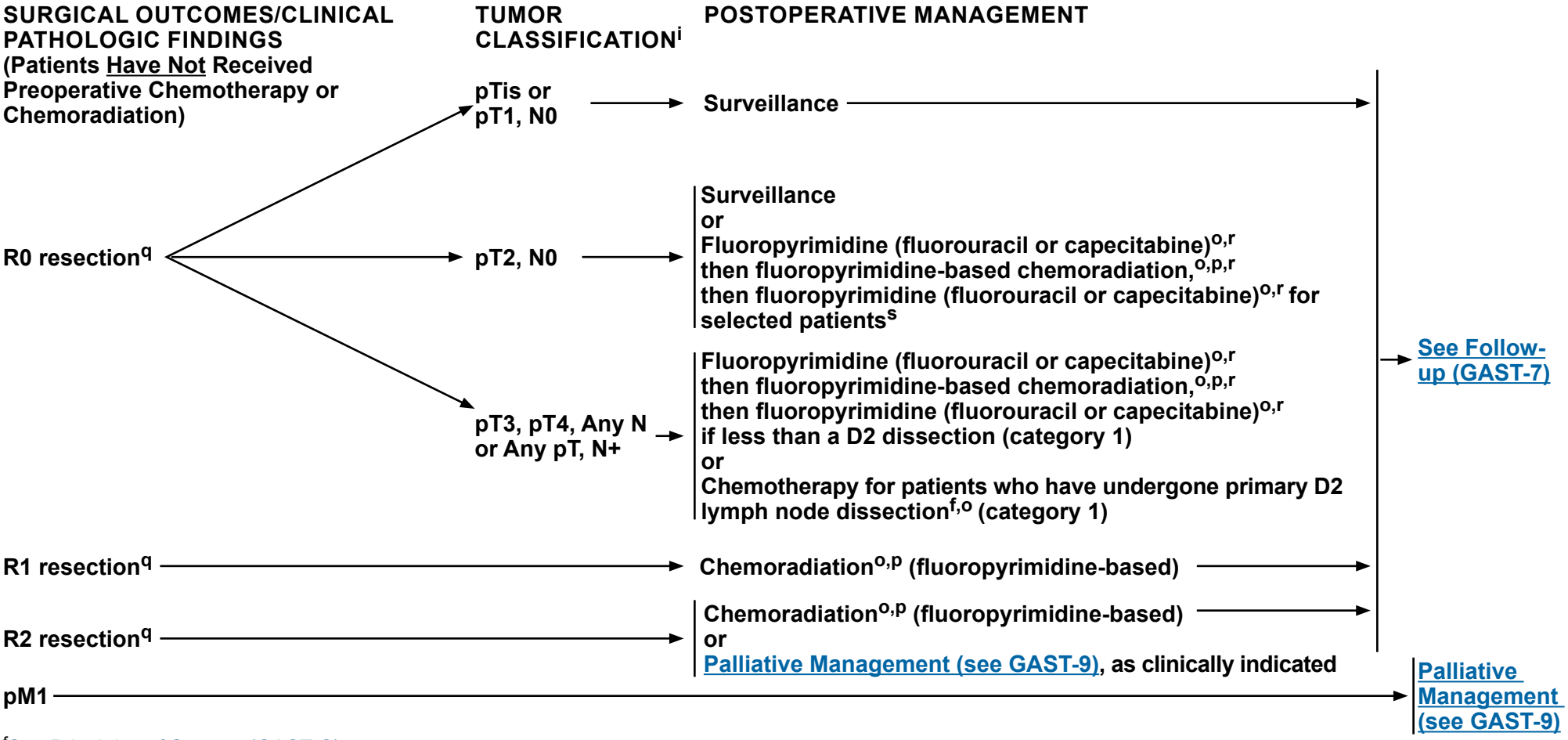


[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[q] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[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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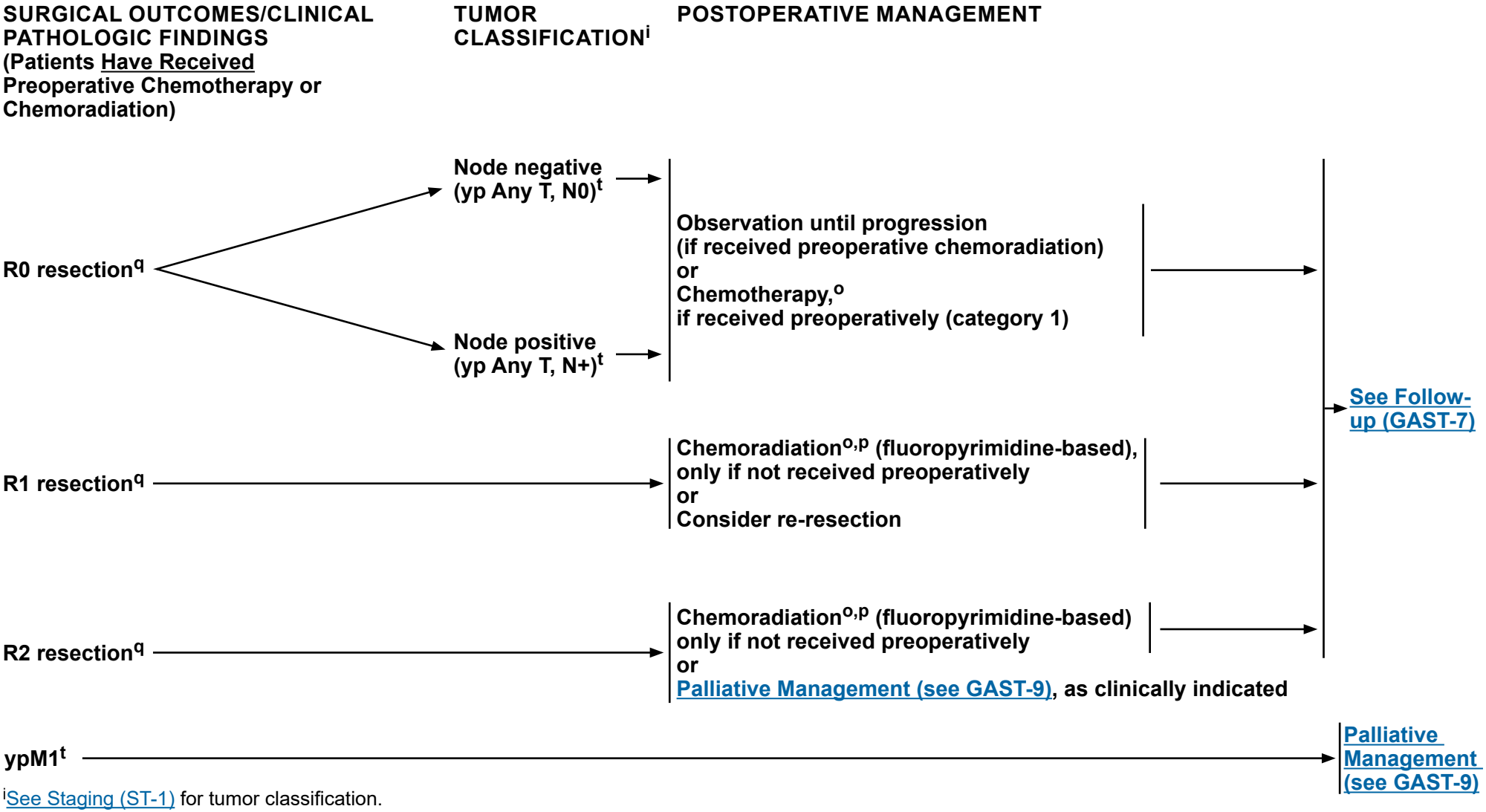


[i] See Staging (ST-1) for tumor classification.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[q] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[t] The yp prefix is used to indicate cases in which staging is performed following preoperative therapy.

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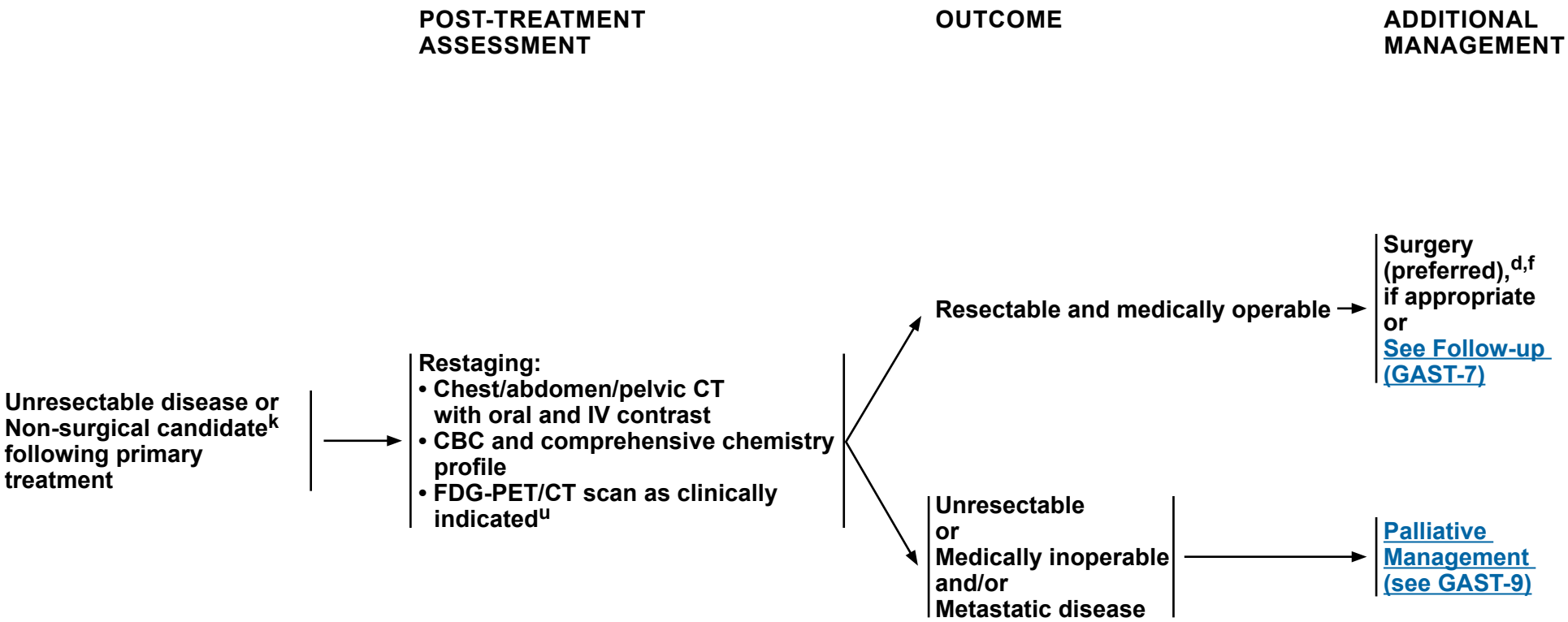


[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[k] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[u] In cases of renal insufficiency or allergy to CT contrast.

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### FOLLOW-UP/SURVEILLANCE[w]

**Tis (successfully treated by ER)[v]** →
- H&P every 3–6 mo for 1–2 y, every 6–12 mo for 3–5 y, and annually thereafter
- CBC and chemistry profile as clinically indicated
- Upper GI endoscopy (EGD) every 6 mo for 1 y, then annually for 3 y
- Routine imaging (CT chest/abdomen/pelvis with oral and IV contrast) as clinically indicated based on symptoms and concern for recurrence

**p stage I (T1a, T1b, N0-1 treated by surgical resection or T1a treated by ER)[v]** →
- H&P every 3–6 mo for 1–2 y, every 6–12 mo for 3–5 y, and annually thereafter
- CBC and chemistry profile as clinically indicated
- For patients treated by ER, EGD every 6 mo for 1 y, then annually for up to 5 years
  - Thereafter, as needed based on symptoms and/or radiographic findings
- For patients treated by surgical resection, EGD as clinically indicated
- CT chest/abdomen/pelvis with oral and IV contrast as clinically indicated[x]
- Monitor for nutritional deficiency (eg, $B_{12}$ and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated

**p stage II/III or yp stage I-III (treated with neoadjuvant ± adjuvant therapy)[v]** →
- H&P every 3–6 mo for 1–2 y, every 6–12 mo for 3–5 y, and annually thereafter
- CBC and chemistry profile as clinically indicated
- For patients who had partial or subtotal gastrectomy, EGD as clinically indicated
- CT chest/abdomen/pelvis with oral and IV contrast (preferred) every 6–12 months for first 2 years, then annually up to 5 years[x] and/or can consider FDG-PET/CT as clinically indicated
- Monitor for nutritional deficiency (eg, $B_{12}$ and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated

→ **Recurrence** (See GAST-8) **or Survivorship[y]**

[v]For patients undergoing total gastrectomy for curative intent, surveillance should follow these recommendations except for endoscopy. Endoscopy has no role in routine surveillance for total gastrectomy unless patients are symptomatic.
[w]See Principles of Surveillance (GAST-H).
[x]After 5 years, additional follow-up may be considered based on risk factors and comorbidities.
[y]See Principles of Survivorship (GAST-I).

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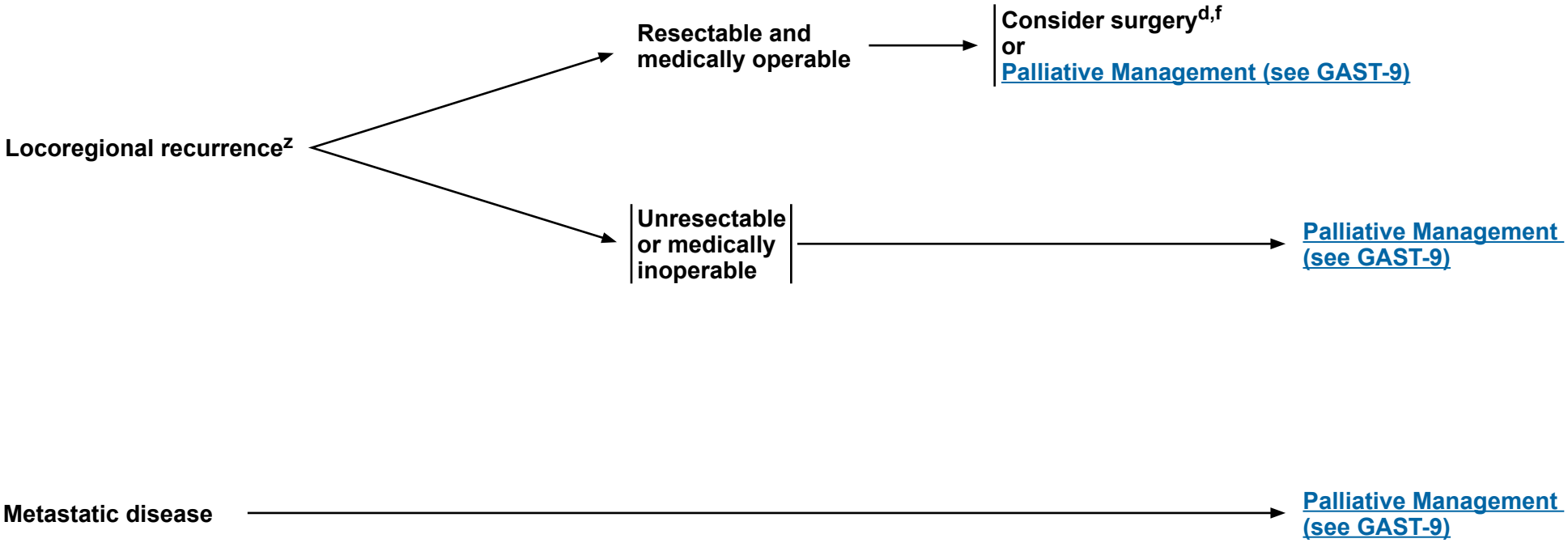
**RECURRENCE**




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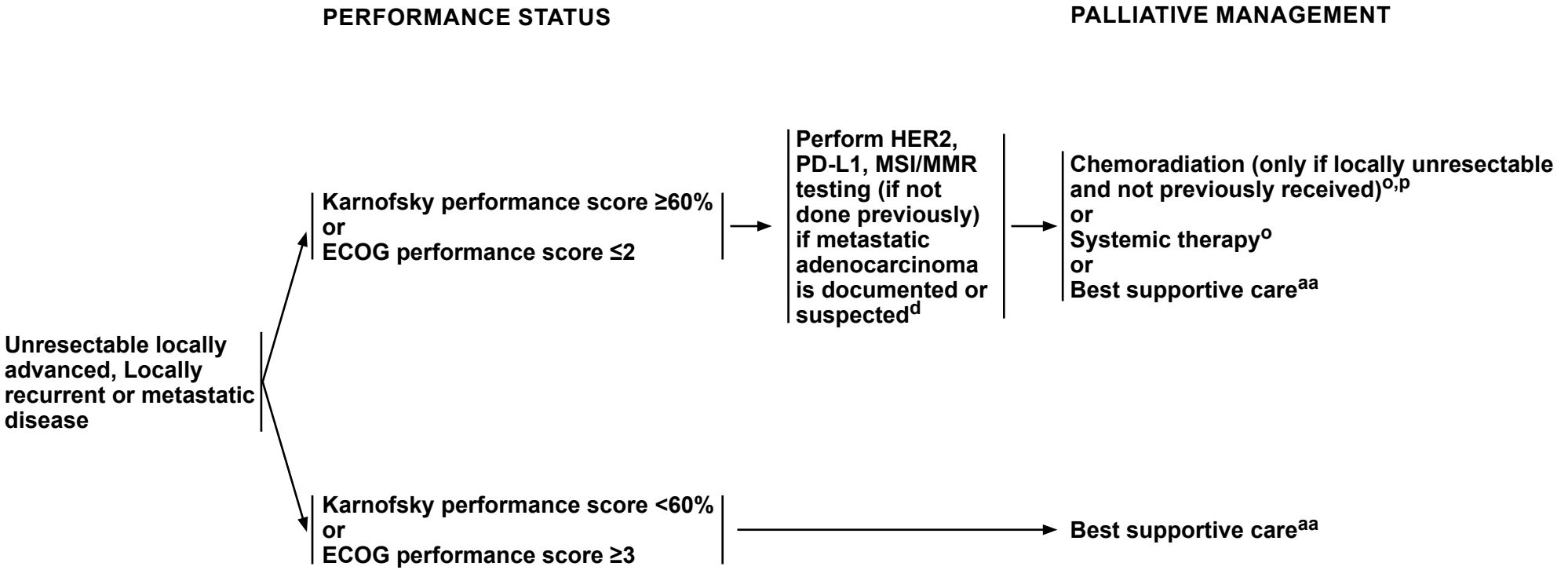


[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[o] See Principles of Systemic Therapy (GAST-F).
[aa] See Principles of Palliative Care/Best Supportive Care (GAST-J).

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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 adequately 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.**

**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 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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References

### 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, 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-J]).[13,14]
- Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic- or radiographic-assisted placement of a feeding gastrostomy tube in carefully selected cases where the distal stomach is uninvolved by tumor, or the placement of a feeding jejunostomy tube.[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 detecting recurrent disease.[16] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

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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.
[2]Graham DY Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. Gastroenterology 1982;82:228-231.
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### PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

**Pathologic Review**
**Table 1**

| Specimen Type | Analysis/Interpretation/Reporting[a] |
|---|---|
| **Biopsy** | **Include in pathology report:**<br>**• Invasion, if present**<br>**• Histologic type[b]**<br>**• Grade** |
| **Endoscopic mucosal resection** | **Include in pathology report:**<br>**• Invasion, if present**<br>**• Histologic type[b]**<br>**• Grade**<br>**• Depth of tumor invasion**<br>**• Vascular/lymphatic invasion**<br>**• Status of mucosal and deep margins** |
| **Gastrectomy, without prior chemoradiation** | **For pathology report, include all elements as for endoscopic mucosal resection plus**<br>**• Location of tumor midpoint in relationship to EGJ[c]**<br>**• Whether tumor crosses EGJ**<br>**• 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**<br><br>**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]Midpoint of tumors arising in the proximal 2 cm of the stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas, while those with the epicenter located greater than 2 cm into the proximal stomach are staged as gastric carcinomas.[2]

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### PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

**Assessment of Treatment Response**

**Response of the primary tumor and lymph node metastases to previous chemotherapy and/or radiation therapy should be reported. Although scoring systems for tumor response in gastric cancer have not been uniformly adopted, in general, 3-category systems provide good reproducibility among pathologists. The following system developed for rectal cancer 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 viable cancer cells, including lymph nodes |
| 1 (Near complete response) | Single cells or rare small groups of cancer cells |
| 2 (Partial response) | Residual cancer cells with evident tumor regression but more than single cells or rare small groups of cancer cells |
| 3 (Poor or no response) | Extensive residual cancer with no evident tumor regression |

**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 Shi C, Berlin J, Branton PA, et al. Protocol for the examination of specimens from patients with carcinoma of the stomach. In: Cancer Protocol Templates. Northfield, IL: College of American Pathologists; 2017. (available at http://www.cap.org).

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### PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

**Assessment of Overexpression or Amplification of HER2 in Gastric Cancer**

**For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach 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]**

**Table 3: Immunohistochemical Criteria for Scoring HER2 Expression in Gastric Cancer[#,*]**

| | 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 | Cluster of five or more cancer cells 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 | Cluster of five or more cancer cells 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 HER2 immunohistochemistry (IHC) be ordered/performed first, followed by in situ hybridization methods in cases showing 2+ (equivocal) expression by IHC. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. Cases with HER2:CEP17 ratio ≥2 or an average HER2 copy number ≥6.0 signals/cell are considered positive by ISH/FISH.**

*Reprinted and adapted from Bartley AN, Washington MK, Colasacco C, 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. J Clin Oncol. 2017;35:446-464 with permission from the American Society of Clinical Oncology.

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### PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

**Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing[d]**

- **MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic gastric carcinoma,[7] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.**

**PD-L1 Testing**

- **PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric carcinomas in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on FFPE tissue is available as an aid in identifying gastric and gastroesophageal junction adenocarcinoma patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.**
- **Assessment of PD-L1 Protein Expression in Gastric Cancers**
  - **This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in FFPE tissues from gastric adenocarcinoma. A specimen is considered to have PD-L1 expression if the Combined Positive Score (CPS) ≥1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.**

**Next Generation Sequencing (NGS):**

- **At present, three targeted therapeutic agents, trastuzumab, ramucirumab, and pembrolizumab have been approved by the FDA for use in gastric cancer. Trastuzumab is based on testing for HER2 positivity. Pembrolizumab is based on microsatellite instability and PD-L1 expression by combined positive score (CPS). Although an enhanced understanding of genomics/epigenomics of gastric cancer is needed, there is insufficient data to support the use of NGS at the time of initial diagnosis for clinical decision making. However, NGS-profiling can be used for the identification of treatment and/or clinical trial enrollment. NGS may be useful in patients with advanced cancer in later stages of therapy rather than in the early phases of disease.**

[d]IHC for MMR and polymerase chain reaction (PCR) for MSI are different assays measuring the same biological effect.

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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 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.

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### PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

**Criteria for Further Risk Evaluation for High-Risk Syndromes:**[1-6]

- **Referral to a cancer genetics professional is recommended for an individual with one or more of the following:**
  - **An individual affected with gastric cancer before age 40**
  - **An individual affected with gastric cancer before age 50 who had one first- or second-degree relative affected with gastric cancer**
  - **An individual affected with gastric cancer at any age who has 2 or more first- or second-degree relatives affected with gastric cancer**
  - **An individual affected with gastric cancer and breast cancer with one diagnosis before age 50**
  - **An individual affected with gastric cancer at any age and a family history of breast cancer in a first- or second-degree relative diagnosed before age 50**
  - **An individual affected with gastric cancer at any age and a family history of juvenile polyps or gastrointestinal polyposis**
  - **An individual affected with gastric cancer at any age and a family history of cancers associated with Lynch syndrome (colorectal, endometrial, small bowel, or urinary tract cancer)**

**OR a family history of:**

- **Known mutation in a gastric cancer susceptibility gene in a close relative**
- **Gastric cancer in one first- or second-degree relative who was diagnosed before age 40,**
- **Gastric cancer in 2 first- or second-degree relatives with one diagnosis before age 50,**
- **Gastric cancer in 3 first- or second-degree relatives independent of age, or**
- **Gastric cancer and breast cancer in one patient with one diagnosis before age 50, juvenile polyps, or gastrointestinal polyposis in a close relative**

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## PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

**Risk Assessment/Genetic Counseling**[1-6]

- **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. Genetic counseling/patient education is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited 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**

- **The most efficient strategy to identify a causative gene mutation in a family is to test a close relative with cancer. If the relative is either unwilling or unavailable for testing, then consider testing of an unaffected relative. A detailed discussion of genetic counseling and testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.**
- **A close relative is defined as a first-, second-, or third-degree relative. First-degree relatives include parents, siblings, and offspring. Second-degree relatives include grandparents, aunts, and uncles. Third-degree relatives include cousins and great grandparents.**

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## 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.[7,8] Truncating mutations in *CDH1*, the gene encoding the cell adhesion molecular E-cadherin, are found in 30% to 50% of cases.[9] The lifetime risk for gastric cancer by age 80 is estimated to be at 67% for men and 83% for women.[10] 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 familial adenomatous polyposis (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.**

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## PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

**Screening Recommendations**

**Insufficient evidence exists for screening 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 Screening Recommendations |
|---|---|---|---|
| Hereditary diffuse gastric cancer[1-4] | *CDH1* | Autosomal dominant | • Prophylactic total gastrectomy is recommended between ages 18 and 40 for CDH1 mutation carriers. A baseline endoscopy is indicated prior to prophylactic total 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.<br>• 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.<br>• CDH1 mutation carriers, who elect not to undergo prophylactic gastrectomy, should be offered screening 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 using high-risk guidelines as outlined in the 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). 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

**Screening Recommendations (continued)**

| Syndrome | Gene(s) | Inheritance Pattern | Gastric Screening 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.<br>• 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.<br>• 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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Continued

## 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 screening 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 |
| Cowden syndrome | *PTEN* | Autosomal dominant |

References

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## PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER
### References

[1]van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015 Jun;52(6):361-74. Epub 2015 May 15.
[2]Oliveira C, Pinheiro H, Figueiredo J, et al. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol 2015 Feb;16(2):e60-70.
[3]Syngal S, Brand RE, Church JM, et al. American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263. Epub 2015 Feb 3.
[4]Kluijt I, Sijmons RH, Hoogerbrugge N, et al. Dutch Working Group on Hereditary Gastric Cancer. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer 2012 Sep;11(3):363-9.
[5]Hampel H, Bennett RL, Buchanan A, et al. Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med 2015 Jan;17(1):70-87. Epub 2014 Nov 13.
[6]Petrovchich I, Ford JM. Genetic predisposition to gastric cancer. Semin Oncol 2016 Oct;43(5):554-559. Epub 2016 Sep 22.
[7]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. Erratum appears in J Med Genet. 2011;48(3):216; Note: Van Krieken, Nicola [corrected to Van Grieken, Nicola C].
[8]Dixon M, Seevaratnam R, Wirtzfeld D, et al. A RAND/UCLA appropriateness study of the management of familial gastric cancer. Ann Surg Oncol 2013;20:533-541.
[9]Gayther SA, Gorringe KL, Ramus SJ, et al. Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. Cancer Res 1998;58:4086-4089.
[10]Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001;121:1348-1353.

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

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### PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and 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.**

[1]Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.

[2]Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.

[3]Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-1708.

[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 7 of 12).

[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.

[6]Park SH, Sohn TS, Lee J, et al. Phase III Trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 2015;33:3130-3136.

Continued
References

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## PRINCIPLES OF SYSTEMIC THERAPY

**Perioperative Chemotherapy**

**Preferred Regimens**
- Fluoropyrimidine and oxaliplatin[a]
- Fluorouracil,[c] leucovorin, oxaliplatin, and docetaxel (FLOT)[b] (category 1)[1]

**Other Recomended Regimens**
- Fluorouracil and cisplatin (category 1)[2]

**Preoperative Chemoradiation**
(Infusional fluorouracil[c] can be replaced with capecitabine)

**Preferred Regimens**
- Fluorouracil and oxaliplatin (category 1)[3,4]
- Fluorouracil and cisplatin (category 1)[5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and Paclitaxel (category 2B)[7]

**Other Recommended Regimens**
- Paclitaxel and carboplatin (category 2B)[8]

**Postoperative Chemoradiation**
(For patients who received less than a D2 lymph node dissection (See Principles of Surgery [GAST-C])

- Fluoropyrimidine (infusional fluorouracil[c] or capecitabine) before and after fluoropyrimidine-based chemoradiation[9]

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

- Capecitabine and oxaliplatin[d] (category 1)[10]

**Chemoradiation for Unresectable Disease**
(Infusional fluorouracil[c] can be replaced with capecitabine)

- Fluorouracil and oxaliplatin [3,4]
- Fluorouracil and cisplatin [5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

See Evidence Blocks on GAST-F (EB-1)

[a]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[b]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[d]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

**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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References

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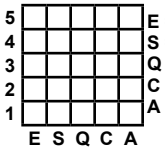
# NCCN Guidelines Version 1.2019
# Gastric Cancer
## NCCN Evidence Blocks™




E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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## EVIDENCE BLOCKS FOR PERIOPERATIVE, PREOPERATIVE, AND POSTOPERATIVE TREATMENT REGIMENS

### Perioperative Chemotherapy (GAST-2 and GAST-4)

| Preferred Regimens | R0 | R1 |
|---|---|---|
| Fluorouracil/oxaliplatin/leucovorin | | |
| Capecitabine/oxaliplatin | | |
| Fluorouracil/leucovorin/oxaliplatin/ docetaxel (FLOT) | | |
| **Other Recommended Regimens** | | |
| Fluorouracil/cisplatin | | |

### Preoperative Chemoradiation (GAST-2)

| Preferred Regimens | |
|---|---|
| Fluorouracil/oxaliplatin + RT | |
| Fluorouracil/oxaliplatin/leucovorin + RT | |
| Capecitabine/oxaliplatin + RT | |
| Fluorouracil/cisplatin + RT | |
| Capecitabine/cisplatin + RT | |
| Paclitaxel/fluorouracil + RT | |
| Paclitaxel/capecitabine + RT | |
| **Other Recommended Regimens** | |
| Paclitaxel/carboplatin + RT | |

### Postoperative Chemoradiation (GAST-3)

| | pT2, N0 tumors | pT3-T4, Any N or Any pT, N+ tumors |
|---|---|---|
| Infusional fluorouracil/leucovorin (before and after chemoradiation) | | |
| Capecitabine (before and after chemoradiation) | | |
| Infusional fluorouracil + RT | | |
| Capecitabine + RT | | |

### Postoperative Chemotherapy (GAST-3)

| | |
|---|---|
| Capecitabine/oxaliplatin | |

### Chemoradiation for Unresectable Disease (GAST-2)

| Preferred Regimens | |
|---|---|
| Fluorouracil/oxaliplatin + RT | |
| Fluorouracil/oxaliplatin/leucovorin + RT | |
| Capecitabine/oxaliplatin + RT | |
| Fluorouracil/cisplatin + RT | |
| Capecitabine/cisplatin + RT | |
| Paclitaxel/fluorouracil + RT | |
| Paclitaxel/capecitabine + RT | |

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### 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 Biomarker Testing [GAST-B])
  - **Combination with fluoropyrimidine and cisplatin (category 1)[11]**
  - **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[c] or capecitabine) and cisplatin[12-15] (category 1)**
- **Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[13,16,17]**

**Other Recommended Regimens**
- **Paclitaxel with cisplatin or carboplatin[18-20]**
- **Docetaxel with cisplatin[21,22]**
- **Fluoropyrimidine[14,23,24] (fluorouracil[c] or capecitabine)**
- **Docetaxel[25,26]**
- **Paclitaxel[27,28]**
- **Fluorouracil[c,e] and irinotecan[29]**
- **DCF modifications**
  - **Docetaxel, cisplatin, and fluorouracil[c,30]**
  - **Docetaxel, oxaliplatin, and fluorouracil[31]**
  - **Docetaxel, carboplatin, and fluorouracil (category 2B)[32]**
- **ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]**
- **ECF modifications (category 2B)[34,35]**
  - **Epirubicin, oxaliplatin, and fluorouracil**
  - **Epirubicin, cisplatin, and capecitabine**
  - **Epirubicin, oxaliplatin, and capecitabine**

See Evidence Blocks on GAST-F (EB-2)

[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.

[e]Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

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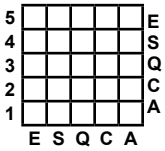
# Gastric Cancer
## NCCN Evidence Blocks™

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## EVIDENCE BLOCKS FOR FIRST-LINE THERAPY FOR UNRESECTABLE LOCALLY ADVANCED, RECURRENT, OR METASTATIC DISEASE

### First-Line Therapy (GAST-8)

| Preferred Regimens | |
|---|---|
| Fluorouracil/cisplatin |  |
| Fluorouracil/cisplatin/leucovorin |  |
| Capecitabine/cisplatin |  |
| Fluorouracil/oxaliplatin/leucovorin |  |
| Capecitabine/oxaliplatin |  |
| **Other Recommended Regimens** | |
| Paclitaxel/cisplatin |  |
| Paclitaxel/carboplatin |  |
| Docetaxel/cisplatin |  |
| Fluorouracil |  |
| Fluorouracil/leucovorin |  |
| Capecitabine |  |
| Docetaxel |  |
| Paclitaxel |  |
| Fluorouracil/irinotecan/leucovorin |  |
| Dose-modified DCF/leucovorin |  |
| Docetaxel/oxaliplatin/fluorouracil |  |
| Docetaxel/carboplatin/fluorouracil |  |
| Epirubicin/cisplatin/fluorouracil |  |
| Epirubicin/oxaliplatin/fluorouracil |  |
| Epirubicin/cisplatin/capecitabine |  |
| Epirubicin/oxaliplatin/capecitabine |  |

### First-Line Therapy for HER2-positive Metastatic Carcinoma (GAST-8)

| Preferred Regimens | |
|---|---|
| Fluorouracil/cisplatin/ trastuzumab |  |
| Fluorouracil/cisplatin/ leucovorin/trastuzumab |  |
| Capecitabine/cisplatin/ trastuzumab |  |
| Fluorouracil/oxaliplatin/ leucovorin/trastuzumab |  |
| Capecitabine/oxaliplatin/ trastuzumab |  |

| Other Recommended Regimens | |
|---|---|
| Paclitaxel/cisplatin/ trastuzumab |  |
| Paclitaxel/carboplatin/ trastuzumab |  |
| Docetaxel/cisplatin/ trastuzumab |  |
| Fluorouracil/trastuzumab |  |
| Fluorouracil/leucovorin/ trastuzumab |  |
| Capecitabine/trastuzumab |  |
| Docetaxel/trastuzumab |  |
| Paclitaxel/trastuzumab |  |
| Fluorouracil/irinotecan/ leucovorin/trastuzumab |  |
| Dose-modified DCF/ leucovorin/trastuzumab |  |
| Docetaxel/oxaliplatin// fluorouracil/trastuzumab |  |
| Docetaxel/carboplatin/ fluorouracil/trastuzumab |  |

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### PRINCIPLES OF SYSTEMIC THERAPY

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

| **Second-Line or Subsequent Therapy**<br>• **Dependent on prior therapy and PS** |
|---|
| **Preferred Regimens**<br>• **Ramucirumab and paclitaxel (category 1)[36]**<br>• **Docetaxel (category 1)[25,26]**<br>• **Paclitaxel (category 1)[27,28,37]**<br>• **Irinotecan (category 1)[37-40]**<br>• **Trifluridine and tipiracil (category 1)[41]**<br>▸ **For third-line or subsequent therapy**<br>• **Fluorouracil[c,e] and irinotecan[38,42,43]**<br>• **Pembrolizumab**<br>▸ **For second-line or subsequent therapy for MSI-H or dMMR tumors[44,45]** |
| **Other Recommended Regimens**<br>• **Ramucirumab (category 1)[46]**<br>• **Irinotecan and cisplatin[16,47]**<br>• **Pembrolizumab**<br>▸ **For third-line or subsequent therapy for PD-L1 positive adenocarcinoma[f,48]**<br>• **Docetaxel and irinotecan (category 2B)[49]** |

See Evidence Blocks on GAST-F (EB-3)

[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.

[e]Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

[f]Pembrolizumab is approved for patients with gastric tumors with PD-L1 expression levels ≥1 as determined by an FDA-approved test.

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Continued
References

### EVIDENCE BLOCKS FOR SECOND-LINE THERAPY (GAST-9)

| Preferred Regimens | |
|---|---|
| Ramucirumab/paclitaxel |  |
| Docetaxel |  |
| Paclitaxel |  |
| Irinotecan |  |
| Trifluridine and tipiracil<br>(for third-line or subsequent therapy) |  |
| Fluorouracil/irinotecan/leucovorin |  |
| Pembrolizumab<br>(second-line or subsequent therapy for MSI-H/dMMR tumors) |  |
| **Other Recommended Regimens** | |
| Ramucirumab |  |
| Irinotecan/cisplatin |  |
| Pembrolizumab<br>(third-line or subsequent therapy for PD-L1 positive adenocarcinoma) |  |
| Docetaxel and irinotecan |  |

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## PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]

### PERIOPERATIVE CHEMOTHERAPY

**PREFERRED REGIMENS**

**Fluoropyrimidine and oxaliplatin**
**(3 cycles preoperative and 3 cycles postoperative)**
**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[16]**

**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[13]**

**Capecitabine 1000 mg/m² PO BID on Days 1–14**
**Oxaliplatin 130 mg/m² IV on Day 1**
**Cycled every 21 days[17]**

**Fluorouracil, leucovorin oxaliplatin, and docetaxel (FLOT)[c]**
**(4 cycles preoperative and 4 cycles postoperative)**
**Fluorouracil 2600 mg/m² IV continuous infusion over 24 hours on Day 1**
**Leucovorin 200 mg/m² IV on Day 1**
**Oxaliplatin 85 mg/m² IV on Day 1**
**Docetaxel 50 mg/m² IV on Day 1**
**Cycled every 14 days[1]**

**OTHER RECOMMENDED REGIMENS**

**Fluorouracil and cisplatin**
**(4 cycles preoperative and 4 cycles postoperative)**
**Fluorouracil 2000 mg/m² IV continuous infusion over 48 hours on Days 1–2**
**Cisplatin 50 mg/m² IV on Day 1**
**Cycled every 14 days**

[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.

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

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Continued
References

## PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]

### PREOPERATIVE CHEMORADIATION

**PREFERRED REGIMENS**

**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[3,h]

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

**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[5]

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[6]

**PREFERRED REGIMENS--CONTINUED**

**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[52]

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

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

**OTHER RECOMMENDED REGIMENS**

**Paclitaxel and carboplatin**
Paclitaxel 50 mg/m² IV on Day 1
Carboplatin AUC 2 IV on Day 1
Weekly for 5 weeks[8]

[g]Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.
[h]This regimen can be individualized and/or attenuated on a patient basis.

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### PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]

**POSTOPERATIVE CHEMORADIATION**
**(for patients who received less than a D2 lymph node dissection)**
**Fluorouracil (bolus) and leucovorin[9,54]**

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

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

**THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[9,54] 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[55]**

- **2 cycles before and 4 cycles after chemoradiation**
  **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**

**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[56]**

**With radiation**
**Capecitabine 625–825 mg/m² PO BID on Days 1–5 or 1–7**
**Weekly for 5 weeks[57]**

**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[10]**

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

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## PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]
## 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[11]
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[12]

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[13,14]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[15]

**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[16]

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[13]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[17]

**OTHER RECOMMENDED 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[18]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[19]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[20]

**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[21,22]

**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[14]

Fluorouracil 800 mg/m² IV continuous infusion
over 24 hours daily on Days 1–5
Cycled every 28 days[23]

Capecitabine 1000–1250 mg/m²
PO BID on Days 1–14
Cycled every 21 days[24]

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

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## PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]
## SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

**FIRST-LINE THERAPY--continued**

**OTHER RECOMMENDED REGIMENS—continued**

**Taxane**

**Docetaxel 75–100 mg/m² IV on Day 1**
**Cycled every 21 days[25,26]**

**Paclitaxel 135–250 mg/m² IV on Day 1**
**Cycled every 21 days[27]**

**Paclitaxel 80 mg/m² IV weekly**
**Cycled every 28 days[28]**

**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[29]**

**OTHER RECOMMENDED 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[30]**

**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[31]**

**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[32]**

**OTHER RECOMMENDED 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[33]**

**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[34,35]**

**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[34,35]**

**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[34,35]**

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

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

### SECOND-LINE AND SUBSEQUENT 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[25,26]

Paclitaxel 135–250 mg/m$^2$ IV on Day 1
Cycled every 21 days[27]

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

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

**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]

**PREFERRED REGIMENS—continued**

**Trifluridine and tipiracil***
Trifluridine and tipiracil 35 mg/m$^2$ up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily on Days 1 – 5 and 8 – 12
Repeat every 28 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]

**Pembrolizumab (for second-line or subseqent therapy for MSI-H/dMMR tumors)**
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[48]

**OTHER RECOMMENDED REGIMENS**

**Ramucirumab**
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[46]

**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[16,47]

**Pembrolizumab (for third-line or subsequent therapy for PD-L1-positive adenocarcinoma)**
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[48]

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

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

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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 oncologists, radiation oncologists, medical oncologists, radiologists, gastroenterologists, and pathologists.
- CT scans, EUS, endoscopy reports, and FDG-PET or FDG-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 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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## PRINCIPLES OF RADIATION THERAPY

**Target Volume (General Guidelines)**

- Preoperative[1]
  - Pre-treatment diagnostic studies (EUS, EGD, FDG-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, FDG-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 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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## 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] | **Heart** |
| • $V_{20Gy}$ ≤ 30%<br>• Mean ≤ 20 Gy | • $V_{30Gy}$ ≤ 30% (closer to 20% preferred)<br>• Mean < 30 Gy |
| **Spinal Cord** | **Left Kidney, Right Kidney (evaluate each one separately):** |
| • Max ≤ 45 Gy | • $V_{20Gy}$ ≤ 33%<br>• Mean < 18 Gy |
| **Bowel** | **Liver** |
| • $V_{45Gy}$ < 195 cc | • $V_{30Gy}$ ≤ 33 %<br>• Mean < 25 Gy |

**RT Dosing**

- **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.**

[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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**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.**

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### PRINCIPLES OF SURVEILLANCE

- **Surveillance strategies after curative intent resection (R0) for gastric cancer remain controversial, with sparse prospective data to construct evidence-based algorithms that balance benefits and risks (including cost) within this cohort.**
- **The guidance provided on GAST-7 for stage-specific surveillance is based on the currently available retrospectively analyzed literature[1-10] and expert consensus.**
- **While the majority of gastric cancer relapses occur within 2 years (70%–80%) and almost all recurrences by 5 years (~90%) after completion of local therapy, it is important to note that occasionally potentially actionable relapses have been recognized more than 5 years after curative intent therapy. Therefore, after 5 years additional follow-up may be considered based on risk factors and comorbidities.**
- **Differences in follow-up for early-stage gastric cancer reflect a heterogeneous potential for relapse and overall survival.[1-10] Whereas R0-resected Tis disease has a prognosis that approximates a non-cancer cohort, T1aN0 and T1b disease do not have such a favorable prognosis. Thus, recommendations vary according to the depth of invasion and treatment modality.**

References

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### PRINCIPLES OF SURVEILLANCE
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### PRINCIPLES OF SURVIVORSHIP

**Surveillance**: (See GAST-7)

- Surveillance should be performed in conjunction with good routine medical care, including routine health maintenance, preventive care, and cancer screening.
- Routine gastric cancer-specific surveillance (ie, radiologic imaging, endoscopic evaluation, tumor markers) is not recommended beyond 5 years.

**Management of Long-Term Sequelae of Disease or Treatment**: (For common survivorship issues, see NCCN Guidelines for Survivorship)

- General issues in gastric cancer survivors:
  - Weight loss:
    - ◊ Monitor weight regularly after gastrectomy to ensure stability
    - ◊ Encourage more frequent feeding and avoiding fluid intake with meals
    - ◊ Consider referral to dietician or nutrition services for individualized counseling
    - ◊ Assess for and address contributing medical and/or psychosocial factors
  - Diarrhea: Consider anti-diarrheal agents, bulk-forming agents, and diet manipulation
  - Chemotherapy-induced neuropathy:
    - ◊ Consider duloxetine for painful neuropathy only (not effective for numbness or tingling)
    - ◊ See NCCN Guidelines for Survivorship (SPAIN-3) and NCCN Guidelines for Adult Cancer Pain (PAIN-3 through PAIN-5 and PAIN-H)
  - Fatigue:
    - ◊ Encourage physical activity and energy conservation measures as tolerated
    - ◊ Assess and address contributing medical and/or psychosocial factors
    - ◊ See NCCN Guidelines for Survivorship (SFAT-1) and NCCN Guidelines for Cancer-Related Fatigue
  - Bone health:
    - ◊ Screen for and manage low bone density at regular intervals as per established national guidelines
    - ◊ Consider vitamin D testing and replacement as clinically indicated

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### PRINCIPLES OF SURVIVORSHIP

**Management of Long-Term Sequelae of Disease or Treatment (For common survivorship issues, see NCCN Guidelines for Survivorship)**

- Issues in subtotal gastrectomy survivors:
  - Indigestion:
    - Avoid foods that increase acid production (ie, citrus juices, tomato sauces, spicy foods) or lower gastroesophageal sphincter tone (ie, caffeine, peppermint, chocolate).
    - Consider proton pump inhibitor
  - Vitamin $B_{12}$ deficiency: (distal gastrectomy only)
    - Monitor CBC and $B_{12}$ levels every 3 months for up to 3 years, then every 6 months up to 5 years, then annually
    - Supplement $B_{12}$ as clinically indicated
  - Iron deficiency: (distal gastrectomy only)
    - Monitor CBC and iron levels at least annually
    - Supplementation with iron as clinically indicated

- Issues in total gastrectomy survivors:
  - Post-prandial fullness or eating dysfunction:
    - Encourage small portions and more frequent eating
    - Avoid fluid intake with meals
  - Dumping syndrome:
    - Early:
      - Occurs within 30 minutes of meal
      - Associated with palpations, diarrhea, nausea, and cramps
    - Late:
      - Occurs within 2–3 hours of a meal
      - Associated with dizziness, hunger, cold sweats, faintness
    - Encourage frequent meals scheduled throughout day
    - Consume a diet high in protein and fiber, and low in simple carbohydrates or concentrated sweets
    - Avoid fluid consumption with meals
  - Vitamin $B_{12}$ deficiency:
    - Monitor CBC and $B_{12}$ levels every 3 months for up to 3 years, then every 6 months up to 5 years, then annually
    - Supplement $B_{12}$ as clinically indicated
  - Iron deficiency:
    - Monitor CBC and iron levels at least annually
    - Supplement iron as clinically indicated; avoid sustained release or enteric-coated formulations if possible
  - Small intestine bacterial overgrowth (blind loop)
    - Consider treatment with antibiotics (rifaximin 550 mg TID x 7–10 days preferred)
    - Consume a diet high in protein and low in carbohydrates

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### PRINCIPLES OF SURVIVORSHIP

**Counseling Regarding Health Behaviors** (See NCCN Guidelines for Survivorship [HL-1])

- Maintain a healthy body weight throughout life
- Adopt a physically activity lifestyle and avoid inactivity. Goal: at least 30 minutes of moderate-intensity activity most days of the week. Modify physical activity recommendations based on treatment sequelae (ie, neuropathy).
- Consume a healthy diet with emphasis on plant sources, with modifications as needed based on treatment sequelae (ie, dumping syndrome, bowel dysfunction).
- Limit alcohol consumption.
- Recommend smoking cessation as appropriate. See NCCN Guidelines for Smoking Cessation.
- Additional preventive health and immunizations should be performed as indicated under the care of or in conjunction with a primary care physician.

**Cancer Screening Recommendations (for average-risk survivors)**

- Breast Cancer: See NCCN Guidelines for Breast Cancer Screening and Diagnosis
- Colorectal Cancer: See NCCN Guidelines for Colorectal Cancer Screening
- Prostate Cancer: See NCCN Guidelines for Prostate Cancer Early Detection
- Lung Cancer: See NCCN Guidelines for Lung Cancer Screening

**Survivorship Care Planning and Coordination of Care** (See NCCN Guidelines for Survivorship (SURV-1 through SURV-B))

- Encourage maintenance of a therapeutic relationship with a primary care physician throughout life. The oncologist and primary care physician should have defined roles in survivorship care, with roles communicated to patient.
- Recommend provision of survivorship care plan that includes:
  - Summary of treatment, including all surgeries, radiation treatment, and chemotherapy received;
  - Description of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment, with anticipated time to development and/or resolution;
- Surveillance recommendations;
- Health behavior recommendations; and
- Delineation of roles of oncologists and primary care, with timing of transfer of care as appropriate

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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.

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### 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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**American Joint Committee on Cancer (AJCC)**
**TNM Staging Classification for Carcinoma of the Stomach (8th ed., 2017)**

***Table 1.*** **Definitions for T, N, M**

| | |
|---|---|
| **T** | **Primary Tumor** |
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma *in situ*: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia |
| **T1** | Tumor invades the lamina propria, muscularis mucosae, or submucosa |
| T1a | Tumor invades the lamina propria or muscularis mucosae |
| T1b | Tumor invades the submucosa |
| **T2** | Tumor invades the muscularis propria* |
| **T3** | Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures**,*** |
| **T4** | Tumor invades the serosa (visceral peritoneum) or adjacent structures**,*** |
| T4a | Tumor invades the serosa (visceral peritoneum) |
| T4b | Tumor invades adjacent structures/organs |

*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 as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as 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 not considered invasion of an adjacent structure, but is classifi ed using the depth of the greatest invasion in any of these sites.

| | |
|---|---|
| **N** | **Regional Lymph Nodes** |
| **NX** | Regional lymph node(s) cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis in one or two regional lymph nodes |
| **N2** | Metastasis in three to six regional lymph nodes |
| **N3** | Metastasis in seven or more regional lymph nodes |
| N3a | Metastasis in seven to 15 regional lymph nodes |
| N3b | Metastasis in 16 or more regional lymph nodes |

| | |
|---|---|
| **M** | **Distant Metastasis** |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |

| | |
|---|---|
| **G** | **Histologic Grade** |
| **GX** | Grade cannot be assessed |
| **G1** | Well differentiated |
| **G2** | Moderately differentiated |
| **G3** | Poorly differentiated, undifferentiated |

Continued

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**American Joint Committee on Cancer (AJCC)**
**TNM Staging Classification for Carcinoma of the Stomach (8th ed., 2017)**

***Table 2.*** **AJCC Prognostic Stage Groups**

**Clinical Staging (cTNM)**

| | cT | cN | M |
|---|---|---|---|
| **Stage 0** | Tis | N0 | M0 |
| **Stage I** | T1 | N0 | M0 |
| | T2 | N0 | M0 |
| **Stage IIA** | T1 | N1, N2, N3 | M0 |
| | T2 | N1, N2, N3 | M0 |
| **Stage IIB** | T3 | N0 | M0 |
| | T4a | N0 | M0 |
| **Stage III** | T3 | N1, N2, N3 | M0 |
| | T4a | N1, N2, N3 | M0 |
| **Stage IVA** | T4b | Any N | M0 |
| **Stage IVB** | Any T | Any N | M1 |

**Pathological Staging (pTNM)**

| | pT | pN | M |
|---|---|---|---|
| **Stage 0** | Tis | N0 | M0 |
| **Stage IA** | T1 | N0 | M0 |
| **Stage IB** | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| **Stage IIA** | T1 | N2 | M0 |
| | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| **Stage IIB** | T1 | N3a | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T4a | N0 | M0 |
| **Stage IIIA** | T2 | N3a | M0 |
| | T3 | N2 | M0 |
| | T4a | N1 or N2 | M0 |
| | T4b | N0 | M0 |
| **Stage IIIB** | T1 | N3b | M0 |
| | T2 | N3b | M0 |
| | T3 | N3a | M0 |
| | T4a | N3a | M0 |
| | T4b | N1 or N2 | M0 |
| **Stage IIIC** | T3 | N3b | M0 |
| | T4a | N3b | M0 |
| | T4b | N3a or N3b | M0 |
| **Stage IV** | Any T | Any N | M1 |

**Post-Neoadjuvant Therapy (ypTNM)**

| | ypT | ypN | M |
|---|---|---|---|
| **Stage I** | T1 | N0 | M0 |
| | T2 | N0 | M0 |
| | T1 | N1 | M0 |
| **Stage II** | T3 | N0 | M0 |
| | T2 | N1 | M0 |
| | T1 | N2 | M0 |
| | T4a | N0 | M0 |
| | T3 | N1 | M0 |
| | T2 | N2 | M0 |
| | T1 | N3 | M0 |
| **Stage III** | T4a | N1 | M0 |
| | T3 | N2 | M0 |
| | T2 | N3 | M0 |
| | T4b | N0 | M0 |
| | T4b | N1 | M0 |
| | T4a | N2 | M0 |
| | T3 | N3 | M0 |
| | 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 05/22/18

**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 indicated.**



**NCCN Categories of Preference**

**Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

**Other recommended intervention:** Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

**Useful in certain circumstances:** Other interventions that may be used for selected patient populations (defined with recommendation).

**All recommendations are considered appropriate.**

## Table of Contents

## Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach constitute a major global health problem. A dramatic shift in the location of upper GI tract tumors has occurred in the United States.[1] Changes in the histology and location of upper GI tract tumors have also been observed in some parts of Europe.[2,3] In Western countries, the proximal lesser curvature, cardia, and EGJ are the most common sites of gastric cancer.[4]

Gastric cancer is one of the least common cancers diagnosed in North America. In contrast, it is rampant in many parts of the world, including Asia. Gastric cancer is the most common type of cancer diagnosed in Japanese men and China has the highest number of newly diagnosed gastric adenocarcinoma patients in the world. Globally, gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths.[5] In 2018, an estimated 26,240 people are likely to be diagnosed and 10,800 people will die of this disease in the United States.[6] In developed countries, the incidence of gastric cancer originating from the cardia follows the distribution of esophageal cancer.[1,3,7] Non-cardia gastric cancer shows marked geographic variation with countries such as Japan, Korea, China, Taiwan, Mongolia, Costa Rica, Peru, Brazil, Chile, and the former Soviet Union reporting high rates.[8] In contrast to the incidence trends in the West, non-proximal tumors continue to predominate in Japan and other parts of the world.[9] The etiology of this shift mainly 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 meta-analysis, there was no appreciable association between moderate alcohol consumption and gastric cancer risk; however, there was a positive association with heavy alcohol use, particularly for non-cardia gastric cancers.[10]

## 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 using the following search terms: gastric cancer, gastric adenocarcinoma, and stomach cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer reviewed biomedical literature.[11]

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 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 at www.NCCN.org.

## 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 1% to 3% are associated with inherited cancer predisposition syndromes. The most common hereditary

cancer predisposition syndromes are discussed in detail below. See *Principles of Genetic Risk Assessment for Gastric Cancer* in the algorithm for criteria that warrant further risk evaluation for high-risk syndromes.

### 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.[12,13] 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.[14,15] 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.[16]

The safety and efficacy of endoscopic surveillance for patients with HDGC have not been established. Additionally, available evidence suggests that endoscopy may not adequately detect the precursor lesions in diffuse gastric cancer.[17-19] Prophylactic total gastrectomy (without a D2 lymph node dissection) is recommended between ages 18 and 40 years for carriers of germline truncating *CDH1* mutations.[20,21] 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 is indicated prior to prophylactic total gastrectomy. Surveillance by upper endoscopy with multiple random biopsies every 6 to 12 months should be offered to *CDH1* mutation carriers who elect not to undergo prophylactic total gastrectomy. Additionally, women with *CDH1* mutations are at an increased risk for developing breast cancer[22] 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.

More than 40% of patients with HDGC do not carry *CDH1* mutations, suggesting the existence of additional susceptibility genes.[23] Known breast cancer predisposition gene *PALB2*, which encodes for an adaptor protein necessary for BRCA2 function, has recently been shown to confer susceptibility to familial gastric cancer.[24,25] In a large genomic study of cancer predisposition variants, five different germline loss-of-function mutations in *PALB2* were identified in gastric adenocarcinoma patients.[25] *PALB2* was also identified as being significantly enriched for loss-of-function variants in a whole-exome sequencing study of families with HDGC not associated with a *CDH1* mutation.[24] Furthermore, *PALB2* loss-of-function variants were found to be substantially more common in families with HDGC than in the general population.[24] These findings suggest a role for *PALB2* in HDGC; however, more sufficient evidence is required to justify routine genetic testing of *PALB2* in families with HDGC without *CDH1* mutations.

### 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, endometrial, and gastric cancers.[26] Lynch syndrome arises from germline mutations in any of the 4 DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6*, and *PMS2*).[27] Deletions of the epithelial cell adhesion molecule (*EPCAM)* gene have also been implicated in Lynch syndrome.[28] Gastric cancer is the second most common extracolonic cancer (after endometrial cancer) in patients with Lynch syndrome. These patients have a 1% to 13% risk of developing gastric cancer, predominantly the intestinal type, which occurs at an earlier age than the general population.[29-32] This risk is higher among Asians than Westerners.

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

distal duodenum or into the jejunum) as a surveillance strategy.[26] 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.[33] JPS arises from a germline mutation in the *SMAD4* or *BMPR1A* genes.[26] The lifetime risk of developing GI cancers in patients with JPS varies from 9% to 50% with the type of mutation.[34] The lifetime risk of developing gastric cancer in individuals with JPS is 21% when the upper GI tract is involved, which is mainly seen in *SMAD4* mutation carriers.[34] EGD may be considered, beginning in the mid-teens and repeated annually if polyps are found or every 2 to 3 years if no polyps are found.[26] 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* tumor suppressor gene,[35,36] which occurs in 30% to 80% of patients.[37] PJS is characterized by mucocutaneous pigmentation and GI polyposis and is associated with an elevated risk of developing GI cancers.[38-42] Individuals with PJS have a 29% lifetime risk of developing gastric cancer and are also at an increased risk for other cancers.[26,38] EGD may be considered, beginning in the late teens and repeated every 2 to 3 years based on gastric polyp burden.[26] 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 germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21.[43,44] 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.[45] The majority (approximately 90%) of gastric polyps are nonadenomatous benign fundic gland polyps, developing in approximately 50% of patients with FAP. Gastric adenomatous polyps, which can lead to gastric cancer, represent 10% of the gastric polyps diagnosed in these patients.[45] Individuals with FAP have a 1% to 2% lifetime risk for developing gastric cancer.

There is no clear evidence to support specific screening recommendations for gastric cancer in patents with FAP. However, given the increased risk of duodenal cancer, the stomach should be examined at the same time of duodenoscopy. Non-fundic gland polyps in the stomach should be managed endoscopically, if possible.[46] Patients with polyps that cannot be removed endoscopically (as in the case of invasive cancers) should be referred for gastrectomy.[46] A baseline EGD with side-viewing endoscope is recommended at age 25 to 30 years and repeated based on duodenal polyp burden. See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.

### Less Common Hereditary Cancer Predisposition Syndromes

In addition to the more common syndromes discussed above, there are a number of hereditary cancer predisposition syndromes that are less commonly associated with a risk of developing gastric cancer. Ataxia-telangiectasia,[47] Bloom syndrome,[48] hereditary breast and ovarian cancer syndrome,[47,49] Li-Fraumeni syndrome,[47,49] Xeroderma pigmentosum,[47] and Cowden syndrome[49] have all been reported to increase the risk of gastric

cancer. However, evidence for gastric cancer surveillance in these patients is insufficient and therefore not recommended at this time.

## Staging

The tumor (T), node (N), and metastasis (M) staging system used by the AJCC is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. The eighth edition of the AJCC Staging Manual provides additional resources for gastric cancer not available in the seventh edition, including the addition of clinical and postneoadjuvant staging groups, to fulfill unmet needs in staging gastric cancer patients under different circumstances. [50] Using this system, tumors involving the EGJ with an epicenter located >2 cm into the proximal stomach are now staged as gastric carcinomas. Tumors crossing the EGJ with an epicenter within 2 cm of the proximal stomach will still be staged as esophageal carcinomas. In addition, the stage groupings and prognostic information for pathologic staging are now based on >25,000 gastric cancer patients who have had surgery with adequate lymph node removal and were followed for a minimum of 5 years. However, limitations of this system include a lack of uniformity in initial clinical stage assessments, the lack of uniform surgical approach, and pathology assessments of yp categories.

Clinical baseline stage provides useful information for the development of an initial treatment strategy. Approximately 50% of patients present with advanced disease at diagnosis and will likely have a poor outcome. Other measures of poor outcome include poor performance status, presence of metastases, and an alkaline phosphatase level ≥100 U/L.[51] 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 and the number of positive lymph nodes has a profound influence on survival.[52]

Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, PET/CT, MRI, and laparoscopic staging.[53-55] EUS is indicated for assessing the depth of tumor invasion.[56] However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.[57] In a large multi-institutional 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.[58] Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.[59] EUS may be useful for differentiating T3 and T4 tumors, but it should be used in combination with other staging modalities.[57,58] EUS is also helpful to identify T1 tumors for potential endoscopic approaches.

CT scan is routinely used for preoperative staging and has an overall accuracy of 43% to 82% for T staging. In contrast, PET has a lower accuracy rate because of the low tracer accumulation in diffuse and mucinous tumor types, which are frequent in gastric cancer.[60] PET also has significantly lower sensitivity compared to CT in the detection of local lymph node involvement (56% vs. 78%), although PET has improved specificity (92% vs. 62%).[61] Thus, combined PET/CT imaging offers several potential advantages over PET or CT scans alone.[62] PET/CT has a significantly higher accuracy rate in preoperative staging (68%) than PET (47%) or CT (53%) alone. Additionally, reports have confirmed that PET alone is not an adequate diagnostic procedure in the detection and preoperative staging of gastric cancer, but can be helpful when used in conjunction with CT.[63,64]

Laparoscopic staging can be used to 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.[65] Distant metastatic disease (M1) was

detected in 31% of 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.[53] Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer and is an independent predictor for identifying patients who are at higher risk for recurrence following curative resection.[66-68] 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.[67] Therefore, positive peritoneal cytology even 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.[65] Laparoscopic staging with peritoneal washings for cytology is indicated for clinical stages higher than T1b (category 2B). The panel recommends laparoscopy to evaluate for peritoneal spread when chemoradiation or surgery is considered. However, laparoscopy is not indicated if a palliative resection is planned.

## Principles of Pathology

### Pathologic Review

A specific diagnosis of gastric adenocarcinoma should be established for staging and treatment purposes. Subclassification of gastric adenocarcinoma as intestinal or diffuse type may have implications for therapy since intestinal type tumors are more likely to overexpress HER2 (see below).[69] In addition to the histologic type and subclassification, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade (required for stage grouping). The pathology report of endoscopic mucosal resection (EMR) specimens should include an assessment of lymphovascular invasion (LVI), depth of tumor invasion, and the status of mucosal and deep margins. Pathology reports of gastrectomy specimens without prior chemoradiation should also document the location of the tumor midpoint in relationship to the EGJ, whether the tumor crosses the EGJ, the 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. The pathology report should include all of the above elements plus assessment of treatment effect.

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.[70] Data from the SEER database showed that the number of lymph nodes examined correlated with overall survival (OS) after gastrectomy. The trend for superior survival based on more lymph nodes examined was confirmed across all stage subgroups.[71]

### Assessment of Treatment Response

Pathologic response and histologic tumor regression after neoadjuvant therapy have been shown to be predictors of survival in patients with gastric adenocarcinoma. Lowy et al reported that clinical response to neoadjuvant chemotherapy was the only independent predictor of OS in patients who underwent curative resection for gastric cancer.[72] In another study, Becker et al demonstrated that histopathologic grading of tumor regression correlated with survival in patients treated with neoadjuvant chemotherapy.[73] Median survival was significantly better for patients with <10% residual tumor compared to those with 10% to 50% or >50%

residual tumor. Additionally, Mansour et al reported that the 3-year disease-specific survival rate was significantly higher for patients with >50% pathologic response to neoadjuvant chemotherapy compared to those with <50% pathologic response (69% and 44%, respectively).[74] Conversely, Smyth et al reported that lymph node metastasis, not pathologic response to therapy, was the only independent predictor of survival in patients who received neoadjuvant chemotherapy as part of the MAGIC trial.[75]

Although tumor regression grading systems for gastric cancer have not been uniformly adopted, the panel recommends using the modified scheme developed by Ryan et al because it generally provides good reproducibility among pathologists.[76] This scheme is based on a 4-tiered classification system: 0 (complete response; no viable cancer cells, including lymph nodes); 1 (near complete response; single cells or rare small groups of cancer cells); 2 (partial response; residual cancer cells with evident tumor regression, but more than single cells or rare small groups of cancer cells); and 3 (poor or no response; extensive residual cancer with no evident tumor regression). Because of the impact of residual nodal metastases on survival, it is recommended that lymph nodes be included in the regression score. 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 Biomarker Testing: Assessment of Treatment Response - Table 2* in the algorithm for more information.

### Assessment of HER2 Overexpression or Amplification

Overexpression or amplification of the human epidermal growth factor receptor 2 (*HER2*) gene and protein have been implicated in the development of gastric adenocarcinomas.[77] The reported rates of HER2 positivity in patients with gastric cancer ranges from 12% to 23%.[78-83] HER2 positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[78,81-83] HER2 positivity is reported in ≤20% of Western patients with metastatic gastric cancer with significantly higher rates in patients with intestinal histology (33% vs. 8% for diffuse/mixed histology; $P = .001$).[83] In the U.S. population, the reported HER2 positivity rate in gastric cancer is 12% and is more often identified in the intestinal subtype rather than the diffuse subtype (19% and 6%, respectively).[82] In the ToGA trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2-positive advanced gastric or EGJ cancers, HER2 positivity rates were 32.2%, 21.4%, 31.8%, and 6.1%, respectively, in patients with EGJ adenocarcinoma, gastric adenocarcinoma, intestinal gastric adenocarcinoma , and diffuse gastric adenocarcinoma.[84] Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

Unlike in breast cancer, the prognostic significance of HER2 status in patients with gastric cancer is unclear. Some studies suggest that HER2 positivity is associated with poor prognosis[80,81,85,86] while 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.[82,83,87] While further studies are needed to assess the prognostic significance of HER2 status in gastric cancer, the addition of HER2 monoclonal antibodies to chemotherapy regimens is a promising treatment option for patients with HER2-positive 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+. The NCCN Guidelines recommend that cases showing 2+ (equivocal) expression of HER2 by IHC should be additionally examined by fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) methods. FISH/ISH results are expressed as the ratio

between the number of copies of the *HER2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (HER2:CEP17). Alternatively, FISH/ISH results may be given as the average *HER2* copy number per cell.

According to the HER2 scoring system for breast cancer proposed by ASCO/College of American Pathologists (CAP), uniform intense membrane staining in >30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to 2 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.[69,88] 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).[89,90] In 2008, Hofmann et al developed a modified 4-tiered HER2 scoring system specifically 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.[69] In a subsequent validation study (n = 447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[88] This modified HER2 scoring system is recommended by the panel.

HER2 testing at the time of diagnosis is recommended for all gastric adenocarcinoma patients if metastatic disease is documented or suspected. The NCCN Guidelines recommend that assessment of HER2 status should be performed first using IHC following the Hofmann-modified scoring system.[69,89] A score of 0 or 1+ is considered to be negative for HER2 overexpression. A score of 2+ is considered equivocal and should be confirmed with FISH/ISH techniques. Cases that have an IHC score of 3+ or an IHC score of 2+ and are FISH/ISH positive (HER2:CEP17 ratio ≥2 or average *HER2* copy number ≥6 signals/cell) are considered positive for HER2 overexpression. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further testing. These guidelines are in agreement with the recommendations for HER2 testing in gastroesophageal adenocarcinoma that were recently published by ASCO, CAP, and the American Society for Clinical Pathology (ASCP).[91] See the *Principles of Pathologic Review and Biomarker Testing: Assessment of Overexpression or Amplification of HER2 in Gastric Cancers - Table 3* in the algorithm.

### New and Emerging Biomarkers

In its first-ever site-agnostic approval, the FDA approved pembrolizumab for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) solid tumors in the second-line or subsequent setting.[92] Therefore, dMMR/MSI-H status should be assessed in all gastric adenocarcinoma patients if metastatic disease is documented or suspected. Results are interpreted as MSI-H or dMMR in accordance with guidelines for colorectal cancer specimens (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal).

In addition, pembrolizumab has been granted accelerated FDA approval as a third- or subsequent-line treatment option for patients with recurrent, locally advanced, or metastatic gastric adenocarcinoma whose tumors express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥1 as determined by an FDA-approved companion diagnostic test.[93] CPS is determined by the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells evaluated, multiplied by 100. Therefore, PD-L1 testing is also recommended for all patients with advanced gastric adenocarcinoma if metastatic disease is documented or suspected.

Tumor Epstein-Barr virus (EBV) status is emerging as a potential biomarker for personalized treatment strategies in gastric cancer, but is

not currently recommended for clinical care. Several studies have shown that gastric cancers that are MSI-H or EBV-positive show higher expression of PD-L1 compared to gastric cancers that do not show these traits.[94-96] Additionally, Derks et al reported that an interferon-γ–driven gene signature was enriched in MSI-H and EBV-positive gastric cancers, suggesting increased sensitivity to PD-1/PD-L1 immunotherapies.[95] Systematic reviews and meta-analyses have shown that MSI-H[97,98] and EBV-positive[99] gastric cancers are associated with good prognosis and longer survival times. Additional data also suggest that patients with EBV-associated localized gastric cancer have the best OS compared to other genotypes.[100]

## Surgery

Surgery is the primary treatment option for patients with early-stage gastric cancer. Complete resection with negative margins 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 chest/abdominal/pelvic CT scan, with or without EUS (if no metastatic disease is seen on CT), should be performed before surgery to assess the extent of the disease and nodal involvement. The primary goal of surgery is to accomplish a complete resection with negative margins (R0 resection); however, only 50% of patients will have an R0 resection of their primary tumor.[101,102] An R1 resection indicates microscopic residual disease and an R2 resection indicates macroscopic residual disease in the absence of distant metastasis.[103] Adequate gastric resection (distal, subtotal, or total gastrectomy) to achieve negative margins (generally ≥4 cm from the gross tumor) is preferred for resectable T1b to T3 tumors, while T4 tumors require en-bloc resection of involved structures.[104] Patients with Tis or T1a tumors may be considered for EMR in experienced centers.

Subtotal gastrectomy is the preferred surgical approach for distal gastric cancers. This procedure has a similar surgical outcome compared to total gastrectomy, although with significantly fewer complications.[105] Proximal gastrectomy and total gastrectomy are both indicated for proximal gastric cancers and are typically associated with postoperative nutritional impairment. Placement of a jejunostomy feeding tube may be considered for select patients, especially those who will be receiving postoperative chemoradiation.

Routine or prophylactic splenectomy should be avoided. In a randomized clinical study, postoperative mortality and morbidity rates were significantly higher in patients who underwent total gastrectomy combined with splenectomy compared to those who underwent total gastrectomy alone.[106] 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.

In patients with incurable disease, gastric resections should be reserved for the palliation of symptoms (obstruction or uncontrollable bleeding) and should not include lymph node dissection.[107,108] Gastric bypass with gastrojejunostomy (open or laparoscopic) is preferable to endoluminal stenting in patients with gastric outlet obstruction, if they are fit for surgery and have a reasonable prognosis due to lower rate of recurrent symptoms.[109] Placement of venting gastrotomy and/or a feeding jejunostomy tube may be also considered.

Gastric adenocarcinomas 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 or invasion/encasement of major vascular structures,

excluding the splenic vessels). Limited gastric resection, even with positive margins, is acceptable for patients with unresectable tumors for the palliation of symptomatic bleeding.

### Lymph Node Dissection

Gastric resection should include the removal of regional lymph nodes (lymphadenectomy). Retrospective analyses have shown that the dissection of ≥15 lymph nodes positively influences survival in patients with advanced gastric cancer.[110,111] In the SEER database analysis that included 1377 patients with advanced gastric cancer, patients who had ≥15 N2 nodes and ≥20 N3 nodes examined had the best long-term survival outcomes.[110] 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.[112] 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 nodes (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 node removal at the time of gastrectomy. D0 refers to incomplete resection of N1 lymph nodes. D1 involves the removal of the greater and lesser omental lymph nodes (which would be the right and left cardiac lymph nodes along lesser and greater curvature and the suprapyloric lymph nodes along the right gastric artery and infra-pyloric area). D2 involves D1 dissection plus the removal of all the lymph 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 dissection of distant lymph nodes contributes to accurate staging of the disease; however, its contribution to the prolongation of survival is unclear.[71,110,113] 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.[114,115] 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.[114] The postoperative morbidity (25% vs. 43%, $P < .001$) and mortality (4% vs. 10%, $P = .004$) rates were higher for patients who underwent D2 lymph node dissection, with no difference in OS (30% vs. 35%, $P = .53$) between the two groups. After a median follow-up of 15 years, D2 lymph node dissection was associated with lower local recurrence (12% vs. 22%), regional recurrence (13% vs. 19%), and gastric cancer-related deaths (37% vs. 48%) than D1 lymph node dissection, but OS rates were similar between the two groups (21% and 29%, respectively, $P = .34$).[116] The British Cooperative trial conducted by the Medical Research Council also failed to demonstrate a survival benefit for D2 over D1 lymph node dissection (5-year OS rates of 35% and 33%, respectively).[115] Therefore, D2 lymph node dissection is considered a recommended but not required procedure in the West. However, there is uniform consensus that the removal of an adequate number of lymph nodes (≥15) is beneficial for staging purposes.

In contrast, other reports from Western countries have suggested 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.[117-119] In an analysis involving patients from the

Intergroup 0116 trial, Enzinger et al assessed the impact of hospital volume on the outcomes of patients who underwent lymph node dissection (54% underwent D0 lymph node dissection and 46% underwent D1 or D2 lymph node dissection).[117] 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 versus D2 lymph node dissection conducted by the Italian Gastric Cancer Study Group involving 267 patients (133 patients allocated to D1 lymph node dissection and 134 patients allocated to D2 lymph node dissection), the 30-day postoperative morbidity and mortality rates were not significantly different between the two groups.[118,119] After a 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, although this difference was not significant ($P$ = .695).[119] D2 lymph node dissection was also associated with a trend towards improved DFS in patients with advanced gastric cancer (pT2 to T4) and positive lymph nodes (59% vs. 38% for D1 lymph node dissection; $P$ = .055).[119]

Investigators have long argued that D2 lymph node dissection may be beneficial in select patients, if the complication rate is decreased. Although pancreatectomy and splenectomy have been widely performed with D2 lymph node dissections in Japan, both of these procedures have been shown to increase postoperative mortality and morbidity.[114,115,120,121] 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 in advanced gastric cancer patients.[120,121] 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 significant ($P$ = .29). Postoperative mortality rates were 0% and 1.3%, respectively, in the D1 and D2 groups. The overall 5-year morbidity rate was 20.9% and the postoperative in-hospital mortality rate was 3.1% for D2 lymph node dissection without pancreatectomy.[121] These rates are comparable with the rates for D1 lymph node dissections in the Dutch and United Kingdom trials.[114,115] Meta-analyses have 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.[122-124]

For patients with localized resectable gastric cancer, the NCCN Guidelines recommend gastrectomy with a D1 or a modified D2 lymph node dissection, with a goal of examining ≥15 lymph nodes.[110,116,120,121] The guidelines emphasize that D2 lymph node dissection should be performed by experienced surgeons in high-volume centers. Routine or prophylactic pancreatectomy is not recommended with D2 lymph node dissection,[106,125] and splenectomy is acceptable only when the 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 to open surgical procedures for patients with gastric cancer.[126-128] A prospective randomized study conducted by Hulscher et al compared early and 5-year clinical outcomes of laparoscopic versus open subtotal gastrectomy in 59 patients with distal gastric cancer.[129] 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 statistically significant. Although these results suggest that laparoscopic resection may be a feasible surgical strategy, the role of this approach in the treatment of gastric cancer requires further investigation in larger randomized clinical trials.

## Endoscopic Therapies

EMR and endoscopic submucosal dissection (ESD) have been used as alternatives to surgery for the treatment of patients with early-stage gastric cancer in Asia. However, 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.[130] 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.[131-135] In a study of 124 patients with mucosal early-stage gastric cancers (<2 cm in diameter), Uedo et al reported 5- and 10-year survival rates of 84% and 64%, respectively, for patients receiving EMR.[132] In another retrospective study of 215 patients with intramucosal gastric cancer, EMR had significantly shorter hospital stays, but was comparable to surgery in terms of risk of death and recurrence.[135] 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.[133]

ESD has also been reported to be a safe and effective procedure for patients with early-stage gastric cancer when performed by experienced endoscopists.[136-143] En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in several studies.[144-149] In a multicenter retrospective study of endoscopic resection (ER) in patients with early-stage gastric cancer, the 3-year recurrence-free rate in the ESD group was significantly higher than that in the EMR group (98% vs. 93%, respectively).[144] The complete resection rates for ESD were significantly better for lesions >5 cm in diameter, whereas the rates were not different between EMR and ESD for lesions <5 cm in diameter regardless of location.[145-147] ESD requires a higher level of skill to perform and is also associated with higher rates of bleeding and perforation complications.[149,150]

As these technologies continue to evolve as promising options for the diagnosis and treatment of early-stage gastric cancers, the NCCN Panel recommends that ER (EMR or ESD) be performed in high-volume medical centers with extensive experience in these techniques.

### Principles of Endoscopy

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

*Diagnosis*

Diagnostic endoscopies are performed to determine the presence and location of gastric neoplasia and to biopsy suspicious lesions. The location of the tumor in the stomach (cardia, fundus, body, antrum, or pylorus) relative to the EGJ should be carefully recorded to assist with treatment planning. Multiple biopsies (6–8), using standard-size endoscopy forceps, should be performed to provide sufficient material for histologic interpretation.[151] Use of larger forceps may improve this yield.

EMR or ESD of focal nodules (≤2 cm) 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 invasion, with the added potential of being therapeutic.[152,153] Cytologic brushings or washings are rarely adequate for the initial diagnosis, but can be useful in confirming persistent disease following treatment.

*Staging*

EUS provides accurate initial clinical staging of locoregional gastric cancer. EUS performed prior to any treatment provides evidence of the depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), and signs of metastasis, such as lesions in surrounding organs (M).[154,155] Accurate clinical staging is especially important in patients who are being considered for ER.[156]

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 can also be confirmed with the use of fine-needle aspiration (FNA) biopsy for cytology assessment.[157] FNA of suspicious lymph nodes should be performed without traversing an area of primary tumor or major blood vessels. The combined use of EUS and FNA (EUS-FNA) is a more accurate method for the diagnosis of gastric submucosal tumors and for differentiating potentially malignant lesions.[158]

*Treatment*

Carcinoma in situ (Tis) and well- to moderately differentiated lesions (pT1a or pT1b) without evidence of LVI, lymph node metastases, or ulceration can be effectively treated with EMR or ESD.[159] The Japanese Gastric Cancer guidelines recommend EMR for early-stage gastric cancer lesions that are ≤2 cm in diameter without associated ulcer formation.[160] EMR or ESD of poorly differentiated gastric cancers with evidence of LVI, invasion into the deep submucosa, lymph node metastases, and positive lateral or deep margins should be considered incomplete and additional therapy (gastrectomy with lymph node dissection) should be considered.[161]

Endoscopic therapies also play a role in palliative care. Endoscopic ablation can be performed for the short-term control of gastric cancer-associated bleeding. Endoscopic insertion of self-expanding metal stents (SEMS) is effective for the long-term relief of tumor obstruction at the EGJ or gastric outlet, though surgical gastrojejunostomy may be more efficacious for those with longer-term predicted survival.[162,163] Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic- or radiographic-assisted placement of a feeding gastrostomy (percutaneous endoscopic gastrostomy [PEG]) tube in patients with EGJ/gastric cardia obstruction or a feeding jejunostomy (percutaneous endoscopic jejunostomy [PEJ]) tube in patients with mid/distal gastric obstruction.[164]

*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. EUS performed in conjunction with endoscopy has a high sensitivity for the detection of recurrent disease.[165] EUS-FNA should be performed if suspicious lymph nodes or areas of wall thickening are observed. EUS performed after chemotherapy or radiation therapy (RT) has a reduced ability to accurately determine the post-treatment stage of disease.[166] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease.[167] See *Principles of Surveillance* in the algorithm for more information.

## Radiation Therapy

RT has been assessed in randomized trials in both the preoperative and postoperative settings in patients with resectable gastric cancer. Smalley et al have reviewed clinical and anatomic issues related to RT and offer

detailed recommendations for the application of RT to the management of patients with gastric cancer.[168]

RT (45–50.4 Gy) as a single modality has minimal value in patients with unresectable gastric cancer.[169] However, RT improved survival when used concurrently with fluorouracil. Moertel et al assessed fluorouracil plus RT compared with RT alone in the treatment of locally advanced unresectable gastric cancer.[170] Patients receiving combined modality treatment had significantly better median survival (13 months vs. 6 months) and 5-year OS (12% vs. none) rates. 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 concurrent bolus fluorouracil followed by maintenance with fluorouracil and lomustine.[171] At 3 years, the survival curve reached a plateau in the combined modality arm while tumor-related deaths continued to occur in the chemotherapy-alone arm, suggesting that a small fraction of patients can be cured with combined modality therapy.

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 either RT or chemotherapy.[172] At the 5-year follow-up, no survival benefit was seen for patients receiving postoperative RT or chemotherapy compared with those who underwent surgery alone. However, 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, which randomized 370 patients to preoperative RT or surgery alone, there was a significant improvement in survival with preoperative RT (30% vs. 20%, $P = .0094$).[173] Resection rates were also higher with preoperative RT (89.5%) compared to surgery alone (79%), suggesting that preoperative RT improves local control and survival. The results from a systematic review and meta-analysis also showed a significant 5-year survival benefit with the addition of RT to surgery in patients with resectable gastric cancer.[174]

Intensity-modulated RT (IMRT) has the potential to reduce radiation-related toxicity by delivering large doses of RT to target tissues while sparing adjacent organs. Several retrospective studies have demonstrated the feasibility of IMRT in the treatment of localized and advanced gastric cancer.[175-179] However, the impact of IMRT on survival of patients with gastric cancer needs to be evaluated in randomized prospective 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 Type I and II tumors should be managed with RT guidelines applicable to esophageal and EGJ cancers (see the NCCN Guidelines for Esophageal and EGJ Cancers). Depending on the clinical situation, Siewert Type III tumors may be 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. A dose range of 45 to 50.4 Gy delivered in fractions of 1.8 Gy per day is recommended by the panel. Higher doses may be used as a boost for positive surgical margins in select patients.

*Simulation and Treatment Planning*

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

IMRT may be used in clinical settings where dose reduction to organs at risk is required and cannot be achieved by 3D techniques.[175-179] Target volumes need to be carefully defined and encompassed when designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion should be taken into account. In designing IMRT for organs at risk, such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses.

*Target Volume*

In the preoperative setting, pretreatment diagnostic studies such as EUS, upper GI endoscopy, PET, and CT scans should be used to identify the primary tumor and pertinent nodal groups. In the postoperative setting, clip placement should be performed in addition to pretreatment diagnostic studies to identify the tumor/gastric bed, the anastomosis or stumps, and pertinent nodal groups. Nodal areas at risk include the 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 into the gastric wall. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity. See *Principles of Radiation Therapy* in the algorithm for more information.

*Normal Tissue Tolerance and Dose Limits*

Treatment planning is essential to reduce unnecessary RT doses to organs at risk (liver, kidneys, small bowel, spinal cord, heart, and lungs) and to limit the volume of organs at risk receiving high RT doses. Effort should be made to keep RT doses to the left ventricle of the heart to a minimum.

Lung dose-volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients treated with concurrent chemoradiation. Although every effort should be made to keep the lung volume and doses to a minimum, it is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances. Optimal criteria for DVH parameters are actively being developed at NCCN Member Institutions.

*Supportive Care*

Careful monitoring and management of acute toxicities with aggressive supportive care is essential to avoid treatment interruptions or dose reductions. Prophylactic antiemetics should be given when appropriate. Additionally, antacid and antidiarrheal medications may be prescribed when needed. If the caloric intake is inadequate (<1500 kcal/d), oral and/or enteral nutrition should be considered. Feeding jejunostomies may be placed if clinically indicated. Adequate enteral and/or IV hydration may be necessary throughout chemoradiation and early recovery.

## Combined Modality Therapy

Combined modality therapy has been shown to significantly increase survival in gastric cancer patients in several studies.[180] Postoperative

chemoradiation or perioperative chemotherapy are the preferred approaches for treatment of localized gastric cancer.

### Preoperative Chemoradiation Therapy

In a pilot study, Lowy et al assessed the feasibility of preoperative chemoradiation (45 Gy of external beam RT [EBRT] with concurrent continuous infusion of fluorouracil) versus intraoperative RT (IORT; 10 Gy) in the treatment of patients with potentially resectable gastric cancer.[181] Significant pathologic response was seen in 63% of patients, and pathologic complete response (pCR) was seen in 11% of patients, who received preoperative chemoradiation. However, the value of preoperative chemoradiation for patients with resectable gastric cancer remains uncertain. The regimens listed in the NCCN Guidelines are derived from phase III trials that have included patients with cancers of the esophagus and/or EGJ.

Results from the multicenter phase III randomized CROSS trial, the largest trial in its class, showed that preoperative chemoradiation with carboplatin and paclitaxel significantly improved OS and DFS compared to surgery alone in patients with resectable (T2-3,N0-1,M0) esophageal or EGJ cancers (n = 368).[182] Median survival time was 49 months in the preoperative chemoradiation arm compared to 24 months in the surgery alone arm. The R0 resection rate was also higher in the preoperative chemoradiation arm compared to the surgery alone arm (92% vs. 69%, respectively).The 1-, 2-, 3-, and 5-year survival rates were 82%, 67%, 58%, and 47%, respectively, in the preoperative chemoradiation arm compared to 70%, 50%, 44%, and 34%, respectively, in the surgery alone arm. A study reporting the long-term results of the CROSS trial verified that median OS was significantly improved in the preoperative chemoradiation group after a median follow-up time of 84.1 months.[183] Additionally, the CALGB 9781 prospective trial that randomized patients with stage I–III esophageal cancers to receive preoperative chemoradiation with cisplatin and fluorouracil or surgery alone also found a survival benefit for preoperative chemoradiation.[184] After a median follow-up time of 6 years, an intent-to-treat analysis showed a median survival of 4.5 years versus 1.8 years in favor of preoperative chemoradiation. Patients receiving preoperative chemoradiation also had a significantly better 5-year OS rate (39% vs. 16%). The panel recommends extension of these regimens, which have confirmed OS benefits in patients with resectable esophageal or EGJ cancers, to patients with resectable gastric cancers.

*Preoperative Sequential Chemotherapy and Chemoradiation Therapy*

Several studies have shown that preoperative sequential chemotherapy followed by chemoradiation yields a pathologic response in patients with locally advanced resectable gastric cancer.[185-189] In the RTOG 9904 trial, preoperative chemotherapy with fluorouracil and cisplatin followed by concurrent chemoradiation with infusional fluorouracil and paclitaxel resulted in a pCR rate of 26% in patients with localized gastric adenocarcinoma. D2 lymph node dissections and R0 resections were achieved in 50% and 77% of patients, respectively.[187] 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.[189] R0 resection was achieved in 65% of patients and the median survival and actuarial 2-year survival rates were 14.5 months and 35%, respectively.[189]

In contrast, the phase III randomized CRITICS trial, which compared perioperative chemotherapy with preoperative chemotherapy followed by postoperative chemoradiation in 788 patients with resectable gastric adenocarcinoma, found that postoperative chemoradiation did not improve overall survival compared with postoperative chemotherapy.[190] Patients were randomized to receive either 3 preoperative and 3 postoperative

cycles of modified ECF regimens (chemotherapy group; n = 393) or RT (45 Gy delivered in 25 fractions of 1.8 Gy) combined with capecitabine and cisplatin (chemoradiation group; n = 395). At a median follow-up of 61.4 months, median OS was 43 months (95% CI, 31–57) in the chemotherapy group and 37 months (95% CI, 30–48) in the chemoradiation group (hazard ratio [HR] = 1.01; 95% CI, 0.84–1.22; *P* = .90). Since there was poor postoperative patient compliance in both treatment groups, preoperative treatment strategies need to be optimized. An ongoing phase II trial (CRITICS II), which will compare 3 preoperative strategies (chemotherapy, concurrent chemoradiation, and sequential chemotherapy and chemoradiation), is actively recruiting participants with resectable gastric cancer (Clinical Trial ID: NCT02931890).

**Postoperative Chemoradiation Therapy**

The landmark Intergroup trial SWOG 9008/INT-0116 investigated the effectiveness of surgery plus postoperative chemoradiation on the survival of patients with resectable gastric or EGJ adenocarcinoma.[191,192] In this trial, 556 patients (stage IB to IV, M0) were randomized to receive surgery plus postoperative chemoradiation (n = 281; bolus fluorouracil and leucovorin before and after concurrent chemoradiation with the same regimen) or surgery alone (n = 275). The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%). Median OS in the surgery-only group was 27 months compared to 36 months in the postoperative chemoradiation group (*P* = .005). The chemoradiation group also had better 3-year OS (50% vs. 41%) and relapse-free survival (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 a median follow-up time of >10 years, survival remained improved in patients treated with postoperative chemoradiation.[192] No increases in late toxic effects were noted.

The results of the INT-0116 trial have established postoperative chemoradiation as a standard of care in patients with completely resected gastric or EGJ adenocarcinoma who have not received preoperative therapy. However, the dosing schedule of chemotherapy agents used in this trial 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% 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. Therefore, the doses and schedule of chemotherapy agents used in the INT-0116 trial are no longer recommended due to concerns regarding toxicity. See *Principles of Systemic Therapy- Regimens and Dosing Schedules* in the algorithm for modifications to this regimen recommended by the panel.

The degree of lymph node dissection during gastrectomy may influence the efficacy of postoperative chemoradiation. A retrospective analysis that compared the outcomes of patients treated with surgery alone to patients treated with postoperative fluoropyrimidine-based chemoradiation reported that 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). However, there was no significant difference in recurrence rates between the two groups following D2 lymph node dissection.[193] The results of the phase III ARTIST trial also showed that postoperative chemoradiation did not significantly reduce recurrence after D2 lymph node dissection in patients with curatively resected gastric cancer (n = 458; stage IB-IV, M0).[194,195] However, in a subgroup analysis of patients with positive lymph nodes, postoperative chemoradiation was associated with a significant prolongation of 3-year DFS compared to postoperative chemotherapy alone (77.5% vs. 72%; *P* = .0365).[194]

## Chemotherapy

### Perioperative Chemotherapy

The survival benefit of perioperative chemotherapy in gastric cancer was first demonstrated in the landmark phase III MAGIC trial.[196] This study, which compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improved OS and PFS in patients with non-metastatic stage II and higher gastric and EGJ adenocarcinoma. In the phase II/III AIO-FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen with a primary endpoint of pCR of the primary tumor.[197] Patients with resectable non-metastatic gastric or EGJ adenocarcinoma (≥cT2 and/or N+) were randomized to receive either 3 preoperative and 3 postoperative cycles of ECF (n = 137) or 4 preoperative and 4 postoperative cycles of FLOT (n = 128). In a report of the findings from the phase II part of the trial, FLOT was associated with significantly higher proportions of patients achieving pCR than was ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; *P* = .02).[197] Additionally, FLOT was associated with a reduction in the percentage of patients experiencing at least one grade 3–4 adverse event, including neutropenia, leucopenia, nausea, infection, fatigue, and vomiting (40% of patients in the ECF group vs. 25% of patients in the FLOT group). Therefore, perioperative chemotherapy with FLOT has largely replaced ECF due to its increased efficacy and similar safety profile. The phase III part of this trial is ongoing (Clinical Trials ID: NCT01216644). However, because of considerable toxicity associated with the FLOT regimen, the panel recommends its use in select patients with good performance status. The preferred perioperative regimen for patients with poor performance status is FOLFOX.

In the FNCLCC ACCORD 07 trial (n = 224 patients; 25% had gastric adenocarcinoma), 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.[198] At the median follow-up time of 5.7 years, the 5-year OS rate was 38% for patients in the perioperative chemotherapy group and 24% for patients in the surgery alone group (*P* = .02). The corresponding 5-year DFS rates were 34% and 19%, respectively. Although this trial was prematurely terminated due to low accrual, the panel feels that fluorouracil and cisplatin is a viable treatment option for patients with locally advanced resectable gastric cancers.

### Postoperative Chemotherapy

Postoperative chemotherapy following complete resection has not been associated with a significant survival benefit in patients with early-stage gastric cancer.[199-203] However, the large, randomized, phase III CLASSIC trial has documented a survival benefit for postoperative chemotherapy after curative D2 lymph node dissection in patients with stage II-IIIB gastric cancer.[204,205]

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 1035 patients with stage II or IIIB gastric cancer.[204,205] In this study, patients were randomized to receive surgery alone (n = 515) or surgery followed by postoperative chemotherapy (n = 520). After a median follow-up of 34.2 months, postoperative chemotherapy with capecitabine and oxaliplatin significantly improved DFS (74%) compared to surgery alone (59%) for all disease stages (*P* < .0001). After a median follow-up of 62.4 months, the estimated 5-year DFS was 68% for the postoperative chemotherapy group compared to 53% for the surgery alone group; the corresponding

estimated 5-year OS rates were 78% and 69%, respectively.[205] These results support the use of postoperative chemotherapy after curative surgery with D2 lymph node dissection in patients with advanced 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 the treatment of choice for this patient population.[191-193]

### 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 or metastatic gastric cancer.[206,207] Chemotherapy regimens including agents such as fluorouracil, cisplatin, irinotecan, paclitaxel, docetaxel, and others have demonstrated activity in patients with advanced gastric cancer.[208-226]

Cisplatin in combination with fluorouracil, with or without docetaxel, has also demonstrated activity in patients with locally advanced or metastatic gastric cancer.[227-230] In a randomized multinational phase III study (V325), 445 untreated patients with advanced gastric cancer were randomized to receive either docetaxel, cisplatin, and fluorouracil (DCF) or cisplatin and fluorouracil (CF) every 3 weeks.[227] The majority of patients had advanced gastric cancer and 19% to 25% of patients had EGJ cancer. At a median follow-up time of 13.6 months, time to progression and OS were significantly longer in the DCF group compared to the CF group (5.6 months vs. 3.7 months and 9.2 months vs. 8.6 months, respectively). At a median follow-up time of 23.4 months, the overall confirmed response rate was also significantly higher with DCF than CF (37% vs. 25%). The 2-year survival rates for DCF and CF were 18% and 9%, respectively. However, DCF was associated with increased myelosuppression and infectious complications. Additionally, grade 3 or 4 toxicities 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 in both treatment arms (DCF vs. CF) were neutropenia (82% vs. 57%), stomatitis (21% vs. 27%), diarrhea (19% vs. 8%), lethargy (19% vs. 14%) and complicated neutropenia (29% vs. 12%).

Various modifications of the DCF regimen have demonstrated efficacy and improved safety in clinical trials of patients with advanced gastric cancer compared to the DCF regimen evaluated in the V325 study.[231-236] In a randomized phase II trial that evaluated the efficacy and tolerability of docetaxel plus oxaliplatin with or without infusional fluorouracil 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 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) or docetaxel, oxaliplatin, and capecitabine (26%, 5.6 months, and 11.3 months, respectively).[235] The frequency of grade 3 or 4 toxicities 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 much lower than the 16.4% reported with DCF in the V325 trial.

In another randomized multicenter phase II study, a dose-modified DCF regimen was less toxic than standard DCF (even when given with growth factors) and was also associated with improved efficacy in previously untreated patients with metastatic gastric or EGJ adenocarcinoma.[236] In this study, 85 patients were randomized to receive dose-modified DCF (docetaxel 40 mg/m$^2$, cisplatin 40 mg/m$^2$, and fluorouracil 2000 mg/m$^2$; n = 54) or the standard DCF regimen (docetaxel 75 mg/m$^2$, cisplatin 75

mg/m$^2$, and fluorouracil 750 mg/m$^2$ with growth factor support; n = 31). The standard DCF arm closed early due to 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 standard 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 NCCN Panel does not recommend the standard DCF regimen as used in the V325 trial.[227] Therefore, dose-modified DCF or other DCF modifications should be used as alternative options for first-line therapy.[232,235,236]

The combination of fluorouracil, oxaliplatin, and leucovorin (FOLFOX) has been evaluated as an alternative to cisplatin-based regimens in patients with advanced or metastatic gastric cancer.[229,237,238] A phase III trial conducted by the German Study Group showed that FOLFOX (referred to as FLO) was associated with significantly less toxicity and showed a trend towards improved median PFS (5.8 vs. 3.9 months) compared to fluorouracil, leucovorin, and cisplatin (FLP) in patients with metastatic esophagogastric cancer.[229] However, there was no significant difference in median OS (10.7 vs. 8.8 months, respectively) between the two groups. In patients >65 years, FOLFOX 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 OS (13.9 vs. 7.2 months) compared with FLP.

Capecitabine-based regimens have also been evaluated in several studies for patients with advanced gastric cancer.[239-242] A phase III randomized trial (ML 17032) evaluated the efficacy of combined capecitabine and cisplatin (XP) compared to fluorouracil and cisplatin (FP) as first-line therapy in patients with previously untreated advanced gastric cancer.[241] 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. However, no difference in median PFS was observed (5.6 months for XP and 5.0 months for FP). 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 to the 664 patients treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.[243] These results suggest that capecitabine is as effective as fluorouracil in the treatment of patients with advanced gastroesophageal cancers.

Irinotecan-based combination regimens have been explored extensively in clinical trials involving patients with advanced or metastatic gastric cancer.[230,244-257] The results of a randomized phase III study comparing irinotecan in combination with fluorouracil and leucovorin (FOLFIRI) to CF in patients with advanced gastric or EGJ adenocarcinoma (n = 337) showed that FOLFIRI was non-inferior to CF in terms of PFS (PFS at 6 and 9 months were 38% and 20%, respectively, for FOLFIRI compared to 31% and 12%, respectively, for CF) but not in terms of OS (9 months vs. 8.7 months) or time to treatment progression (5 months vs. 4.2 months).[252] FOLFIRI was also associated with a more favorable toxicity profile. A more recent phase III trial (French Intergroup Study) compared FOLFIRI with ECF as first-line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[257] In this study, 416 patients (65% 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 ECF (5.1 months vs. 4.2 months; *P* = .008).[257] However, 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%). Importantly, FOLFIRI was less toxic and better tolerated than ECF. Therefore, the NCCN Panel feels that FOLFIRI is an acceptable option for first-line therapy in patients with advanced or

metastatic gastric cancer. Second-line therapy with FOLFIRI was also shown to be active and well-tolerated in patients with metastatic gastric cancer with disease progression on docetaxel-based chemotherapy.[258]

## Targeted Therapies

The targeted therapies trastuzumab, ramucirumab, and pembrolizumab have been approved for the treatment of advanced or metastatic gastric cancer.[89,93,259,260] A variety of investigational agents targeting EGFR and c-MET have also shown encouraging results in patients with advanced or metastatic gastric cancer.[261-263] However, definite results of these ongoing studies are not yet available.

### Trastuzumab

The ToGA trial was 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.[89] In this trial, 594 patients with HER2-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.[89] 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. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone in patients with HER2 overexpression or amplification (13.8 vs. 11 months, respectively; *P* = .046). This study established trastuzumab in combination with chemotherapy as the standard of care for patients with HER2-positive advanced or metastatic gastric or EGJ adenocarcinoma. However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3+ or IHC 2+ and FISH positivity. In a post-hoc subgroup analysis, 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).

In a retrospective study of 34 patients with metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen improved tolerability compared with cisplatin plus fluorouracil in untreated patients with HER2-positive tumors.[264] The ORR with this regimen was 41% and median PFS and OS were 9.0 months and 17.3 months, respectively. The most frequent grade 3 to 4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combination of mFOLFOX6 and trastuzumab is an effective regimen with an acceptable safety profile and warrants further study in patients with HER-2+ gastroesophageal cancers.

### Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown promising results in patients with previously treated advanced or metastatic gastroesophageal cancers in phase III clinical trials.[259,260] An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[259] In this study, 355 patients were randomized to receive ramucirumab (n = 238; 178 had gastric cancer and 60 had EGJ adenocarcinoma) or placebo (n = 117; 87 had gastric cancer and 30 had 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 similar between the two groups.

In a more recent international phase III randomized trial (RAINBOW) that evaluated paclitaxel with or without ramucirumab in patients (n = 665) 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.[260] Patients randomized to receive ramucirumab plus paclitaxel (n = 330) had significantly longer median OS (9.63 months) compared to patients receiving paclitaxel alone (n = 335; 7.36 months; $P < .0001$). The median PFS was 4.4 months and 2.86 months, respectively, for the two treatment groups. Additionally, the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone ($P = .0001$). However, neutropenia and hypertension were more common with ramucirumab plus paclitaxel. Based on the results of these two studies, ramucirumab as a single agent or in combination with paclitaxel was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy.

**Pembrolizumab**

Pembrolizumab is a PD-1 antibody that was approved by the FDA in 2017 for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[92] This first-ever tissue- and site-agnostic approval was based on several clinical trials that demonstrated the efficacy of pembrolizumab in MSI-H/dMMR solid tumors, including the KEYNOTE-016 trial.[265-267]

KEYNOTE-016 is a multicenter, open-label, phase II trial that evaluated the activity of pembrolizumab in patients with metastatic treatment-refractory dMMR colorectal cancers, MMR-proficient colorectal cancers, or dMMR non-colorectal cancers who had received at least two previous lines of chemotherapy. The immune-related ORR for patients with dMMR non-colorectal cancers was 71%, with an immune-related PFS rate of 67% at 20 weeks.[265] Median PFS was 5.4 months. Adverse events of clinical interest included rash or pruritus (24%, any grade), thyroiditis, hypothyroidism, hypophysitis (10%, any grade), and asymptomatic pancreatitis (15%, any grade), which were similar to those reported in other trials involving pembrolizumab. In a recently reported expansion of this study, data from 86 patients with dMMR tumors representing 12 different cancer types achieved an ORR of 53% with 21% of patients achieving a complete response.[266] While median PFS and OS have not yet been reached, estimates of these outcomes at 1 and 2 years are 64% and 53% for PFS and 76% and 64% for OS, respectively. The KEYNOTE-016 trial is still recruiting patients at several institutions (Clinical Trial ID: NCT01876511).

Another 2017 pembrolizumab approval was for the treatment of patients with recurrent, locally advanced, or metastatic PD-L1–positive gastric or EGJ adenocarcinoma who have progressed following two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy.[93] This approval was based on the results of two KEYNOTE studies (KEYNOTE-012 and KEYNOTE-059). KEYNOTE-012 was a multicenter, open-label, phase Ib study that evaluated the safety and activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic gastric or EGJ adenocarcinoma.[268] The ORR was 22% and 13% of patients had grade 3 or 4 treatment-related adverse events including fatigue, pemphigoid, hypothyroidism, peripheral sensory neuropathy, and pneumonitis. The results of this trial justified the study of pembrolizumab monotherapy in cohort 1 of the phase II KEYNOTE-059 trial, which included 259 patients with gastric or EGJ adenocarcinoma who had progressed on two or more prior lines of therapy.[269] Of those with PD-L1–positive tumors (57.1%; n = 143), the ORR was 15.5% (95% CI, 10.1–22.4), with 2% (95% CI, 0.4–5.8) of patients achieving a complete response. The median duration of

response was 16.3 months. Analysis of cohorts 2 and 3 of the KEYNOTE-059 trial, which examine the efficacy of first-line pembrolizumab as a monotherapy or in combination with chemotherapy, is ongoing (Clinical Trial ID: NCT02335411).[270-272]

Based on the KEYNOTE trials, pembrolizumab shows manageable toxicity and promising antitumor activity in patients with heavily pretreated PD-L–-positive or MSI-H/dMMR advanced gastric adenocarcinoma. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing clinical trials of pembrolizumab in patients with gastric cancer.

### Other Immunotherapies

Preliminary studies have demonstrated the activity of nivolumab (a PD-1 antibody) and ipilimumab (a CTLA-4 antibody) for the treatment of advanced, recurrent, or metastatic gastric and EGJ cancers.[263,273-275] While these data are encouraging, the panel considers these studies too preliminary for inclusion in the guidelines and will reevaluate once more mature data become available.

CheckMate-032 is an ongoing phase I/II open-label study to evaluate the safety and activity of nivolumab alone or in combination with ipilimumab for advanced or metastatic gastric, esophageal, and EGJ cancers.[263] Patients, irrespective of PD-L1 status, were treated with nivolumab 3 mg/kg (N3, n = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1 + I3, n = 49), or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3 + I1, n = 52). The ORR for each treatment group was 12%, 24%, and 8% for N3, N1+I3, and N3+I1, respectively. Among PD-L1–positive patients, the ORR was 19%, 40%, and 23%, respectively, in each treatment group. OS among PD-L1–positive patients was 6.2 and 5.6 months, respectively, for N3 and N3+I1, while OS was not reached in the N1+I3 treatment group. Treatment-related adverse events were consistent with previous reports, with serious events occurring in 10%, 43%, and 23% of patients treated with N3, N1+I3, and N3+I1, respectively. Although encouraging in combination with nivolumab, ipilimumab monotherapy has not shown any benefit in the treatment of gastric or EGJ cancers. A phase II trial comparing ipilimumab to best supportive care for treatment of gastric or EGJ cancers following first-line chemotherapy showed no significant improvement in OS or PFS for patients treated with ipilimumab.[275]

## 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.[108] Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of patients with gastric cancer. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the patient. See *Principles of Multidisciplinary Team Approach for Esophagogastric Cancers* in the algorithm for more information.

### Workup

Newly diagnosed patients should undergo a complete history and physical examination, complete blood count (CBC), comprehensive chemistry profile, and upper GI endoscopy with biopsy of the primary tumor. CT scan (with oral and IV contrast) of the chest, abdomen, and pelvis should also be performed. PET/CT evaluation from skull base to mid-thigh is recommended, if clinically indicated and if metastatic disease 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.[276-279] EUS is preferred if early-stage disease is suspected or if early-stage versus locally advanced disease needs to be determined.

HER2, MSI-H/dMMR, and PD-L1 testing are recommended if metastatic disease is documented or suspected. Assessment of Siewert tumor type should also be included as part of the initial workup. The guidelines also recommend screening for family history of gastric cancers. Referral to a cancer genetics professional is recommended for those with a family history or a known high-risk syndrome associated with gastric cancer. See *Principles of Genetic Risk Assessment for Gastric Cancer* in the algorithm for more information.

Initial workup enables patients to be classified into three clinical stage groups:

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

### Additional Evaluation

Additional evaluations are warranted to assess a patient's medical condition, his/her ability to tolerate major surgery, and the feasibility of resection. These evaluations may include pulmonary function studies, cardiac testing, and nutritional assessment. Laparoscopy with cytology (category 2B) may be performed to evaluate for peritoneal spread when considering chemoradiation and/or surgery for patients with unresectable locoregional disease, but is not indicated if palliative resection is planned. Laparoscopy with cytology is indicated for clinical stage T1b or higher.

Additional evaluation enables patients with locoregional cancer to be further classified into the following groups:

- Medically fit patients with potentially resectable disease
- Medically fit patients with unresectable disease
- Non-surgical candidates (medically unable to tolerate major surgery or medically fit patients who decline surgery)

### Primary Treatment

*Medically Fit Patients*

ER or surgery are the primary treatment options for patients with localized (cTis or cT1a) tumors. Surgery is the primary treatment option for patients with potentially resectable locoregional tumors (cT1b or higher, any N). However, since surgery alone is insufficient for most patients with cT2 or higher tumors, perioperative chemotherapy (category 1; preferred) or preoperative chemoradiation (category 2B) should be considered.[187,188,197,198] Chemoradiation, systemic therapy, or palliative management are the recommended treatment options for patients whose locoregional cancer is found to be surgically unresectable after laparoscopic staging.[170,280]

All patients diagnosed with metastatic disease should be treated with palliative/best supportive care. See the *Principles of Palliative Care/Best Supportive Care* in the algorithm for more information.

*Non-surgical Candidates*

ER is recommended for non-surgical candidates with cTis or cT1a tumors. Definitive chemoradiation or palliative management are the recommended treatment options for patients with locoregional disease. All patients diagnosed with metastatic disease should be treated with palliative/best supportive care. See the *Principles of Palliative Care/Best Supportive Care* in the algorithm for more information.

### Response Assessment and Additional Management

Additional management options are based on the assessment of response to primary treatment. Therefore, chest/abdominal/pelvic CT scan with contrast should be performed after the completion of perioperative

chemotherapy or preoperative chemoradiation. Surgery is preferred for patients with no evidence of disease. Surveillance should be offered only to those patients who refuse surgery. Patients with persistent local disease should be managed with surgery (preferred) or palliative management while those with unresectable or metastatic disease should receive palliative management only.

Following primary treatment, non-surgical candidates should be restaged using chest/abdominal/pelvic CT scan with contrast. A CBC and comprehensive chemistry profile is also recommended. PET/CT scan should be performed as clinically indicated. Surgery is preferred, if appropriate, for patients found to have resectable, medically operable disease at restaging. Patients with unresectable, medically inoperable, or metastatic disease at restaging should receive palliative management.

**Postoperative Management**

Postoperative management is based on pathologic tumor stage, nodal status, surgical margins, the extent of lymph node dissection, and previous treatment.

*Patients Who Have Not Received Preoperative Chemotherapy or Chemoradiation*

The benefit of postoperative chemoradiation for patients who have not received preoperative therapy has been established in randomized studies.[191,192,194,195] Therefore, postoperative chemoradiation is recommended for all patients following an R1 or R2 resection, patients with pT3-pT4, any N or any pT, N+ tumors who received less than a D2 dissection (category 1), and select high-risk patients with pT2, N0 tumors following an R0 resection. High-risk features include poorly differentiated or higher grade cancer, LVI, neural invasion, age <50 years, and not undergoing D2 lymph node dissection.[281] Palliative management, as clinically indicated, is an alternate option for patients with R2 resection. Patients with metastatic disease (pM1) should receive palliative management only.

Based on the results of the INT-0116 trial, the panel has included chemotherapy before and after chemoradiation for patients with pT3-pT4, any N or any pT, N+ tumors if they received less than a D2 dissection (category 1), as well as high-risk patients with pT2, N0 tumors.[191,192] However, the panel does not recommend the doses and schedule of chemotherapy agents as used in the INT-0116 trial due to concerns regarding toxicity. Instead, the panel recommends the use infusional fluorouracil or capecitabine before and after fluoropyrimidine-based chemoradiation. Patients with pT3-pT4, any N or any pT, N+ tumors who have undergone primary D2 lymph node dissection may alternatively receive chemotherapy (category 1).[204,205]

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 pTis or pT1, N0 tumors, the panel does not recommend postoperative chemoradiation for this group of patients, except for select high-risk patients with pT2, N0 tumors. Therefore, surveillance is recommended for patients with pTis tumors and non–high-risk patients with pT2, N0 tumors, following R0 resection.

*Patients Who Have Received Preoperative Chemotherapy or Chemoradiation*

Patients who have received preoperative chemoradiation should be observed until disease progression following R0 resection, regardless of tumor stage or nodal status. However, patients who have received preoperative chemotherapy could receive postoperative chemotherapy following R0 resection (category 1). In the absence of distant metastases, chemoradiation is recommended for patients with R1 or R2 resection, only if not received preoperatively. Although this approach has not been evaluated in prospective studies, the panel feels this is a reasonable

treatment option given the significantly worse prognosis associated with margin-positive resections, especially in patients who have not received preoperative chemoradiation. Alternative treatment options following R1 resection include chemotherapy (if received preoperatively) or re-resection, if feasible. Palliative management should be offered to all patients with metastatic disease and may also be offered to patients with R2 resection, if clinically indicated.

### Follow-up/Surveillance

All patients should be followed systematically. However, surveillance strategies after curative intent (R0) resection for gastric cancer remain controversial with sparse prospective data to construct evidence-based recommendations that balance the benefits and risks, including costs, within this cohort. The surveillance strategies provided in this guideline are based on the currently available retrospectively analyzed literature[282-291] and expert consensus. While studies have shown that most gastric cancer recurrences occur within the first 2 years after the completion of local therapy and almost all recurrences occur by 5 years,[282,284,289] a study of 1573 patients who underwent curative intent therapy showed that 7.6% of recurrences occurred >5 years after treatment.[285]Therefore, additional follow-up after 5 years may be considered based on risk factors and comorbidities. Differences in follow-up for early-stage gastric cancer reflect a heterogeneous potential for relapse and OS.[282-286,289,290] For example, whereas R0 resected Tis disease has a prognosis that approximates a non-cancer cohort, T1a, N0 and T1b disease do not perform as well. Thus, surveillance recommendations vary according to the depth of invasion and treatment modality.

In general, surveillance for all patients should include a complete history and physical examination every 3 to 6 months for the first 2 years, every 6 to 12 months for years 3 to 5, and then annually thereafter. CBC and chemistry profile should be obtained as clinically indicated. Patients with early-stage (Tis or T1a) tumors treated by ER should be surveilled with EGD every 6 months for the first year, and then annually for either 3 years (Tis) or 5 years (T1a). EGD surveillance beyond 5 years for patients with T1a tumors should be based on symptoms and/or radiographic findings. Patients with stage I disease (T1a or T1b) treated with surgery should receive EGD as clinically indicated. Patients with Tis or stage I tumors should also receive routine imaging (CT scan of the chest/abdomen and pelvis with contrast) as clinically indicated. Patients with stage II or III disease should be imaged with chest/abdominal/pelvic CT scan with contrast every 6 to 12 months for the first 2 years, then annually for up to 5 years. PET/CT can be considered as clinically indicated. EGD should also be performed as clinically indicated for patients who had partial or subtotal gastrectomy. Surveillance for patients undergoing curative intent total gastrectomy should follow these surveillance recommendations, except for endoscopy. Endoscopy has no role in the routine surveillance of these patients and should only be used if patients are symptomatic. Surgically resected patients with stage I–III disease should also be monitored for nutritional deficiencies (eg, $B_{12}$ and iron), especially after total gastrectomy, and treated as indicated.

### Unresectable Locally Advanced, Recurrent, or Metastatic Disease

When locoregional recurrence develops after prior therapy, the clinician should determine whether surgery is an appropriate option. Surgery should be considered in medically fit patients with isolated resectable locoregional recurrences. Palliative management, which includes chemoradiation (only if locally unresectable and if not previously received), systemic therapy, and best supportive care, is recommended for patients with unresectable or metastatic recurrence.

Best supportive care is always indicated for patients with unresectable locally advanced, recurrent, or metastatic disease. The decision to offer best supportive care alone or with systemic therapy is dependent upon 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 of patients with cancer.[292-294] ECOG PS is a 5-point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher ECOG PS scores are considered to have worse performance status. KPS is an ordered scale with 11 levels (0%–100%) in which patients are classified based on their degree of functional impairment (activity, work, and self-care). Lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score <60% or an ECOG PS score ≥3 should be offered best supportive care only. Systemic therapy can be offered in addition to best supportive care for patients with better performance status (KPS score of ≥60% or ECOG PS score ≤2). See *Best Supportive Care* below for more information.

First-line palliative systemic therapy with two-drug chemotherapy regimens is preferred for patients with advanced disease because of their lower toxicity. 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.[89] The use of trastuzumab in combination with an anthracycline is not recommended.

The selection of regimens for second-line or subsequent therapy for patients with advanced or metastatic disease is dependent upon prior therapy and performance status. Based on the available data and FDA approvals, the guidelines have included ramucirumab as a single-agent or in combination with paclitaxel (both category 1) as preferred options for second-line or subsequent therapy.[259,260] Irinotecan or docetaxel as single agents are also included as category 1 preferred options for second-line therapy.[295-297] Fluorouracil in combination with irinotecan may be considered as a preferred second-line option if not previously used in first-line therapy.[298-300] Other regimens for second-line therapy include irinotecan plus cisplatin[301,302] and docetaxel plus irinotecan[303] (category 2B). Pembrolizumab is an option for second-line and subsequent therapy for MSI-H/dMMR tumors.[265,268] Third-line and subsequent therapy options include pembrolizumab for PD-L1–positive adenocarcinoma[269] as well as regimens recommended for second-line therapy that were not previously used.

The survival benefit of palliative systemic therapy compared to best supportive care alone for patients with metastatic or advanced gastric cancer has been demonstrated in randomized trials.[295,297,304,305] In a comparison between chemotherapy and best supportive care versus best supportive care alone, OS (8 months vs. 5 months, though not statistically significant) and time to progression (5 months vs. 2 months) were longer in patients receiving chemotherapy for advanced gastric cancer.[304] More patients in the chemotherapy group (45%) had an improved or prolonged quality of life for a minimum of 4 months compared to those who received best supportive care alone (20%). In a randomized phase III study, second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n = 40).[295] The study was closed prematurely due to poor accrual. Median survival was 4 months in the irinotecan arm compared to 2.4 months in the best supportive care only arm. In a 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 alone in patients with advanced gastric cancer.[305] In a 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, or stomach that had

progressed on or within 6 months of treatment with platinum fluoropyrimidine–based combination chemotherapy.[297] In this study, patients (n = 168) with an ECOG PS score of 0 to 2 were randomized 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 in the docetaxel group compared to 3.6 months for those in the active symptom control group (*P* = .01). Docetaxel was associated with higher incidence of grade 3/4 neutropenia, infection, and febrile neutropenia. However, disease-specific, health-related quality-of-life measures showed benefits for docetaxel in reducing dysphagia and abdominal pain.

See *Principles of Systemic Therapy* in the algorithm for a full list of specific regimens for unresectable, locally advanced, recurrent, or metastatic disease. Some of the chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

### Leucovorin Shortage

There is currently a shortage of leucovorin in the United States.[306] 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.[307-309] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. Under this circumstance, a modest increase in fluorouracil dose (in the range of 10%) may be considered for patients who can tolerate this without grade 2 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, best supportive care provides symptom relief and may result in prolongation of life, improvement in nutritional status, and overall quality of life.

#### *Bleeding*

Acute bleeding is common in patients with gastric cancer and may be tumor-related or a consequence of therapy.[310] Therefore, a multidisciplinary approach is required for the proper diagnosis and management of GI bleeding in patients with gastric cancer. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment. The efficacy of endoscopic treatment for bleeding in patients with gastric cancer is not well-studied, but limited available data suggest that while endoscopic therapies may be as effective as initial treatment, the rate of recurrent bleeding is very high.[311,312] 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 modalities.[311] Angiographic embolization techniques may be useful in situations where endoscopy is not helpful. Additionally, EBRT has been shown to effectively manage acute and chronic GI bleeding.[313,314] Proton pump inhibitors can also be prescribed to reduce the risk of bleeding from gastric cancer; however, there are no definitive 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 select patients), EBRT, chemotherapy, and endoscopic placement of enteral stent for relief of gastric outlet obstruction or esophageal stent for EGJ/cardia obstruction are treatment options 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.[315-318] In a systematic review, patients treated with endoscopic placement of SEMS were more likely to tolerate oral intake and had shorter hospital stays than patients treated with gastrojejunostomy.[319] The results of another systematic review suggest that SEMS 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.[109] A randomized trial also reported similar findings.[320] However, these results need to be confirmed in larger randomized trials.

When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy.[321] Percutaneous, endoscopic, surgical, or interventional radiology gastrostomy tube placement may be performed for gastric decompression, if tumor location permits. Percutaneous decompressive gastrostomy has been associated with palliative benefit for patients with gastric outlet obstruction.[322,323] Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.[324,325] Feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or jejunal feeding tubes 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 EBRT or chemotherapy. 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 with immediate endoscopic removal of the stent.

*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 obstruction is present.

**Survivorship**

In addition to survivorship care relevant to all cancer survivors (see NCCN Guidelines for Survivorship), gastric cancer survivors have special long-term care needs due to the nature of their illness and treatments. Survivors who underwent gastrectomy are at particular risk for long-term health issues—particularly for patients who underwent total gastrectomy as they are shown to have greater restrictions and a significantly worse quality of life than those who were treated with partial gastrectomy.[326-328] A prospective study of 254 patients who were followed for 5 years following gastrectomy (partial or total) as treatment for gastric cancer found that symptoms including diarrhea, dysphagia, reflux, eating restrictions, physical functioning, cognitive functioning, and fatigue negatively impacted the patients' long-term quality of life.[329] Therefore, screening and management of these long-term sequelae are important for all gastric cancer survivors.

Due to a lack of large, randomized trials on long-term sequelae in gastric cancer survivors, the screening and management recommendations provided by the NCCN Panel are based on smaller studies and clinical experience. Gastric cancer survivors, particularly those who underwent gastrectomy, have unique nutritional needs due to frequent vitamin and mineral deficiencies and other GI dysfunctions.[330] Studies have shown that long-term anemia, iron deficiency, and vitamin $B_{12}$ deficiency are common after gastrectomy in patients treated for gastric cancer.[331,332] Other studies have shown that supplementation of vitamin $B_{12}$[333] and iron[334] is safe and effective for reversing these deficiencies. Osteopenia/osteoporosis is another common long-term sequelae following gastrectomy, caused by deficiencies in vitamin D, calcium, phosphorus, and other vitamins and minerals. Supplementation with vitamin D, and treatment with other therapies, has been shown to improve bone health in these patients.[335,336]

Dumping syndrome, which results from rapid emptying of the stomach to the small bowel, is another common side effect of gastrectomy. A large study of 1153 gastrectomy patients treated for gastric cancer reported that 67.6% and 38.4% of patients experienced early and late dumping, respectively.[337] The panel recommends dietary changes to help manage dumping syndrome as well as other GI dysfunctions. See *Principles of Survivorship* in the algorithm for specific recommendations.

## 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 a cancer genetics professional is recommended for an individual with a genetic predisposition. The NCCN Panel strongly recommends multidisciplinary team management as essential for the management of patients with gastric cancer. Best supportive care is an integral part of treatment, especially in patients with metastatic and locally advanced 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 and T2 or higher, any N tumors. Perioperative chemotherapy is preferred (category 1) for patients with resectable 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 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. 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 management.

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, as a single agent or in combination with paclitaxel, and pembrolizumab (for MSI-H/dMMR tumors) are included as options for second-line therapy for patients with unresectable locally advanced, recurrent, or metastatic gastric cancer. Pembrolizumab is also included as a third-line or subsequent therapy option for PD-L1–positive gastric adenocarcinoma.

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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