National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 2.2022 — January 11, 2022

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Gastric Cancer

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¤ Gastroenterology
Δ Genetics
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Gastric Cancer

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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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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Discussion

Updates in Version 2.2022 of the NCCN Guidelines for Gastric Cancer from Version 1.2022 include:

MS-1

- **The Discussion has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2022 of the NCCN Guidelines for Gastric Cancer from Version 5.2021 include:

GAST-1

- **Workup**
  - **9th Bullet revised: Universal testing for MSI by ~~PCR/MMR PCR~~/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients**
  - **11th Bullet revised: ~~If sufficient tissue is available after the above testing has been completed,~~ NGS may be considered**
  - **New bullet added: *If anemia is suspected, See NCCN Guidelines for Hematopoietic Growth Factors***
- **Clinical Stage; Locoregional (cM0) pathway; Additional Evaluation: "Consider laparoscopy with cytology (category 2B) " was recommended for all patients in this pathway. This recommendation was changed as follows:**
  - **Medically fit, potentially resectable: Changed to, *Recommend laparoscopy with cytology*.**
  - **Medically fit, surgically unresectable: Consider laparoscopy with cytology changed from category 2B to category 2A**
  - **Non-surgical candidate: Changed to, *Palliative Management (see GAST-9)***

GAST-2

- **Locoregional disease (cM0) pathway; Medically fit, potentially resectable; cT2 or higher, Any N; Primary Treatment: Revised, Perioperative chemotherapy (category 1) ~~(preferred)~~ (Also for GAST-3)**

GAST-9

- **Unresectable locally advanced, Locally recurrent or metastatic disease; Third column revised**
  - **Perform HER2, PD-L1, ~~MSI by PCR/MMR~~ *and microsatellite* ~~by IHC~~ testing (if not done previously) if metastatic ~~adenocarcinoma~~ *cancer* is documented or suspected**
  - **Bullet revised: ~~If sufficient tissue is available after the above testing has been completed,~~ NGS may be considered *via a validated assay***

GAST-B Principles of Pathologic Review and Biomarker Testing

GAST-B 1 of 6

- **Pathologic Review Table; Analysis/Interpretation/Reporting column: PCR/MMR changed to *PCR/NGS or MMR* throughout the table.**

GAST-B Principles of Pathologic Review and Biomarker Testing (continued)

GAST-B 3 of 6

- **Assessment of Overexpression or Amplification of HER2 in Gastric Cancer**
  - **Revised: "...a traditional biopsy. ~~It should be noted that NGS has several inherent limitations and thus whenever possible,~~ The use of ~~gold-standard assays (~~IHC/ISH~~)~~ should be ~~performed~~ *considered* first, ~~and if sufficient tissue is available,~~ *followed by* additional NGS testing ~~may be considered~~ *as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic gastric adenocarcinoma.*"**

GAST-B 4 of 6

- **Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing**
  - **Revised: "Universal testing for MSI by polymerase chain reaction (PCR), *NGS,* or MMR ...in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines. ~~MMR or MSI~~ *T*esting should be performed only in CLIA-approved laboratories."**
- **Footnote h: " PCR*/NGS* for MSI and IHC for MMR proteins ..."**

GAST-B 5 of 6

- **Next-Generation Sequencing (NGS)**
  - **At present, ~~three~~ *several* targeted therapeutic agents, trastuzumab, ~~ramucirumab, and~~ pembrolizumab*/nivolumab, and entrectinib/larotrectinib* have been approved by the FDA for use in gastric cancer. Trastuzumab is based on testing for HER2 ~~positivity~~ *overexpression*. Pembrolizumab*/nivolumab* ~~is~~ *are* based on testing for MSI by ~~PCR/MMR~~ *PCR or NGS/MMR* by IHC, PD-L1 immunohistochemical expression ~~by CPS~~, or high tumor mutational burden (TMB) by NGS...In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI *status*, MMR ~~mutations~~ *deficiency*, TMB, and *NTRK* gene fusions. ~~It should be noted that NGS has several inherent limitations and thus whenever possible,~~ *T*he use of ~~gold-standard assays (~~IHC/FISH/targeted PCR~~)~~ should be ~~performed~~ *considered* first ~~and if sufficient tissue is available,~~ *followed by* additional NGS testing ~~may be considered as appropriate~~.**

Continued

UPDATES

GAST-B 5 of 6 Principles of Pathologic Review and Biomarker Testing (continued)

- **Liquid Biopsy: Revised, "...Liquid biopsy is being used more frequently in patients with advanced disease*, particularly those* who are unable to have a clinical biopsy for disease surveillance and management...Therefore, for patients who have metastatic or advanced gastric cancer ~~and are~~ *who may be* unable to undergo a traditional biopsy, *or for disease progression monitoring,* testing using a validated NGS-based comprehensive genomic profiling assay..."**

Principles of Systemic
GAST-F 1 of 16

- **4th Bullet revised: Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. ~~Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation~~. *The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations*.**
- **8th Bullet revised: ~~Perioperative chemotherapy or postoperative chemotherapy plus chemoradiation4 is the preferred approach for localized gastric cancer.~~ *Perioperative therapy is a category 1 recommendation for localized gastric cancer. Postoperative chemotherapy plus chemoradiation is an alternative option for patients who received less than a D2 lymph node dissection*.**

Principles of Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease
GAST-F 3 of 16

- **First-Line Therapy; Useful in Certain Circumstances; HER2 overexpression negative: Revised, Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ~~1-4~~ <*5*) (category 2B)**

GAST-F 4 of 16

- **Footnote k revised: For patients ~~that have progressed~~ *whose cancer is progressing* on or following prior treatment *(that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i)* and who have no satisfactory alternative treatment options. *Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly*.**

Principles of Systemic Therapy-Regimens and Dosing Schedules
GAST-F 5 of 16

- **Perioperative Chemotherapy; Preferred Regimens**
  - **Fluoropyrimidine and oxaliplatin: Revised, (~~3~~ *4* cycles preoperative and ~~3~~ *4* cycles postoperative)**

GAST-F 7 of 16

- **Postoperative Chemoradiation: Dosing for Fluorouracil and Capecitabine were revised to include the following statement, *For cycles after chemoradiation, begin chemotherapy 1 month after chemoradiation*.**

GAST-F 10 of 16

- **First-line therapy; Other recommended regimens:**
  - **Paclitaxel with or without cisplatin or carboplatin**
    - ◊ **The cisplatin dose was revised as follows: Cisplatin 75 mg/m² IV on Day ~~2~~ *1***

Principles of Systemic Therapy-References
GAST-F 14 of 16 through GAST-F 16 of 16

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

GAST-G Principles of Radiation
GAST-G 1 of 5

- **Simulation and Treatment Planning; First bullet revised: CT simulation and conformal treatment planning should be used *with either 3D conformal radiation (3D-CRT) or* ~~.~~ *i*ntensity-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~~.**

GAST-G 3 of 5

- **Normal Tissue Tolerance Dose-Limits: This section was extensively revised**
- **RT Dosing revised: 45–50.4 Gy (1.8 Gy/day) *(total 25–28 fractions)***

GAST-G 5 of 5

- **References were updated.**

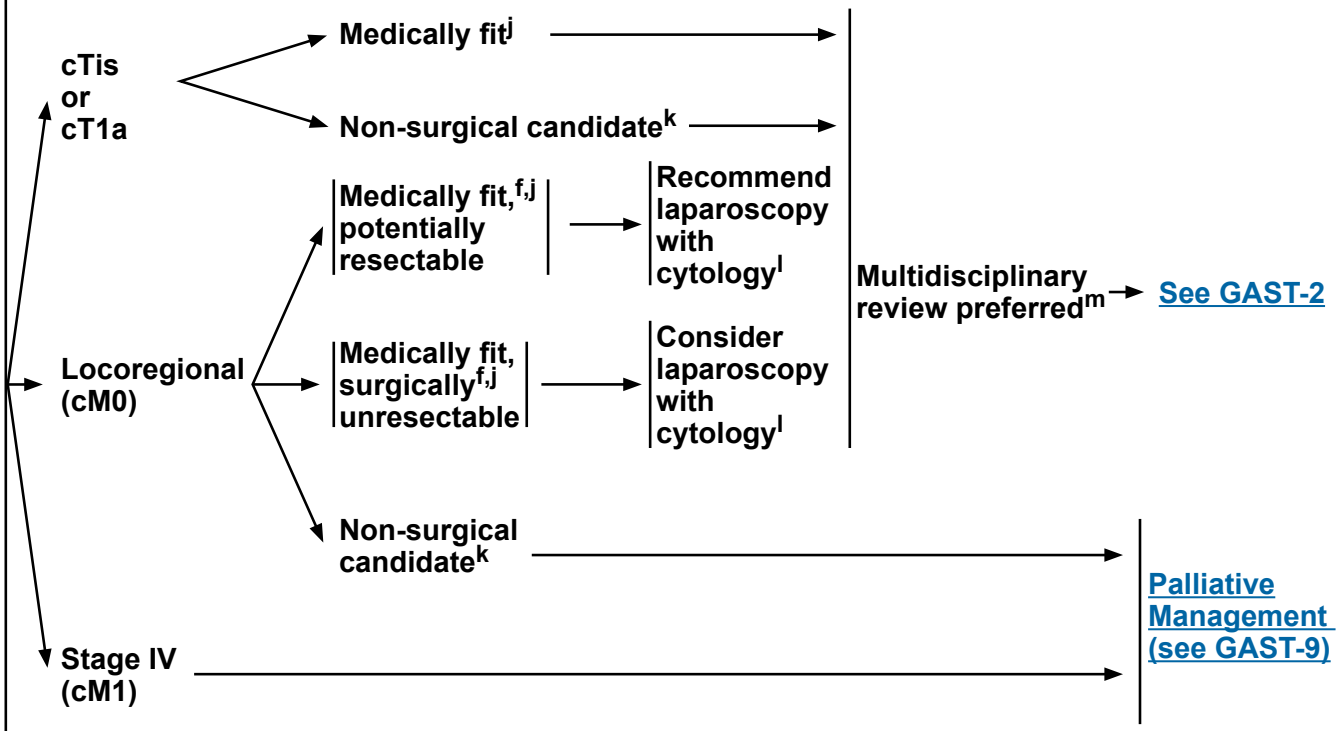
UPDATES

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] Early-stage cancers can best be diagnosed by ER.
- Biopsy of metastatic disease as clinically indicated
- Universal testing for MSI by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patientsd
- HER2 and PD-L1 testing if metastatic adenocarcinoma is documented/suspected[d,e]
- NGS may be considered[d]
- Assess Siewert category[f]
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated[g]
- Screen for family history[h]
- If anemia is suspected, See NCCN Guidelines for Hematopoietic Growth Factors

CLINICAL STAGE[i]

ADDITIONAL EVALUATION



See Footnotes on GAST-1A

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

FOOTNOTES FOR GAST-1

[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[b] May not be appropriate for T1.
[c] ER 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, Ovarian and Pancreatic.
[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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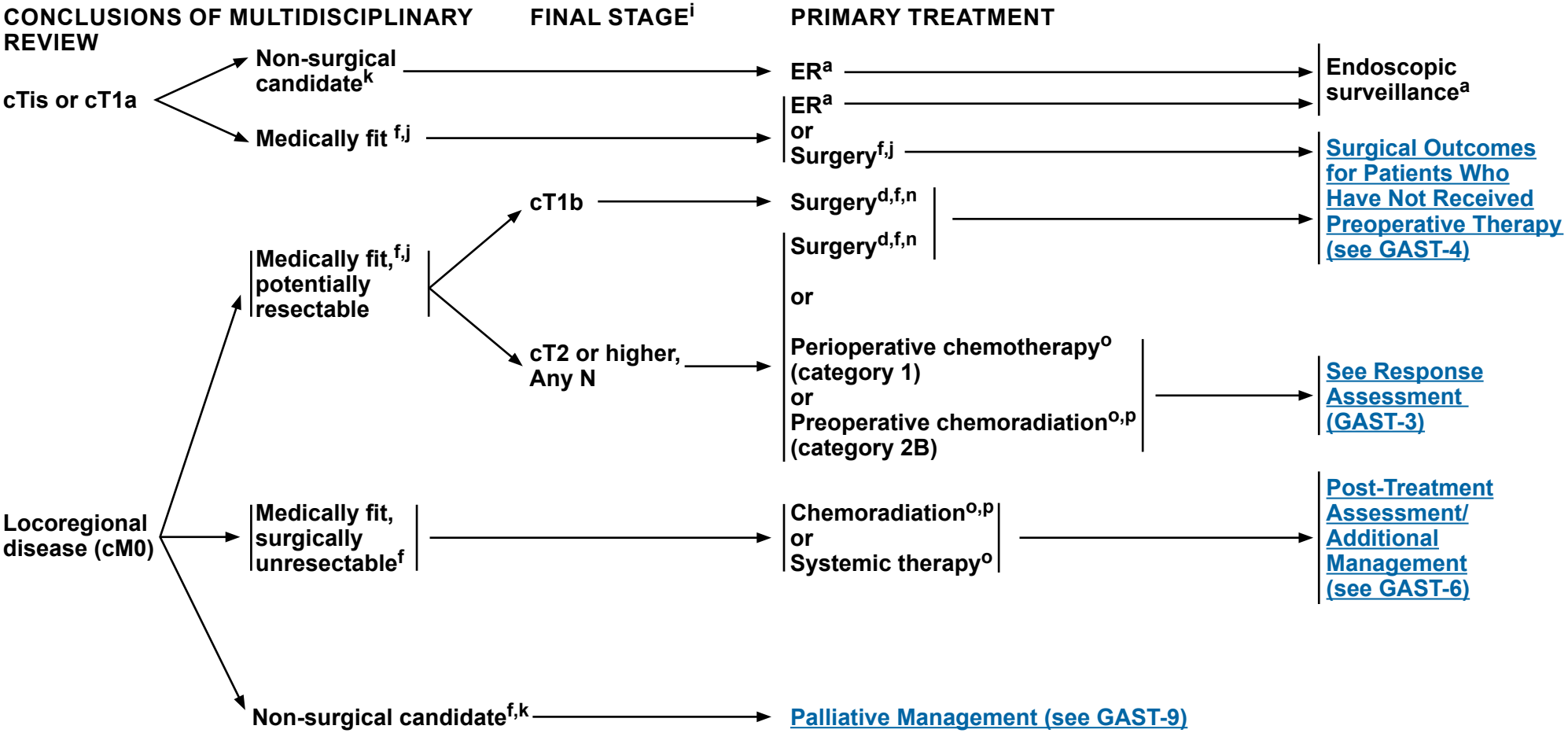

[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[j] Medically able to tolerate major surgery.
[k] Medically unable to tolerate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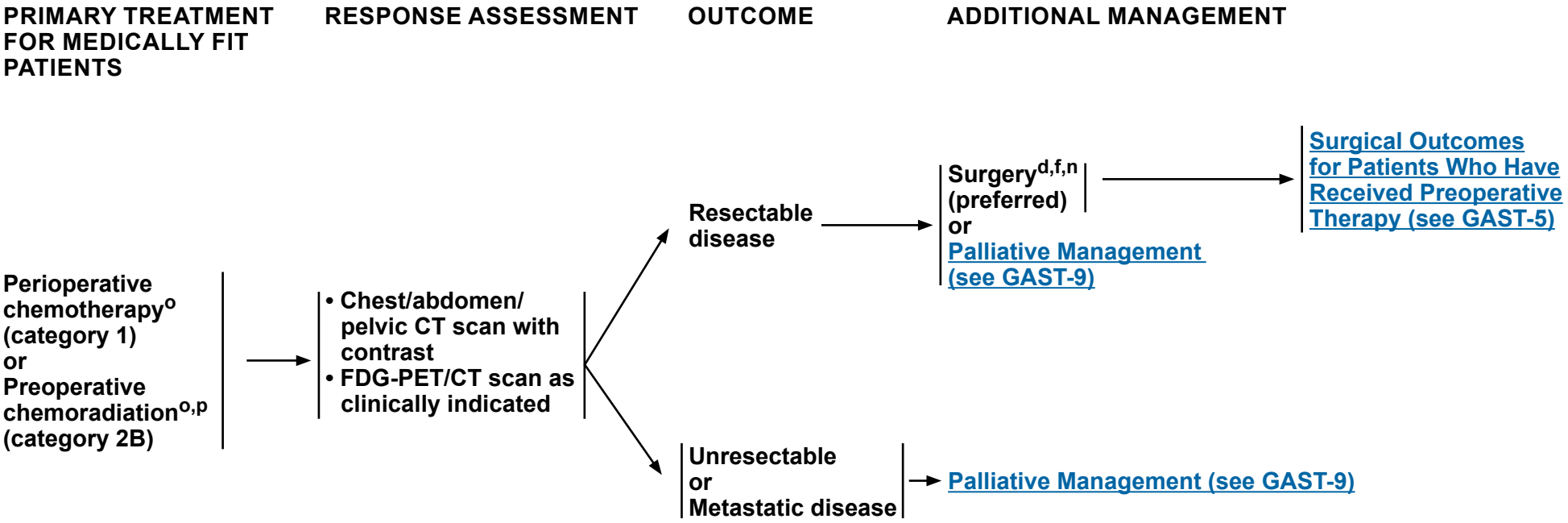

[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[n] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See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

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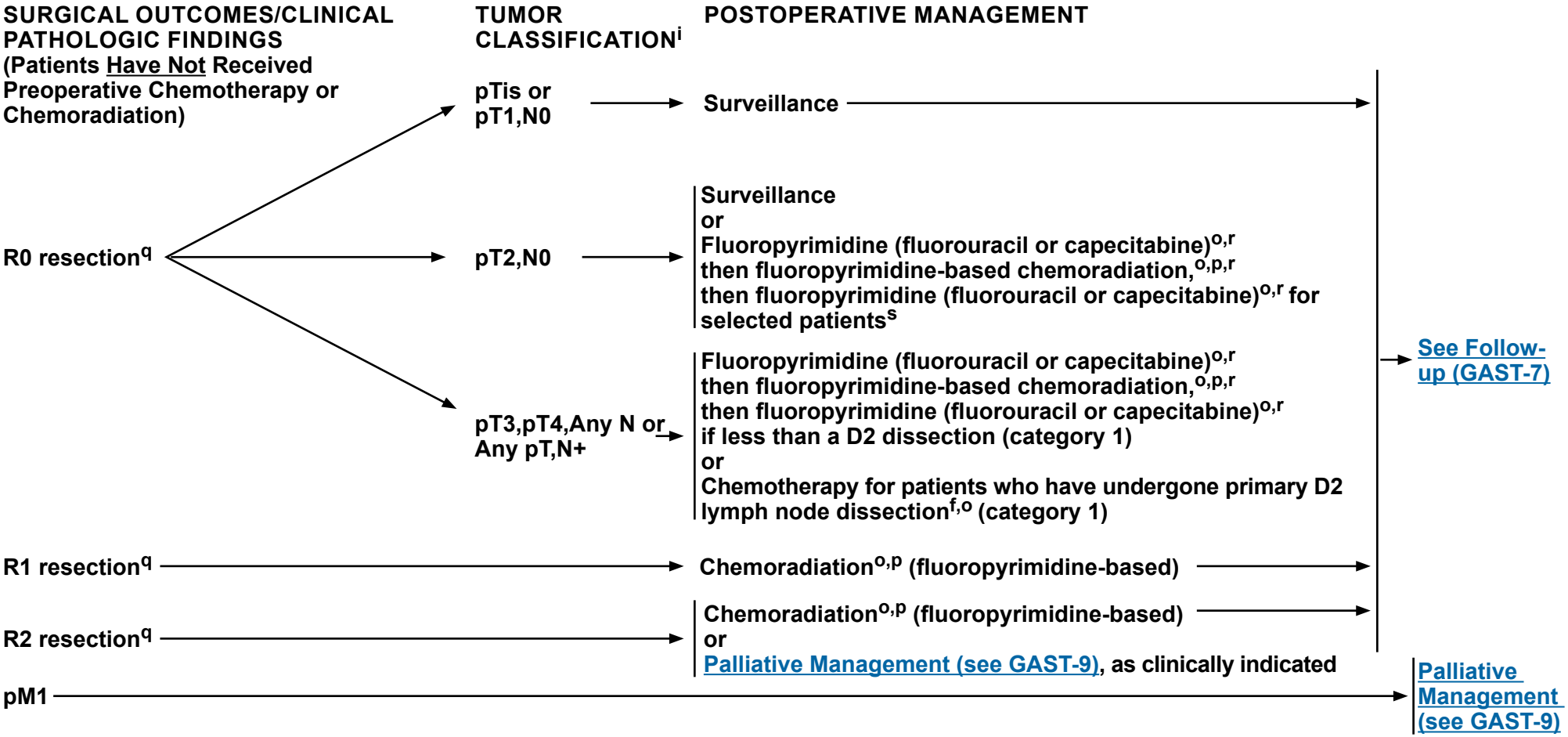

[f] See Principles of Surgery (GAST-C).
[i] See Staging (ST-1) for tumor classification.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[q] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.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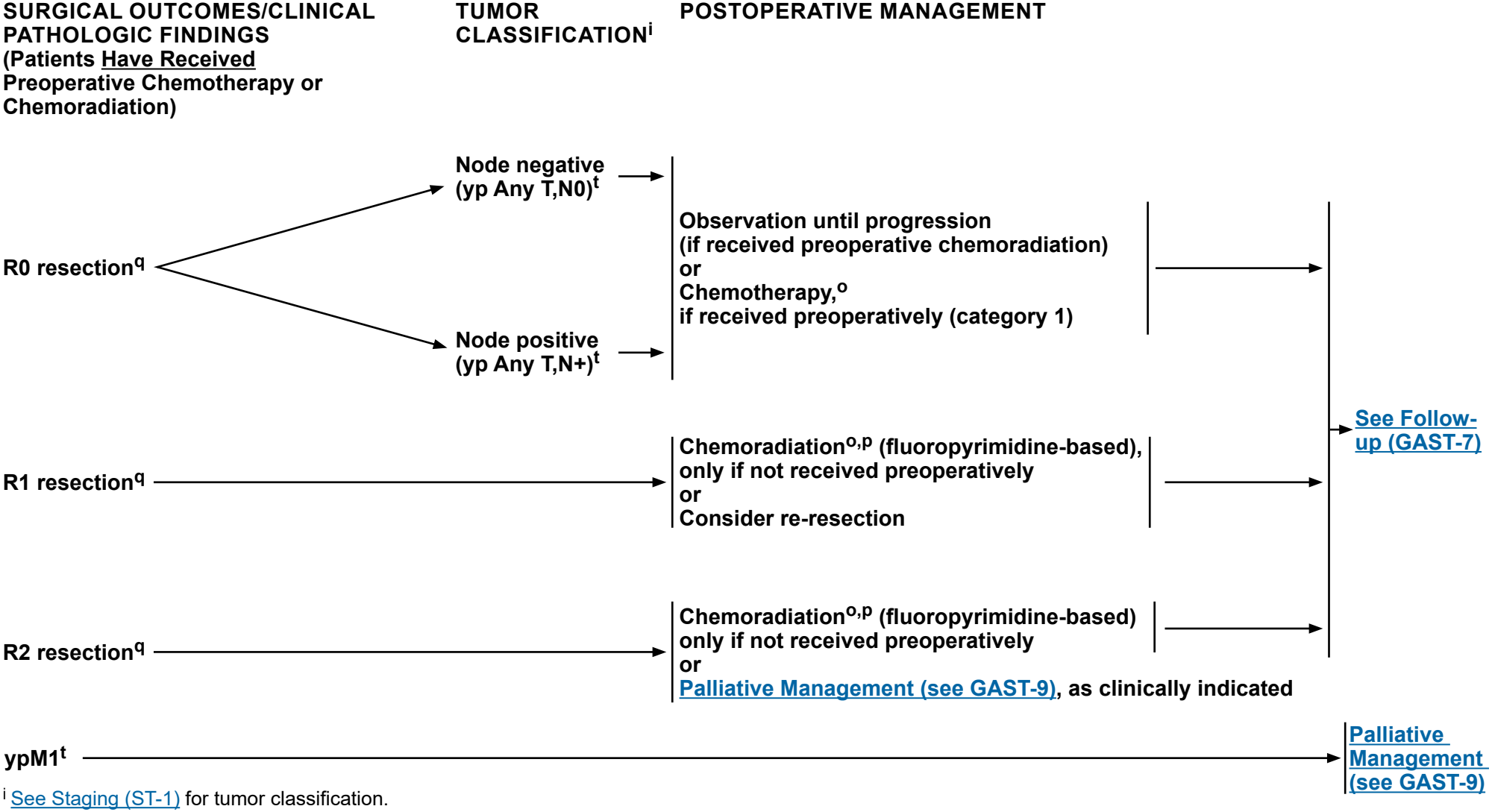

[i] See Staging (ST-1) for tumor classification.
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[q] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[t] The yp prefix is used to indicate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

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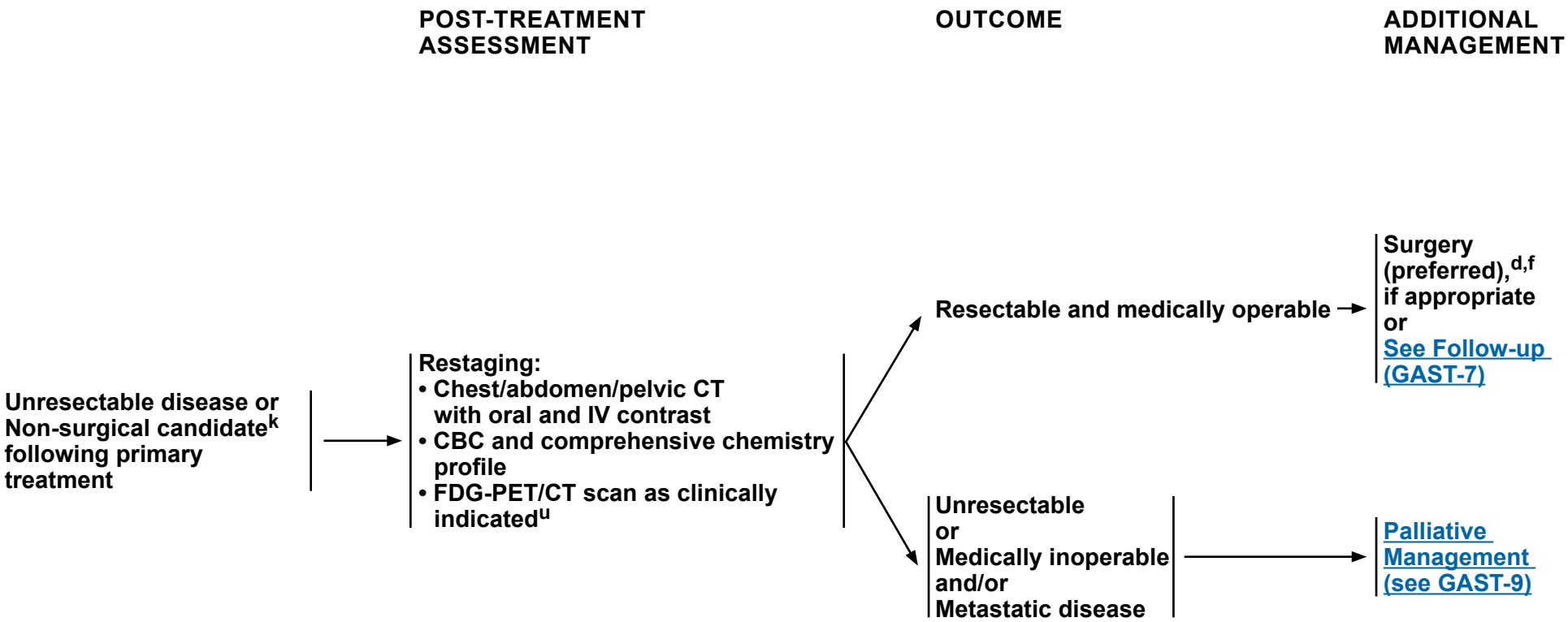

[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] See Principles of Surgery (GAST-C).
[k] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[u] In cases of renal insufficiency or allergy to CT contrast.

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FOLLOW-UP/SURVEILLANCE[w]

Tis (successfully treated by ER)[v] →
- H&P every 3–6 months for 1–2 years, every 6–12 months for 3–5 y, and annually thereafter
- CBC and chemistry profile as clinically indicated
- Upper GI endoscopy (EGD) every 6 months for 1 year, then annually for 3 years
- 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 months for 1–2 years, every 6–12 months for 3–5 years, and annually thereafter
- CBC and chemistry profile as clinically indicated
- For patients treated by ER, EGD every 6 months for 1 year, 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 months for 1–2 years, every 6–12 months for 3–5 years, 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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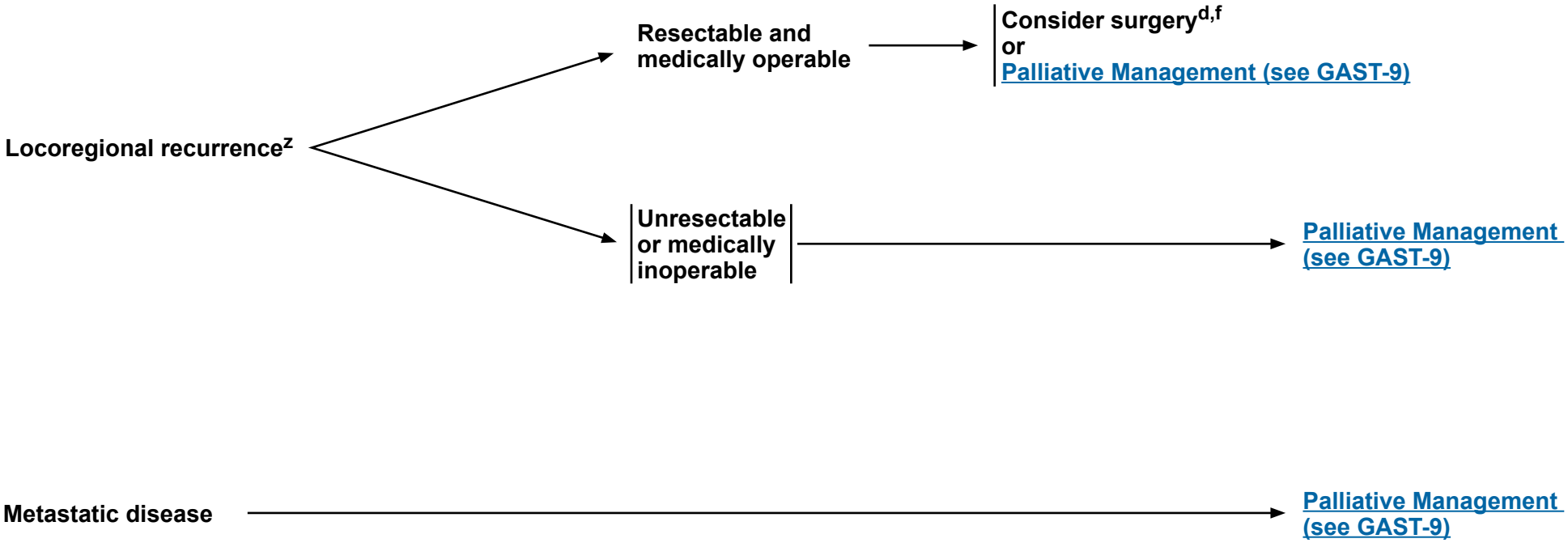
RECURRENCE



[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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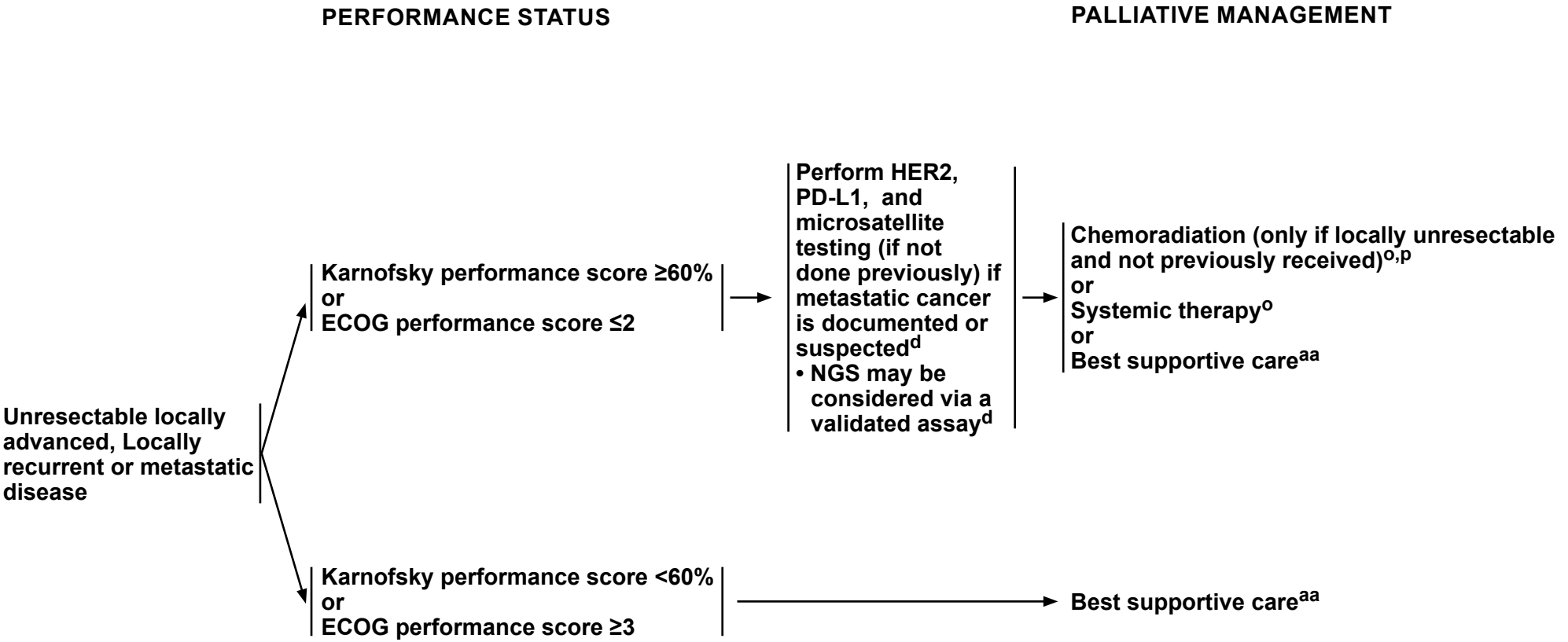

[d] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[o] See Principles of Systemic Therapy (GAST-F).
[p] See Principles of Radiation Therapy (GAST-G).
[aa] See Principles of Palliative Care/Best Supportive Care (GAST-J).

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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 corresponds 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.**

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Continued
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, or 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 (J-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 PATHOLOGIC REVIEW AND BIOMARKER TESTING

Pathologic Review
Table 1

Specimen Type	Analysis/Interpretation/Reporting[a]
Biopsy	Include in pathology report: • Invasion, if present • Histologic type[b] • Grade • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
Endoscopic mucosal resection	Include in pathology report: • Invasion, if present • Histologic type[b] • Grade • Depth of tumor invasion • Vascular/lymphatic invasion • Status of mucosal and deep margins • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
Gastrectomy, without prior chemoradiation	For pathology report, include all elements as for endoscopic mucosal resection plus • Location of tumor midpoint in relationship to EGJ[c] • Whether tumor crosses EGJ • Lymph node status and number of lymph nodes recovered • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients, if not previously performed
Gastrectomy, with prior chemoradiation	• Tumor site should be thoroughly sampled for specimens s/p neoadjuvant therapy without grossly obvious residual tumor • For pathology report, include all elements as for resection without prior chemoradiation plus assessment of treatment effect

[a] Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at http://www.cap.org) for reporting pathologic findings is recommended.
[b] Subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy, as intestinal type cancers may be more likely to overexpress HER2.[1]
[c] 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[d]

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

- **Although it is suggested that at least 16 regional lymph nodes be pathologically assessed, removal and assessment of over 30 lymph nodes is desirable.[2]**

[d] 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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References

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[e] therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) method is recommended.[4] NGS offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and microsatellite instability (MSI) status. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by additional NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic gastric adenocarcinoma.

Table 3: Immunohistochemical Criteria for Scoring HER2 Expression in Gastric Cancer[f,g]

	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

[e] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[f] The NCCN Guidelines Panel recommends that HER2 IHC be ordered/performed first, followed by ISH 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.

[g] 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[h]

- **Universal testing for MSI by polymerase chain reaction (PCR), NGS, or MMR by IHC should be performed for all newly diagnosed gastric cancers.[5] The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[6] Testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors may be referred to a genetics counselor for further assessment in the appropriate clinical context.**

  - **MMR Interpretation**
    - ◊ **No loss of nuclear expression of MMR proteins: No evidence of dMMR (low probability of MSI-H)**
    - ◊ **Loss of nuclear expression of one or more MMR proteins: dMMR**

  - **MSI Interpretation**
    - ◊ **MSI-Stable (MSS)**
    - ◊ **MSI-Low (MSI-L)**
      - **1%–29% of the markers exhibit instability**
      - **1 of the 5 National Cancer Institute (NCI) or mononucleotide markers exhibits instability**
    - ◊ **MSI-H**
      - **≥30% of the markers exhibit instability**
      - **2 or more of the 5 NCI or mononucleotide markers exhibit instability**

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 should be used on FFPE tissue as an aid in identifying 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 minimum of 100 tumor cells must be present in the PD-L1-stained slide for the specimen to be considered adequate for PD-L1 evaluation. 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.**

[h] PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by dMMR function.

References

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

- **At present, several targeted therapeutic agents, trastuzumab,[e] pembrolizumab/nivolumab,[i] and entrectinib/larotrectinib have been approved by the FDA for use in gastric cancer. Trastuzumab is based on testing for HER2 overexpression. Pembrolizumab/nivolumab are based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. The FDA granted approval for the use of select TRK inhibitors for *NTRK* gene fusion-positive solid tumors. When limited tissue is available for testing, or the patient is unable to undergo a traditional biopsy, sequential testing of single biomarkers or use of limited molecular diagnostic panels may quickly exhaust the sample. In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC/ISH/targeted PCR should be considered first followed by additional NGS testing as appropriate.**

Liquid Biopsy[7,8]

- **The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced gastric cancer who may be unable to undergo a traditional biopsy, or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.**

[e] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[i] See Guidelines for Management of Immunotherapy-Related Toxicities.

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PRINCIPLES OF SURGERY

N Category Determination

- Determine extent of disease by CT scan (chest, abdomen, and pelvis) ± 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 esophagus) with the epicenter 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 epicenter within 1 cm above and 2 cm below the EGJ.
  - Siewert Type III: subcardial carcinoma with the tumor epicenter between 2 cm and 5 cm below the 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)

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References
Continued

PRINCIPLES OF SURGERY

Resectable Tumors

- Tis or T1[7] tumors limited to mucosa (T1a) may be candidates for EMR or ESD if they meet appropriate criteria (in experienced centers).[8]
- T1b–T3[9]: Adequate gastric resection to achieve negative microscopic margins along with lymphadenectomy.
  - Distal gastrectomy
  - Subtotal gastrectomy
  - Total gastrectomy
- T4b 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 16 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, and splenic artery.
- Routine splenectomy is not indicated unless the spleen is involved or extensive hilar adenopathy is noted.[13]
- Consider placing feeding tube in select patients undergoing total gastrectomy (especially if postoperative chemoradiation appears a likely recommendation).
- Minimally invasive surgical (MIS) approaches may be considered for selected cases based on the following criteria:
  - The surgeon has experience performing laparoscopic or robotic foregut procedures and has experience in lymphadenectomy.
  - Both early and locally advanced gastric cancers can be considered for laparoscopic or robotic gastrectomy given evidence that supports equivalent oncologic outcomes from the East and West.[14-17]
  - Minimally invasive approaches are generally not recommended for T4b or N2 bulky gastric cancer.
- Hyperthermic intraperitoneal chemotherapy (HIPEC) or laparoscopic HIPEC may be a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials and is under further clinical investigation.[18-20]

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.[21]
- 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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References

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, Ovarian, and Pancreatic.**
- **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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References

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. Females 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:[a]**
    - ◊ **Two gastric cancer cases in a family, one confirmed diffuse gastric cancer (DGC) regardless of age**
      OR
    - ◊ **DGC diagnosed before age 50 years without a family history**
      OR
    - ◊ **Personal or family history of DGC and lobular breast cancer, one diagnosed before age 70 years**
      OR
    - ◊ **Two cases of lobular breast cancer in family members before 50 years of age**
      OR
    - ◊ **DGC at any age in individuals of Māori ethnicity, or with a personal or family history of cleft lip/cleft palate**
      OR
    - ◊ **Bilateral lobular breast cancer before age 70 years**

[a] Adapted and reproduced with permission from Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer updated clinical practice guidelines. Lancet Oncol 2020;21:e386-e397.

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

Continued
References

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

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

- **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-Jeghers 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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Continued
References

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. • Prophylactic gastrectomy prior to 18 years of age is not recommended, but may be considered for certain patients, especially those with family members diagnosed with gastric cancer before 25 years of age. • *CDH1* mutation carriers, who elect not to undergo prophylactic gastrectomy, should be offered 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, Ovarian, and Pancreatic. • For those patients without a strong family history of DGC, genetics counseling with multidisciplinary review is indicated.
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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Continued
References

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

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Continued
References

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
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[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;52:361-374.
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[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.
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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.**

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

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[a] should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.**
- **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 therapy[2,3] is a category 1 recommendation for localized gastric cancer. Postoperative chemotherapy plus chemoradiation[4] is an alternative option for patients who received less than a D2 lymph node dissection.**
- **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.**

Footnotes

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

References

[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.

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

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy

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

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

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

Preferred Regimens
- None

Other Recommended Regimens
- Paclitaxel and carboplatin (category 2B)[3]
- Fluorouracil[b] and oxaliplatin (category 2B)[4,5]
- Fluorouracil and cisplatin (category 2B)[6,7]
- Fluoropyrimidine (fluorouracil or capecitabine) (category 2B)

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

- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[8]

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

Preferred Regimens
- Capecitabine and oxaliplatin[e] (category 1)[9]
- Fluorouracil[b] and oxaliplatin[e]

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

Preferred Regimens
- Fluorouracil[b] and oxaliplatin [4,5]
- Fluorouracil and cisplatin [6,7]

Other Recommended Regimens
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[10]

[b] 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.
[c] Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[d] The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[e] 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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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

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

First-Line Therapy
- **Oxaliplatin is generally preferred over cisplatin due to lower toxicity.**

Preferred Regimens
- **HER2 overexpression positive adenocarcinoma[f]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]**
- **HER2 overexpression negative[f]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]**

Other Recommended Regimens
- **HER2 overexpression positive adenocarcinoma[f]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]**
- **Fluorouracil[b,i] and irinotecan[j,20]**
- **Paclitaxel with or without cisplatin or carboplatin[j,21-25]**
- **Docetaxel with or without cisplatin[j,26-29]**
- **Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)**
- **Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]**
- **Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]**

Useful in Certain Circumstances
- **HER2 overexpression negative[f]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[g,h,12]**

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] 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.
[f] See Principles of Pathologic Review and Biomarker Testing (GAST-B).
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[j] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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Continued
References

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 • **Dependent on prior therapy and PS**
Preferred Regimens • **Ramucirumab and paclitaxel (category 1)[35]** • **Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]** • **Docetaxel (category 1)[28,29]** • **Paclitaxel (category 1)[24,25,37]** • **Irinotecan (category 1)[37-40]** • **Fluorouracil[b,i] and irinotecan[38,41,42]** • **Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]**
Other Recommended Regimens • **Ramucirumab (category 1)[44]** • **Irinotecan and cisplatin[14,45]** • **Fluorouracil and irinotecan + ramucirumab[b,i,46]** • **Irinotecan and ramucirumab[47]** • **Docetaxel and irinotecan (category 2B)[48]**
Useful in Certain Circumstances • **Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]** • **Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]** • **Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[54]** • **Dostarlimab-gxly[g,h,k] for MSI-H or dMMR tumors[55]**

[b] 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] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[k] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[l]

PERIOPERATIVE CHEMOTHERAPY

PREFERRED REGIMENS

Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[b]
(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]

Fluoropyrimidine and oxaliplatin[b]
(4 cycles preoperative and 4 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[14]

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[15]

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

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

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[l]

PREOPERATIVE CHEMORADIATION

PREFERRED REGIMENS

- None

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[3]

Fluorouracil and oxaliplatin[b]
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[m,4]

Fluorouracil 300 mg/m² IV continuous infusion over 24 hours daily for 4 days (over 96 hours) weekly
Oxaliplatin 85 mg/m² IV over 2 hours on Day 1
Cycled every 14 days for 3 cycles with radiation[56]

Capecitabine and oxaliplatin
Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID on Days 1–5 weekly for 5 weeks[57]

OTHER RECOMMENDED REGIMENS–CONTINUED

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

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

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[58]

Fluoropyrimidine (fluorouracil or capecitabine)
Fluorouracil 200–250 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Weekly for 5 weeks[59]

Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[60]

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[l]

POSTOPERATIVE CHEMORADIATION

(for patients who received less than a D2 lymph node dissection)

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[8,61] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE DOSES AND SCHEDULE OF CYTOTOXIC AGENTS SPECIFIED IN THIS TRIAL DUE TO CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

Fluorouracil[b]

2 cycles before and 4 cycles after chemoradiation. For cycles after chemoradiation, begin chemotherapy 1 month 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
Weekly for 5 weeks[59]

Capecitabine

1 cycle before and 2 cycles after chemoradiation. For cycles after chemoradiation, begin chemotherapy 1 month after chemoradiation.
Capecitabine 750–1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[62]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[60]

POSTOPERATIVE CHEMOTHERAPY

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

PREFERRED

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[9]

Fluoropyrimidine and oxaliplatin[b]

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[14]

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]

[b] 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.

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

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

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PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[l]

CHEMORADIATION FOR UNRESECTABLE DISEASE

(Infusional fluorouracil[b] can be replaced with capecitabine)

PREFERRED REGIMENS

Fluorouracil and oxaliplatin[b]

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

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

Capecitabine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Days 1, 15, and 29 for 3 doses
Capecitabine 625 mg/m² PO BID
on Days 1–5 weekly for 5 weeks[57]

Fluorouracil and cisplatin

Cisplatin 75–100 mg/m² IV on Day 1
Fluorouracil 750–1000 mg/m² IV continuous infusion
over 24 hours daily on Days 1–4
Cycled every 28 days for 2 cycles with radiation
followed by 2 cycles without radiation[63]

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[58]

OTHER RECOMMENDED REGIMENS

Paclitaxel and fluoropyrimidine

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

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

[b] 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.

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

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References

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

FIRST-LINE THERAPY

Trastuzumab[a] with chemotherapy (See GAST-F [3 of 16] for list of regimens)
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 oxaliplatin[b]
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[14]

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[15]

Capecitabine 625 mg/m² PO BID on Days 1–14[n]
Oxaliplatin 85 mg/m² IV on Day 1
Cycled every 21 days[64]

PREFERRED REGIMENS—continued

Fluoropyrimidine and cisplatin[b]
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[16]

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[13,17]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[18]

PREFERRED REGIMENS—continued

Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin and nivolumab[b,h]
Nivolumab 360 mg IV on Day 1
Capecitabine 1000 mg/m² PO BID every Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[12]

Nivolumab 240 mg IV on Day 1
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[12]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] 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.
[h] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[l] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.
[n] Based on consensus opinion, the panel revised the doses and schedule studied in level C of the GO2 trial.

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

FIRST-LINE THERAPY–continued

OTHER RECOMMENDED REGIMENS

Fluorouracil and irinotecan[b]

Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[20]

Irinotecan 80 mg/m² IV on Day 1
Leucovorin 500 mg/m² IV on Day 1
Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours on Day 1
Weekly for 6 weeks followed by 2 weeks off treatment[65]

Paclitaxel with or without cisplatin or carboplatin

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

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[22]

Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[23]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[25]

Paclitaxel 80 mg/m² IV weekly
Cycled every 28 days[24]

OTHER RECOMMENDED REGIMENS–continued

Docetaxel with or without cisplatin

Docetaxel 70–85 mg/m² IV on Day 1
Cisplatin 70–75 mg/m² IV on Day 1
Cycled every 21 days[26,27]

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[28,29]

Fluoropyrimidine[b]

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[17]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[30]

Capecitabine 1000–1250 mg/m²
PO BID on Days 1–14
Cycled every 21 days[31]

OTHER RECOMMENDED REGIMENS–continued

Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b]

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

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

Docetaxel, carboplatin and fluorouracil

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

[b] 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.

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

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

FIRST-LINE THERAPY–continued

OTHER RECOMMENDED REGIMENS—continued

Trastuzumab[a] and pembrolizumab[h] with fluoropyrimidine and oxaliplatin or cisplatin (only for HER2 overexpression positive adenocarcinoma)

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

Pembrolizumab 200 mg IV on Day 1
Cycled every 3 weeks
or
Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks[19]

OTHER RECOMMENDED REGIMENS—continued

Fluoropyrimidine and oxaliplatin[b]

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[14]

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[15]

Capecitabine 625 mg/m² PO BID on Days 1–14[n]
Oxaliplatin 85 mg/m² IV on Day 1
Cycled every 21 days[64]

OTHER RECOMMENDED REGIMENS—continued

Fluoropyrimidine and cisplatin[b]

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[16]

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[13,17]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[18]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] 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.
[h] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[l] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.
[n] Based on consensus opinion, the panel revised the doses and schedule studied in level C of the GO2 trial.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[l]
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[35]

Fam-trastuzumab deruxtecan-nxki
(for HER2 overexpression positive adenocarcinoma)
6.4 mg/kg IV on Day 1
cycled every 21 days[o,36]

Taxane
Docetaxel 75–100 mg/m^2 IV on Day 1
Cycled every 21 days[28,29]

Paclitaxel 135–250 mg/m^2 IV on Day 1
Cycled every 21 days[25]

Paclitaxel 80 mg/m^2 IV weekly
Cycled every 28 days[24]

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

PREFERRED REGIMENS—continued

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

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

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

Fluorouracil and irinotecan[b]
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]

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[43]

[b] 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.
[l] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.
[o] Fam-trastuzumab deruxtecan-nxki is approved for metastatic HER2-positive breast cancer at a different dose of 5.4 mg/kg IV on Day 1, cycled every 21 days.

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

OTHER RECOMMENDED REGIMENS

Ramucirumab
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[44]

Irinotecan and cisplatin
Irinotecan 65 mg/m² IV on Days 1 and 8
Cisplatin 25–30 mg/m² IV on Days 1 and 8
Cycled every 21 days[14,45]

Fluorouracil and irinotecan + ramucirumab[b]
Ramucirumab 8 mg/kg IV on Day 1
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 1,200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[66]

Irinotecan and ramucirumab
Irinotecan 150 mg/m2 IV on Day 1
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[47]

Docetaxel and irinotecan
Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days[48]

USEFUL IN CERTAIN CIRCUMSTANCES

Entrectinib or Larotrectinib (For *NTRK* gene fusion-positive tumors)
Entrectinib 600 mg PO once daily[49]
or
Larotrectinib 100 mg PO twice daily[50]

Pembrolizumab[g,h] **(for MSI-H/dMMR tumors or TMB-high (≥10 mutations/megabase) tumors)**
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[67]

Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks[68]

Dostarlimab-gxly[g,h] **(for MSI-H/dMMR tumors)**
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1,000 mg IV every 6 weeks[55]

[b] 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] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[l] 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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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 pretreatment 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 with either 3D conformal radiation (3D-CRT) or. intensity-modulated radiation therapy (IMRT).**
- **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]
  - Pretreatment 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]
  - Pretreatment 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[6,7]

- **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_{40Gy} ≤ 10% • V_{30Gy} ≤ 15% • V_{20Gy} ≤ 20% • V_{10Gy} ≤ 40% • V_{05Gy} ≤ 50% • Mean < 20 Gy	• V_{30Gy} ≤ 30% (closer to 20% preferred) • Mean < 30 Gy (closer to 26 Gy preferred)
Spinal Cord	**Left Kidney, Right Kidney (evaluate each one separately):**
• Max ≤ 45 Gy	• V_{20Gy} ≤ 33% • Mean < 18 Gy
Bowel	**Liver**
• Max dose < 54 Gy • V_{45Gy} < 195 cc	• V_{30Gy} ≤ 33 % • Mean < 25 Gy

RT Dosing

- **45–50.4 Gy (1.8 Gy/day) (total 25–28 fractions)**
  - **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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PRINCIPLES OF RADIATION THERAPY

Supportive Therapy

- **Treatment interruptions or dose reductions for manageable acute toxicities should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment 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/day, oral and/or enteral nutrition should be considered. When indicated, feeding jejunostomies (J-tubes) or nasogastric feeding tubes may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.**
- **Adequate enteral and/or IV hydration is necessary during chemoradiation and 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.**

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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)
    - ◊ Consider referral to occupational, rehabilitation, and/or physical therapy for patients with chemotherapy-induced neuropathy at risk for falls
    - ◊ 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 for 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:**
  - **Postprandial 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 for 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 active 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 measures 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)
- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections
- Encourage maintenance of a therapeutic relationship with a primary care physician (PCP) throughout life. The oncologist and PCP should have defined roles in survivorship care, with roles communicated to patient.
- Planning for ongoing survivorship care[a]
  - Information on treatment received including all surgeries, radiation therapy, and systemic therapies
  - Information regarding follow-up care, surveillance, and screening recommendations
  - Information on post-treatment needs, including information regarding acute, late, and long-term treatment-related effects and health risks when possible (See NCCN Disease-Specific Guidelines)
  - Delineation regarding roles of oncologists, PCPs, and subspecialty care physicians in long-term care and the timing of transfer of care if appropriate
  - Healthy behavior recommendations (See NCCN Guidelines for Survivorship [HL-1])
  - Periodic assessment of ongoing needs and identification of appropriate resources

[a] From Commission on Cancer. Optimal Resources for Cancer Care (2020 Standards): https://www.facs.org/-/media/files/quality-programs/cancer/coc/optimal_resources_for_cancer_care_2020_standards.ashx and NCCN Guidelines for Survivorship.

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

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.[b]

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 (EBRT) 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.**
  - **EBRT may be used for chronic blood loss due to gastric cancer.[4,5]**

[a] See NCCN Guidelines for Palliative Care.
[b] For patients who have immune-mediated toxicity, See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

Continued
References

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]**
  - **EBRT**
  - **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

- **EBRT**
- **Chemotherapy[c]**
- **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.
[c] See Principles of Systemic Therapy (GAST-F).

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

References

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE
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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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 classified 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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Gastric Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Gastric Cancer. Last updated on January 11, 2022.

Table of Contents

Overview

The incidence of gastric cancer has decreased substantially in the United States and Western Europe over the past several decades.[1-4] However, gastric cancer still constitutes a major global health problem, especially in East Asian countries.[5,6] Globally, there were more than 1 million cases resulting in greater than 768,000 deaths in 2020, making gastric cancer the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths in the world.[7,8] The global incidence of gastric cancer shows wide geographic variation, with a 15- to 20-fold difference between high- and low-incidence regions.[1] The highest gastric cancer incidence rates occur in Northeast Asia, South and Central America, and Eastern Europe.[5,6] Rates are particularly high in Japan and Korea, where gastric cancer is the most commonly diagnosed cancer in males, and in China, where gastric cancer is a leading cause of cancer-related mortality.[5,6,9] In contrast, gastric cancer is one of the least commonly diagnosed cancers in Western Europe, sub-Saharan Africa, Australia, and North America.[6] In the United States, an estimated 26,560 people were to be diagnosed and 11,180 people were expected to die of this disease in 2021, making gastric cancer the 16th most commonly diagnosed cancer and the 17th leading cause of cancer-related death in the United States.[4,10,11] Despite overall declining rates, recent evidence suggests that the incidence of early-onset gastric cancer may be rising in the United States.[12]

Over 95% of gastric cancers are adenocarcinomas, which are typically classified based on anatomic location (cardia/proximal or non-cardia/distal) and histologic type (diffuse or intestinal).[3] The diffuse type, which is characterized by poorly differentiated and discohesive tumor cells with a signet-ring or non-signet-ring morphology diffusely infiltrating the gastric wall in a desmoplastic stroma, is more prevalent in low-risk areas and is mostly associated with heritable genetic abnormalities.[3,9,13-15] The intestinal type, which tends to form a mass lesion and is characterized by variably differentiated tumor cells arranged in a tubular or glandular pattern with scattered goblet cells present, occurs more frequently in high-risk areas and accounts for most of the geographic variation seen with this disease. Intestinal type gastric cancer is often related to environmental factors such as *Helicobacter pylori* (*H. pylori*) infection, tobacco smoking, high salt intake, and other dietary factors.[3,9,13-15] However, the role of alcohol as a risk factor for gastric cancer is without consensus. While the results of several meta-analyses have shown no appreciable association between light or moderate alcohol consumption and gastric cancer risk, they did show a positive association between heavy alcohol use and gastric cancer, particularly non-cardia gastric cancer.[16-19]

A dramatic shift in the type and location of upper gastrointestinal (GI) tract tumors has occurred in North America and Europe.[2,20,21] There has been a marked decline in intestinal type gastric cancers of the distal stomach in North American and Western European countries over the past several decades, mainly due to enhanced access to clean drinking water, improved food preservation, an average diet with low promotion of gastric cancer, and *H. pylori* eradication.[1-4,15] However, incidence rates of diffuse type gastric cancer of the proximal stomach are rising.[1-3] The etiology of this increase remains elusive and may be multifactorial. In contrast to the incidence trends in high income countries, tumors of the distal stomach continue to predominate in low and middle income countries.[2] Gastric cancer generally carries a poor prognosis since it is often diagnosed at an advanced stage. In Japan and South Korea, where population screening is performed widely, early detection often results in improved outcomes.[1,6] In the United States, survival rates from gastric cancer remain poor as early detection continues to pose a major challenge for health care professionals.

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 published since the last Guidelines update, 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 peer reviewed biomedical literature.[22]

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 (eg, e-publications ahead of print, meeting abstracts). 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 Cancer

While most gastric cancers are considered sporadic, it is estimated that 3% to 5% of gastric cancers are associated with inherited cancer predisposition syndromes. Referral to a cancer genetics professional is recommended for individuals with a known high-risk syndrome associated with gastric cancer. 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 diffuse gastric cancers at a young age.[23,24] 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.[25,26] The average age at diagnosis is 37 years, and the lifetime risk for the development of gastric cancer by the age of 80 years has been estimated to be 67% for men and 83% for women.[27] In a recent analysis of 75 families with pathogenic *CDH1* mutations, the extrapolated cumulative incidence of gastric cancer by the age of 80 years was estimated to be 42% for men and 33% for women, suggesting that the lifetime risk of gastric cancer in *CDH1* mutation carriers may be significantly lower than previously reported.[28]

Prophylactic total gastrectomy (without a D2 lymph node dissection) is recommended between the ages of 18 and 40 years for carriers of germline truncating *CDH1* mutations.[29,30] 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 age 25. A baseline endoscopy is indicated prior to prophylactic total gastrectomy. Screening 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. However, available evidence suggests that endoscopy may not adequately detect the precursor lesions in diffuse gastric cancer.[31-33] Additionally, women with germline truncating *CDH1* mutations are at an increased risk for developing breast cancer[34] and should be followed using

high-risk guidelines as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Genetic counseling with multidisciplinary review is recommended for *CDH1* mutation carriers without a strong family history of HDGC.

More than 40% of patients with HDGC do not carry *CDH1* mutations, suggesting the existence of additional susceptibility genes.[35] 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.[36,37] In a large genomic study of cancer predisposition variants, five different germline loss-of-function mutations in *PALB2* were identified in gastric adenocarcinoma patients.[37] *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.[36] Furthermore, *PALB2* loss-of-function variants were found to be substantially more common in families with HDGC than in the general population.[36] These findings suggest a putative 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.[38] Lynch syndrome arises from germline mutations in any of the four DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6*, and *PMS2*).[39] Deletions of the epithelial cell adhesion molecule (*EPCAM)* gene have also been implicated in Lynch syndrome.[40] 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.[41-44] This risk is higher among Asians than Westerners. In a recent analysis of data from 3828 carriers of Lynch syndrome-associated mutations, personal history of gastric cancer was found to be independently associated with male sex, older age, mutations in *MLH1* or *MSH2*, and number of first-degree relatives with gastric cancer.[45]

Esophagogastroduodenoscopy (EGD) with extended duodenoscopy (to the distal duodenum or into the jejunum) may be considered as a screening strategy in select individuals or those of Asian descent.[38] 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.[46] JPS arises from a germline mutation in the *SMAD4* or *BMPR1A* genes.[38] The lifetime risk of developing GI cancers in patients with JPS varies from 9% to 50% with the type of mutation.[47] 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.[47] Screening with 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.[38] 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,[48,49] which occurs in 30% to 80% of patients.[50] PJS is characterized by mucocutaneous pigmentation and GI polyposis and is associated with an

elevated risk of developing GI cancers.[51-55] Individuals with PJS have a 29% lifetime risk of developing gastric cancer and are also at an increased risk for other cancers.[38,51] Screening with EGD may be considered, beginning in the late teens and repeated every 2 to 3 years based on gastric polyp burden.[38] 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.[56,57] 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.[58] The majority (~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.[58] Individuals with FAP have a 1% to 2% lifetime risk of 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.[59] Patients with polyps that cannot be removed endoscopically (as in the case of invasive cancers) should be referred for gastrectomy.[59] 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,[60] Bloom syndrome,[61] hereditary breast and ovarian cancer syndrome,[60,62] Li-Fraumeni syndrome,[60,62] Xeroderma pigmentosum,[60] and Cowden syndrome[62] have all been reported to increase the risk of gastric cancer. However, evidence for gastric cancer screening 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 American Joint Committee on Cancer (AJCC) is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. Staging recommendations for gastric cancer presented in the Eighth Edition of the AJCC Cancer Staging Manual include clinical staging (cTNM; newly diagnosed, not-yet-treated patients), pathologic staging (pTNM; patients undergoing resection without prior treatment), and post neoadjuvant pathologic staging (ypTNM; patients receiving preoperative therapy).[63] The Eighth Edition also introduced modifications regarding tumors located at the esophagogastric junction (EGJ) and within the gastric cardia. Using this system, tumors involving the EGJ with an epicenter located greater than 2 cm into the proximal stomach are now staged as gastric carcinomas. Tumors involving the EGJ with an epicenter less than or equal to 2 cm into the proximal stomach will still be staged as esophageal carcinomas. Cancers located within the gastric cardia that do not involve the EGJ are staged as gastric carcinomas.

The Eighth Edition of the AJCC Cancer Staging Manual provides additional resources for gastric cancer not available in the Seventh Edition, including the addition of new cTNM and ypTNM stage groupings,

to fulfill unmet needs in staging patients under different circumstances. Due to the lack of an official clinical stage classification in the past, treating physicians have typically used the pathologic stage to clinically stage patients. Furthermore, due to the lack of yp stage groupings, pathologic staging was also applied to patients who had received preoperative therapy. The use of pathology assessments to establish cTNM and ypTNM stages has never been validated and may not be appropriate. Therefore, new cTNM and ypTNM stage groupings and prognostic information were added to the Eighth Edition to overcome these issues. New clinical stage groupings and prognostic information are based on datasets from the National Cancer Database (NCDB), representing patients treated surgically or nonsurgically in the United States, and the Shizuoka Cancer Center dataset, representing patients treated surgically in Japan, for a total of 4091 patients. These clinical stage groupings are different from groupings used for pathologic or post neoadjuvant staging. The prognostic value of the newly proposed cTNM stage criteria has been externally validated in a cohort of 4374 surgically treated gastric cancer patients in Japan.[64] Newly provided prognostic information for ypTNM staging is presented using only the four broad stage categories (stage I–IV) due to the limited number of patients (n = 700) available for analysis. The addition of this new ypTNM stage grouping system fulfills an unmet need in the clinics since many gastric cancer patients are now treated with preoperative therapy. Furthermore, the stage groupings and prognostic information for pTNM staging presented in the Eighth Edition are now based on data from more than 25,000 gastric cancer patients from the International Gastric Cancer Association (IGCA) database who have had surgery with adequate lymph node removal. Patients treated with preoperative therapy were not included in the analysis. Pathologic stage groupings were refined based on 5-year survival data. Although most (84.8%) of the eligible cases from the IGCA database came from Japan and Korea, the predictive ability and accuracy of parameters used in the Eighth Edition for pTNM staging of gastric cancer have been validated for U.S. populations.[65,66] The new pTNM staging classification criteria have also been externally validated in a cohort with a higher proportion of advanced disease than the IGCA cohort (49% had stage III disease compared to 26% in the IGCA cohort, $P < .001$).[67] However, limitations of this dataset still remain, including a lack of uniformity in initial clinical stage assessments, the lack of a uniform surgical approach, and the use of pTNM assessments for ypTNM staging.[63]

Baseline clinical stage provides useful information for the development of an initial treatment strategy. The availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, 18-fluorodeoxyglucose (FDG)-PET/CT, and laparoscopy has greatly improved baseline clinical staging of gastric cancer.[68-70] EUS is indicated for assessing the depth of tumor invasion (T category) as well as nodal involvement (N category).[71] However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.[72] 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 category and 66.7% for N category.[73] Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.[74] EUS may be useful for differentiating T3 and T4 tumors, but it should be used in combination with other staging modalities.[72,73] EUS is also useful to identify superficial tumors for potential endoscopic approaches. Therefore, EUS should be used if early-stage disease is suspected or if early versus locally advanced disease needs to be determined.

CT scan is routinely used for preoperative staging and has an overall accuracy of 43% to 82% for measuring depth of invasion. In contrast, FDG-PET has a lower accuracy rate because of low FDG uptake in diffuse and mucinous tumor types, which are common in gastric cancer.[75,76] FDG-PET also has significantly lower sensitivity compared to CT in the detection of local lymph node involvement (56% vs. 78%), although FDG-

PET has improved specificity (92% vs. 62%).[77] Thus, combined FDG-PET/CT imaging offers several potential advantages over FDG-PET or CT scans alone.[78] FDG-PET/CT has a significantly higher accuracy rate in preoperative staging (68%) than FDG-PET (47%) or CT (53%) alone. Additionally, reports have confirmed that FDG-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.[79,80] FDG-PET does not take the place of staging laparoscopy given its failure to detect peritoneal disease.

Pretreatment diagnostic laparoscopy can be used to detect occult metastases. In a study conducted at Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a period of 10 years.[81] Metastatic disease (M1) was detected in 31% of patients. However, 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.[68] Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer and is an independent predictor for recurrence following curative resection.[82-84] 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.[83] 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. 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. The panel recommends performing diagnostic laparoscopy to assess the peritoneal cavity (with biopsies as needed) and cytology of peritoneal washings in medically fit patients with potentially resectable stage cT1b or higher locoregional disease when considering preoperative chemoradiation and/or surgery. [81] Laparoscopy with cytology can be considered for medically fit patients with surgically unresectable disease.

In most countries, where screening programs for early detection of gastric cancer are not in use or practical because of low incidence, diagnosis is often made late in the disease course. 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.[85] Additionally, nearly 80% of patients have involvement of the regional lymph nodes and the number of positive lymph nodes has a profound influence on survival.[86] In patients with localized resectable disease, outcome depends on the surgical stage of the disease.

Pathologic Review and Biomarker Testing

Pathologic review and biomarker testing play important roles in the diagnosis, classification, and molecular characterization of gastric cancer. Classification based on histologic subtype and molecular features helps improve early diagnosis and has implications for therapy. An accumulation of genetic aberrations occurs during gastric carcinogenesis, including overexpression of growth factors and/or receptors, alterations in DNA damage response, and loss of genomic stability. Characterization of these pathways has enabled the application of molecular pathology to aid in the diagnosis, classification, and treatment of gastric cancer.[15]

Principles of 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 be HER2 overexpression positive (see below). In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade, which are required for staging. Universal testing for microsatellite instability (MSI) by polymerase chain reaction (PCR)/next-generation sequencing (NGS) or MMR deficiency by immunohistochemistry (IHC) is recommended in all newly diagnosed patients. The pathology report of endoscopic mucosal resection (EMR) specimens should include an assessment of lymphovascular invasion (LVI), depth of tumor invasion, tumor diameter, 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 an assessment of treatment effect.

Assessment of Treatment Response

Response of the primary tumor and involved lymph nodes to previous chemotherapy and/or RT should be reported. 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 response to neoadjuvant chemotherapy was the only independent predictor of OS in patients who underwent curative resection for gastric cancer.[87] Additionally, Mansour et al reported that the 3-year disease-specific survival rate was significantly higher for patients with greater than 50% pathologic response to neoadjuvant chemotherapy compared to those with less than 50% pathologic response (69% and 44%, respectively).[88] In another study, Becker et al demonstrated that histopathologic grading of tumor regression was correlated with survival in patients treated with neoadjuvant chemotherapy.[89] 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.[90]

Tumor response scoring systems for gastric cancer have not been uniformly adopted. The panel recommends using the modified scheme developed by Ryan et al[91,92] because it generally provides good reproducibility among pathologists, but other systems may also be used. The following scheme is suggested: 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.

Although it is suggested that at least 16 regional lymph nodes be pathologically assessed, removal and assessment of over 30 lymph nodes is desirable.[63,93] Analysis of data from the SEER database and NCDB showed a trend for improved overall survival (OS) with a higher number of lymph nodes examined after gastrectomy.[93-95] The trend for superior survival based on more lymph nodes examined was confirmed across all stage subgroups.

Principles of Biomarker Testing

Presently, IHC and/or molecular testing for HER2/*ERBB2* status, MSI or MMR status, PD-L1 expression, tumor mutational burden-high (TMB-H) status, and neurotrophic tropomyosin-related kinase (*NTRK*) gene

fusions are implicated in the clinical management of advanced gastric cancer. When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated NGS assay performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved environment may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC, in situ hybridization (ISH), or targeted PCR should be considered first, followed by NGS testing as appropriate.

Assessment of HER2 Overexpression

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of gastric adenocarcinoma.[96] However, unlike in breast cancer, the prognostic significance of HER2 status in gastric cancer is unclear. Some studies suggest that HER2 positivity is associated with poor prognosis[97-102] 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.[103-105] 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 overexpression-positive disease.

The reported rates of HER2 positivity in patients with gastric cancer range from 12% to 23%.[98,99,104-107] HER2 positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[99,104-106] HER2 positivity is reported in less than or equal 20% of European and U.S. patients with metastatic gastric cancer with significantly higher rates seen in patients with intestinal histology (33% vs. 8% for diffuse/mixed histology; $P = .001$).[104] 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).[105] The HER-EAGLE study, which examined the HER2 positivity rate in a large multinational population of nearly 5000 patients with gastric or EGJ adenocarcinoma, reported that 14.2% of samples were HER2 overexpression positive.[108] HER2 positivity was significantly higher in males versus females, in EGJ tumors versus stomach tumors, and in intestinal subtypes versus diffuse subtypes. In the ToGA trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2 overexpression-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.[109,110] Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

HER2 testing is recommended for all gastric cancer patients at the time of diagnosis if metastatic disease is documented or suspected. In concordance with HER2 testing guidelines from the College of American Pathologists (CAP), the American Society for Clinical Pathology (ASCP), and the American Society for Clinical Oncology (ASCO),[111] the NCCN Guidelines recommend using IHC and, if needed, ISH techniques to assess HER2 status in gastric cancer. NGS offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, fusions, deletions, TMB, and MSI status. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression of advanced or metastatic disease.

IHC evaluates the membranous immunostaining of tumor cells, including the intensity and extent of staining and the percentage of

immunoreactive tumor cells, with scores ranging from 0 (negative) to 3+ (positive). In 2008, Hofmann et al refined this 4-tiered scoring system to assess HER2 status in gastric cancer by using a cut-off of greater than or equal to 10% immunoreactive tumor cells.[110,112] In a subsequent validation study (n = 447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[113] This modified HER2 scoring system is therefore recommended by the panel. A score of 0 (membranous reactivity in <10% of cancer cells) or 1+ (faint membranous reactivity in ≥10% of cancer cells) is considered to be HER2-negative. A score of 2+ (weak to moderate membranous reactivity in ≥10% of cancer cells) is considered equivocal and should be additionally examined by fluorescence in situ hybridization (FISH) or other ISH methods. FISH/ISH results are expressed as the ratio between the number of copies of the *ERBB2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (*ERBB2*:CEP17). Alternatively, FISH/ISH results may be given as the average *ERBB2* copy number per cell. Cases that have an IHC score of 3+ (strong membranous reactivity in ≥10% of cancer cells) or an IHC score of 2+ and are FISH/ISH positive (*ERBB2*:CEP17 ratio ≥2 or average *ERBB2* copy number ≥6 signals/cell) are considered HER2 overexpression positive. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. See *Principles of Pathologic Review and Biomarker Testing: Assessment of Overexpression or Amplification of HER2 in Gastric Cancer - Table 3* in the algorithm for more information.

MSI and MMR Testing

Universal testing for MSI by PCR/NGS or MMR by IHC should be performed for all newly diagnosed gastric cancer patients. MSI status is assessed by PCR to measure gene expression levels of microsatellite markers (ie, *BAT25*, *BAT26*, *MONO27*, *NR21*, *NR24*).[114] MMR deficiency is evaluated by IHC to assess nuclear expression of proteins involved in DNA mismatch repair (ie, MLH1, MSH2, MSH6, PMS2).[115] PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by deficient MMR function. Testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or MMR-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[116] Testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment in the appropriate clinical context.

PD-L1 Testing

PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric cancers in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test should be used to identify patients for treatment with PD-1 inhibitors. The companion diagnostic test is a qualitative IHC assay using anti-PD-L1 antibodies for the detection of PD-L1 protein levels in FFPE tumor tissue. A minimum of 100 tumor cells must be present in the PD-L1–stained slide for the specimen to be adequately evaluated. Combined positive score (CPS) is determined by the number of PD-L1–stained cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells evaluated, multiplied by 100. A specimen is considered to have PD-L1 expression if the CPS is greater than or equal to 1. PD-L1 testing should be performed only in CLIA-approved laboratories. Tumor proportion score (TPS) is also considered and reported in some trials.

Liquid Biopsy

The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of “liquid biopsy.”[101,117] Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical

biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. In one study, a complete or partial response to immunotherapy was achieved by 63% of patients with advanced gastric carcinoma who tested positive for MSI by cell-free DNA analysis.[117] In another study that analyzed the genomic alterations of 55 patients with advanced gastroesophageal adenocarcinomas using NGS performed on plasma-derived ctDNA, 69% of patients had 1 or more characterized alterations theoretically targetable by an FDA-approved agent (on- or off-label).[101] Therefore, for patients who have advanced or metastatic gastric cancer and who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations, or amplifications.

Emerging Biomarker: Tumor Epstein-Barr Virus

Tumor Epstein-Barr virus (EBV) status is emerging as a potential biomarker for personalized treatment strategies in gastric cancer. An estimated 8% to 10% of gastric cancers are associated with EBV infection, making EBV-positive gastric cancer the largest group of EBV-associated malignancies.[118,119] EBV-positive tumors occur preferentially in the proximal stomach and are associated with diffuse-type histology and early onset.[12] Although the prognostic value of EBV status on the survival of gastric cancer patients remains a subject of debate, several studies suggest that patients with EBV-positive gastric cancer have better OS rates compared to other genotypes.[120-124] Additional studies have shown that expression of PD-L1 is elevated in EBV-positive gastric cancers and is associated with decreased OS rates.[125-127] Furthermore, Derks et al reported that an interferon-γ–driven gene signature was enriched in EBV-positive gastric cancers, suggesting increased sensitivity to PD-1/PD-L1 immunotherapies.[126] Therefore, PD-1/PD-L1 immunotherapies may be a viable option to treat EBV-positive gastric cancer patients; however, more data are needed to substantiate this claim. Due to the lack of prospective trials and limited understanding of the exact association between EBV and gastric cancer, testing for EBV status is not currently recommended for routine clinical care.

Surgery

Surgery is the primary treatment option for patients with localized gastric cancer. Complete resection with negative margins is widely considered as a standard goal, whereas the type of resection (subtotal vs. total gastrectomy) and the extent of lymph node dissection remain subjects 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 degree of 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.[128,129] An R1 resection indicates microscopic residual disease and an R2 resection indicates macroscopic residual disease in the absence of distant metastasis.[130] Adequate gastric resection to achieve negative microscopic margins along with lymphadenectomy is preferred for resectable T1b to T3 tumors, while T4b tumors require en-bloc resection of involved structures.[131] Patients with Tis or T1a tumors may be considered for EMR or ESD if they meet appropriate criteria (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.[132] Proximal gastrectomy and total gastrectomy are both indicated for proximal gastric cancers and are typically associated with postoperative nutritional impairment. Placement of a feeding tube should be considered for select patients undergoing total gastrectomy, especially those who will be receiving postoperative chemoradiation.

Routine splenectomy is not indicated unless the spleen is involved or extensive hilar adenopathy is noted. 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.[133] A recently published meta-analysis of randomized controlled trials also concluded that splenectomy should not be recommended for proximal gastric cancer since it increases operative morbidity without improving OS when compared to spleen-preserving procedures.[134] The results of these studies do not support the use of prophylactic splenectomy or removal of 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 (eg, obstruction or uncontrollable bleeding) and should not include lymph node dissection.[135,136] 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 rates of recurrent symptoms.[137,138] Placement of venting gastrotomy and/or a feeding jejunostomy tube may also be 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). 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 dissection refers to an incomplete resection of lymph nodes along the lesser and greater curvature of the stomach. D1 dissection involves the removal of the greater and lesser omenta (which includes 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, and splenic artery. The technical aspects of performing a D2 lymph node dissection require a significant degree of training and expertise. Therefore, D2 dissections should be performed in centers experienced with this technique.

Gastrectomy with D2 lymph node dissection is the standard treatment for curable gastric cancer in East 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.[94,139,140] 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.[141,142] 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.[141] 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).[143] 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).[142] Therefore, D2 lymph node dissection is considered a recommended but not required procedure in the West.

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 survival when performed in high-volume centers that have sufficient experience with the operation and postoperative management.[144-147] 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).[144] 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.[145,146] 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).[146]

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.[141,142,148,149] 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.[148,149] 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.[149] These rates are comparable with the rates for D1 lymph node dissections in the Dutch and United Kingdom trials.[141,142] 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 in patients who did not undergo resection of the spleen or pancreas.[150-152]

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 16 or more lymph nodes.[139,143,148,149] The guidelines emphasize that D2 lymph node dissections should be performed by experienced surgeons in high-volume centers. Routine or prophylactic pancreatectomy is not recommended with D2 lymph node dissection,[133,153] and splenectomy is acceptable only when the spleen is involved or extensive hilar adenopathy is noted.

Laparoscopic Resection

Laparoscopic resection is an emerging surgical approach that offers several potential 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 gastric cancer.[154-156] In a propensity score-matched analysis of 692 patients who underwent total gastrectomy for gastric cancer, patients who received laparoscopic resection had less blood loss, shorter mean operation time, and a higher number of retrieved lymph nodes compared to patients who received an open procedure.[157] The 3-year cumulative survival rates after a median follow-up of 45 months were similar between the two groups. Results of a meta-analysis involving 9337 advanced gastric cancer patients (5000 received laparoscopic gastrectomy and 4337 received open gastrectomy) showed that the laparoscopic procedure resulted in less intraoperative blood loss and faster recovery times.[158] However, there was no difference in operative time, number of harvested lymph nodes, postoperative mortality, or 5-year OS.

The safety and efficacy of laparoscopic resection versus standard open resection have been evaluated in several clinical trials in Asia. In the phase III CLASS-01 trial, 1056 Chinese patients with locally advanced gastric cancer (cT2 to cT4a) were randomized to receive laparoscopic or open distal gastrectomy, both with D2 lymph node dissection.[159] After 3 years, the DFS rate was 76.5% in the laparoscopic group and 77.8% in the open group (hazard ratio [HR] for recurrence = 1.069). The 3-year OS rates and cumulative incidence of recurrence were also similar between the two groups (83.1% and 18.8%, respectively, in the laparoscopic group and 85.2% and 16.5% in the open group), suggesting that the long-term oncologic outcomes of laparoscopic distal gastrectomy were non-inferior to those of the conventional open surgery for patients with advanced gastric cancer. The randomized CLASS-02 trial compared the safety of laparoscopic and open total gastrectomy with lymphadenectomy in 277 patients with early-stage gastric cancer.[160] The rates of overall morbidity and mortality, intraoperative complications, and overall postoperative complications were not significantly different between the groups. Although one patient in the laparoscopic group died from intra-abdominal bleeding secondary to splenic artery hemorrhage, there was no significant difference in mortality between the laparoscopic and open groups. These results showed that the safety of laparoscopic total gastrectomy with lymphadenectomy by experienced surgeons for early-stage gastric cancer was comparable to that of an open procedure.

The randomized phase III KLASS-01 trial reported the long-term outcomes of 1416 Korean patients with stage I gastric cancer randomized to receive laparoscopic or open gastrectomy.[161] The 5-year OS rates were 94.2% in the laparoscopic group and 93.3% in the open surgery group (P = .64), and 5-year cancer-specific survival rates were 97.1% and 97.2%, respectively (P = .91). Intention-to-treat analysis confirmed the non-inferiority of laparoscopic gastrectomy compared with the open approach. Although these results suggest that laparoscopic resection may be a feasible surgical strategy, the role of this approach in the treatment of gastric cancer in Western countries requires further investigation. The randomized phase III KLASS-02 trial reported the long-term outcomes of laparoscopic or open subtotal distal gastrectomy with D2 lymphadenectomy in 974 Korean patients with locally advanced gastric cancer.[162] Compared to the open surgery group, the laparoscopy group suffered fewer early complications (15.7% vs. 23.4%; P = .0027) and late complications (4.7% vs. 9.5%; P = .0038). The 3-year relapse-free survival rate was 80.3% for the laparoscopy group and 81.3% for the open group (P = .726). Therefore, the outcomes of laparoscopic distal gastrectomy with D2 lymphadenectomy were comparable to those of open surgery in patients with locally advanced gastric cancer.

Based on these and other data suggesting equivalent oncologic outcomes in the East and West, the panel suggests that minimally invasive

approaches may be considered for selected cases provided that the surgeon has experience in performing laparoscopic or robotic foregut procedures and has experience in lymphadenectomy.[163] Minimally invasive approaches are generally not recommended for T4b or N2 bulky gastric cancer.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The HIPEC procedure involves the continuous circulation of a heated sterile chemotherapy–containing solution throughout the peritoneal cavity following cytoreductive surgery. HIPEC enables the infusion of high doses of chemotherapy directly into the abdominal cavity, where traditional methods of chemotherapy cannot effectively reach. This procedure can potentially improve long-term outcomes and provide more treatment options for patients with advanced gastric cancer. This technique is currently under investigation in clinical trials.

In the CYTO-CHIP study, which included 277 patients with peritoneal metastases from gastric cancer who underwent cytoreductive surgery with HIPEC (n = 180) or cytoreductive surgery alone (n = 97), the addition of HIPEC improved OS and recurrence-free survival, without increasing morbidity or mortality.[164] However, the median peritoneal cancer index remained higher in the HIPEC group following treatment. Therefore, cytoreductive surgery with HIPEC may be effective for strictly selected patients with limited peritoneal metastases.

In a phase II trial, 20 patients with gastric adenocarcinoma and positive peritoneal cytology or carcinomatosis who had completed systemic chemotherapy and laparoscopic HIPEC underwent cytoreduction, gastrectomy, and HIPEC. The 90-day morbidity and mortality rates were 70% and 0%, respectively. Median OS from the date of cytoreduction, gastrectomy, and HIPEC was 16.1 months; 1-, 2-, and 3-year OS rates from the diagnosis of metastatic disease were 90%, 50%, and 28%, respectively.[165] In a phase III trial, 68 patients with gastric cancer and peritoneal carcinomatosis were randomized to receive cytoreductive surgery alone or cytoreductive surgery with HIPEC.[166] At a median follow-up of 32 months, death occurred in 97% of cases in the surgery alone group and 85% of cases in the surgery plus HIPEC group. The median survival was 6.5 months and 11 months, respectively (P = 0.046). Four patients (11.7%) in the surgery alone group and 5 (14.7%) in the HIPEC group developed serious adverse events (P = .839). Multivariate analysis found that the addition of HIPEC to cytoreductive surgery is an independent predictor for better survival.

Based on the available data, the NCCN Panel recommends HIPEC or laparoscopic HIPEC as a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials only.

Endoscopic Therapies

Endoscopy has become an important tool in the diagnosis, staging, treatment, and palliation of patients with gastric cancer. 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 disease.

Principles of Endoscopy

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) and 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.[167,168] 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.[169,170] 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 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).[171,172] Accurate clinical staging is especially important in patients who are being considered for endoscopic resection (ER).[173]

Hypoechoic (dark) expansion of the gastric wall layers identifies the location of the tumor, with gradual loss of the layered pattern of the normal stomach wall corresponding with greater depths of tumor infiltration and thus higher T-categories. Perigastric lymph nodes are readily seen by EUS, and the identification of enlarged, hypoechoic, homogeneous, well-circumscribed, rounded structures around the stomach 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.[174] FNA of suspicious lymph nodes should be performed, without traversing an area of primary tumor or major blood vessels, if it will impact treatment decisions. FNA should also be considered to rule out peritoneal spread of disease.

Treatment

EMR represents a major advancement in minimally invasive approaches for the management of patients with early-stage gastric cancer.[175] Most of the experience with EMR for early-stage disease has been gained by countries with a high incidence of gastric cancer and an active screening program.[176-180] In a study of 124 patients with early-stage mucosal gastric cancers, Uedo et al reported 5- and 10-year survival rates of 84% and 64%, respectively, for patients receiving EMR.[177] In another retrospective study of 215 patients with intramucosal gastric cancer, EMR resulted in significantly shorter hospital stays, but was comparable to surgery in terms of risk of death and recurrence.[180] The 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.[178]

ESD has also been reported to be a safe and effective procedure for patients with early-stage gastric cancer when performed by experienced endoscopists.[181-188] En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in several studies.[189-196] In a multicenter retrospective study of 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).[189] The complete resection rates for ESD were significantly better for lesions greater than 5 cm in diameter, whereas the rates were not different between EMR and ESD for lesions less than 5 cm in diameter regardless of location.[190-192] ESD requires a higher level of skill to perform and is also associated with higher rates of bleeding and perforation complications.[194-197] 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.

Early-stage gastric cancer that is less than or equal to 2 cm in diameter, well to moderately differentiated, does not invade the deep submucosa, does not exhibit LVI or lymph node metastases, and has clear lateral and deep margins can be effectively treated with EMR or ESD.[170,196,198] EMR or ESD of poorly differentiated gastric cancers with evidence of LVI, invasion into the deep submucosa, and positive lateral or deep margins should be considered incomplete and additional therapy (gastrectomy with lymph node dissection) should be considered.[199]

Endoscopic therapies also play a role in palliative care. Endoscopic tumor 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.[200,201] 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.[202]

Surveillance

Endoscopic surveillance following definitive treatment of gastric cancer requires careful attention to detail for mucosal surface changes. Multiple (4–6) biopsies of any visualized abnormalities should be performed. Additionally, strictures should also be biopsied to rule out neoplastic cause. EUS performed in conjunction with endoscopy exams has a high sensitivity for detecting recurrent disease.[203] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are observed. It should be noted that EUS performed after chemotherapy or radiation therapy (RT) has a reduced ability to accurately determine the post-treatment stage of disease.[204] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease.[205]

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.[206]

RT as a single modality has minimal value in patients with unresectable gastric cancer.[207] However, early studies showed that RT improved survival when used concurrently with chemotherapy. Moertel et al assessed fluorouracil plus RT compared with RT alone in the treatment of locally advanced unresectable gastric cancer.[208] Patients receiving combined modality treatment had significantly better median OS (13 months vs. 6 months) and 5-year OS (12% vs. 0%) rates compared to those receiving RT alone. 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 lomustine or split-course RT with concurrent bolus fluorouracil followed by maintenance with fluorouracil and lomustine.[209] 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.

Randomized clinical trials have also been conducted to compare surgery alone to surgery plus RT in patients with resectable gastric cancer. In a trial conducted by the British Stomach Cancer Group, 432 patients were randomized to undergo surgery alone or surgery followed by either RT or

chemotherapy.[210] 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 another 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).[211] Resection rates were also higher with preoperative RT (89.5%) compared to surgery alone (79%), suggesting that preoperative RT improves local control. 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.[212]

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. Retrospective studies have shown that IMRT can lead to improved organ sparing and lower toxicity, compared to 3D conformal techniques.[213-216]

Principles of Radiation Therapy

General Guidelines

RT treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team, which should include medical oncologists, radiation oncologists, surgical oncologists, radiologists, gastroenterologists, and pathologists. Imaging studies and endoscopy reports should be reviewed by this multidisciplinary team to ensure an informed determination of treatment volume and field borders prior to simulation. 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. 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.

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

CT simulation and conformal treatment planning should be used. IV and/or oral contrast may be used for CT simulation to aid in target localization when clinically appropriate. It is optimal to treat patients in the supine position, as this setup is generally more stable and reproducible. 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.[213-216] Target volumes need to be carefully defined and encompassed when designing IMRT plans. Uncertainties from variations in stomach filling and respiratory motion should be considered. In designing IMRT for organs at risk, 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, EGD, FDG-PET, and CT scans should be used to identify the primary tumor and pertinent nodal groups.[206,217] 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.[206,218] Treatment of the remaining stomach should depend on a balance of the normal tissue morbidity and the risk of local recurrence in the residual stomach.

The relative risk of nodal metastases at a specific location is dependent on the site of the primary tumor and other factors including the depth of invasion into the gastric wall. Nodal areas at risk include the perigastric, celiac, left gastric artery, splenic artery, splenic hilar, hepatic artery, porta hepatic, suprapyloric, subpyloric, and pancreaticoduodenal lymph nodes. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity. See *Principles of Radiation Therapy- Target Volume* 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. Particular effort should be made to keep RT doses to the left ventricle of the heart to a minimum. Additionally, lung dose-volume histogram (DVH) parameters can be used as predictors of pulmonary complications in patients treated with concurrent chemoradiation. Although every effort should be made to minimize RT doses to organs at risk, it is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances.

Supportive Care

Careful monitoring and management of acute toxicities with aggressive supportive care is essential to avoid treatment interruptions or dose reductions. During an RT treatment course, patients' vital signs, weight, and blood counts should be measured at least once per week. Prophylactic antiemetics should be given when appropriate. Additionally, antacid and antidiarrheal medications may be prescribed when needed. If the estimated caloric intake is inadequate (<1500 kcal/day), oral and/or enteral nutrition should be considered. Feeding jejunostomy tubes or nasogastric feeding tubes may be placed to ensure adequate caloric intake. Adequate enteral and/or IV hydration is necessary throughout chemoradiation and recovery.

Combined Modality Therapy

Combined modality therapy has been shown to significantly increase survival in gastric cancer patients with locoregional disease.[219-221] Perioperative chemotherapy is recommended for localized resectable disease (category 1).[220,222-225] Postoperative chemoradiation is recommended for patients who received less than a D2 lymph node dissection.[218,226,227] Other treatment options include preoperative chemoradiation (category 2B) [217,228,229] or postoperative chemotherapy (for patients who have undergone primary D2 lymph node dissection).[230-232] Chemoradiation alone should be reserved for patients with unresectable disease or those who decline surgery.

Perioperative Chemotherapy

The survival benefit of perioperative chemotherapy in gastric cancer was first demonstrated in the landmark phase III MAGIC trial.[225] This study, which compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improves progression-free survival (PFS) and OS in patients with non-metastatic stage II and higher gastric or EGJ adenocarcinoma. In the randomized controlled phase II/III FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen in patients with resectable non-metastatic gastric or EGJ adenocarcinoma

(≥cT2 and/or N+).[222,233] In the phase II part of the study, 265 patients were randomized to receive either three preoperative and postoperative cycles of ECF (n = 137) or four preoperative and postoperative cycles of FLOT (n = 128). Results showed that 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).[233] 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). In the phase III part of the trial, 716 patients were randomized to receive FLOT (n = 356) or ECF (n = 360).[222] Results showed that median OS was increased in the FLOT group compared with the ECF group (50 months vs. 35 months; HR, 0.77; 95% CI, 0.63–0.94). The percentage of patients with serious chemotherapy-related adverse events was the same in the two groups (27% in the ECF group vs. 27% in the FLOT group). Therefore, ECF should no longer be recommended in this setting. However, because of considerable toxicity associated with the FLOT regimen, the panel recommends its use in select patients with good performance status. The perioperative regimen for most patients who have good to moderate performance status is fluorouracil and oxaliplatin (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 significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer.[223] At a median follow-up 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 perioperative fluorouracil and cisplatin is a viable treatment option for patients with locally advanced resectable gastric cancer.

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 OS compared with postoperative chemotherapy.[224] Patients were randomized to receive either three preoperative and three postoperative cycles of modified ECF regimens (chemotherapy group; n = 393) or capecitabine and cisplatin with concurrent RT (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 (HR, 1.01; 95% CI, 0.84–1.22; *P* = .90). After a median follow-up of 6.7 years, the 5-year OS was 58% in the chemotherapy group versus 46% in the chemoradiation group (HR, 1.62; *P* = .0004).[234] Therefore, adding RT to postoperative chemotherapy confers no survival benefit following adequate preoperative chemotherapy and surgery. Since there was poor postoperative patient compliance in both treatment groups, optimization of preoperative treatment strategies is integral. An ongoing phase II trial (CRITICS II), which will compare three preoperative strategies (chemotherapy, concurrent chemoradiation, and sequential chemotherapy and chemoradiation), is actively recruiting participants with resectable gastric cancer (Clinical Trial ID: NCT02931890).[235]

Preoperative Chemoradiation Therapy

Several small, single-arm studies have demonstrated the ability of preoperative chemoradiation to produce a pathologic response in resectable gastric cancer.[236-239] However, the value of preoperative chemoradiation in treating resectable gastric cancer remains uncertain since phase III randomized controlled trials demonstrating a survival

benefit in gastric cancer are lacking. The regimens listed in the guidelines for preoperative chemoradiation are largely derived from phase II/III trials involving patients with cancers of the esophagus and/or EGJ.[217,228,240-243]

Results from the multicenter phase III randomized CROSS trial showed that preoperative chemoradiation with paclitaxel and carboplatin significantly improved OS and DFS compared to surgery alone in patients with resectable (T2–3,N0–1,M0) esophageal or EGJ cancers (n = 368).[228] 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.[229]

A small trial of 38 patients with stage II–IV esophageal carcinoma showed that FOLFOX combined with RT is safe and well-tolerated in the preoperative setting, with 38% of patients achieving pCR.[242] The CALGB 9781 prospective trial that randomized patients (n = 56) with stage I–III esophageal cancers to receive preoperative chemoradiation or surgery alone found a survival benefit for preoperative chemoradiation with fluorouracil and cisplatin.[241] After a median follow-up of 6 years, median OS was 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%). In a randomized phase III trial (PRODIGE5/ACCORD17), 267 patients with unresectable esophageal cancer or those medically unfit for surgery were randomized to receive chemoradiation with either FOLFOX or fluorouracil and cisplatin.[240] The median PFS was 9.7 months in the FOLFOX group compared to 9.4 months in the fluorouracil and cisplatin group (P = .64). Although FOLFOX was not associated with a PFS benefit compared to fluorouracil and cisplatin, the investigators suggest that FOLFOX might be a more convenient option for patients who may not be candidates for surgery. Since patients with gastric cancer were not included in these trials, paclitaxel and carboplatin, FOLFOX, and fluorouracil plus cisplatin are category 2B recommendations in this setting. Single-agent fluoropyrimidine (fluorouracil or capecitabine) is also a category 2B recommendation for preoperative chemoradiation.

Preoperative Sequential Chemotherapy and Chemoradiation Therapy

Several studies have shown that preoperative sequential chemotherapy followed by chemoradiation and surgery yields a pathologic response in patients with resectable gastric cancer.[217,237-239,244] In the phase II RTOG 9904 trial, preoperative chemotherapy with fluorouracil and cisplatin followed by concurrent chemoradiation with infusional fluorouracil and paclitaxel resulted in a pathologic complete response (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.[217] 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.[239] R0 resection was achieved in 65% of patients and the median OS and actuarial 2-year survival rates were 14.5 months and 35%, respectively.[239] Therefore, induction chemotherapy prior to preoperative chemoradiation therapy is feasible and may be appropriate for select patients. However, this approach needs to further evaluated in phase III randomized clinical trials.

Postoperative Chemoradiation Therapy

The landmark INT-0116 trial investigated the effectiveness of surgery followed by postoperative chemotherapy plus chemoradiation on the survival of patients with resectable gastric or EGJ adenocarcinoma.[218,226] In this trial, 556 patients (stage IB to IV, M0) who had not received preoperative therapy were randomized to receive surgery followed by postoperative chemotherapy plus chemoradiation (n = 281; bolus fluorouracil and leucovorin before and after concurrent chemoradiation with the same regimen) or surgery alone (n = 275).[218] The majority of patients had T3 or T4 tumors (69%) and node-positive disease (85%). After a median follow-up of 5 years, median OS in the surgery-only group was 27 months compared to 36 months in the postoperative chemotherapy plus chemoradiation group (*P* = .005). The postoperative chemotherapy plus chemoradiation group also had better 3-year OS (50% vs. 41%) and RFS rates (48% vs. 31%) than the surgery-only group. There was also a significant decrease in local failure as the first site of failure in the chemoradiation group (19% vs. 29%). After a median follow-up of greater than 10 years, survival remained improved in patients treated with postoperative chemoradiation.[226]

The results of the INT-0116 trial established the efficacy of postoperative chemoradiation in patients with completely resected gastric or EGJ adenocarcinoma who have not received preoperative therapy. However, the dosing and schedule of chemotherapy agents used in this trial were associated with high rates of grade 3–4 hematologic and GI toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group, 17% discontinued treatment and three patients died as a result of chemoradiation-related toxicities, including pulmonary fibrosis, cardiac events, and myelosuppression. Therefore, the doses and schedule of chemotherapy agents used in the INT-0116 trial are not recommended by the panel due to concerns regarding toxicity. See *Principles of Systemic Therapy—Regimens and Dosing Schedules* in the algorithm for recommended modifications to this regimen.

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. However, there was no significant difference in recurrence rates between the two groups following D2 lymph node dissection.[227] The results of the phase III ARTIST trial confirmed that postoperative chemoradiation did not significantly reduce recurrence rates after D2 lymph node dissection in patients with curatively resected gastric cancer compared to postoperative chemotherapy.[231,245] Interestingly, postoperative chemoradiation was associated with a significant prolongation of 3-year DFS compared to postoperative chemotherapy in a subgroup (ad-hoc) of patients with positive lymph nodes (78% vs. 72%; *P* = .0365).[245] However, the phase III ARTIST II trial demonstrated no survival benefit for the addition of radiation to postoperative chemotherapy in 546 patients with node-positive, D2-resected gastric cancer (3-year DFS of 74.3% vs. 72.8% for postoperative chemotherapy and postoperative chemoradiation, respectively; HR, .971; *P* = .879).[246] Therefore, postoperative chemoradiation is recommended for patients who received less than a D2 lymph node dissection while patients who received a D2 lymph node dissection should be treated with postoperative adjuvant chemotherapy.

Postoperative Chemotherapy

The phase III CLASSIC trial (conducted in South Korea, China, and Taiwan) evaluated postoperative chemotherapy with capecitabine and oxaliplatin after curative gastrectomy with D2 lymph node dissection in 1035 patients with stage II or IIIB gastric cancer.[230,232] In this study,

patients were randomized to receive either 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 3-year DFS (74%) compared to surgery alone (59%) for all disease stages ($P < .0001$).[232] After a median follow-up of 62.4 months, the estimated 5-year DFS rate 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.[230] Therefore, the panel supports the use of postoperative chemotherapy with capecitabine and oxaliplatin after D2 lymph node dissection in patients with advanced resectable gastric cancer. The panel also endorses the use of FOLFOX in this setting. However, it should be noted that the benefit of postoperative chemotherapy 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.[218,226,227]

Chemoradiation for Unresectable Disease

Chemoradiation alone may be offered to medically fit patients with unresectable disease. Since there are limited data in gastric cancer, the panel recommends extrapolation of fluorouracil-based chemoradiation regimens with proven efficacy in esophageal carcinoma (See *Preoperative Chemoradiation Therapy* above). Preferred regimens in this setting include FOLFOX as well as fluorouracil and cisplatin. Another recommended regimen is fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B). Chemoradiation with either FOLFOX or fluorouracil and cisplatin were shown to be effective in a randomized phase III trial of patients with unresectable esophageal cancer.[240] A trial of patients with stage II–IV esophageal carcinoma confirmed the safety and efficacy of FOLFOX combined with RT with or without surgery.[242] In the FFCD 9102 trial, survival was similar for patients with esophageal cancer receiving fluorouracil and cisplatin-based chemoradiation with or without surgery.[243] Additionally, patients may receive a fluoropyrimidine combined with paclitaxel, which has proven efficacy in yielding a pathologic response in resectable gastric cancer.[217] Following primary treatment, patients should be re-staged to determine whether surgery is an option. Surgery is preferred for patients with resectable disease after chemoradiation while those found to still have unresectable disease should receive palliative management.

Systemic Therapy for Locally Advanced or Metastatic Disease

First-Line Therapy

Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic gastric cancer.[247-250] First-line systemic therapy regimens with two cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.[251] Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Trastuzumab should be added to first-line chemotherapy for patients with HER2 overexpression-positive adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred [category 1 for cisplatin;[110] category 2A for oxaliplatin]). An FDA-approved biologic medical product that is similar to trastuzumab (a biosimilar) is an appropriate substitute. Pembrolizumab can also be added to this regimen for treatment of HER2 overexpression-positive adenocarcinoma.[252] Preferred regimens for HER2 overexpression-negative disease include nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin for tumors with PD-L1 expression levels by CPS of greater than or equal to 5 (category 1).[253] Nivolumab is useful under certain

circumstances for tumors with CPS of less than 5 (category 2B). See *Targeted Therapies* below for more information on trastuzumab, nivolumab, and pembrolizumab.

The preferred regimens for HER2-negative disease also include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin[254-256] or cisplatin.[254,257-259] A phase III trial conducted by the German Study Group compared treatment with fluorouracil and cisplatin to FOLFOX in patients (n = 220) with previously untreated advanced adenocarcinoma of the stomach or EGJ.[254] Results 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; *P* = .77) compared to fluorouracil and cisplatin (FLP).[254] However, there was no significant difference in median OS (10.7 vs. 8.8 months, respectively) between the two groups. FOLFOX resulted in significantly superior response rates (41.3% vs. 16.7%; *P* = .12), time to treatment failure (5.4 vs. 2.3 months; *P* < .001), PFS (6.0 vs. 3.1 months; *P* = .029), and improved OS (13.9 vs. 7.2 months) compared with FLP in patients older than 65 years (n = 94). Therefore, FOLFOX offers reduced toxicity and similar efficacy compared to fluorouracil plus cisplatin and may also be associated with improved efficacy in older adult patients. The safety and efficacy of FOLFOX have also been demonstrated in other studies.[255,260,261]

Regimens combining a platinum agent with capecitabine have also been evaluated in several studies for patients with advanced gastric cancer.[259,262,263] A phase III randomized trial (ML 17032) that evaluated the efficacy of combined capecitabine and cisplatin (XP) compared to fluorouracil and cisplatin (FP) found that capecitabine was noninferior to fluorouracil as first-line therapy in patients with advanced gastric cancer.[259] Two phase II trials concluded that capecitabine in combination with oxaliplatin is active and well-tolerated as first-line therapy for advanced gastric cancer.[262,263] Furthermore, results of a meta-analysis suggest that OS was superior in advanced gastroesophageal cancer patients treated with capecitabine-based combinations compared to patients treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.[264] Another meta-analysis reported that treatment with oxaliplatin-based regimens significantly improved the partial response rate, disease progression rate, and 1-year OS rate of patients with gastric cancer as compared to cisplatin-based regimens.[265] Therefore, capecitabine and oxaliplatin is also a preferred regimen for first-line treatment of patients with advanced gastric cancers. The GO2 phase III trial demonstrated that a low-dose capecitabine and oxaliplatin regimen (60% of the standard dose) was non-inferior in terms of PFS and resulted in significantly lower toxicities and better overall treatment utility in elderly and/or frail patients with advanced gastroesophageal cancers (n = 514).[266] Therefore, this low-dose regimen is recommended as an alternative to standard-dose capecitabine and oxaliplatin for elderly and/or frail patients with advanced or metastatic disease. See *Principles of Systemic Therapy—Regimens and Dosing Schedules* in the algorithm for recommended modifications to this regimen.

First-line treatment with irinotecan-based regimens has been explored extensively in clinical trials involving patients with advanced or metastatic gastroesophageal cancers.[258,267-278] The results of a randomized phase III study comparing irinotecan and fluorouracil (FOLFIRI) to cisplatin and fluorouracil (CF) in patients with advanced gastric or EGJ adenocarcinoma (n = 337) showed that FOLFIRI was non-inferior to CF in terms of PFS, but not in terms of OS or time to progression.[273] FOLFIRI was also associated with a more favorable safety profile. A phase III trial (French Intergroup Study) compared FOLFIRI with ECF as first-line treatment in patients (n = 416) with advanced or metastatic gastric or EGJ adenocarcinoma.[278] 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).[278] 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, FOLFIRI may be recommended as an option for first-line therapy in patients with advanced or metastatic gastric cancer.

Docetaxel, cisplatin, and fluorouracil (DCF) has also demonstrated activity in patients with locally advanced or metastatic gastric cancer.[279,280] An international phase III study (V325) that randomized 445 patients with untreated advanced gastric or EGJ cancer to receive either DCF or CF found that the addition of docetaxel to CF significantly improved time to progression, OS, and overall response rate (ORR).[279] However, DCF was associated with increased toxicities including myelosuppression and infectious complications. Various modifications of the DCF regimen have demonstrated improved safety in clinical trials of patients with advanced gastric cancer compared to the DCF regimen evaluated in the V325 study.[281-286] Therefore, due to concerns regarding toxicity, dose-modified DCF or other DCF modifications should be used as alternative options to the standard DCF regimen for first-line therapy.[282,285,286] Other recommended regimens for first-line therapy include paclitaxel with either cisplatin or carboplatin,[287-289] docetaxel with cisplatin,[290,291] or single-agent fluoropyrimidine (fluorouracil or capecitabine),[258,292,293] docetaxel,[248,294] or paclitaxel.[295,296] Docetaxel, carboplatin, and fluorouracil[282] is a category 2B recommendation in this setting.

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Ramucirumab in combination with paclitaxel (preferred) or as a single agent are category 1 recommendations for second-line or subsequent therapy.[297,298] Fam-trastuzumab deruxtecan-nxki is a second-line treatment option for HER2 overexpression-positive adenocarcinoma patients who had received prior trastuzumab-based therapy.[299] See *Targeted Therapies* below for more information on ramucirumab and fam-trastuzumab deruxtecan-nxki.

Single-agent docetaxel,[248,294] paclitaxel,[295,296,300] and irinotecan[249,300-302] are also category 1 preferred options for second-line or subsequent therapy. In a randomized phase III trial (COUGAR-02) single-agent docetaxel was shown to significantly increase 12-month OS compared to active symptom control alone (5.2 months vs. 3.6 months, respectively; HR, 0.67; *P* = .01).[248] A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the two groups (9.5 months in the paclitaxel group vs. 8.4 months in the irinotecan group; HR, 1.13; *P* = .38).[300]

FOLFIRI is a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy.[269,302-305] A phase II trial investigating the efficacy and toxicity of FOLFIRI in patients (n = 40) with recurrent or metastatic gastric cancer reported an ORR of 29% and median OS of 6.4 months.[305] Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in advanced gastric cancer patients (n = 59) treated with FOLFIRI in the second-line setting.[302] Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.[303] In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%).

The trifluridine and tipiracil regimen was approved by the FDA in 2019 for previously treated recurrent or metastatic gastric and EGJ adenocarcinoma,[306] based on results from the global phase III TAGS trial, in which 507 patients with heavily pretreated metastatic gastric or EGJ cancer were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n = 337) or placebo plus best supportive care (n = 170).[307] This study reported an improvement in median OS by 2.1 months

(5.7 vs. 3.6 months) with the trifluridine and tipiracil regimen compared to placebo (HR, 0.69; 95% CI, 0.56–0.85; *P* = .0003). PFS was significantly longer in the trifluridine and tipiracil group (2.0 vs. 1.7 months; HR, 0.57; 95% CI, 0.47–0.70; *P* < .0001). The efficacy benefits of trifluridine and tipiracil were observed regardless of whether or not the patient had undergone previous gastrectomy.[308] The most frequently reported grade 3–4 toxicities were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%). Patients aged greater than or equal to 65 years had a higher incidence of moderate renal impairment compared to the overall study population (31% vs. 17%).[309] Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic gastric cancer in the third-line or subsequent setting. However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume gastric cancer who have minimal or no symptoms and the ability to swallow pills.

Other recommended regimens for second-line or subsequent therapy include irinotecan and cisplatin,[255,310] ramucirumab combined with irinotecan[311] or FOLFIRI,[312] and irinotecan and docetaxel (category 2B).[313] Options that are useful in certain circumstances include pembrolizumab[115,314,315] or dostarlimab-gxly[316] for MSI-H/dMMR tumors, pembrolizumab for TMB-H (≥10 mutations/megabase) tumors,[317] and entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors.[318,319] See *Targeted Therapies* below for more information on pembrolizumab, dostarlimab-gxly, entrectinib, and larotrectinib.

Targeted Therapies

At present, several targeted therapeutic agents, trastuzumab, pembrolizumab/nivolumab, and entrectinib/larotrectinib, have been approved by the FDA for use in advanced gastric cancer. Treatment with trastuzumab is based on the presence of HER2 overexpression.[110] Treatment with pembrolizumab/nivolumab is based on testing for MSI by PCR/NGS or MMR by IHC, PD-L1 expression by IHC, or high TMB by NGS.[115,253,314,315,317,320,321] Treatment with the tropomyosin receptor kinase (TRK) inhibitors entrectinib and larotrectinib is based on testing for *NTRK* gene fusions.[322,323] When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC/ISH/targeted PCR should be considered first, followed by NGS testing as appropriate.

Trastuzumab

The ToGA trial was the first randomized prospective phase III trial that evaluated the efficacy and safety of trastuzumab in patients with HER2 overexpression-positive advanced gastric or EGJ adenocarcinoma.[110] In this trial, 594 patients with HER2 overexpression-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.[110] 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 in HER2 overexpression-positive patients (13.8 vs. 11 months, respectively; *P* = .046). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment for patients with HER2 overexpression-positive advanced gastroesophageal adenocarcinoma. In a post-hoc subgroup analysis, the addition of trastuzumab to chemotherapy further 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).

The phase II HERXO trial assessed the combination of trastuzumab with capecitabine and oxaliplatin in the first-line treatment of patients with HER2 overexpression-positive advanced gastric or EGJ adenocarcinoma (n = 45).[324] At a median follow-up of 13.7 months, PFS and OS were 7.1 and 13.8 months, respectively, and 8.9%, 37.8%, and 31.1% of patients achieved a complete response, partial response, and stable disease. The most frequently reported grade 3 or higher adverse events were diarrhea (26.6%), fatigue (15.5%), nausea (20%), and vomiting (13.3%). In a retrospective study of 34 patients with HER2 overexpression-positive metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2 overexpression-positive tumors.[325] 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 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combinations of trastuzumab with capecitabine and oxaliplatin or with modified FOLFOX are effective regimens with acceptable safety profiles in patients with HER2 overexpression-positive gastroesophageal cancers. Therefore, trastuzumab should be added to first-line chemotherapy in combination with a fluoropyrimidine and a platinum agent (oxaliplatin is preferred over cisplatin due to lower toxicity) in patients with HER2 overexpression-positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab may be combined with other chemotherapy agents for first-line therapy, but should not be continued in second-line therapy.[326]

Pembrolizumab can also be added to first-line fluoropyrimidine, platinum, and trastuzumab based on an interim analysis of the first 264 patients enrolled in the KEYNOTE-811 trial, which showed an improved ORR (74% vs. 52%; *P* = .0001) and median duration of response (10.6 vs. 9.5 months) with the addition of pembrolizumab to chemotherapy plus trastuzumab compared to the addition of placebo in patients with HER2 overexpression-positive adenocarcinoma.[252]

Fam-trastuzumab deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of trastuzumab and a cytotoxic topoisomerase I inhibitor connected by a cleavable tetrapeptide-based linker. The efficacy and safety of fam-trastuzumab deruxtecan-nxki in advanced or metastatic gastric or EGJ adenocarcinoma was evaluated in the phase II DESTINY-Gastric01 trial, which included 188 patients with progressive disease following at least two prior lines of therapy, including trastuzumab.[299] Patients were randomized 2:1 to receive either fam-trastuzumab deruxtecan-nxki or physician's choice of chemotherapy (paclitaxel or irinotecan). The confirmed ORR for patients on fam-trastuzumab deruxtecan-nxki was 40.5% compared to 11% for those on chemotherapy. OS (12.5 vs. 8.4 months; *P* = .0097), median PFS (5.6 vs. 3.5 months), and duration of response (11.3 vs. 3.9 months) were also higher in the fam-trastuzumab deruxtecan-nxki group compared to the chemotherapy group. Fam-trastuzumab deruxtecan-nxki resulted in more toxicities than systemic chemotherapy in this trial. The most common adverse events (grade 3 or higher) were a decreased neutrophil count (51% of the fam-trastuzumab deruxtecan-nxki group and 24% of the chemotherapy group), anemia (38% and 23%, respectively), and decreased white blood cell count (21% and 11%). Fam-trastuzumab deruxtecan-nxki–related interstitial lung disease or pneumonitis occurred in 12 patients resulting in 1 drug-related death (due to pneumonia). No drug-related deaths occurred in the physician's choice group. The FDA has approved fam-trastuzumab derextecan-nxki to treat HER2 overexpression-positive tumor patients in second-line or subsequent therapy. Therefore, fam-trastuzumab deruxtecan-nxki may be used as a second-line or subsequent treatment

option for patients with HER2 overexpression-positive adenocarcinoma following failure of prior treatment with a trastuzumab-based regimen. However, careful patient selection and close monitoring of patients for excessive toxicity is recommended.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.[297,298] 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.[297] In this study, 355 patients were randomized to receive ramucirumab (n = 238) or placebo (n = 117). 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 placebo (16% vs. 8%), whereas rates of other adverse events were similar.

An international phase III randomized trial (RAINBOW) evaluated paclitaxel with or without ramucirumab in patients (n = 665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.[298] 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, and the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone (P = .0001). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel. An exposure-response analysis revealed that ramucirumab was a significant predictor of OS and PFS in both studies.[327] Based on these results, 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. The guidelines recommend ramucirumab as a single agent (category 1) or in combination with paclitaxel (category 1; preferred) as treatment options for second-line or subsequent therapy in patients with advanced or metastatic gastric adenocarcinoma.[297,298]

Ramucirumab combined with FOLFIRI can be an option for second-line or subsequent therapy. In a multi-institutional retrospective analysis of 29 patients with advanced gastric or EGJ adenocarcinoma who received FOLFIRI plus ramucirumab in the second-line setting, the ORR was 23% with a disease control rate of 79%.[312] Median PFS was 6 months and median OS was 13.4 months. Six- and 12-month OS were 90% and 41%, respectively. No new safety signals were observed with the combination treatment, making FOLFIRI plus ramucirumab a safe, non-neurotoxic alternative to ramucirumab plus paclitaxel. Ramucirumab combined with irinotecan is also an option for second-line or subsequent therapy for patients with advanced gastric cancer.[311]

Due to the results of the international phase III RAINFALL trial, in which treatment with ramucirumab did not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma, the addition of ramucirumab to first-line chemotherapy is not recommended at this time.[328]

Nivolumab

Nivolumab is a monoclonal PD-1 antibody that was approved by the FDA in April 2021, in combination with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with advanced or metastatic gastric cancer.[329] This approval was based on results from the phase III Checkmate-649 trial, which randomized 1581 patients with previously untreated, HER2-negative, unresectable gastric, EGJ, or esophageal adenocarcinoma to receive chemotherapy alone or nivolumab

plus chemotherapy (capecitabine and oxaliplatin or modified FOLFOX).[253] The addition of nivolumab to chemotherapy resulted in significant improvements in OS (14.4 vs. 11.1 months; HR = .71; *P* < .0001) and PFS (7.7 vs. 6 months; HR = .68; *P* < .0001) compared to chemotherapy alone in patients with a PD-L1 CPS of ≥5 (n = 955). Additional results also showed some improvement in OS and PFS in patients with a PD-L1 CPS of ≥1 (n = 1296; OS = 14 vs. 11.3 months, HR = .77; PFS = 7.5 vs. 6.9, HR = .74) and in all randomly assigned patients (OS = 13.8 vs. 11.6, HR = .8; PFS = 7.7 vs. 6.9, HR = .77). Among all patients, 59% of those in the nivolumab plus chemotherapy group and 44% of those in the chemotherapy alone group experienced grade 3–4 treatment-related adverse events. The most common any-grade treatment-related adverse events were nausea, diarrhea, and peripheral neuropathy across both groups. Sixteen treatment-related deaths occurred in the nivolumab plus chemotherapy group compared to 4 in the chemotherapy alone group. Therefore, nivolumab plus fluoropyrimidine- and oxaliplatin-based chemotherapy is a preferred first-line treatment option for patients with HER2-negative gastric tumors with PD-L1 expression levels by CPS of ≥5 (category 1) and is useful under certain circumstances for tumors with a CPS of <5 (category 2B).

Pembrolizumab

Pembrolizumab is a PD-1 antibody that was FDA approved 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.[330] This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across five multicenter single-arm clinical trials.[115,314,315] The ORR was 39.6% and responses lasted ≥6 months for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses, and the ORR was similar irrespective of cancer type.

In June 2020, the FDA approved pembrolizumab for the treatment of patients with metastatic TMB-H solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[331] This approval was based on a retrospective analysis of 102 patients enrolled in the KEYNOTE-158 trial who had tumors identified as TMB-H.[317] The ORR for these patients was 29%, with a 4% complete response rate. The median duration of response was not reached, with 50% of patients having response durations for ≥24 months. Based on these data, pembrolizumab may be used for the second-line or subsequent treatment of MSI-H/dMMR or TMB-H gastroesophageal tumors. However, it should be noted that no patients with gastroesophageal cancer were included in the KEYNOTE-158 trial.

Additional trials of pembrolizumab in gastric and EGJ cancers are ongoing. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing KEYNOTE clinical trials for pembrolizumab in patients with gastric and EGJ cancers.

Dostarlimab-gxly

Dostarlimab-gxly, an anti-PD-1 antibody, was approved by the FDA in August 2021 for the treatment of patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment, who have no satisfactory alternative treatment options, and who had not previously received a PD-1 or PD-L1 inhibitor.[332] This approval was based on data from the nonrandomized phase 1 multi-cohort GARNET trial that evaluated the safety and antitumor activity of dostarlimab-gxly in 209 patients with dMMR solid tumors who had not received prior PD-1, PDL-1, or CTLA4 inhibitors.[316,333] The majority of patients had endometrial or GI cancers. The ORR was 42%, with a 9% complete response rate and 33% partial response rate, and the median duration of response was 35 months. The most common treatment-related

adverse events were fatigue, anemia, diarrhea, and nausea. Immune-mediated adverse events also occurred, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities. Based on these data, dostarlimab-gxly may be used to treat patients with MSI-H/dMMR gastric tumors.

Entrectinib and Larotrectinib

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode TRK fusion proteins (TRKA, TRKB, TRKC), which have increased kinase function and are implicated in the oncogenesis of many solid tumors including head and neck, thyroid, soft tissue, lung, and colon.[319,334] Although believed to be extremely rare in gastroesophageal cancers, one case report provides evidence that *NTRK* gene fusions do occur in gastric adenocarcinoma and may be associated with an aggressive phenotype.[335-337]

In 2018, the FDA granted accelerated approval of the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged 12 years and older) with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[323] This second-ever tissue-agnostic FDA approval for the treatment of patients with cancer was based on data from three multicenter single-arm clinical trials. Patients with prospectively identified *NTRK* gene fusion-positive cancers were enrolled into one of three protocols: a phase I trial involving adults (LOXO-TRK-14001), a phase I–II trial involving children (SCOUT), and a phase II trial involving adolescents and adults (NAVIGATE).[319] A total of 55 patients with unresectable or metastatic solid tumors harboring an *NTRK* gene fusion who experienced disease progression following systemic therapy were enrolled across the three trials and treated with larotrectinib. The most common cancer types represented were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR across the three trials was 75%, with a complete response rate of 22%. At a median follow-up of 9.4 months, 86% of the patients with a response were either continuing treatment with larotrectinib or had undergone curative-intent surgery. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Response duration was ≥6 months for 73%, ≥9 months for 63%, and ≥12 months for 39% of patients. At the time of data analysis, the median duration of response and PFS had not been reached. Adverse events were predominantly grade 1, the most common being increased aspartate aminotransferase (AST) levels, vomiting, constipation, and dizziness. The SCOUT (Clinical Trial ID: NCT02637687) and NAVIGATE (Clinical Trial ID: NCT02576431) trials are still actively recruiting patients with *NTRK* gene fusion-positive tumors.

In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.[322] The approval of entrectinib for the treatment of *NTRK* gene fusion-positive tumors was based on data from three multicenter single-arm phase I and phase II clinical trials. A total of 54 patients aged 18 years or older with metastatic or locally advanced *NTRK* gene fusion-positive solid tumors were enrolled into one of the three protocols (ALKA-372-001, STARTRK-1, and STARTRK-2).[318] The most common cancer types represented were sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal. The ORR across the three trials was 57%, with a complete response rate of 7%. Response duration was ≥6 months for 68% of patients and ≥12 months for 45% of patients. The median duration of response was 10 months. The most common grade 3–4 treatment-related adverse events were increased weight and

anemia while the most common serious treatment-related adverse events were nervous system disorders. STARTRK-2 (Clinical Trial ID: NCT02568267) is still actively recruiting patients with *NTRK* gene fusion-positive tumors.

These data demonstrate that entrectinib and larotrectinib induce durable and clinically meaningful responses in patients with *NTRK* gene fusion-positive tumors with manageable safety profiles. Therefore, entrectinib and larotrectinib are recommended as second-line or subsequent treatment options for patients with *NTRK* gene fusion-positive gastric tumors.

Treatment Guidelines

The management of patients with gastric cancer requires the expertise of several disciplines, including surgical oncology, medical oncology, radiation oncology, gastroenterology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines is also desirable.[136] 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. See *Principles of Multidisciplinary Team Approach for Esophagogastric Cancers* in the algorithm for more information.

Workup

Newly diagnosed patients should receive 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. FDG-PET/CT evaluation from skull base to mid-thigh is recommended, if clinically indicated and if metastatic disease is not evident (may not be appropriate for T1 disease). EUS should be performed if early-stage disease is suspected or if early-stage versus locally advanced disease needs to be determined (preferred). ER is essential for the accurate staging of early-stage cancers (T1a or T1b); early-stage cancers can best be diagnosed by ER. ER may also be therapeutic for early-stage disease. Biopsy of metastatic disease should be performed as clinically indicated. Assessment of Siewert tumor type should also be included as part of the initial workup in all patients with EGJ adenocarcinoma.[338,339] Nutritional assessment and counseling as well as smoking cessation advice, counseling, and pharmacotherapy (as indicated) are recommended for all patients.

Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients. HER2 and PD-L1 testing are recommended at the time of diagnosis if metastatic disease is documented or suspected. NGS may be considered via a validated assay. 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 (stages cTis or cT1a)
- Locoregional cancer (stages cT1b–cT4a; cM0)
- Metastatic cancer (stage cT4b; cM1)

Additional Evaluation

Additional evaluations are warranted to assess a patient's medical condition, their ability to tolerate major surgery, and the feasibility of resection. These evaluations may include pulmonary function studies,

cardiac testing, and nutritional assessment. Laparoscopy with assessment of cytology with or without biopsies is recommended to evaluate for peritoneal spread when considering chemoradiation and/or surgery for medically fit patients with stage cT1b or higher potentially resectable locoregional disease. Laparoscopy with cytology can be considered for medically fit patients with surgically unresectable disease.

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 preferred treatment option for patients with potentially resectable cT1b or cT2, N0 tumors. However, since surgery alone is insufficient for most patients with cT2, N+ or cT3 or higher, any N tumors, perioperative chemotherapy (category 1) or preoperative chemoradiation (category 2B) is recommended.[217,222,223,244] Chemoradiation or systemic therapy are the recommended treatment options for medically fit patients whose locoregional cancer is found to be surgically unresectable after laparoscopic staging.[208,340]

Non-surgical Candidates

ER is recommended for non-surgical candidates with cTis or cT1a tumors. Non-surgical candidates with locoregional disease should receive palliative management/best supportive care. All patients diagnosed with metastatic disease are considered non-surgical candidates and should be treated with palliative management/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 in medically fit patients after the completion of preoperative therapy (chemotherapy or chemoradiation) and before surgical intervention. FDG-PET/CT scan can be performed as clinically indicated. Patients found to have resectable disease on imaging should proceed with surgery (preferred) or palliative management while those found to have unresectable or metastatic disease after primary treatment should receive palliative management.

Non-surgical candidates should also be restaged using chest/abdominal/pelvic CT scan with oral and IV contrast following primary treatment. FDG-PET/CT scan can be performed as clinically indicated in cases of renal insufficiency or allergy to CT contrast. A CBC and comprehensive chemistry profile are also recommended. 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 therapy for patients who have not received preoperative therapy has been established in randomized trials.[218,226,231] Therefore, postoperative chemoradiation is recommended for all patients following an R1 or R2 resection. Palliative management, as clinically indicated, is an alternative option for patients following an R2 resection. Postoperative chemoradiation is also recommended following an R0 resection for select patients with pT2, N0 tumors and high-risk features (eg, poorly differentiated or higher grade cancer, LVI, neural invasion, age <50 years, and not undergoing D2 lymph node dissection)[341] and for patients with pT3–pT4, any N or any pT, N+ tumors who received less than a D2 dissection (category 1). Patients with pT2, N0 tumors without high-risk features should receive surveillance. Patients with pT3–pT4, any N or any pT, N+ tumors who have undergone primary D2 lymph node dissection should receive postoperative chemotherapy (category 1).[230,232] 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 following R0 resection, the panel recommends surveillance for this group of patients.

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 should receive postoperative chemotherapy following R0 resection (category 1). In the absence of distant metastases, chemoradiation is recommended for patients following R1 or R2 resection, only if it was 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 therapy. Re-resection, if feasible, can also be considered following R1 resection. Palliative management should be offered to all patients with new metastatic disease and may also be offered to patients with R2 resection, as 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[342-351] and expert consensus. While studies have shown that most gastric cancer recurrences occur within the first 2 years after the completion of local therapy (70%–80%) and almost all recurrences occur by 5 years (~90%),[342,344,349] a study of 1573 patients who underwent curative intent therapy showed that 7.6% of recurrences occurred more than 5 years after treatment.[345] 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.[342-351] 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 received by the patient.

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. EGD should also be performed as clinically indicated in patients who had partial or subtotal gastrectomy. Patients with Tis or stage I disease may receive CT scan of the chest, abdomen, and pelvis with contrast as clinically indicated based on symptoms and concern for recurrence. Patients with stage II or III disease should receive chest/abdominal/pelvic CT scan with oral and IV contrast (preferred) every 6 to 12 months for the first 2 years, then annually for up to 5 years. FDG-PET/CT can also be considered as clinically indicated. Surveillance for patients undergoing curative intent total gastrectomy should follow these 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 recurrences. Palliative management, which may include chemoradiation (only if locally unresectable and not previously received), systemic therapy, and/or best supportive care, is recommended for patients with unresectable or metastatic recurrence. If not done previously, HER2, PD-L1, and MSI or MMR testing should be performed in patients with documented or suspected metastatic adenocarcinoma. NGS may be considered via a validated assay.

Management of unresectable or metastatic disease may include either systemic therapy and/or chemoradiation, with the goal of providing symptom relief and delaying progression, and should incorporate symptom-directed best supportive care (See *Palliative/Best Supportive Care* below). The decision to offer palliative/best supportive care alone or with systemic therapy is dependent upon the patient's performance status. The Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[352-354] Patients with higher ECOG PS scores are considered to have worse performance status while lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score less than 60% or an ECOG PS score greater than or equal to 3 should be offered palliative/best supportive care only. Systemic therapy or chemoradiation (only if locally unresectable and not previously received) can be offered in addition to palliative/best supportive care for patients with better performance status (KPS score of ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared to palliative/best supportive care alone for patients with advanced gastric cancer has been demonstrated in several randomized trials.[247-250] In an early comparison between chemotherapy and best supportive care versus best supportive care alone, OS (8 vs. 5 months) and time to progression (5 vs. 2 months) were longer in patients receiving chemotherapy in addition to best supportive care for advanced gastric cancer.[247] 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, the addition of 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).[249] Median survival was 4 months in the irinotecan and best supportive care group compared to 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual. In a larger randomized trial (n = 193), second-line chemotherapy with irinotecan (or docetaxel) was also found to significantly improve OS compared to best supportive care alone (5.1 vs. 3.8 months) in patients with advanced gastric cancer.[250] In another phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n = 33), EGJ (n = 59), or stomach (n = 76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine-based combination chemotherapy.[248] After a median follow-up of 12 months, the median OS was 5.2 months for patients in the docetaxel and best supportive care group compared to 3.6 months for those in the best supportive care alone group (*P* = .01). Therefore, the addition of systemic therapy to best supportive care can improve the quality of life and may prolong survival in patients with advanced gastric cancer.

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 regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

Leucovorin Shortage

Leucovorin is indicated with certain fluorouracil-based regimens. However, there is currently a shortage of leucovorin in the United States.[355] There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. 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.[356-358] However, the panel recommends use of these regimens without leucovorin in situations where leucovorin is not available.

Palliative/Best Supportive Care

The goals of palliative/best supportive care are to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of the stage of the disease or the need for other therapies. In patients with advanced or metastatic gastric cancer, palliative/best supportive care provides symptom relief and improvement in overall quality of life, and may result in prolongation of life. This is especially true when a multimodality interdisciplinary approach is pursued. Therefore, a multimodality interdisciplinary approach to palliative/best supportive care of gastric cancer patients is encouraged.

Bleeding

Acute bleeding is common in patients with gastric cancer and may be tumor-related or a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment.[359] 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 effective as initial treatment, the rate of recurrent bleeding is very high.[360,361] Widely available options for endoscopic therapies include injection therapy, mechanical therapy (eg, endoscopic clip placement), ablative therapy (eg, argon plasma coagulation or other laser therapy), or a combination of modalities.[360] Interventional radiology with angiographic embolization techniques may be useful in situations where endoscopy is not helpful.[362] Additionally, external beam RT (EBRT) has been shown to effectively

manage acute and chronic GI bleeding.[363,364] 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. Management of malignant gastric obstruction should be individualized, and treatment options should be selected as clinically appropriate. Treatment options used to alleviate or bypass obstruction include surgery (gastrojejunostomy[137] or gastrectomy in select patients[135]), EBRT, chemotherapy, and endoscopic placement of an enteral stent for relief of gastric outlet obstruction[137] or esophageal stent for EGJ/cardia obstruction. Endoscopic placement of a SEMS is a safe and effective minimally invasive palliative treatment for patients with luminal obstruction due to advanced gastric cancer.[365-368] In a systematic review, patients treated with endoscopic placement of a SEMS were more likely to tolerate oral intake and had shorter hospital stays than patients treated with gastrojejunostomy.[369] 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.[137] A randomized trial also reported similar findings.[370] 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.[371] 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.[372,373] Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.[374,375] Feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or jejunal feeding tubes for patients with mid 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. Therefore, screening and management of long-term sequelae are important for all gastric cancer survivors. However, due to a lack of large randomized trials, the survivorship management recommendations provided by the panel are based on smaller studies and clinical experience. Survivorship care planning should include appropriate timing of transfer of care to a primary care physician and maintenance of a therapeutic relationship with the primary care physician throughout life.

The oncology team and primary care physician should have clearly delineated roles in survivorship care, with these roles communicated to the patient. In general, routine gastric cancer-specific surveillance is not recommended for more than 5 years following the end of treatment. Surveillance should be performed in conjunction with good routine medical care, including routine health maintenance, preventive care, and cancer screening. Gastric cancer survivors should be counseled to maintain a healthy body weight, adopt a physically active lifestyle, consume a healthy diet with an emphasis on plant-based sources, and limit alcohol intake. Smoking cessation should also be encouraged, as appropriate. Additional preventive health measures and immunizations should be performed as indicated under the care of or in conjunction with a primary care physician.

Common issues facing gastric cancer survivors include weight loss, diarrhea, chemotherapy-induced neuropathy, and fatigue. Weight loss and fatigue can be effectively managed by monitoring patients' weight regularly, encouraging more frequent consumption of smaller meals without fluid intake, and encouraging physical activity and energy conservation measures. Anti-diarrheal medications, bulk-forming agents, or diet manipulation can be considered to treat diarrhea. Duloxetine can be considered to treat painful chemotherapy-induced neuropathy, but is ineffective for numbness or tingling. Referral to occupational, rehabilitation, and/or physical therapy should be considered for patients with chemotherapy-induced neuropathy at risk for falls. Osteopenia/osteoporosis is another common long-term sequelae in gastric cancer survivors, 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.[376,377] Therefore, bone density should be screened at regular intervals and low bone density should be managed as per established national guidelines.[378]

In addition to the issues discussed above, gastric cancer survivors who underwent gastrectomy face other long-term health issues including indigestion and nutritional deficiencies. Patients experiencing indigestion should be counseled to avoid foods that increase acid production (eg, citrus, tomato sauce, spicy foods) or lower gastroesophageal sphincter tone (eg, caffeine, peppermint, chocolate). Use of a proton pump inhibitor can also be considered. Gastrectomy survivors also have unique nutritional needs due to frequent vitamin and mineral deficiencies and other GI dysfunctions.[379] Studies have shown that long-term anemia, iron deficiency, and vitamin B_{12} deficiency are common in patients treated with gastrectomy for gastric cancer.[380,381] Supplementation of vitamin B_{12}[382] and iron[383] is safe and effective for reversing these deficiencies. If needed, referral to a dietician or nutritional services for individualized counseling can be considered.

Survivors who underwent total gastrectomy are at particular risk for long-term health issues, as they have been shown to have greater restrictions and a significantly worse quality of life compared to those who received partial gastrectomy.[384-386] 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.[387] Dumping syndrome, which results from rapid emptying of the stomach into the small bowel, is another concern for total gastrectomy survivors. Patients suffering from early dumping syndrome (within 30 minutes of eating a meal) may experience palpitations, diarrhea, nausea, and cramps while those with late dumping syndrome (within 2–3 hours of eating a meal) may experience dizziness, hunger, cold sweats, and faintness. A large study of 1153 total gastrectomy survivors reported that 67.6% and 38.4% of patients experienced early and late dumping, respectively.[388] To help manage the symptoms of dumping syndrome, the panel recommends

making dietary changes including frequent eating throughout the day, avoiding fluid intake with meals, and consuming a diet high in protein and fiber and low in simple carbohydrates and sugars.

The panel recommends the development of a survivorship care plan that includes information on treatments received (surgeries, RT, and systemic therapies), follow-up care, surveillance, screening recommendations, and post-treatment needs regarding acute, late, and long-term treatment-related effects and health risks. Roles of oncologists, primary care physicians, and subspecialty care physicians in the survivorship care plan should be clearly delineated. Long-term survivorship care plans should also include a periodic assessment of ongoing needs and identification of appropriate resources, including timing of transfer of care, if appropriate.

Summary

Gastric cancer is rampant in many parts of the world and is often diagnosed at an advanced stage. Risk factors for gastric cancer include *H. pylori* infection, smoking, and high salt intake. Some 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 localized gastric cancer. Best supportive care is an integral part of treatment, especially in patients with unresectable locally advanced, recurrent, or metastatic disease.

ER (EMR or ESD) is the primary treatment option for patients with early-stage (Tis or T1a) tumors. Medically fit patients with resectable T1b or higher, any N tumors should receive surgery with D2 lymph node dissection. Perioperative chemotherapy is a category 1 recommendation for patients with resectable T2 or higher, any N tumors (surgery is preferred for patients with T2, N0 tumors); preoperative chemoradiation may also be considered for these patients (category 2B). Patients with unresectable or metastatic disease may be offered best supportive care and palliative management with or without systemic therapy or chemoradiation, depending on performance status and prior treatment.

Following an R0 resection, postoperative chemoradiation is recommended for patients with T3–T4, any N tumors or any T, N+ tumors in patients who had received less than a D2 lymph node dissection and had not received previous chemoradiation or chemotherapy (category 1). Selected patients with T2, N0 tumors and high-risk features can also be considered for postoperative chemoradiation. Postoperative chemotherapy should be reserved for patients with T3–T4, any N and or any T, N+ tumors who had received D2 lymph node dissection (category 1). Postoperative chemoradiation is recommended for all patients with residual disease at surgical margins, if it was not received previously. Options for patients who have received previous chemotherapy or chemoradiation include chemotherapy (category 1 if received preoperatively) or observation (if preoperative chemoradiation was received) following R0 resection. Patients with R1 resection can be considered for re-resection while patients with R2 resection should receive 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 overexpression-positive tumors. Nivolumab combined with chemotherapy is recommended as first-line therapy for tumors with PD-L1 expression levels by CPS of greater than or equal to 5 (category 1) or CPS of less than 5 (category 2B). Ramucirumab, as a single agent or in combination with paclitaxel (preferred), and pembrolizumab (for MSI-H/dMMR or TMB-H tumors) are included as options for second-line or subsequent therapy for patients with metastatic gastric cancer. Dostarlimab-gxly is an alternative option to pembrolizumab for MSI-H/dMMR tumors. Entrectinib and larotrectinib are recommended for second-line or subsequent therapy for *NTRK* gene fusion-positive tumors.

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The NCCN Guidelines for Gastric Cancer are based on evidence- and consensus-based treatment approaches 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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