National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 2.2025 — April 4, 2025

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NCCN Gastric Cancer Guidelines Panel Members
Summary of the Guidelines Updates

Workup and Additional Evaluation (GAST-1)
Conclusions of Multidisciplinary Review, Primary Treatment (GAST-2)
Response Assessment, Additional Management (GAST-3)
Surgical Outcomes/Clinical Pathologic Findings for Patients Who Have Not Received Systemic Therapy (GAST-4)
Surgical Outcomes/Clinical Pathologic Findings for Patients Who Have Received Systemic Therapy (GAST-5)
Post-Treatment Assessment/Additional Management (GAST-6)
Follow-up/Surveillance (GAST-7)
Recurrence (GAST-8)
Palliative Management (GAST-9)
Peritoneal Carcinoma As Only Disease (GAST-10)

Principles of Endoscopic Staging and Therapy (GAST-A)
Principles of Pathologic Review and Biomarker Testing (GAST-B)
Principles of Surgery (GAST-C)
Principles of Genetic Risk Assessment for Gastric Cancer (GAST-D)
Principles of Multidisciplinary Team Approach for Esophagogastric Cancers (GAST-E)
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Principles of Radiation Therapy (GAST-G)
Principles of Surveillance (GAST-H)
Principles of Survivorship (GAST-I)
Principles of Palliative Care/Best Supportive Care (GAST-J)
Staging (ST-1)
Abbreviations (ABBR-1)

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

See NCCN Categories of Evidence and Consensus.

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See NCCN Categories of Preference.

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Updates in Version 2.2025 of the NCCN Guidelines for Gastric Cancer from Version 1.2025 include:

MS-1
• The Discussion has been updated to reflect the changes in the algorithm.

Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

General
• Upper GI gastrointestinal (GI) endoscopy changed to Esophagogastroduodenoscopy (EGD) throughout the algorithm.

GAST-1
• Workup; Last bullet revised: ~~Assess H. pylori status and conduct genetic testing as needed~~ *Test for H. pylori infection and eradicate in all patients with early gastric cancer if positive. Conduct genetic testing as needed and recommend H. pylori testing of close family members*

GAST-1A
• Footnote i revised: Added link to Principles of Surveillance (GAST-H).
• Footnote m revised: "...performed to evaluate for peritoneal spread when considering ~~chemoradiation or surgery~~ *local therapy*. Laparoscopy..."

GAST-2
• Locoregional disease: Medically fit potentially resectable, cT2 or higher, Any N: Preoperative chemoradiation (category 2B) removed as a primary treatment option. (Also for first column; top pathway on GAST-3)

GAST-2A
• Footnote q revised: "...perioperative immunotherapy ~~or surgery alone~~ should be considered in consultation with a multidisciplinary team. *The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear.*" (Also for GAST-3)
• Footnote removed: The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear. The role for surgery in the setting of favorable neoadjuvant response should be carefully discussed. (Also for GAST-3)

GAST-3
• Primary Treatment for Patients who are medically fit
  ▸ Top pathway revised: Perioperative chemotherapy (category 1) ~~or Preoperative chemoradiation (category 2B)~~
  ▸ Neoadjuvant or perioperative ICI if tumor is microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR)
    ◊ Outcome clarified: No evidence *of disease*
    ◊ Additional Management for patients with no evidence of disease; Revised: Observation *or Surgery*
• Footnote removed: Principles of Radiation Therapy (GAST-C)
• Footnote removed: If surgery is not being considered for management, upper GI endoscopy and biopsy should be done.

GAST-4
• Column header revised: Surgical Outcomes/Clinical Pathologic Findings (Patients Have Not Received ~~Preoperative Chemoradiation or~~ Systemic Therapy

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

GAST-5
- Column header Revised: Surgical Outcomes/Clinical Pathologic Findings (Patients Have Received ~~Preoperative Chemoradiation or~~ Systemic Therapy)
- Postoperative Management:
  - R0 resection:
    - Observation (if received preoperative chemoradiation) removed as an option
    - Revised: Systemic therapy~~, if received preoperatively~~ (category 1)
  - R1 resection revised: Chemoradiation (fluoropyrimidine-based)~~, only if not received preoperatively~~. Also for R2 resection.

GAST-7
- Footnote bb revised: For patients undergoing total gastrectomy for curative intent, surveillance should follow these recommendations except for endoscopy. Endoscopy ~~has no role in~~ *as clinically indicated for* routine surveillance for total gastrectomy unless patients are symptomatic.

GAST-9
- 3rd column; Bullet revised: NGS ~~may~~ *should* be considered via a validated assay

GAST-A 3 of 4
- Treatment
  - New bullet and sub-bullets added
    - Several Japanese and American guidelines have expanded the indications for ESD to include:
      - Well to moderately differentiated cancer of any size, without ulceration
      - Well or moderately differentiated with submucosal (sm) layer invasion <500 micrometers
      - Well or moderately differentiated <3 cm with ulceration
      - Poorly differentiated <2 cm without ulceration
  - New bullet added: This may potentially be considered curative resection if the margins are negative, there is no LVI, and curative resection is limited to sm1. However, there is still a very small risk of lymph node involvement, so such decisions should be made following multidisciplinary discussions and careful explanation to the patient.

GAST-B 1 of 7
- Pathologic review; Specimen type
  - 3rd row revised: Gastrectomy~~, without prior chemoradiation~~
  - 4th row
    - Revised: Gastrectomy, with prior chemoradiation *in unresectable gastric cancer treated with chemoradiation followed by surgery*
    - Analysis/Interpretation/Reporting revised
      - 1st bullet revised: Tumor site should be thoroughly sampled for specimens s/p ~~neoadjuvant therapy~~ *chemoradiation* without grossly obvious residual tumor
      - 2nd bullet revised: For pathology report, include all elements ~~as for~~ *of* resection ~~without prior chemoradiation plus~~ *and* assessment of treatment effect
- New footnote d added: For patients with surgically managed cancer, ≥16 regional lymph nodes are removed and pathologically examined during resection for curative intent therapy.

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

GAST-B 2 of 7
- Assessment of Treatment Response revised: "Response of the primary tumor and lymph node metastases to previous chemotherapy ~~and/~~or RT should be reported..."

GAST-B 3 of 7
- Assessment of Overexpression or Amplification of HER2 in Gastric Cancer revised: "...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 additional NGS testing as appropriate~~. *IHC/ISH/targeted PCR is the preferred approach to assess biomarkers initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing.* Repeat biomarker testing may be considered..."
- Footnote f revised: ~~An FDA-approved biosimilar is an appropriate substitute for trastuzumab.~~ *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.*

GAST-B 5 of 7
- Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing; 1st bullet revised: "...Patients with MSI-H or dMMR tumors ~~may~~ *should* be referred to a genetics counselor for further assessment in the appropriate clinical context."

GAST-B 6 of 7
- Next-Generation Sequencing revised
  - "...by the FDA for use in gastric cancer. ~~Immunohistochemistry/in situ hybridization/targeted PCR should be considered first for the identification of biomarkers, followed by NGS testing. If limited tissue is available, or the patient is unable to undergo a traditional biopsy, sequential testing of single biomarkers/limited molecular diagnostic panels will exhaust the sample. In these scenarios, or at the discretion of the treating physician, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory should be considered.~~ *IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing*.
  - PD-L1 expression ~~by immunohistochemistry~~
- Liquid Biopsy revised: 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 *or fusions* in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, *when limited tissue is available or* for patients who have metastatic or advanced gastric cancer who ~~may be unable~~ *are not able* 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.~~

GAST-C 4 of 5
- Palliative Procedures: Gastric resections should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease *when non-surgical options are not feasible such as endoscopic or interventional radiology procedures (ie, endoscopic stenting)*.

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

Principles of Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease
GAST-F 1 of 20
- New bullets added
  - An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
  - A checkpoint inhibitor should be added to first-line chemotherapy for patients with advanced disease with PD-L1 CPS ≥1.
  - Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
  - Footnote removed: An FDA-approved biosimilar is an appropriate substitute for trastuzumab. (Also for all GAST-F pages)

GAST-F 3 of 20
- The regimens for preoperative chemoradiation were removed. The corresponding dosing schedules were also removed.
  - Paclitaxel and carboplatin (category 2B)
  - Fluorouracil and oxaliplatin (category 2B)
  - Fluorouracil and cisplatin (category 2B)
  - Fluoropyrimidine (fluorouracil or capecitabine) (category 2B)
- Footnote removed: Cisplatin may not be used interchangeably with oxaliplatin in this setting.

GAST-F 4 of 20
- First-line Therapy revised
  - Preferred Regimens; HER2 overexpression negative
    - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab ~~(PD-L1 CPS ≥5) (category 1)~~ *for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)*
    - Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ~~≥ 10~~ *≥5* ~~; category 2B for PD-L1 CPS 1 to <10~~)
    - New regimen added: Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)
    - Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ~~≥10~~ *≥5* ~~; category 2B for PD-L1 CPS 1 to <10~~)
    - New regimen added: Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)
  - Useful in Certain Circumstances
    - New systemic therapy options added: Entrectinib, larotrectinib, or repotrectinib for NTRK gene fusion-positive tumors (category 2B)
    - Removed: Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B).

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

GAST-F 4A of 20
- Footnote e revised: If *no prior checkpoint inhibitor therapy or no t*umor progression while on therapy with a checkpoint inhibitor. (Applies to all GAST-F pages)
- Footnote h revised: Trastuzumab should be added to first-line chemotherapy for HER2 overexpression-positive adenocarcinoma. ~~An FDA-approved biosimilar is an appropriate substitute for trastuzumab~~.

Principles of Systemic Therapy-Regimens and Dosing Schedules
GAST-F 11 of 20
- First-line therapy; Preferred Regimens; Dosing revised:
  - HER2 Overexpression Negative, CLDN18.2 Positive
    - ◊ Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and zolbetuximab-clzb

      ~~Oxaliplatin 85 mg/m2 IV on Day 1~~
      Oxaliplatin 85 mg/m² IV on Day 1 (per study maximum of 12 doses)
      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
      Zolbetuximab-clzb 800 mg/m² IV (first-dose only)
      on Day 1 (subsequent doses 400 mg/m²)
      Cycled every 14 days

      Capecitabine 850–1000 mg/m² PO BID on Days 1–14
      ~~Oxaliplatin 130 mg/m2 IV on Day 1~~
      Oxaliplatin 130 mg/m² IV on Day 1 (per study maximum of 8 doses)
      Zolbetuximab-clzb 800 mg/m² IV (first-dose only)
      on Day 1 (subsequent doses 600 mg/m²)
      Cycled every 21 days

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

Principles of Systemic Therapy-Regimens and Dosing Schedules
GAST-F 12 of 20
- First-line Therapy; Preferred Regimens; New dose schedule added:
  - Tislelizumab-jsgr with fluoropyrimidine and oxaliplatin or cisplatin
    Tislelizumab 200 mg IV on Day 1 every 21 days
    in combination with:

    Fluoropyrimidine and oxaliplatin
    Oxaliplatin 85 mg/m^2 IV on Day 1
    Leucovorin 200 mg/m^2 IV on Day 1
    Fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on Days 1 and 2
    Cycled every 14 days for 12 cycles

    Capecitabine 850–1000 mg/m2 PO BID on Days 1–14
    Oxaliplatin 130 mg/m^2 IV on Day 1
    Cycled every 21 days (per study maximum of 6 doses)

    Fluoropyrimidine and cisplatin
    Cisplatin 60–80 mg/m^2 IV on Day 1
    Fluorouracil 750–800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1–5
    Cycled every 21 days for 6 cycles

    Cisplatin 60–80 mg/m^2 IV on Day 1 (per study maximum of 6 doses)
    Capecitabine 850–1000 mg/m^2 PO BID on Days 1–14
    Cycled every 21 days

GAST-F 14 of 20
- First-line therapy; Useful in Certain Circumstances, new dosing added:
  - Entrectinib, larotrectinib, or repotrectinib (for NTRK gene fusion-positive tumors)
    Entrectinib 600 mg PO once daily

    Larotrectinib 100 mg PO twice daily

    Repotrectinib
    160 mg PO daily Days 1–14 of cycle 1
    160 mg PO BID Days 15–28 of cycle 1
    160 mg PO BID Days 1–28 of cycle 2 and beyond
    Cycled every 28 days

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Updates in Version 1.2025 of the NCCN Guidelines for Gastric Cancer from Version 5.2024 include:

Principles of Systemic Therapy-References
GAST-F 17 of 20 through GAST-F 20 of 20
• The reference pages were updated to reflect the changes in the algorithm.

GAST-G 2 of 5
• Target Volume (General Guidelines)
  ▸ Preoperative chemoradiation section along with sub-bullets below removed
    ◊ Pretreatment diagnostic studies (EUS, EGD, FDG-PET, and CT scans) should be used to identify the tumor and pertinent nodal groups.
    ◊ 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.

GAST-G 5 of 5
• Reference removed: Ajani AJ, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. J Clin Oncol 2006;24:3953-3958.

GAST-H 1 of 2
• New bullet added: All patients with H. pylori infection who underwent curative ER or gastric subtotal resection must receive an H. pylori eradication regimen. The choice and duration of the eradication regimen should follow the recommendations of the latest American (American College of Gastroenterology) or international (Maastricht consensus report) H. pylori guidelines.

GAST-H 2 of 2
• Reference 1 is new: Choi IJ, Kook MC, Kim YI, et al. Helicobacter pylori therapy for the prevention of metachronous gastric cancer. N Engl J Med 2018;378:1085-1095.

GAST-I 3 of 4
• Survivorship Care Planning and Coordination of Care; 4th bullet; 3rd sub-bullet revised: "...NCCN ~~Disease-Specific~~ Guidelines: *Treatment by Cancer Type"*

GAST-J 2 of 3
• Pain; 3rd bullet, New sub-bullet added: Severe uncontrolled pain following gastric stent placement should be treated with endoscopic removal of the stent once the uncontrollable nature of the pain is established.

ABBR-1
• The abbreviations page was updated as appropriate.

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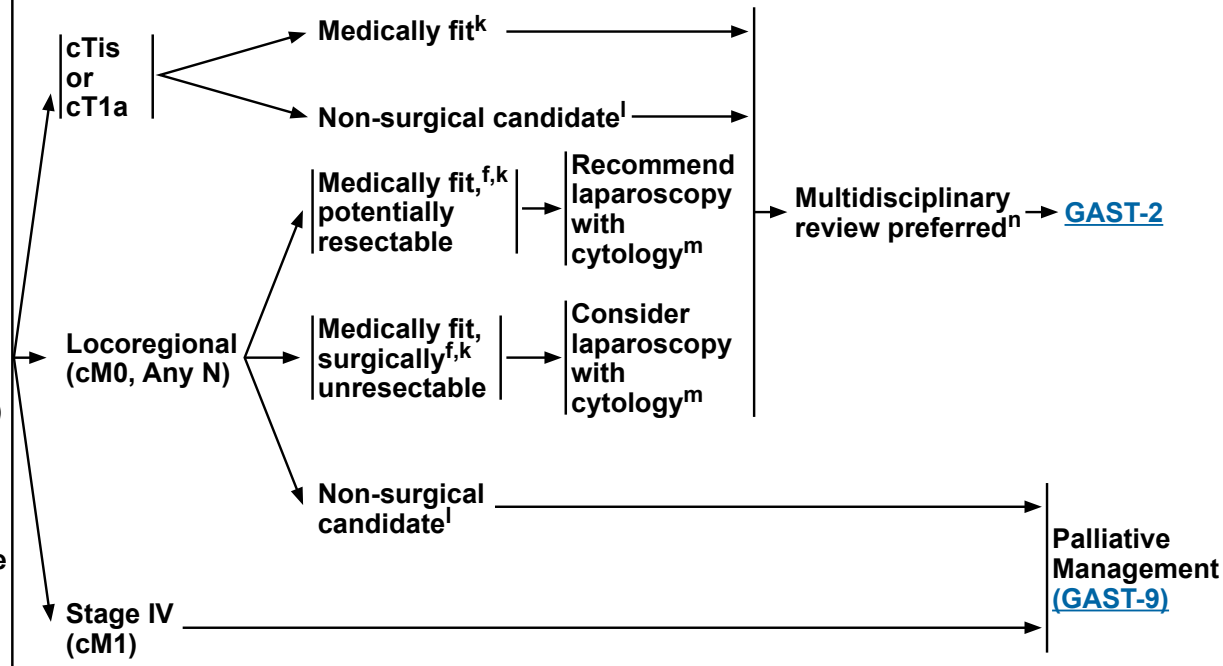
WORKUP

- History and physical (H&P)
- Esophagogastroduodenoscopy (EGD) and biopsy[a]
- Chest/abdomen/pelvis CT with oral and IV contrast
- FDG-PET/CT evaluation (skull base to mid-thigh) for locally advanced or metastatic disease[b] or if clinically indicated
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS) is recommended 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 microsatellite instability (MSI) by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients[d]
- HER2 and PD-L1 testing if advanced/metastatic disease is documented/suspected[d,e]
- CLDN18.2 testing if advanced/metastatic disease is documented/suspected[d]
- NGS should 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]
- Test for *H. pylori* infection and eradicate in all patients with early gastric cancer if positive. Conduct genetic testing as needed and recommend *H. pylori* testing of close family members[i]



Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on GAST-1A

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FOOTNOTES FOR GAST-1

[a] 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] 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. EBV testing should be performed if the morphology of the tumor contains prominent lymphoid stroma.
[f] Principles of Surgery (GAST-C).
[g] 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 Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.
[i] If H. pylori testing is positive, discuss recommendations with family members as appropriate. See Principles of Surveillance (GAST-H).
[j] See Staging (ST-1) for tumor classification.
[k] Medically able to tolerate major surgery.
[l] Patients who are medically unable to tolerate major surgery or patients who are medically fit, but decline surgery.
[m] Laparoscopy with cytology is performed to evaluate for peritoneal spread when considering local therapy. Laparoscopy with cytology is not indicated if a palliative resection is planned. Laparoscopy with cytology is indicated for clinical stage T1b or higher.
[n] Principles of Multidisciplinary Team Approach (GAST-E).

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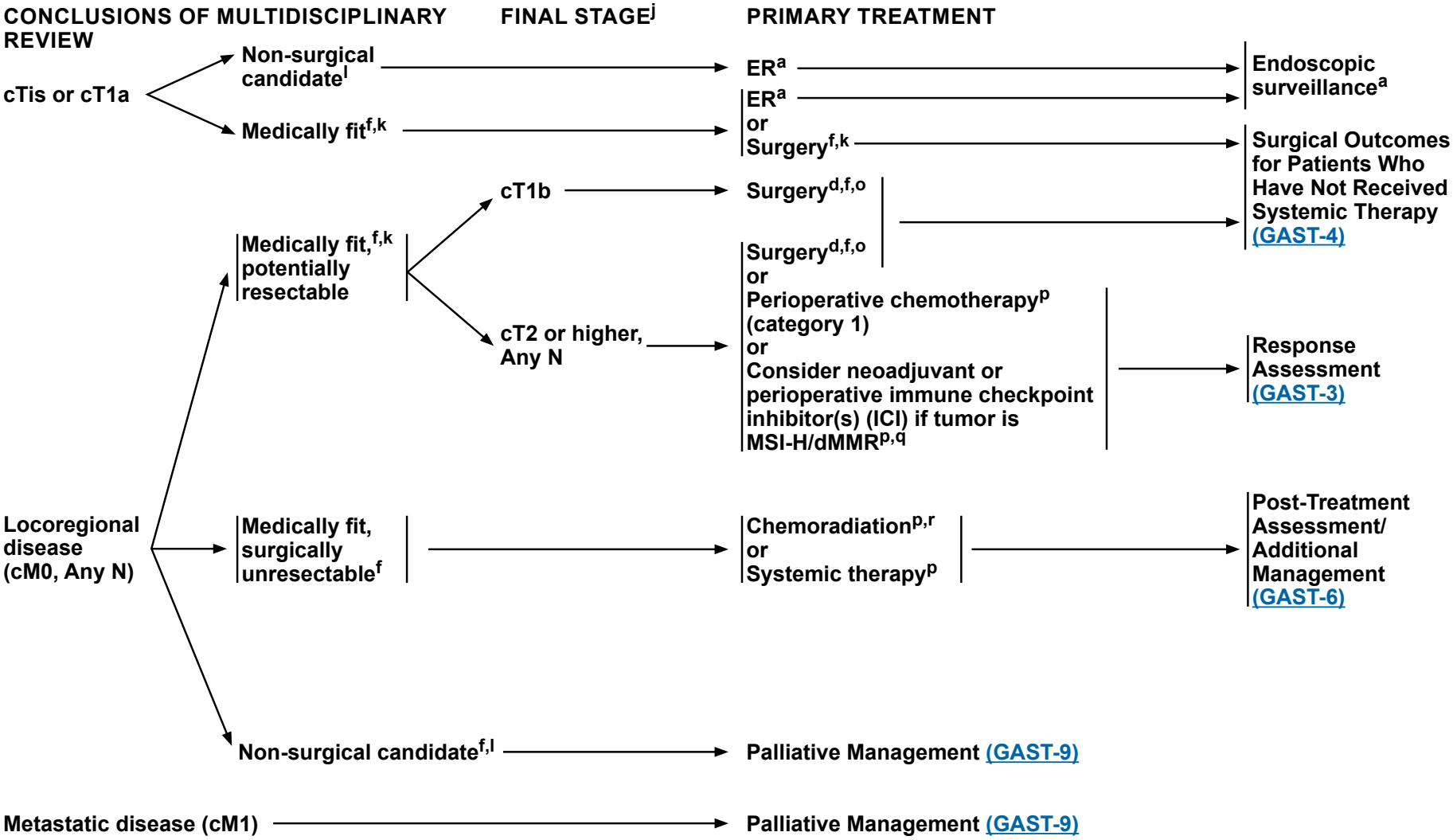

Footnotes on GAST-2A

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Footnotes for GAST-2

[a] Principles of Endoscopic Staging and Therapy (GAST-A).
[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] Principles of Surgery (GAST-C).
[j] See Staging (ST-1) for tumor classification.
[k] Medically able to tolerate major surgery.
[l] Patients who are medically unable to tolerate major surgery or patients who are medically fit, but decline surgery.
[o] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[p] Principles of Systemic Therapy (GAST-F).
[q] In patients with a microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) tumor, perioperative immunotherapy should be considered in consultation with a multidisciplinary team. The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear.
[r] Principles of Radiation Therapy (GAST-G).

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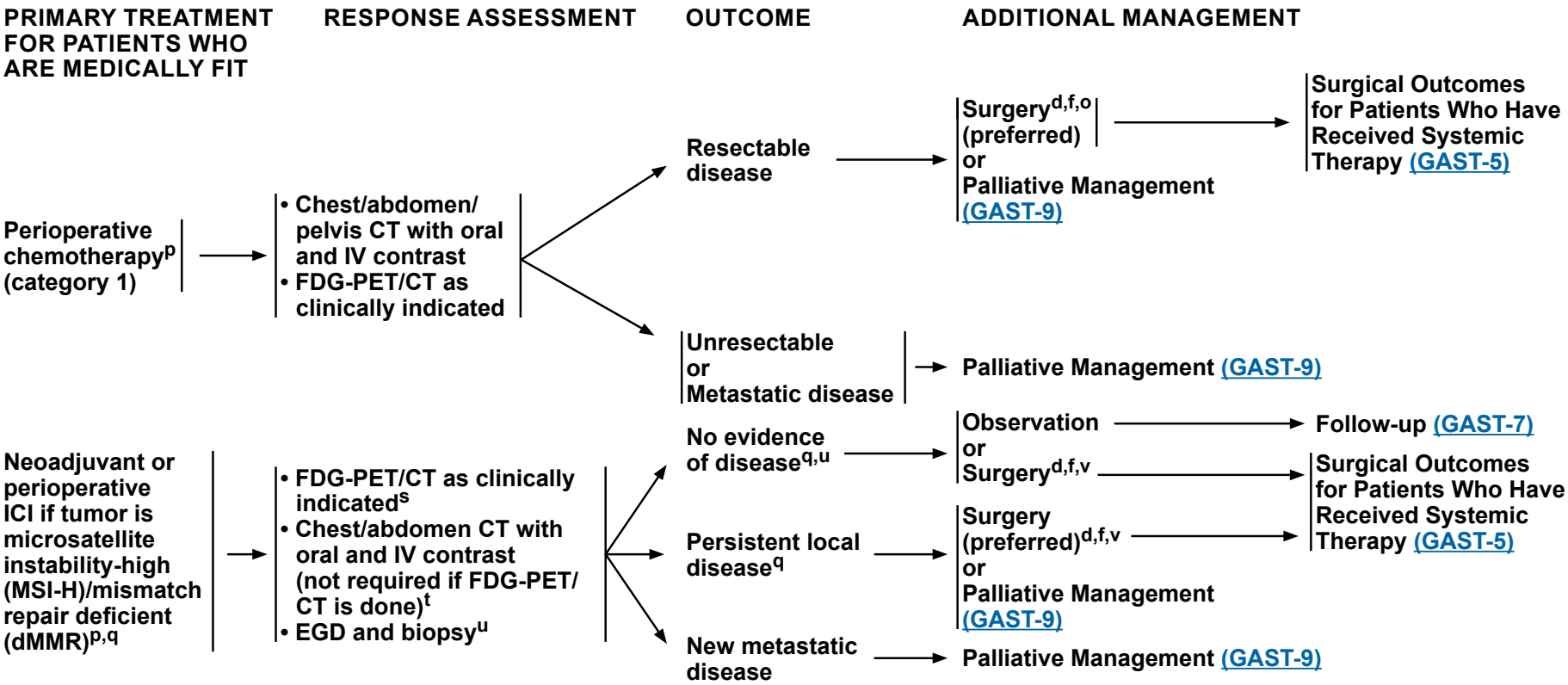

[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] Principles of Surgery (GAST-C).
[o] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[p] Principles of Systemic Therapy (GAST-F).
[q] In patients with an MSI-H/dMMR tumor, perioperative immunotherapy should be considered in consultation with a multidisciplinary team. The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear.
[s] Assessment ≥5 to 8 weeks after completion of preoperative therapy.
[t] Pelvis CT if clinically indicated.
[u] See Post-Treatment Surveillance in Principles of Endoscopic Staging and Therapy (GAST-A 3 of 4).
[v] Feeding jejunostomy for postoperative nutritional support, generally preferred.

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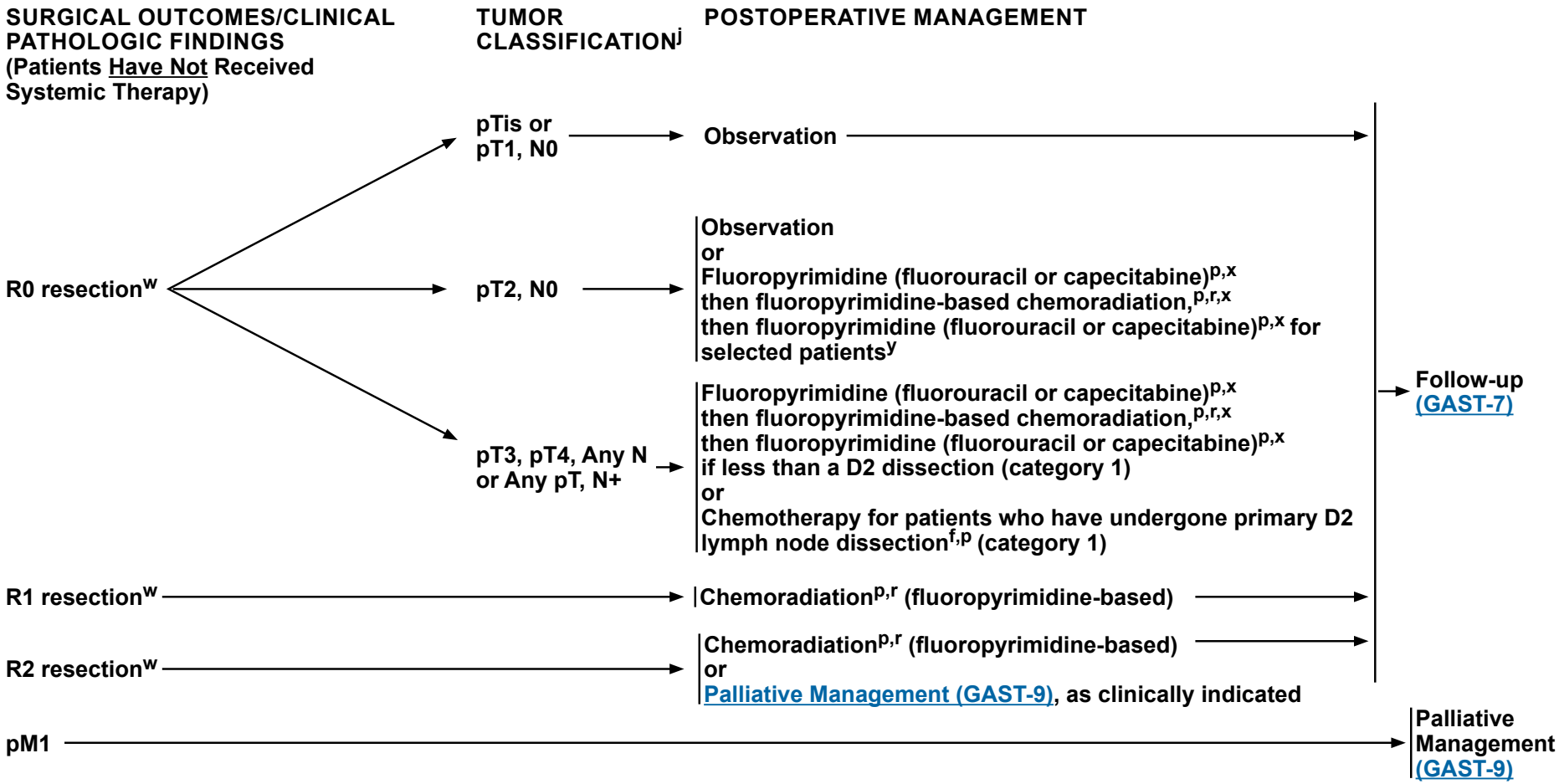

[f] Principles of Surgery (GAST-C).
[j] See Staging (ST-1) for tumor classification.
[p] Principles of Systemic Therapy (GAST-F).
[r] Principles of Radiation Therapy (GAST-G).
[w] R0 = No cancer at resection margins, R1 = Microscopic residual cancer, R2 = Macroscopic residual cancer or M1.
[x] Smalley SR, et al. J Clin Oncol 2012;30:2327-2333. See Principles of Systemic Therapy (GAST-F).
[y] High-risk features include poorly differentiated or higher grade cancer, lymphovascular invasion (LVI), neural invasion, or <50 years of age or patients who did not undergo D2 lymph node dissection.

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS (Patients Have Received Systemic Therapy)	TUMOR CLASSIFICATION[j]	POSTOPERATIVE MANAGEMENT	
R0 resection[w]	→	Systemic therapy,[p] (category 1)	→ Follow-up (GAST-7)
R1 resection[w]	→	Chemoradiation[p,r] (fluoropyrimidine-based) or Consider re-resection	→ Follow-up (GAST-7)
R2 resection[w]	→	Chemoradiation[p,r] (fluoropyrimidine-based) or Palliative Management (GAST-9), as clinically indicated	→ Follow-up (GAST-7)
ypM1[z]	→		Palliative Management (GAST-9)

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

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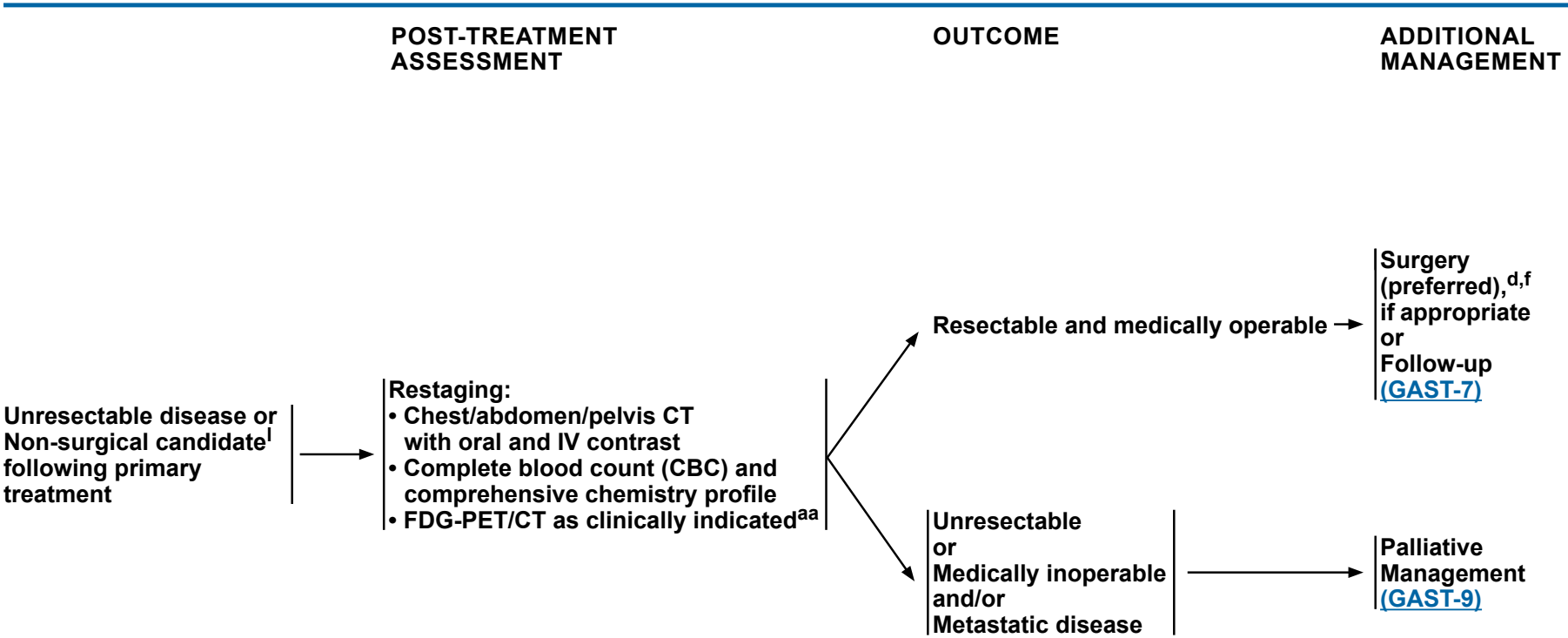

[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] Principles of Surgery (GAST-C).
[l] Patients who are medically unable to tolerate major surgery or patients who are medically fit, but decline surgery.
[aa] In cases of renal insufficiency or allergy to CT contrast.

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FOLLOW-UP/SURVEILLANCE[cc]

Tis (successfully treated by ER)[bb] →

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- CBC and chemistry profile as clinically indicated
- Upper gastrointestinal (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 treated by surgical resection or T1a treated by ER)[bb] →

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- 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[dd,ee]
- Monitor for nutritional deficiency in patients who have undergone surgical resection (especially after total gastrectomy) and treat as indicated[ff]

p stage II/III or yp stage I–III (treated with neoadjuvant ± adjuvant therapy)[bb] →

- H&P every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years
- 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 every 6 months for first 2 years, then annually for up to 5 years[dd,ee]
- Monitor for nutritional deficiency in patients who have undergone surgical resection (especially after total gastrectomy) and treat as indicated[ff]

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

[bb] For patients undergoing total gastrectomy for curative intent, surveillance should follow these recommendations except for endoscopy. Endoscopy as clinically indicated for routine surveillance for total gastrectomy unless patients are symptomatic.
[cc] Principles of Surveillance (GAST-H).
[dd] After 5 years, additional follow-up may be considered based on risk factors and comorbidities.
[ee] CT scan preferred. For patients who cannot undergo CT scan, alternative imaging such as PET/CT or MRI as clinically indicated.
[ff] Follow-up with appropriate practitioners or specialists should be established for lifelong monitoring and management of potential nutritional sequelae of gastrectomy, which may include, but are not limited to, vitamin B_{12}, iron, zinc, calcium, and vitamin D deficiencies. Consider routine supplementation with a daily multivitamin/mineral complex, vitamin B_{12}, calcium, and vitamin D. See Principles of Survivorship (GAST-I 2 of 4).
[gg] Principles of Survivorship (GAST-I).

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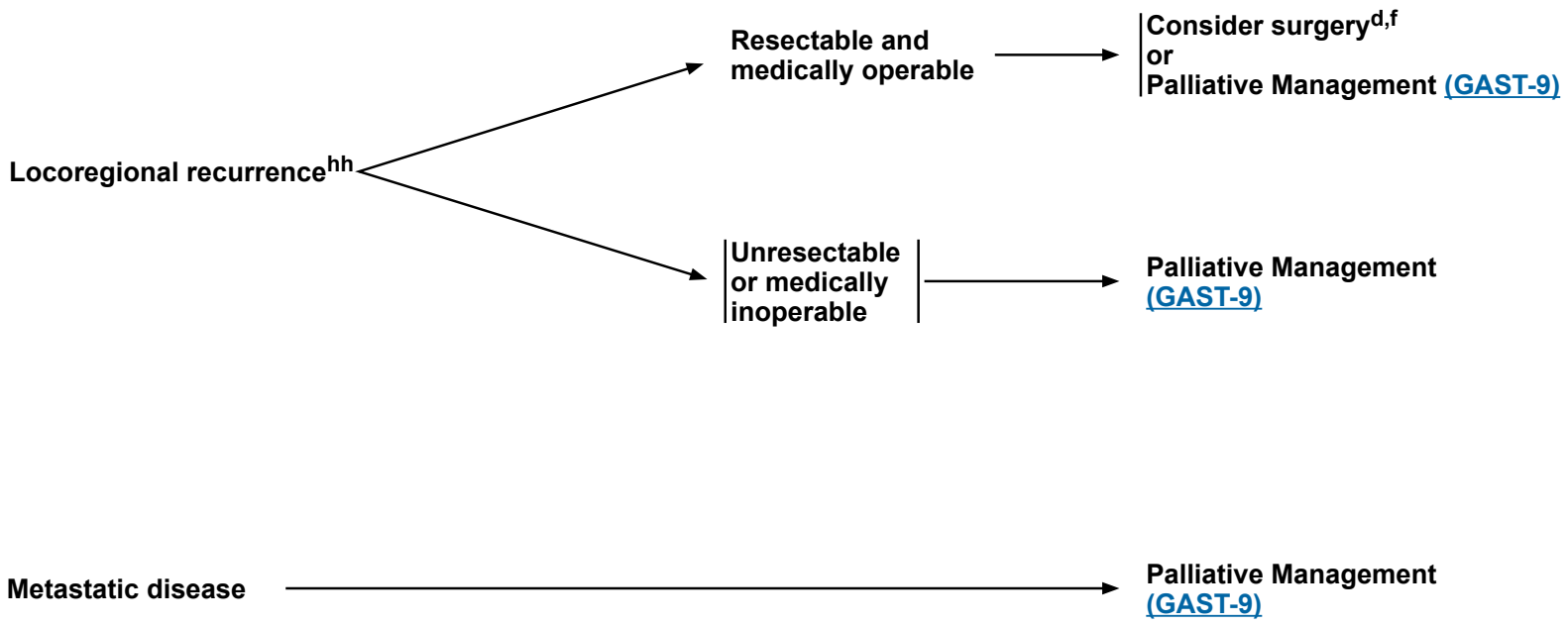
RECURRENCE



[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] Principles of Surgery (GAST-C).
[hh] Review if surgery is appropriate for patients with isolated local recurrences. Surgery should be considered as an option for locoregional recurrence in patients who are medically fit.

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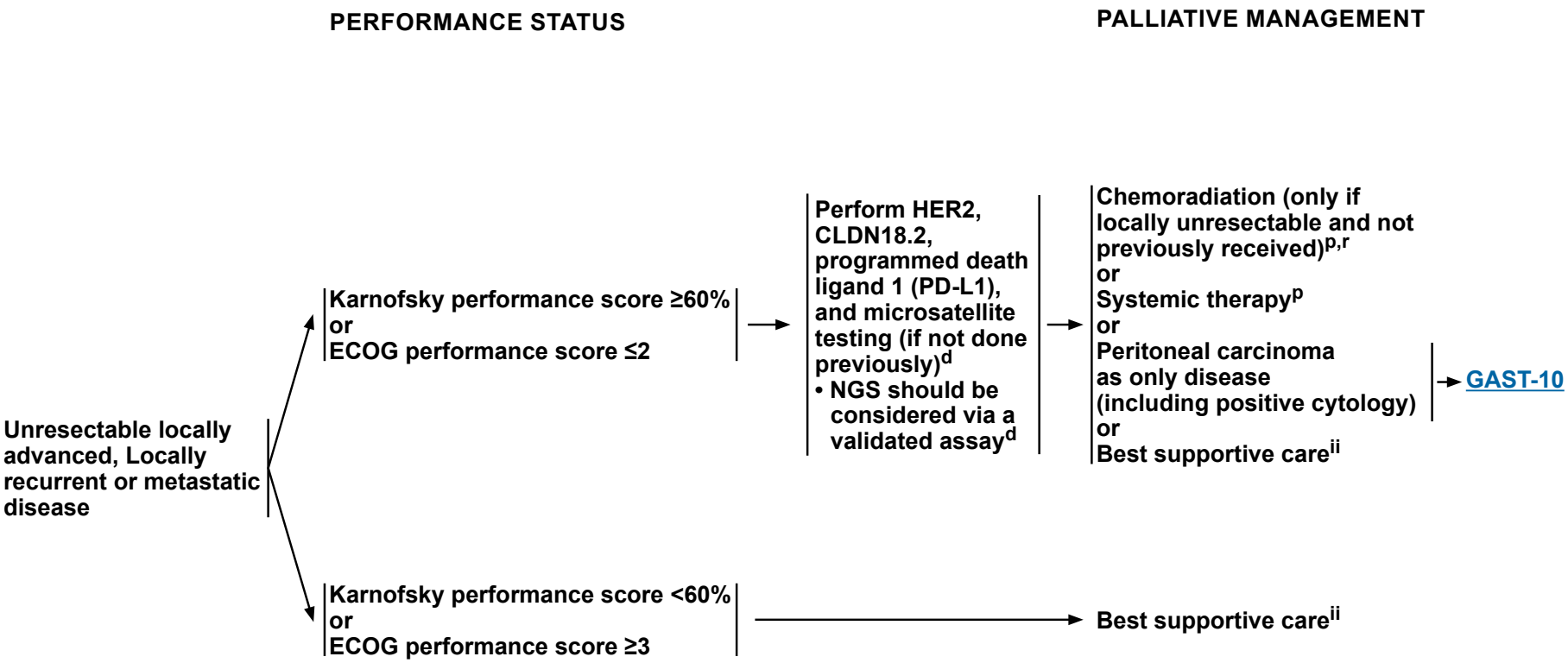

[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[p] Principles of Systemic Therapy (GAST-F).
[r] Principles of Radiation Therapy (GAST-G).
[ii] Principles of Palliative Care/Best Supportive Care (GAST-J).

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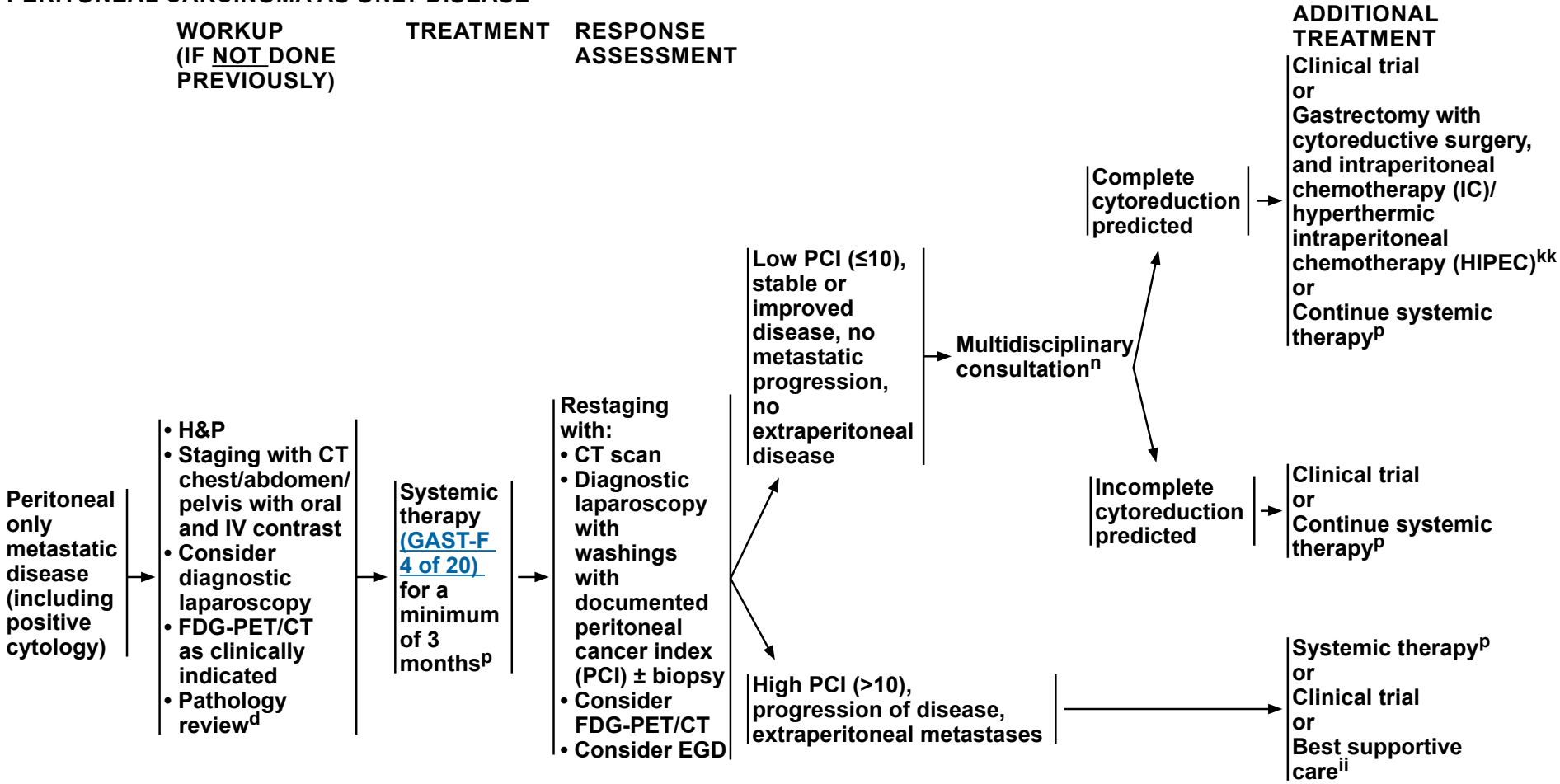
PERITONEAL CARCINOMA AS ONLY DISEASE[jj]



[d] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[n] Principles of Multidisciplinary Team Approach (GAST-E).
[p] Principles of Systemic Therapy (GAST-F).
[ii] Principles of Palliative Care/Best Supportive Care (GAST-J).
[jj] Chicago Consensus Working Group. Ann Surg Oncol 2020;27:1768-1773.
[kk] Principles of Surgery (GAST-C 3 of 5).

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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.

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 and molecular 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]**

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 ER (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.**

Continued
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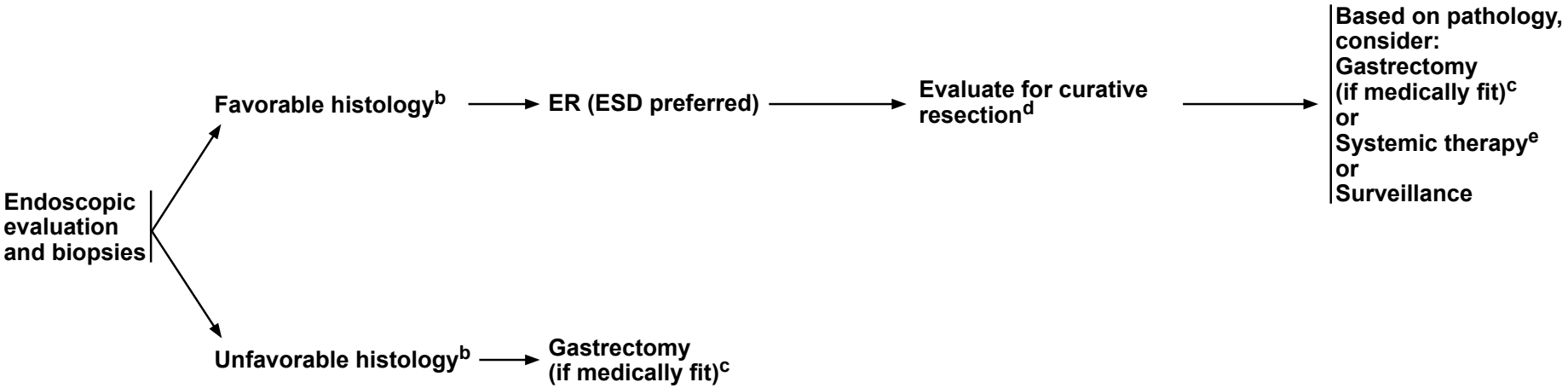
PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Endoscopic Therapy for Early-Stage Gastric Adenocarcinoma[a,9,10]



[a] Endoscopic features suggestive of deep submucosal invasion include converging folds, irregular surface pattern, and ulceration in a large gastric mass.
[b] Unfavorable histologic features include: poorly differentiated or diffuse type (compared to intestinal) histology.
[c] Principles of Surgery (GAST-C).
[d] The resected endoscopy specimen should be evaluated by a pathologist with expertise in GI pathology. Curative ER features include: submucosal invasion <500 µm, but without poorly or undifferentiated pathology, and without LVI.
[e] See Postoperative Chemotherapy in Principles of Systemic Therapy (GAST-F 3 of 20).

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Continued
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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY

Treatment

- EMR or ESD of early-stage gastric cancer can be considered adequate therapy when the lesion is ≤2 cm in diameter, is shown on histopathology to be well or moderately well differentiated, does not penetrate beyond the superficial submucosa, does not exhibit LVI, and has clear lateral and deep margins. En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in curing small early-stage gastric cancer, but requires greater skills and instrumentation to perform and has a significant risk of complications including perforation.[11]
- 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]
- Several Japanese and American guidelines have expanded the indications for ESD to include:
  - Well to moderately differentiated cancer of any size, without ulceration
  - Well or moderately differentiated with submucosal (sm) layer invasion <500 micrometers
  - Well or moderately differentiated <3 cm with ulceration
  - Poorly differentiated <2 cm without ulceration
- This may potentially be considered curative resection if the margins are negative, there is no LVI, and curative resection is limited to sm1. However, there is still a very small risk of lymph node involvement, so such decisions should be made following multidisciplinary discussions and careful explanation to the patient.
- 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.[12]
- EUS performed after chemotherapy or radiation therapy (RT) has a reduced ability to accurately determine the post-treatment stage of disease.[13] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease but still provide useful information.[14]
- 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, although surgical gastrojejunostomy may be more efficacious for those with longer-term survival (Principles of Palliative Care/Best Supportive Care [GAST-J]).[15,16]
- 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).[17]

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.[18] EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen.

References

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PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY
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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 (EMR)	**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	**For pathology report, include all elements as for EMR plus:** **• Location of tumor midpoint in relationship to EGJ[c]** **• Whether tumor crosses EGJ** **• Lymph node status and number of lymph nodes recovered[d]** **• 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 in unresectable gastric cancer treated with chemoradiation followed by surgery	**• Tumor site should be thoroughly sampled for specimens s/p chemoradiation without grossly obvious residual tumor** **• For pathology report, include all elements of resection and assessment of treatment effect**

[a] Use of a standardized minimum dataset 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 >2 cm into the proximal stomach are staged as gastric carcinomas.[2]
[d] For patients with surgically managed cancer, ≥16 regional lymph nodes are removed and pathologically examined during resection for curative intent therapy.

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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 or RT 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[e]

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 ≥16 regional lymph nodes be pathologically assessed, removal and assessment of >30 lymph nodes is desirable.[2]**

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Overexpression or Amplification of HER2 in Gastric Cancer

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom trastuzumab[f] 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 mutational burden (TMB), and MSI status. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing. 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[g,h]

	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

[f] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[g] 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.
[h] 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

Assessment of Positivity of Claudin 18 Isoform 2 (CLDN18.2) in Gastric Cancer[5-7]

- **For patients with untreated inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom zolbetuximab therapy is being considered**

Table 4: Immunohistochemical Criteria for Assessing CLDN18.2 Expression in Gastric Cancer

CLDN18.2 Assessment	Biopsy or Surgical Specimen Expression Pattern by IHC
Positive	≥75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining (2+ or 3+ intensity)
Negative	<75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

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

- **Universal testing for MSI by polymerase chain reaction (PCR), NGS, or MMR by IHC should be performed for all newly diagnosed gastric cancers.[8] The testing is performed on formalin-fixed paraffin-embedded (FFPE) tissue and results are interpreted as MSI-H or dMMR in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[9] Testing should be performed only in Clinical Laboratory Improvement Amendments (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.**

  - **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**
    - ◊ **Microsatellite 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 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 programmed cell death protein 1 (PD-1) inhibitors. A 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 IHC 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) is ≥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.**

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

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PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

- **At present, several targeted therapeutic agents (GAST-F) have been approved by the FDA for use in gastric cancer. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing. The list of targeted biomarkers includes:**
  - **HER2 overexpression/amplification**
  - **PD-L1 expression**
  - **MSI**
  - **CLDN18.2**
  - **TMB**
  - ***NTRK* gene fusion**
  - ***RET* gene fusion**
  - ***BRAF* V600E mutation**

Liquid Biopsy[10,11]

- **The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." The detection of mutations/alterations or fusions in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, when limited tissue is available or for patients who have metastatic or advanced gastric cancer who are not able to undergo a traditional biopsy, 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.**

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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 is planned as a separate procedure, peritoneal washings with cytology 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 Esophagogastric Junction 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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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 ≥16 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 the 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 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.

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PRINCIPLES OF SURGERY

Resectable Tumors–continued

- **IC/HIPEC/Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC)[18-21]**
  - **The evidence for the use of IC/HIPEC/PIPAC is limited. There are no randomized trials to demonstrate efficacy, and results are limited to case reports and small series. However, IC/HIPEC may be effective in selected patients with low burden of tumor. The decision to pursue IC/HIPEC should be made only after multidisciplinary discussion.**
  - **PIPAC is investigational and should only be done in the context of a clinical trial.**
  - **IC/HIPEC may be a therapeutic alternative for carefully selected patients with peritoneal carcinoma as only disease.**
    - ◊ **Patients who are being considered for IC/HIPEC should undergo pre-treatment evaluation with a chest/abdomen/pelvis CT, diagnostic laparoscopy with washings to assess for PCI and/or cytology-positive disease, and consider a PET scan to rule out distant metastatic disease. Patients with documented peritoneal metastatic disease should begin with systemic therapy given for a minimum of 3 months. Then patients should undergo re-staging and demonstrate stable or improving disease to be considered for further therapy. Treatment decisions should be made in the context of a multidisciplinary tumor board. In this setting:**
      - **IC/HIPEC can be used in conjunction with cytoreductive surgery[a] for patients with low PCI (≤10) who are candidates to undergo complete cytoreduction.**
      - **In patients with a higher burden of peritoneal disease (PCI >10), IC/HIPEC may be considered in the setting of a clinical trial.**
      - **The role of prophylactic IC/HIPEC/PIPAC is currently investigational for patients with non-metastatic cancers and should only be performed in the setting of a clinical trial.**

[a] Cytoreduction of all visible nodules/plaques.

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PRINCIPLES OF SURGERY

Palliative Procedures

- **Gastric resections should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease when non-surgical options are not feasible such as endoscopic or interventional radiology procedures (ie, endoscopic stenting).**
- **Lymph node dissection is not required.**
- **In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) or endoluminal stenting are options. Except for rare cases that may have slow growth, endoluminal stenting is preferred in patients with gastric outlet obstruction/ disease and very minimal metastatic disease, in the liver or other area not affecting the GI tract. If longer term palliation is needed, surgical bypass may be considered.[22,23]**
- **Venting gastrostomy and/or feeding tube may be considered.**

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PRINCIPLES OF GENETIC RISK ASSESSMENT FOR GASTRIC CANCER

See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric - Hereditary Diffuse Gastric Cancer for information on:

- **Testing Criteria for Hereditary Diffuse Gastric Cancer**
- ***CDH1* Gastric Cancer Risks**
- **Management of Gastric Cancer in *CDH1* Pathogenic Variant Carriers**

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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 2 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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PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal adenocarcinoma, EGJ adenocarcinoma, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.**
- **Trastuzumab should be added to first-line chemotherapy for advanced 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 patients who are medically fit 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 systemic 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 systemic therapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.**
- **An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.**
- **A checkpoint inhibitor should be added to first-line chemotherapy for patients with advanced disease with PD-L1 CPS ≥1.**
- **Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.**

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.
[2] Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-1721.
[3] Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.
[4] Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-2333 (GAST-F 7 of 20).
[5] Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1389-1396.
[6] Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 2015;33:3130-3136.

Note: All recommendations are category 2A unless otherwise indicated.

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PRINCIPLES OF SYSTEMIC THERAPY

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

Perioperative Chemotherapy

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

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

Neoadjuvant or Perioperative Immunotherapy

Useful in Certain Circumstances
- MSI-H/dMMR tumors[c]
  - Nivolumab and ipilimumab followed by nivolumab[d,3]
  - Pembrolizumab[d,4,5]
  - Tremelimumab and durvalumab for neoadjuvant therapy only[d,6,7]

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

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

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

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

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

Preferred Regimens
- Fluorouracil[a] and oxaliplatin[10,11]
- Fluorouracil and cisplatin[12,13]

Other Recommended Regimens
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[14]

[a] 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.
[b] The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[c] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[d] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Note: All recommendations are category 2A unless otherwise indicated.

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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 preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and trastuzumab
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,f,15-16]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and trastuzumab (category 1)[17]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)[e,f,15-16]
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[e,f,18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[e,f,19]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[e,f,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and zolbetuximab-clzb for CLDN18.2 positive[c] (category 1)[21,22]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[23-25]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[e,f,19]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)[e,f,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[23,26-28]
- MSI-H/dMMR tumors (independent of PD-L1 status)[c]
  - Pembrolizumab[e,f,29-31]
  - Dostarlimab-gxly[e,f,32]
  - Nivolumab and ipilimumab[e,f,18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[e,f,18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[e,f,30,31]

Other Recommended Regimens
- Fluorouracil[a,g] and irinotecan[h,33]
- Paclitaxel with or without carboplatin or cisplatin[h,34-38]
- Docetaxel with or without cisplatin[h,39-42]
- Fluoropyrimidine[h,27,43,44] (fluorouracil[a] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a,h,45,46]

Useful in Certain Circumstances
- Entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors (category 2B)[47-49]

Footnotes on GAST-F (4A of 20)

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

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FOOTNOTES FOR GAST-F 4 OF 20

[a] 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] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[h] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression-positive adenocarcinoma.

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PRINCIPLES OF SYSTEMIC THERAPY

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

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1)[50] • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression-positive adenocarcinoma[51] • Docetaxel (category 1)[41,42] • Paclitaxel (category 1)[37,38,52] • Irinotecan (category 1)[52-55] • Fluorouracil[a,g] and irinotecan[53,56,57] • Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[58]
Other Recommended Regimens • Ramucirumab (category 1)[59] • Irinotecan and cisplatin[24,60] • Fluorouracil and irinotecan + ramucirumab[a,g,61] • Irinotecan and ramucirumab[62] • Docetaxel and irinotecan (category 2B)[63]
Useful in Certain Circumstances • Entrectinib, larotrectinib, or repotrectinib[i] for *NTRK* gene fusion-positive tumors[47-49] • Pembrolizumab[e,f] for MSI-H/dMMR tumors[64-66] • Nivolumab and ipilimumab[e,f] for MSI-H/dMMR tumors[18] • Pembrolizumab[e,f] for TMB-high (TMB-H) (≥10 mutations/megabase) tumors[67] • Dostarlimab-gxly[e,f,j] for MSI-H/dMMR tumors[32] • Dabrafenib and trametinib for *BR*AF V600E-mutated tumors[68] • Selpercatinib for *RET* gene fusion-positive tumors[69]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[i] Repotrectinib can be used in patients whose disease progressed on a prior *NTRK*-targeted therapy.
[j] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PD-L1i, 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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Note: All recommendations are category 2A unless otherwise indicated.

References

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

PERIOPERATIVE CHEMOTHERAPY

PREFERRED REGIMENS

Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT)[a]
(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[a]
(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[24]

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[23]

Capecitabine 1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[25]

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

NEOADJUVANT OR PERIOPERATIVE IMMUNOTHERAPY

USEFUL IN CERTAIN CIRCUMSTANCES
(MSI-H/dMMR tumors)

Nivolumab and ipilimumab followed by nivolumab[f]
Nivolumab 240 mg IV every 2 weeks,
Ipilimumab 1 mg/kg IV every 6 weeks
(preoperative for at least 12 total weeks),
followed by surgery and
adjuvant nivolumab 480 mg IV every 4 weeks for 9 cycles[3]

Pembrolizumab[f]
Pembrolizumab 200 mg IV every 3 weeks for at least 12 total weeks
followed by surgery and adjuvant pembrolizumab 200 mg IV
every 3 weeks x 16 cycles[4,5]

Tremelimumab and durvalumab
(for neoadjuvant therapy only)[f]
Tremelimumab 300 mg IV on Day 1
Durvalumab 1500 mg IV on Days 1, 29, and 57
for 12 weeks preoperatively for 1 cycle only[6,7]

[a] 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] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

Note: All recommendations are category 2A unless otherwise indicated.

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References

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

POSTOPERATIVE CHEMORADIATION
(for patients who received less than a D2 lymph node dissection)
THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[8,70] 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[a]
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[71]

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[72]

With radiation
Capecitabine 625–825 mg/m² PO BID on Days 1–5
Weekly for 5 weeks[73]

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]

Fluorouracil and oxaliplatin[a]
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[24]

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[23]

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

Note: All recommendations are category 2A unless otherwise indicated.

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

CHEMORADIATION FOR UNRESECTABLE DISEASE
(Infusional fluorouracil[a] can be replaced with capecitabine)
PREFERRED REGIMENS
Fluorouracil and oxaliplatin[a]
Oxaliplatin 85 mg/m² IV
on Days 1, 15, and 29 for 3 doses
Fluorouracil 180 mg/m² IV daily on Days 1–33[11]

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[10]

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[74]

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[75]

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[76]

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[14]

Paclitaxel 45–50 mg/m² IV on Day 1
Capecitabine 625–825 mg/m² PO BID
on Days 1–5
Weekly for 5 weeks[14]

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

Note: All recommendations are category 2A unless otherwise indicated.

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

FIRST-LINE THERAPY
HER2 overexpression-positive
Trastuzumab with chemotherapy
(See GAST-F [4 of 20] 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[17]
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[a]
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[24]

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[23]

Capecitabine 850–1000 mg/m²
PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[25]

Capecitabine 625 mg/m² PO BID on Days 1–14[l,m]
Oxaliplatin 85 mg/m² IV on Day 1
Cycled every 21 days[77]

PREFERRED REGIMENS—continued
Fluoropyrimidine and cisplatin[a]
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[26]

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[23,27]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 850–1000 mg/m²
PO BID on Days 1–14
Cycled every 21 days[28]

PREFERRED REGIMENS—continued
Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab[a,f]
Nivolumab 360 mg IV on Day 1
(per study maximum of 2 years)
Capecitabine 850–1000 mg/m²
PO BID Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[18]

Nivolumab 240 mg IV on Day 1
(per study maximum of 2 years)
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[18]

[a] 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] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.
[l] Based on consensus opinion, the Panel revised the doses and schedule studied in level C of the GO2 trial.
[m] This regimen is recommended for patients who are frail and/or older.

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

FIRST-LINE THERAPY–continued

PREFERRED REGIMENS—continued

Trastuzumab and pembrolizumab[f] 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[16,17]
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[15,16]

PREFERRED REGIMENS—continued

Fluoropyrimidine and oxaliplatin[a]

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[24]

Capecitabine 850–1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days[25]

PREFERRED REGIMENS—continued

Fluoropyrimidine and cisplatn

Cisplatin 80 mg/m² IV on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days[15]

Cisplatin 80 mg/m² IV daily on Day 1
Capecitabine 850–1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[28]

[a] 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] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

Note: All recommendations are category 2A unless otherwise indicated.

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

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS—continued
HER2 Overexpression Negative
Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[e,f]
Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Capecitabine 850–1000 mg/m² PO BID Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
Cycled every 21 days for up to 6 cycles (total 18 weeks)[19]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
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 for up to 9 cycles (total 18 weeks)[19]

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS—continued
HER2 Overexpression Negative
Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab[e,f]
Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Cisplatin 80 mg/m² IV on Day 1
Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for up to 6 cycles[19]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Cisplatin 80 mg/m² IV on Day 1
Capecitabine 850–1000 mg/m² PO twice daily on Days 1–14
Cycled every 21 days for up to 6 cycles (total of 18 weeks)[19]

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS—continued
HER2 Overexpression Negative, CLDN18.2 Positive
Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and zolbetuximab-clzb
Oxaliplatin 85 mg/m² IV on Day 1
(per study maximum of 12 doses)
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
Zolbetuximab-clzb 800 mg/m² IV (first-dose only) on Day 1 (subsequent doses 400 mg/m²)
Cycled every 14 days[21]

Capecitabine 850–1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1
(per study maximum of 8 doses)
Zolbetuximab-clzb 800 mg/m² IV (first-dose only) on Day 1 (subsequent doses 600 mg/m²)
Cycled every 21 days[22]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

Note: All recommendations are category 2A unless otherwise indicated.

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

FIRST-LINE THERAPY
PREFERRED REGIMENS
Tislelizumab-jsgr[e,f] with fluoropyrimidine and oxaliplatin or cisplatin
(see GAST-F [4 of 20 and 5 of 20] for list of regimens)
Tislelizumab 200 mg IV on Day 1 every 21 days[20]
in combination with:

Fluoropyrimidine and oxaliplatin[a]
Oxaliplatin 85 mg/m² IV on Day 1
Leucovorin 200 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 for 12 cycles[20]

Capecitabine 850–1000 mg/m² PO BID on Days 1–14
Oxaliplatin 130 mg/m² IV on Day 1 (per study maximum of 6 doses)
Cycled every 21 days[20]

PREFERRED REGIMENS–continued
Fluoropyrimidine and cisplatin
Cisplatin 60–80 mg/m² IV on Day 1
Fluorouracil 750–800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 21 days for 6 cycles[20]

Cisplatin 60–80 mg/m2 IV on Day 1 (per study maximum of 6 doses)
Capecitabine 850–1000 mg/m²
PO BID on Days 1–14
Cycled every 21 days[20]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

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

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS–continued
MSI-H/dMMR tumors (independent of PD-L1 status)

Pembrolizumab[e,f]
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days (up to 2 years)[29]
or
Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks (up to 2 years)[30,78]

Dostarlimab-gxly[e,f]
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks[32]

Nivolumab and ipilimumab[e,f]
Nivolumab 1 mg/kg IV on Day 1
Ipilimumab 3 mg/kg IV on Day 1
Cycled every 21 days for 4 cycles
followed by
Nivolumab 240 mg IV every 14 days
(maximum to 2 years)[18]
THE PANEL ACKNOWLEDGES THAT THE CHECKMATE-649 TRIAL[18] FORMED THE BASIS FOR FIRST-LINE THERAPY STRATEGY FOR METASTATIC OR LOCALLY ADVANCED CANCER. HOWEVER, THE PANEL DOES NOT RECOMMEND THE DOSES AND SCHEDULE OF AGENTS SPECIFIED IN THIS TRIAL DUE TO CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS THE FOLLOWING MODIFICATIONS INSTEAD:
Nivolumab and ipilimumab[e,f]
Nivolumab 240 mg IV every 2 weeks
Ipilimumab 1 mg/kg IV every 6 weeks
For 16 weeks, followed by
Nivolumab 240 mg IV every 2 weeks or
Nivolumab 480 mg IV every 4 weeks
(maximum of 2 years)

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS–continued
MSI-H/dMMR tumors (independent of PD-L1 status)

Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[e,f]
Nivolumab 360 mg IV on Day 1
(per study maximum of 2 years)
Capecitabine 850–1000 mg/m^2
PO BID Days 1–14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days[18]

Nivolumab 240 mg IV on Day 1
(per study maximum of 2 years)
Oxaliplatin 85 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[18]

FIRST-LINE THERAPY–continued
PREFERRED REGIMENS–continued
MSI-H/dMMR tumors (independent of PD-L1 status)

Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[e,f]
Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Capecitabine 850–1000 mg/m^2 PO BID Days 1–14
Oxaliplatin 130 mg/m^2 IV on Day 1
Cycled every 21 days for up to 6 cycles
(total 18 weeks)[30]

Pembrolizumab 200 mg IV
every 21 days for up to 2 years
Oxaliplatin 85 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 for up to 9 cycles
(total 18 weeks)[30]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

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

FIRST-LINE THERAPY–continued

OTHER RECOMMENDED REGIMENS

Fluorouracil and irinotecan[a]
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[33]

Paclitaxel with or without carboplatin or cisplatin
Paclitaxel 200 mg/m² IV on Day 1
Carboplatin AUC 5 IV on Day 1
Cycled every 21 days[36]

Paclitaxel 135–200 mg/m² IV on Day 1
Cisplatin 75 mg/m² IV on Day 1
Cycled every 21 days[34]

Paclitaxel 90 mg/m² IV on Day 1
Cisplatin 50 mg/m² IV on Day 1
Cycled every 14 days[35]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[38]

Paclitaxel 80 mg/m² IV weekly
Cycled every 28 days[37]

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[39,40]

Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[41,42]

Fluoropyrimidine[a]
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[27]

Fluorouracil 800 mg/m² IV continuous infusion over 24 hours daily on Days 1–5
Cycled every 28 days[43]

Capecitabine 850–1000 mg/m² PO BID on Days 1–14
Cycled every 21 days[44]

OTHER RECOMMENDED REGIMENS–continued

Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a]
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[45]

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[46]

USEFUL IN CERTAIN CIRCUMSTANCES

Entrectinib, larotrectinib, or repotrectinib (For NTRK gene fusion-positive tumors)
Entrectinib 600 mg PO once daily[47]

Larotrectinib 100 mg PO twice daily[48]

Repotrectinib[49]
160 mg PO Daily Days 1–14 of cycle 1
160 mg PO BID Days 15–28 of cycle 1
160 mg PO BID Days 1-28 of cycle 2 and beyond
Cycled every 28 days

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

Note: All recommendations are category 2A unless otherwise indicated.

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

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 IV on Days 1, 8, and 15
Cycled every 28 days[50]

Fam-trastuzumab deruxtecan-nxki (for HER2 overexpression-positive adenocarcinoma)
6.4 mg/kg IV on Day 1
cycled every 21 days[n,51]

Taxane
Docetaxel 75–100 mg/m^2 IV on Day 1
Cycled every 21 days[41,42]

Paclitaxel 135–250 mg/m^2 IV on Day 1
Cycled every 21 days[38]

Paclitaxel 80 mg/m^2 IV weekly
Cycled every 28 days[37]

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

PREFERRED REGIMENS—continued

Irinotecan
Irinotecan 150–180 mg/m^2 IV on Day 1
Cycled every 14 days[52,53]

Irinotecan 125 mg/m^2 IV on Days 1 and 8
Cycled every 21 days[55]

Irinotecan 250–350 mg/m^2 IV on Day 1
Cycled every 21 days[54]

Fluorouracil and irinotecan[a]
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[53]

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[58]

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

Note: All recommendations are category 2A unless otherwise indicated.

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

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[59]

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[24,60]

Fluorouracil and irinotecan + ramucirumab[a]
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 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[79]

Irinotecan and ramucirumab
Irinotecan 150 mg/m² IV on Day 1
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[62]

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[63]

USEFUL IN CERTAIN CIRCUMSTANCES

Entrectinib, larotrectinib, or repotrectinib (for *NTRK* gene fusion-positive tumors)
Entrectinib 600 mg PO once daily[47]

Larotrectinib 100 mg PO twice daily[48]

Repotrectinib[g,49]
160 mg PO daily Days 1–14 of cycle 1
160 mg PO BID Days 15–28 of cycle 1
160 mg PO BID Days 1–28 of cycle 2 and beyond
Cycled every 28 days

Pembrolizumab[e,f] (for MSI-H/dMMR tumors or TMB-H [≥10 mutations/megabase] tumors)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[29]

Pembrolizumab 400 mg IV on Day 1
Cycled every 6 weeks[78]

Nivolumab and ipilimumab[e,f] (for MSI-H/dMMR tumors)
Nivolumab 1 mg/kg IV on Day 1
Ipilimumab 3 mg/kg IV on Day 1
Cycled every 21 days for 4 cycles
followed by
Nivolumab 240 mg IV every 14 days
(maximum to 2 years)[18]

THE PANEL ACKNOWLEDGES THAT THE CHECKMATE-649[18] FORMED THE BASIS FOR THERAPEUTIC STRATEGY FOR METASTATIC OR LOCALLY ADVANCED CANCER. HOWEVER, THE PANEL DOES NOT RECOMMEND THE DOSES AND SCHEDULE OF AGENTS SPECIFIED IN THIS TRIAL DUE TO CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS THE FOLLOWING MODIFICATIONS INSTEAD:

Nivolumab and ipilimumab[e,f]
Nivolumab 240 mg IV every 2 weeks
Ipilimumab 1 mg/kg IV every 6 weeks
For 16 weeks, followed by
Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks
(maximum to 2 years)

USEFUL IN CERTAIN CIRCUMSTANCES-continued

Dostarlimab-gxly[e,f,j] (for MSI-H/dMMR tumors)
Dostarlimab-gxly 500 mg IV
every 3 weeks for 4 doses
followed by 1000 mg IV every 6 weeks[32]

Dabrafenib and trametinib (for *BRAF* V600E-mutated tumors)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily[68]

Selpercatinib (for *RET* gene fusion-positive tumors)
Selpercatinib
Patients ≥50 kg: 160 mg PO twice daily
Patients <50 kg: 120 mg PO twice daily[69]

Footnotes on GAST-F (16A of 20)

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FOOTNOTES FOR GAST-F 16 OF 20

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e] If no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] Repotrectinib can be used in patients whose disease progressed on a prior *NTRK*-targeted therapy.
[j] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PD-L1i, 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.
[k] Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

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PRINCIPLES OF RADIATION THERAPY

General Guidelines

- **Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical oncologists, radiation oncologists, medical oncologists, radiologists, gastroenterologists, and pathologists.**
- **CT scans, EUS, endoscopy reports, and FDG-PET or FDG-PET/CT scans, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders prior to simulation.**
- **All available information from pretreatment diagnostic studies should be used to determine the target volume.**
- **In general, Siewert I and II tumors should be managed with RT guidelines applicable to esophageal and EGJ cancers. Depending on the clinical situation, Siewert III tumors may be more appropriately managed with RT guidelines applicable to either esophageal and EGJ 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 three-dimensional conformal radiation therapy (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.**
- **Four-dimensional (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)

- **Postoperative**[1]
  - **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.**[4]
  - **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[5,6]

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

Lungs[a] • V_{40Gy} ≤10% • V_{30Gy} ≤15% • V_{20Gy} ≤20% • V_{10Gy} ≤40% • V_{05Gy} ≤50% • Mean <20 Gy	**Heart** • V_{30Gy} ≤30% (closer to 20% preferred) • Mean <30 Gy (closer to 26 Gy preferred)
Spinal Cord • Max ≤45 Gy	**Left Kidney, Right Kidney (evaluate each one separately)**: • V_{20Gy} ≤33% • Mean <18 Gy
Bowel • Max dose <54 Gy • V_{45Gy} <195 cc	**Liver** • 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 patients with gastric/EGJ cancer 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 patients with gastric/EGJ cancer 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 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

- **All patients with *H. pylori* infection who underwent curative ER or gastric subtotal resection must receive an *H. pylori* eradication regimen. The choice and duration of the eradication regimen should follow the recommendations of the latest American (American College of Gastroenterology) or international (Maastricht consensus report) *H. pylori* guidelines.[1]**
- **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[2-11] 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 >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.[2-11] 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 SURVIVORSHIP

Surveillance: (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-F)**
  - **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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Continued
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PRINCIPLES OF SURVIVORSHIP[1-4]

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

- **Issues in gastrectomy survivors:[a,b]**
  - **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:**
    - ◊ **Supplement B_{12} following local practice for route of administration and monitoring levels**
    - ◊ **Monitor B_{12} level at least every 6 months (if not on parenteral B_{12} supplement)**
  - **Iron deficiency:**
    - ◊ **Monitor CBC and iron levels at least annually**
    - ◊ **Supplement iron orally or intravenously as clinically indicated and according to local practice; 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**
  - **Other micronutrient deficiencies:**
    - ◊ **Supplement with a daily multivitamin and mineral complex, to include vitamins A, C, E, D, folate, thiamine, magnesium, zinc, selenium, copper, and iron, with monitoring levels as clinically indicated**
  - **Vitamin D and calcium supplementation**
    - ◊ **Supplement vitamin D, following local practice for dose and monitoring levels**
    - ◊ **Ensure adequate calcium intake**
  - **Osteopenia/osteoporosis screening**
    - ◊ **Consider bone density testing at 3 years post-gastrectomy and in individuals who are post-menopausal or >50 years of age**

[a] Follow-up with appropriate practitioners or specialists should be established for lifelong monitoring and management of potential nutritional sequelae of gastrectomy, which may include, but are not limited to, vitamin B_{12}, iron, zinc, calcium, and vitamin D deficiencies. Consider routine supplementation with a daily multivitamin/mineral complex, vitamin B_{12}, calcium, and vitamin D.

[b] Patients with subtotal gastrectomy are at decreased risk of postoperative complications including nutritional deficiencies, and thus the protocol for monitoring and replacement in these patients can be individualized.

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PRINCIPLES OF SURVIVORSHIP

Counseling Regarding Health Behaviors (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: NCCN Guidelines for Breast Cancer Screening and Diagnosis**
- **Colorectal Cancer: NCCN Guidelines for Colorectal Cancer Screening**
- **Prostate Cancer: NCCN Guidelines for Prostate Cancer Early Detection**
- **Lung Cancer: 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 the patient.**
- **Planning for ongoing survivorship care[a]**
  - **Information on treatment received including all surgeries, RT, 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 (NCCN Guidelines: Treatment by Cancer Type)**
  - **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 (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.

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PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE[a]

The goal of best supportive care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. For gastric cancer, interventions undertaken to relieve major symptoms may result in prolongation of life. This appears to be particularly true when a multimodality interdisciplinary approach is pursued, and, therefore, a multimodality interdisciplinary approach to palliative care of the patient with gastric cancer 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.**
  - **Palliative gastrectomy in select patients**
- **Chronic blood loss from gastric cancer**
  - **Although proton pump inhibitors can be prescribed to reduce bleeding risk from gastric cancer, there are no definite data supporting its use at this time.**
  - **External beam RT (EBRT) has been shown to effectively manage acute and chronic GI bleeding in multiple small series.[4,5]**

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

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Continued
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PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE[a]

Obstruction

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

- **Alleviate or bypass obstruction**
  - **Endoscopy**
    - **Placement of enteral stent for relief of outlet obstruction,[6] or esophageal stent for EGJ/gastric cardia obstruction (NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers)**
  - **Surgery**
    - **Gastrojejunostomy[6]**
    - **Gastrectomy in select patients[7]**
  - **EBRT**
  - **Chemotherapy[c]**
- **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.**
  - **Severe uncontrolled pain following gastric stent placement should be treated with endoscopic removal of the stent once the uncontrollable nature of the pain is established.**

Nausea/Vomiting

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

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

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References

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

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

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

*A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.
**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
***Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is 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

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

Table 2. **AJCC Prognostic Stage Groups**

Clinical Staging (cTNM)

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

Pathological Staging (pTNM)

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

Post-Neoadjuvant Therapy (ypTNM)

	ypT	ypN	M
Stage I	T1	N0	M0
	T2	N0	M0
	T1	N1	M0
Stage II	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage III	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy
4D-CT	four-dimensional computed tomography therapy
AUC	area under the curve
CBC	complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CPS	combined positive score
ctDNA	circulating tumor DNA
dMMR	mismatch repair deficient
DVH	dose-volume histogram
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EGD	esophagogastroduodenoscopy
EGJ	esophagogastric junction
EMR	endoscopic mucosal resection
ER	endoscopic resection
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasound
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
GI	gastrointestinal
H&P	history and physical
HIPEC	hyperthermic intraperitoneal chemotherapy
IC	intraperitoneal chemotherapy
ICI	immune checkpoint inhibitor
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
ISH	in situ hybridization
J-tube	jejunostomy tube
LVI	lymphovascular invasion
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSI-L	microsatellite instability-low
MSS	microsatellite stable
NGS	next-generation sequencing
PCR	polymerase chain reaction
PCI	peritoneal cancer index
PCP	primary care physician
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PIPAC	pressurized intraperitoneal aerosolized chemotherapy
PS	performance status
sm	submucosal
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

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Discussion

This discussion corresponds to the NCCN Guidelines for Gastric Cancer. Last updated on April 4, 2025.

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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 968,000 new cases resulting in approximately 660,000 deaths in 2022, making gastric cancer the fifth most frequently diagnosed cancer and the fifth 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] Based on SEER data for 2024, gastric cancer is the 15th most commonly diagnosed cancer and the 15th leading cause of cancer-related death in the United States.[4] In the United States for 2025, an estimated 30,300 people will be diagnosed and 10,780 people are expected to die of this disease.[10] Despite overall declining rates, evidence suggests that the incidence of early-onset gastric cancer may be rising in the United States and other western countries.[11,12] A recent global meta-analysis suggests factors that may contribute to risk of early-onset gastric cancer include family history, *Helicobacter pylori*, infection, and diet.[13]

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.[3,9,14-16] 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 *H. pylori* infection, tobacco smoking, high salt intake, and other dietary factors.[2,3,9,14-16] 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 showed a positive association between heavy alcohol use and gastric cancer, particularly non-cardia gastric cancer.[17-20]

A dramatic shift in the type and location of upper gastrointestinal (GI) tract tumors has occurred in North America and Europe.[2,21,22] 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.[1,3,16,23] However, incidence rates of diffuse type gastric cancer of the proximal stomach are rising.[1,3,23] 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.[23] 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.

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Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Clinical Practice Guidelines (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.

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; Practice 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.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[24] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Hereditary Cancer Predisposition Syndromes Associated with Gastric Cancer

While most gastric cancers are considered sporadic, it is estimated that 1% to 3% of gastric cancers are associated with inherited cancer predisposition syndromes. These syndromes include hereditary diffuse gastric cancer, Lynch syndrome, juvenile polyposis syndrome, and familial adenomatous polyposis syndrome. See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at www.nccn.org) for hereditary diffuse gastric cancer testing, *CDH1* risk assessment, and more information on these syndromes.

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

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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).[25] 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 >2 cm into the proximal stomach are now staged as gastric carcinomas. Tumors involving the EGJ with an epicenter ≤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 patients in Japan surgically treated for gastric cancer.[26] 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 patients with gastric cancer 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 >25,000 patients with gastric cancer 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.[27,28] 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; $P < .001$).[29] 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.[25]

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.[30-32] EUS is indicated for assessing the depth of tumor invasion (T category) as well as nodal involvement (N category).[33] However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.[34] In a large

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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.[35] Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.[36] EUS may be useful for differentiating T3 and T4 tumors, but it should be used in combination with other staging modalities.[34,35] EUS is also useful to identify superficial tumors for potential endoscopic approaches. Therefore, EUS is recommended 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.[37,38] 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%).[39] Thus, combined FDG-PET/CT imaging offers several potential advantages over FDG-PET or CT scans alone.[40] 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.[41,42] FDG-PET does not replace staging laparoscopy given its inability 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.[43] 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.[30] Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer and is an independent predictor for recurrence following curative resection.[44-46] 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.[45] 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 patients who are medically fit with potentially resectable stage cT1b or higher locoregional disease when considering perioperative therapy and/or surgery.[43] Laparoscopy with cytology can be considered for patients who are medically fit 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.[47] 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.[48] In patients with localized resectable disease, outcome depends on the surgical stage of the disease.

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Overview of Treatment Guidelines

The comprehensive care of patients with gastric cancer requires expertise in 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.[49] 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 esophagogastroduodenoscopy (EGD) 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 for locally advanced or metastatic disease or if clinically indicated. However, this may not be appropriate for T1 disease. EUS is recommended if early-stage disease is suspected or if early-stage 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). 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.[50,51]

Universal testing for microsatellite instability (MSI) status by polymerase chain reaction (PCR)/next-generation sequencing (NGS) or mismatch repair (MMR) status by immunohistochemistry (IHC) is recommended in all newly diagnosed patients. HER2, programmed death ligand 1 (PD-L1), and claudin 18 isoform 2 (CLDN18.2) testing are recommended at the time of diagnosis if advanced/metastatic disease is documented or suspected. NGS should be considered via a validated assay. See *Principles of Pathologic Review and Biomarker Testing* below for more information.

Nutritional assessment and counseling as well as smoking cessation advice, counseling, and pharmacotherapy (as indicated) are recommended for all patients. The guidelines also recommend screening for family history of gastric cancers. See *Hereditary Cancer Predisposition Syndromes Associated with Gastric Cancer* above. Testing/screening for *H. pylori* and genetic testing should be considered as needed. The Panel recommends testing for *H. pylori* infection and to eradicate in all patients with early gastric cancer, if positive. If testing is positive, recommendations should be discussed with family members as appropriate. For close family members, *H. pylori* testing should be recommended, and genetic testing should be performed as needed.

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

- Localized cancer (stages cTis or cT1a)
- Locoregional cancer (stages cT1b–cT4a; cM0, Any N)
- 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

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peritoneal spread when considering local therapy for patients who are medically fit with stage cT1b or higher potentially resectable locoregional disease. Laparoscopy with cytology can be considered for patients who are medically fit with surgically unresectable disease. It is not indicated if a palliative resection is planned.

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

- Medically fit with potentially resectable disease
- Medically fit with surgically unresectable disease
- Nonsurgical candidates (medically unable to tolerate major surgery or medically fit but decline surgery)

Primary Treatment

Patients Who Are Medically Fit

ER or surgery are the primary treatment options for patients who are medically able to tolerate major surgery with localized (cTis or cT1a) tumors. Surgery is the treatment option for patients with potentially resectable cT1b tumors. For patients with cT2 or higher, any N tumors, surgery or perioperative chemotherapy (category 1) are recommended options.[52-54] For patients whose tumors are cT2 or higher, any N and are MSI-high (MSI-H)/MMR deficient (dMMR), preoperative or perioperative immune checkpoint inhibitor (ICI) therapy may be considered. See the *Combined Modality Therapy* section for important considerations on ICIs in this setting. Chemoradiation or systemic therapy are the recommended treatment options for patients who are medically fit whose locoregional cancer is found to be surgically unresectable after laparoscopic staging.[55,56] See *Combined Modality Therapy* below for more information.

Nonsurgical Candidates

ER is recommended for nonsurgical candidates with cTis or cT1a tumors. Nonsurgical candidates with locoregional disease (cM0, any N) should receive palliative management/best supportive care. All patients diagnosed with metastatic disease are considered nonsurgical 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/abdomen/pelvis CT scan with contrast (oral and IV) should be performed in patients who are medically fit after the completion of perioperative chemotherapy 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.

For those patients with MSI-H/dMMR tumors who received preoperative or perioperative ICI, response assessment should include an FDG-PET/CT (5–8 weeks after therapy) as clinically indicated and EGD and biopsy. A chest/abdomen CT with oral and IV contrast (including pelvis CT, if clinically indicated) is recommended but not required if FDG-PET/CT is performed. Patients with no evidence of disease should be discussed by a multidisciplinary team and may undergo observation or surgery. However, patients with persistent local disease have the option of surgery (preferred) or palliative management. Palliative management is recommended for patients with new metastatic disease.

Nonsurgical candidates should also be restaged using chest/abdomen/pelvis CT scan with oral and IV contrast following primary

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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 Systemic Therapy

The benefit of postoperative therapy for patients who have not received preoperative therapy has been established in randomized trials.[57-59] 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, lymphovascular invasion [LVI], neural invasion, age <50 years, and not undergoing D2 lymph node dissection)[60] 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 undergo observation. 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).[61,62] Given the relatively good prognosis combined with the lack of evidence from randomized clinical trials showing any survival benefit from postoperative chemoradiation for patients with pTis or pT1, N0 tumors following R0 resection, the Panel recommends observation for this group of patients.

Patients Who Have Received Systemic Therapy

Patients who have received preoperative systemic therapy should receive postoperative systemic therapy (perioperative therapy) following R0 resection (category 1). In the absence of distant metastases, chemoradiation is recommended for patients following R1 or R2 resection. 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. 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

Patients who are positive for *H. pylori* and who underwent curative endoscopic resection or gastric subtotal resection should receive an *H. pylori* eradication regimen. Choice of regimen and duration should be based on the latest American College of Gastroenterology or Maastricht Consensus Report *H. pylori* guidelines.[63] 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[64-73] 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%),[64,66,71] a study of 1573 patients who underwent curative intent therapy showed that 7.6% of recurrences

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occurred >5 years after treatment.[67] 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 overall survival (OS).[64-73] 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 and then every 6 to 12 months for years 3 to 5. 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/abdomen/pelvis CT scan with oral and IV contrast every 6 months for the first 2 years, then annually for up to 5 years. For stage I–III, CT scan is preferred, but alternative imaging such as FDG-PET/CT or MRI can be considered as clinically indicated for patients who cannot undergo CT scan. Surveillance for patients undergoing curative intent total gastrectomy should follow these recommendations, except for endoscopy. Endoscopy is an option as clinically indicated for routine surveillance and should be used if patients are symptomatic. Patients with stage I–III disease who underwent surgical resection should also have lifelong monitoring and management for nutritional deficiencies, especially after total gastrectomy, as indicated. See the *Survivorship* section for more details on nutritional deficiencies following gastrectomy.

Principles of Endoscopy

Endoscopy has become an important tool in the diagnosis, staging, treatment, and palliation of patients with gastric cancer. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been used as alternatives to surgery for the treatment of patients with early-stage gastric cancer in Asia. However, the applicability of these techniques in the United States is limited because of the low incidence of early-stage disease. 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 and follow-up. Multiple biopsies (6–8), using standard-size endoscopy forceps, should be performed to provide sufficient material for histologic and molecular interpretation.[74,75] 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.[76,77]

Staging

EUS provides accurate initial clinical staging of locoregional gastric cancer. EUS performed prior to any treatment provides evidence of the

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depth of tumor invasion (T), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N), signs of metastasis, such as lesions in surrounding organs (M), or the presence of ascites.[78,79] Accurate clinical staging is especially important in patients who are being considered for ER.[80]

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. See *Principles of Endoscopic Staging and Therapy* in the algorithm for detailed information on 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.[81] 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 comprehensive care of patients with early-stage gastric cancer.[82] 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.[83-87] 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.[84] 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.[87] 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.[85]

ESD has also been reported to be a safe and effective procedure for patients with early-stage gastric cancer when performed by experienced endoscopists.[88-95] En-bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in several studies.[96-103] 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).[96] The complete resection rates for ESD were significantly better for lesions >5 cm in diameter, whereas the rates were not different between EMR and ESD for lesions <5 cm in diameter regardless of location.[97-99] ESD requires a higher level of skill to perform and is also associated with higher rates of bleeding and perforation complications.[101-104] 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 ≤2 cm in diameter with favorable histology that is 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.[77,103,105-107] ESD is preferred. A GI pathologist should then evaluate the specimen for features of curative resection, which include submucosal (sm) invasion <500 μm without poorly or undifferentiated pathology and with no evidence of LVI. The Panel recognizes many American and Japanese guidelines have expanded ESD indications, which are outlined in the algorithm. If margins are negative, curative resection is limited to

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sm1 invasion, and there is no LVI, then these have potential to be curative resections. Importantly, there is a very small risk of lymph node involvement, so these decisions should be made after multidisciplinary discussion and careful explanation to the patient. Further treatment such as gastrectomy for patients who are medically fit, systemic therapy (ie, postoperative chemotherapy) or surveillance should be considered, depending on pathology.[106,107]

EMR or ESD of gastric cancers with unfavorable histology (poorly differentiated or diffuse type 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 for patients who are medically fit.[106-108]

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, although surgical gastrojejunostomy may be more efficacious for those with longer-term predicted survival.[109,110] 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.[111]

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.[112] 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.[113] Similarly, biopsies performed after chemotherapy or RT may not accurately diagnose the presence of residual disease but still provide useful information.[114]

Principles of 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, resulting in overexpression of growth factors and/or receptors, loss of certain tumor suppressor genes, alterations in the cell cycle, and changes in the DNA repair and damage response.[115,116] Genome instability, which includes increased chromosomal instability and MSI, is often associated with some of these changes and can contribute to tumorigenesis.[116-118] Additionally, MSI-H in gastric tumors is frequently associated with an increase in immune checkpoint ligand expression.[118-120] A genomic stable subtype has also been identified by The Cancer Genome Atlas (TCGA) data.[115] Characterization of these alterations and pathways has enabled the application of molecular pathology to aid in the diagnosis, classification, and treatment of gastric cancer.

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

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pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade, which are required for staging. Universal testing for MSI by PCR/NGS or MMR deficiency by IHC is recommended in all newly diagnosed patients. The pathology report of EMR specimens should include an assessment of LVI, depth of tumor invasion, tumor diameter, and the status of mucosal and deep margins. Pathology reports of gastrectomy specimens 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 (≥16). In patients who undergo gastrectomy following treatment with chemoradiation for unresectable gastric cancer, and without grossly obvious residual tumor, the tumor site should be thoroughly sampled to detect microscopic residual disease. The pathology report should include all 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 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.[121] Additionally, Mansour et al reported that the 3-year disease-specific survival rate was significantly higher for patients with >50% pathologic response to preoperative chemotherapy compared to those with <50% pathologic response (69% and 44%, respectively).[122] In another study, Becker et al demonstrated that histopathologic grading of tumor regression was correlated with survival in patients treated with neoadjuvant chemotherapy.[123] 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.[124]

Tumor response scoring systems for gastric cancer have not been uniformly adopted. The Panel recommends using the modified scheme developed by Ryan et al[125,126] because it generally provides good reproducibility among pathologists, but other systems may also be used. The following scheme is suggested: 0 (complete response [CR]; no viable cancer cells, including lymph nodes); 1 (near CR; 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 ≥16 regional lymph nodes be pathologically assessed, removal and assessment of >30 lymph nodes is desirable.[25,127] Analysis of data from the SEER database and NCDB showed a trend for improved OS with a higher number of lymph nodes examined after gastrectomy.[127-129] 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* overexpression/amplification, MSI or MMR status, PD-L1 expression, CLDN18.2 positivity, tumor mutational burden-high (TMB-H) status, *NTRK* gene fusion, *RET* gene fusion, and *BRAF* V600E mutation are implicated in the clinical management of advanced gastric cancer. IHC, in situ hybridization (ISH), or targeted PCR is preferred to evaluate biomarkers. However, a validated NGS assay performed in a Clinical

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Laboratory Improvement Amendments (CLIA)-approved laboratory may be considered later in the clinical course of a patient with sufficient tumor tissue available. NGS can assess several mutations and other molecular events simultaneously. Specific recommendations for HER2, PD-L1, MSI/MMR status, and CLDN18.2 are outlined in the following sections. The biomarkers that will define additional subsets are expected to grow.

Assessment of HER2 Overexpression

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of gastric adenocarcinoma.[130] 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[131-136] 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.[137-139] 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.[140]

The reported rates of HER2 positivity in patients with gastric cancer range from 12% to 23%.[131,132,138,139,141,142] HER2 positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[132,136,138,139,141] HER2 positivity is reported in ≤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; $P = .001$).[138] 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).[139] 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.[143] 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, which 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.[144,145] Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

HER2 testing is recommended for all patients with gastric cancer at the time of diagnosis if advanced/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),[146] the NCCN Guidelines® for Gastric Cancer recommend using IHC and, if needed, ISH techniques to assess HER2 status in gastric cancer. As stated above, IHC/ISH/targeted PCR is preferred, followed by NGS later in the clinical course 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 ≥10% immunoreactive tumor cells.[145,147] In a subsequent validation study (n = 447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[148] This modified HER2 scoring system is therefore recommended by the

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Panel. A score of 0 (membranous reactivity in <10% of cancer cells) or 1+ (faint membranous reactivity in ≥10% of cancer cells) is considered HER2-negative.[146] 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)[146] 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/or MMR Testing

It is well-established that MSI-H or dMMR can occur in various malignancies. Microsatellites are mutational hotspots, and loss of functional MMR facilitates elevated mutation events at these sites.[117] Prevalence of MSI-H/dMMR in gastric cancer can vary depending on factors including disease stage, sex and age, histologic type, and tumor location. Specifically, MSI-H/dMMR status is associated with earlier stage, ≥68 years of age, intestinal subtype, and if the tumor is in the distal stomach.[115,118,149-152] Analysis of gastric adenocarcinoma data from TCGA showed an incidence of 22% for MSI-H tumors.[115] Similarly, a pan-cancer whole-exome sequencing analysis of numerous tumor-normal pairs from both TCGA and the Therapeutically Applicable Research to Generate Effective Treatments project reported an incidence of 19% in MSI-H/dMMR in gastric tumors.[153] Better prognosis has been reported with MSI-H/dMMR gastric tumors compared to microsatellite stable/MMR-proficient tumors,[149,150,154] including for those with MSI-H/dMMR who receive immunotherapy.[155,156]

Universal testing for MSI by PCR/NGS or MMR by IHC should be performed for all newly diagnosed patients with gastric cancer. PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by dMMR function. MSI status of the tumor can be assessed by PCR to determine shifts in validated microsatellite markers (eg, mononucleotide repeats *BAT25*, *BAT26*, *MONO27*, *NR21*, *NR24*).[157] MMR deficiency is evaluated by IHC to assess nuclear expression of proteins involved in DNA MMR (ie, MLH1, MSH2, MSH6, PMS2).[158] Testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-H or dMMR in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.[159] 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

Binding of the programmed cell death protein 1 (PD-1) receptor by its ligand PD-L1 is a critical immune checkpoint blockade that negatively affects T cell function and proliferation. Tumor cells can express PD-L1 and exploit PD-1/L1 binding to facilitate immune evasion, tumor growth/survival, and moderate activity of different immune cell types and signaling.[160-162] This makes PD-1/L1 a valuable target, and PD-1/L1 inhibitors have emerged as beneficial therapeutic options for certain patients (see *Targeted Therapies*).

PD-L1 expression has been frequently observed in the intestinal subtype,[163-165] though some studies have not observed a significant

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association with histologic subtype.[166] PD-L1 is reportedly associated with MSI-H and Epstein-Barr virus (EBV) positivity in gastric tumors.[115,163,164,166,167] The prognostic significance of PD-L1 in gastric cancer remains unclear. This may be due to different factors such as PD-L1 testing variability or small sample size. Currently, some studies suggest a significant favorable association with survival outcomes,[156,164,165] while others showed an unfavorable or no relationship between PD-L1 and survival.[166,168]

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. A 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 ≥1. PD-L1 testing should be performed only in CLIA-approved laboratories. Tumor proportion score (TPS) and tumor area positivity (TAP) score are also considered and reported in some trials, but they are not included in these Guidelines.

Claudin 18 Isoform 2

CLDN18.2 is a tight junction transmembrane protein that is typically expressed in normal gastric epithelia and is retained during malignant transformation.[169,170] CLDN18.2-positive tumors represent 24% to 38% of advanced gastric and EGJ adenocarcinomas.[171-174] However, due to variations in detection methods, assays used, and differing definitions of CLDN18.2 positivity, the percentage of CLDN18.2-positive tumors can vary across the literature.[175] CLDN18.2 expression has been observed in intestinal-type gastric tumors, but is more commonly seen in the diffuse subtype.[171,172,174,176] CLDN18.2 positivity has been shown independent of other established molecular subtypes (eg, dMMR, HER2 status) and PD-L1.[172-174] Association between CLDN18.2 and EBV status is unclear, as certain studies have reported a significant correlation between the two,[171,172] while another study reported no significance.[173]

Changes in tumor cell adhesion and polarity expose the normally inaccessible CLDN18.2 protein, which makes it a unique molecular target.[177,178] Testing is recommended for untreated patients who have unresectable locally advanced, recurrent, or metastatic gastric adenocarcinoma and zolbetuximab is being considered. Tumors are considered CLDN18.2 positive if ≥75% of viable tumor cells demonstrate moderate to strong membranous CLDN18.2 staining (2+ or 3+ intensity) by a qualitative IHC assay for FFPE tumor tissue.[169,179]

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.”[134,180] The detection of mutations/alterations or fusions 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.[180] 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 one or more characterized alterations theoretically targetable by a U.S. Food and Drug Administration (FDA)-approved agent (on- or off-label).[134] Therefore, when limited tissue is available or for patients who have advanced or metastatic gastric cancer who are not able

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to undergo a traditional biopsy, 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 a tumor.

Emerging Biomarkers

Tumor Epstein-Barr Virus

Tumor 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.[181,182] EBV-positive tumors occur preferentially in the proximal stomach and are associated with diffuse-type histology and early onset.[11] Although the prognostic value of EBV status on the survival of patients with gastric cancer remains a subject of debate, several studies suggest that patients with EBV-positive gastric cancer have better OS rates compared to other genotypes.[183-187] Additional studies have shown that expression of PD-L1 is elevated in EBV-positive gastric cancers and is associated with decreased OS rates.[188-190] 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.[189] Therefore, PD-1/PD-L1 immunotherapies may be a viable option to treat patients with EBV-positive gastric cancer; 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. However, EBV testing should be performed if the morphology of the tumor contains prominent lymphoid stroma.

Principles of 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.

Clinical staging using chest/abdomen/pelvis 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.[191,192] An R1 resection indicates microscopic residual disease and an R2 resection indicates macroscopic residual disease in the absence of distant metastasis.[193] 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.[194] Patients with Tis or T1a tumors may be considered for EMR or ESD if they meet appropriate criteria (in experienced centers).

Subtotal gastrectomy has a similar surgical outcome compared to total gastrectomy for distal gastric cancers, although with significantly fewer complications.[195] 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 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

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compared to those who underwent total gastrectomy alone.[196] 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.[197] 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) when nonsurgical options are not feasible such as endoscopic or interventional radiology procedures (ie, endoscopic stenting). Also, it does not need to include lymph node dissection.[49,198] In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) or endoluminal stenting are options. Except for rare cases that may have slow growth, endoluminal stenting is preferred in patients with gastric outlet obstruction/disease and very minimal metastatic disease in the liver or other area not affecting the GI tract. If longer-term palliation is needed, surgical bypass may be considered.[199,200] Venting gastrostomy and/or a feeding tube may also be considered.

Gastric adenocarcinoma is considered unresectable if there is evidence of peritoneal involvement (including positive peritoneal cytology), distant metastases, or locally advanced disease (N3 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.[128,201,202] Results from two large randomized trials performed in Western countries did not demonstrate a significant survival benefit for D2 over D1 lymph node dissection.[203,204] 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.[203] 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; $P = .34$).[205] The British Cooperative trial conducted by the Medical Research Council also did not demonstrate a survival benefit for D2 over D1 lymph node

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dissection (5-year OS rates of 35% and 33%, respectively).[204] 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.[206-209] 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).[206] High-volume centers had no 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.[207,208] 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).[208]

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.[203,204,210,211] 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 patients with advanced gastric cancer.[210,211] 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.[211] These rates are comparable with the rates for D1 lymph node dissections in the Dutch and United Kingdom trials.[203,204] 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.[212-214]

For patients with localized resectable gastric cancer, the NCCN Guidelines for Gastric Cancer recommend gastrectomy with a D1 or a modified D2 lymph node dissection, with a goal of examining ≥16 lymph nodes.[201,205,210,211] 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,[196,215] 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.[216-218] 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

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received an open procedure.[219] 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 patients with advanced gastric cancer (5000 received laparoscopic gastrectomy and 4337 received open gastrectomy) showed that the laparoscopic procedure resulted in less intraoperative blood loss and faster recovery times.[220] 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.[221] 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 noninferior 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.[222] 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.[223] 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 noninferiority 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.[224] 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.[225] Minimally invasive approaches are generally not recommended for T4b or N2 bulky gastric cancer.

Principles of Radiation Therapy

RT has been assessed in randomized trials in both the preoperative and postoperative settings in patients with resectable gastric cancer. Smalley

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et al have reviewed clinical and anatomic issues related to RT and offer detailed recommendations for the application of RT to the comprehensive care of patients with gastric cancer.[226]

RT as a single modality has minimal value in patients with unresectable gastric cancer.[227] 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.[55] Patients receiving combined modality treatment had significantly better median OS (13 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.[228] 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.[229] 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% for surgery vs. 10% for surgery plus RT and 19% for surgery plus chemotherapy). 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.[230]

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.[231-234]

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 [available at www.nccn.org]). 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

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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.[231-234] 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 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.[57,226] 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 patients with gastric cancer with locoregional disease.[235-237] Perioperative chemotherapy is recommended for localized resectable disease (category 1).[52,54,236,238,239] Postoperative chemoradiation is recommended for patients who received less than a D2 lymph node

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dissection.[57,58,240] Other treatment options include postoperative chemotherapy for patients who have undergone primary D2 lymph node dissection.[59,61,62] Chemoradiation alone should be reserved for patients with unresectable disease or those who decline surgery. Preoperative or perioperative ICIs can be considered for certain patients with an MSI-H/dMMR gastric tumor. Importantly, for MSI-H/dMMR tumors, a multidisciplinary team should be consulted for perioperative immunotherapy. The role of surgery following biopsy proven and confirmed radiologic/metabolic CR after preoperative immunotherapy is unclear.

Perioperative Chemotherapy

The survival benefit of perioperative chemotherapy in gastric cancer was first demonstrated in the landmark phase III MAGIC trial.[239] 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+).[54,241] 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 pathologic CR than was ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; *P* = .02).[241] Additionally, FLOT was associated with a reduction in the percentage of patients experiencing at least one grade 3–4 adverse event (AE), 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).[54] Results showed that median OS was increased in the FLOT group compared with the ECF group (50 vs. 35 months; HR, 0.77; 95% CI, 0.63–0.94). The percentage of patients with serious chemotherapy-related AEs 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 (category 1). 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.[52] 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 (category 1).

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.[238] 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

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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).[242] Therefore, adding RT to postoperative chemotherapy confers no survival benefit following adequate preoperative chemotherapy and surgery. Since there was poor postoperative adherence in both treatment groups, optimization of preoperative treatment strategies is integral. An ongoing phase II trial (CRITICS II) is comparing three preoperative strategies (chemotherapy, concurrent chemoradiation, and sequential chemotherapy and chemoradiation) in participants with resectable gastric cancer (Clinical Trial ID: NCT02931890).[243]

Preoperative or Perioperative Immunotherapy

For certain patients with MSI-H/dMMR gastric tumors, immunotherapy in the neoadjuvant or perioperative setting may be an option. The GERCOR NEONIPIGA phase II trial investigated the use of neoadjuvant nivolumab (monoclonal PD-1 antibody) plus ipilimumab (monoclonal CTLA-4 antibody) followed by adjuvant nivolumab in 32 patients with locally advanced gastric or EGJ adenocarcinoma and confirmed MSI-H/dMMR.[244] Following neoadjuvant therapy, 29 patients underwent R0 resection and a little more than half (~59%) had a pathologic CR. Of the 31 patients evaluated for survival, 97% had a survival benefit.[244] The Panel recommends nivolumab plus ipilimumab followed by nivolumab as a category 2A option useful in certain circumstances for patients with MSI-H/dMMR gastric tumors in the neoadjuvant or perioperative settings.

In another phase II trial, 35 patients with locally advanced MSI-H/dMMR solid tumors (most with stage III colorectal cancer) received neoadjuvant pembrolizumab (monoclonal PD-1 antibody).[245] Among 33 patients assessed, the overall response rate (ORR) was 82% and CR was observed in 30% of patients. Out of 17 patients whose tumors were surgically resected, 65% had a pathologic CR.[245] Individual case reports have also shown certain patients with MSI-H/dMMR gastric cancer may benefit from neoadjuvant pembrolizumab.[246] Based on these data, the Panel recommends pembrolizumab as a category 2A option useful in certain circumstances for patients with MSI-H/dMMR gastric tumors in the neoadjuvant or perioperative settings.

The combination of tremelimumab, a CTLA-4 inhibitor, and durvalumab, a PD-L1 inhibitor, was previously approved by the FDA for unresectable hepatocellular carcinoma and for certain patients with metastatic non-small cell lung cancer (NSCLC). These ICIs have also been investigated in combination in gastric cancer. In a randomized phase Ib/II trial, previously treated patients with gastric or EGJ cancer received either tremelimumab monotherapy, durvalumab monotherapy, or the combination.[247] There was no significant difference in ORR and PFS between the combination and either durvalumab or tremelimumab monotherapy, and median OS between the same treatment arms was 9.2, 3.4, and 7.7 months, respectively. The most common AEs regardless of treatment were fatigue, decreased appetite, diarrhea, and pruritis.[247] In the ongoing phase II INFINITY trial, patients with resectable MSI-H/dMMR gastric or EGJ adenocarcinoma received preoperative or definitive tremelimumab/durvalumab. Primary endpoint analysis showed a pathologic CR rate of 60% in the preoperative arm, and those who had pathologic CR were negative for ctDNA prior to surgery.[248] The Panel recommends tremelimumab and durvalumab as preoperative therapy only (category 2A, useful in certain circumstances).

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.[57,58] In this trial, 556 patients (stage IB to IV, M0) who had not received

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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).[57] 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 >10 years, survival remained improved in patients treated with postoperative chemoradiation.[58]

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.[240] 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.[59,249] 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).[249] 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).[250] 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 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.[61,62] 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).[61] 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

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group; the corresponding estimated 5-year OS rates were 78% and 69%, respectively.[62] 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 (category 1). 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.[57,58,240]

Peritoneal Carcinoma as Only Disease

For many patients with locally advanced or metastatic gastric cancer, there is a high risk of peritoneal disease, which confers a poor prognosis. The blood-peritoneal barrier presents challenges in effectively treating the disease.[251,252] For selected patients with only peritoneal metastatic disease, see *Peritoneal Carcinoma As Only Disease* in the algorithm for Panel recommendations. Briefly, following workup (if not previously done), selected patients should be given systemic therapy for a minimum of 3 months. Before considering further therapy, patients should undergo restaging. Multidisciplinary discussion is then recommended for patients with low peritoneal cancer index (PCI) (≤10), improved or stable disease, and no metastasis/extraperitoneal disease to determine status for cytoreduction. Regardless of whether complete or incomplete cytoreduction is predicted, these patients have the option of clinical trial participation or continuing systemic therapy. Only patients who are likely to have complete cytoreduction of all visible nodes/plaques have the option of gastrectomy with cytoreductive surgery and intraperitoneal chemotherapy (IC)/hyperthermic intraperitoneal chemotherapy (HIPEC). For patients with high PCI (>10) and disease progression or extraperitoneal disease, the Panel recommends systemic therapy, clinical trial participation, or best supportive care.

IC/HIPEC

Only case reports and small series are available to support the use of IC/HIPEC/pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in resectable gastric tumors. 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. Similarly, PIPAC is the introduction of chemotherapy directly to the abdomen but via aerosol. Note that PIPAC is considered investigational and should only be performed in the context of a clinical trial. Therefore, the focus of this section is on HIPEC and the Panel's recommendations.

HIPEC can potentially improve long-term outcomes and provide more treatment options for certain 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.[253] However, the median PCI 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 completed systemic chemotherapy and laparoscopic HIPEC underwent cytoreduction, gastrectomy, and HIPEC. The 90-day morbidity and mortality rates were 70% and 0%, respectively. A median OS of 16.1 months was observed from the time of cytoreduction, gastrectomy, and HIPEC. The OS rates for 1, 2, and 3 years from the diagnosis of metastatic disease were 90%,

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50%, and 28%, respectively.[254] 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.[255] 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 = .046). Four patients (11.7%) in the surgery alone group and 5 (14.7%) in the HIPEC group developed serious AEs (P = .839). Multivariate analysis found that the addition of HIPEC to cytoreductive surgery is an independent predictor for better survival.

A recent phase III trial, GASTRIPEC-I, investigated cytoreductive surgery with and without HIPEC following preoperative chemotherapy in patients with gastric or EGJ cancers and peritoneal metastasis. No significant differences were observed in OS between the two approaches (HR, 0.72; P = .1647).[256] Median PFS (7.1 vs. 3.5 months; P = .0472) and other distant metastasis-free survival (10.2 vs. 9.2 months; P = .0286) were improved with the addition of HIPEC. Of note, some patients were excluded from further treatment and complete cytoreduction after initial preoperative chemotherapy due to disease progression, among other causes, and almost half had a PCI of ≥7.[256] Additionally, an ongoing Dutch study, PERISCOPE II, is investigating gastrectomy followed by cytoreductive surgery plus HIPEC versus systemic treatment in resectable cT3–cT4 gastric cancer with limited peritoneal carcinoma (PCI <7). The primary endpoint is OS and secondary endpoints are PFS, toxicity, and quality of life.[257]

Due to limited evidence and a lack of randomized clinical trials to support the use of these methods in resectable tumors, the Panel recommends that IC/HIPEC should be pursued only in select circumstances and after multidisciplinary discussion. Any patient considered for IC/HIPEC should undergo pretreatment evaluation as described in the algorithm for those with documented peritoneal carcinoma as the only disease. This includes staging with chest/abdomen/pelvis CT, diagnostic laparoscopy with washings for PCI and/or cytology-positive disease evaluation, and consideration of a PET scan to rule out distant metastases. For certain patients with PCI ≤10 and candidates for complete cytoreduction, IC/HIPEC in conjunction with cytoreductive surgery is an option. For certain patients with PCI >10, IC/HIPEC may be considered in a clinical trial. All treatment decisions should be made in the context of a multidisciplinary tumor board.

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 patients who are medically fit 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, CLDN18.2, and MSI/MMR testing should be performed. NGS should 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.[258-260] 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

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<60% or an ECOG PS score ≥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.[261-264] 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.[261] 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).[262] 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.[263] 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.[264] 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.

Chemoradiation for Unresectable Disease

Chemoradiation alone may be offered to certain patients who are medically fit with unresectable disease and if not received previously. Since there are limited data in gastric cancer, the Panel recommends extrapolation of fluorouracil-based chemoradiation regimens with proven efficacy in esophageal carcinoma. 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.[265] 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. 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.[265] A trial of patients with stage II–IV esophageal carcinoma confirmed the safety and efficacy of FOLFOX combined with RT with or

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without surgery.[266] In the FFCD 9102 trial, survival was similar for patients with esophageal cancer receiving fluorouracil and cisplatin-based chemoradiation with or without surgery.[267] Additionally, patients may receive a fluoropyrimidine combined with paclitaxel, which has proven efficacy in yielding a pathologic response in resectable gastric cancer.[268] Following primary treatment, patients should be restaged to determine whether surgery is an option. Surgery is preferred if appropriate for patients with resectable and medically operable disease after chemoradiation, while those found to still have unresectable or medically inoperable and/or metastatic disease should receive palliative management.

First-Line Therapy

Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic gastric cancer.[261-264] 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 patients who are medically fit with excellent PS and easy access to frequent toxicity evaluations.[269] Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

For HER2 overexpression-positive disease, the addition of trastuzumab to chemotherapy with or without pembrolizumab is a treatment option for certain patients in this setting. Preferred regimens for HER2 overexpression-negative disease include certain ICIs combined with fluoropyrimidine and platinum-based therapies. Specifically, an ICI should be added to first-line chemotherapy for patients with PD-L1 CPS ≥1. For MSI-H/dMMR tumors, treatment options also include certain ICIs. See *Targeted Therapies* below for more information and specific Panel recommendations.

The preferred regimens for HER2-negative disease also include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin[270-272] or cisplatin.[270,273-275] 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.[270] 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, leucovorin, and cisplatin (FLP).[270] 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 >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.[271,276,277]

Regimens combining a platinum agent with capecitabine have also been evaluated in several studies for patients with advanced gastric cancer.[275,278,279] A phase III randomized trial (ML 17032) that evaluated the efficacy of combined capecitabine and cisplatin compared to fluorouracil and cisplatin found that capecitabine was noninferior to fluorouracil as first-line therapy in patients with advanced gastric cancer.[275] Two phase II trials concluded that capecitabine in combination with oxaliplatin is active and well-tolerated as first-line therapy for advanced gastric cancer.[278,279] Furthermore, results of a meta-analysis suggest that OS was superior in patients with advanced gastroesophageal cancer treated with capecitabine-based combinations compared to patients treated with fluorouracil-based combinations, although no significant difference in PFS

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between treatment groups was seen.[280] 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.[281] 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 noninferior in terms of PFS and resulted in significantly lower toxicities and better overall treatment utility in patients who are older and/or frail with advanced gastroesophageal cancers (n = 514).[282] Therefore, this low-dose regimen is recommended as an alternative to standard-dose capecitabine and oxaliplatin for patients who are older and/or frail 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.[274,283-294] 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 noninferior to CF in terms of PFS, but not in terms of OS or time to progression.[289] 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.[294] After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECF (5.1 vs. 4.2 months; P = .008).[294] However, there were no significant differences in median PFS (5.3 vs. 5.8 months; P = .96), median OS (9.5 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.[295,296] 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 ORR.[295] 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.[297-302] 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.[298,301,302] Other recommended regimens for first-line therapy include fluorouracil plus irinotecan,[294] paclitaxel with either cisplatin or carboplatin,[303-305] docetaxel with cisplatin,[306,307] docetaxel plus oxaliplatin and fluorouracil,[308] and single-agent fluoropyrimidine (fluorouracil or capecitabine),[274,309,310] docetaxel,[264,311] or paclitaxel.[312,313]

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Ramucirumab plus paclitaxel,[314] as well as single-agent docetaxel,[264,311] paclitaxel,[312,313,315] and irinotecan[262,315-317] are category 1 preferred options for second-line or subsequent therapy. Fam-trastuzumab deruxtecan-nxki is an option for HER2 overexpression-positive adenocarcinoma. See *Targeted Therapies* below for more information on and specific recommendations for ramucirumab and fam-trastuzumab deruxtecan-nxki. In a randomized phase III trial (COUGAR-02) single-agent docetaxel was shown to

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significantly increase 12-month OS compared to active symptom control alone (5.2 vs. 3.6 months, respectively; HR, 0.67; *P* = .01).[264] 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).[315]

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.[285,317-320] 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.[320] Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in patients with advanced gastric cancer (n = 59) treated with FOLFIRI in the second-line setting.[317] 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.[318] 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, 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).[321] 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. 1.8 months; HR, 0.57; 95% CI, 0.47–0.70; *P* < .0001).[321,322] The efficacy benefits of trifluridine and tipiracil were observed regardless of whether or not the patient had undergone previous gastrectomy.[323] The most frequently reported grade 3–4 toxicities were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%).[321] Patients ≥65 years had a higher incidence of moderate renal impairment compared to the overall study population (31% vs. 17%).[322] In the trifluridine and tipiracil arm versus the placebo arm, the ORR was 4.5% versus 2.1%, respectively, and the disease control rate was 44.1% versus 14.5%.[321] However, trifluridine and tipiracil 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. 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.

Other recommended regimens for second-line or subsequent therapy include single-agent ramucirumab (category 1),[324] irinotecan and cisplatin,[271,325] ramucirumab combined with irinotecan[326] or FOLFIRI,[327] and irinotecan and docetaxel (category 2B).[328] Options that are useful in certain circumstances include pembrolizumab,[158,329,330] nivolumab and ipilimumab,[331] or dostarlimab-gxly[332] for MSI-H/dMMR tumors; pembrolizumab for TMB-H (≥10 mutations/megabase) tumors[333]; entrectinib, larotrectinib, or repotrectinib for *NTRK* gene fusion-positive tumors[334-336]; dabrafenib and trametinib for *BRAF* V600E-mutated tumors[337]; and selpercatinib for *RET* gene fusion-positive tumors.[338] See *Targeted Therapies* below for more information on these agents.

Targeted Therapies

At present, several targeted therapeutic agents, including HER2-directed therapies, ICIs, and various kinase inhibitors, have been approved by the FDA for advanced gastric cancer. See *Principles of Biomarker Testing* above for details on testing recommendations.

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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.[145] 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.[145] 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 patients with HER2 overexpression-positive disease (13.8 vs. 11 months, respectively; $P = .046$). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as a treatment option 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 vs. 11.8 months; HR, 0.65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 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).[339] 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 CR, partial response, and stable disease. The most frequently reported grade 3 or higher AEs 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.[340] 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 mFOLFOX are effective regimens with acceptable safety profiles in patients with HER2 overexpression-positive gastroesophageal cancers. Trastuzumab should be added to first-line chemotherapy for patients with advanced HER2 overexpression-positive adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred [category 1 for cisplatin[145]; category 2A for oxaliplatin]). Pembrolizumab can also be added to this regimen for treatment of advanced HER2 overexpression-positive adenocarcinoma [341] (see *Pembrolizumab* below). Trastuzumab may be combined with other chemotherapy agents for first-line therapy, but should not be continued in second-line therapy.[342]

Pembrolizumab

HER2 Overexpression-Positive Tumors

Pembrolizumab is a PD-1 antibody that can be added to first-line fluoropyrimidine, platinum, and trastuzumab therapy for patients with advanced HER2 overexpression-positive gastric cancer. The phase III KEYNOTE-811 trial compared pembrolizumab to placebo in combination with trastuzumab and the investigator's choice of chemotherapy with fluorouracil and cisplatin or capecitabine and oxaliplatin in patients with previously untreated advanced HER2-positive gastric or EGJ adenocarcinoma.[343] Median PFS in patients in the pembrolizumab arm was longer than in the placebo arm (10 vs. 8.1 months; $P = .0002$).[344] In the subgroup analyses at the second interim (median ~28 months), patients with PD-L1 CPS ≥1 treated in the pembrolizumab arm had longer

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median PFS compared to placebo (10.8 vs. 7.2 months; HR, 0.70), which was not observed in patients with PD-L1 CPS <1 (9.5 vs. 9.6 months; HR, 1.17). Median OS was 20 months in the pembrolizumab arm compared to 16.9 months in the placebo arm (HR, 0.87; 95% CI, 0.72–1.06; *P* = .084), with the PD-L1 subgroup analysis following a similar trend to the PFS analysis.[344] The third interim analysis was consistent with the second. Improved ORR (72.6% vs. 59.8%) and median duration of response (11.2 vs. 9 months) was observed with the addition of pembrolizumab compared to placebo. CRs were also more frequent in the pembrolizumab group compared to placebo (14% vs. 11%).[344] Similar incidence of AEs was observed in the pembrolizumab and placebo groups, the most common being diarrhea, nausea, and anemia.[343,344] Based on KEYNOTE-811, in 2021 the FDA approved pembrolizumab in combination with trastuzumab plus fluoropyrimidine- and platinum-containing chemotherapy for locally advanced, unresectable or metastatic HER2-positive gastric or EGJ adenocarcinoma in first-line. The approval was modified in 2023 for patients in this setting whose tumor has PD-L1 CPS ≥1. Therefore, pembrolizumab combined with trastuzumab and fluoropyrimidine and platinum-based chemotherapy is a category 1 preferred first-line therapy option for treatment of patients with advanced HER2 overexpression-positive adenocarcinoma and PD-L1 CPS ≥1.

HER2 Overexpression-Negative Tumors

The randomized phase III KEYNOTE-859 trial investigated pembrolizumab plus chemotherapy versus placebo plus chemotherapy in treatment-naïve patients with advanced HER2-negative gastric or EGJ adenocarcinoma.[345] At a median 31-month follow-up, OS and PFS were favorable for the pembrolizumab combination versus placebo. More specifically, in the PD-L1 CPS ≥10 subgroup, median OS was significantly longer with pembrolizumab compared with placebo (15.7 vs. 11.8 months; HR, 0.65; *P* < .0001), and median PFS was also longer with pembrolizumab (8.1 vs. 5.6 months; HR, 0.62; *P* < .0001). Objective responses were observed in 61% of patients with pembrolizumab versus 43% with placebo.[345] In the PD-L1 CPS ≥1 subgroup, median OS was 13 months versus 11.4 months (HR, 0.74; *P* < .0001) and median PFS was 6.9 months versus 5.6 months (HR, 0.72; *P* < .0001) for pembrolizumab versus placebo, respectively. Objective responses were observed in 52% compared to 43%. Incidence of AEs were similar between the two treatment arms, with the most common grade 3–5 AEs being anemia and decreased neutrophils.[345] Based on this study, the FDA granted approval for pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy for locally advanced, unresectable, or metastatic HER2-negative gastric or EGJ cancer in first-line therapy.

The Panel includes pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy as a preferred option for first-line treatment of advanced HER2 overexpression-negative gastric cancer with PD-L1 CPS ≥1 if no prior ICI therapy or no tumor progression while on an ICI. This is a category 1 preferred option when PD-L1 CPS is ≥5.

MSI-H/dMMR Tumors

Pembrolizumab 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. 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.[158,329,330] The ORR was 39.6% and responses lasted ≥6 months for 78% of those whose disease responded to pembrolizumab. There were 11 CRs and 48 partial responses, and the ORR was similar irrespective of cancer type. In an updated analysis of cohort K in KEYNOTE-158, 351 patients were enrolled with 28 tumor types represented.[346] By independent central radiologic review, the ORR was 30.8%, with 27 patients having a CR, and median duration of response

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(DOR) was 47.5 months. Among the 42 patients with gastric cancer, the ORR was 31%.[346]

A few studies investigating pembrolizumab monotherapy and/or plus chemotherapy in advanced gastric or EGJ adenocarcinoma included patients whose tumors were MSI-H. In the phase II KEYNOTE-059 trial of a cohort of previously treated recurrent or metastatic gastric and EGJ cancers, four out of seven patients with an MSI-H tumor obtained an objective response with pembrolizumab monotherapy, with an ORR of 57.1%. Median OS and PFS were not reached among these same patients.[155,347] Previously treated patients in the phase III KEYNOTE-061 trial received either pembrolizumab or paclitaxel.[348] Among the 5.3% of patients with MSI-H tumors, median OS was not reached with pembrolizumab compared to 8.1 months with paclitaxel only. Median PFS was 17.8 months and ORR was 46.7% in patients with MSI-H tumor who received pembrolizumab versus 3.5 months and 16.7%, respectively, with paclitaxel alone.[155,348] In the phase III KEYNOTE-062 trial, treatment-naïve patients received pembrolizumab ± chemotherapy.[349] Similar to the other trials, median OS was not reached in the 7% of patients with MSI-H untreated locally advanced/unresectable or metastatic disease who received pembrolizumab ± chemotherapy versus 8.5 months with chemotherapy. Median PFS was 11.2 months among these patients with pembrolizumab and not reached with pembrolizumab plus chemotherapy versus 6.6 months with chemotherapy alone.[155,349] ORR was 57.1% and 64.7% with pembrolizumab and pembrolizumab plus chemotherapy, respectively, compared to 36.8% with chemotherapy alone.[155] Similar incidences of treatment-related all-grade or grade 3–5 AEs were observed with pembrolizumab and were lower than chemotherapy in the two phase III trials.[348-350]

Both pembrolizumab monotherapy and pembrolizumab in combination with fluoropyrimidine and oxaliplatin are recommended as category 2A preferred first-line therapy options for patients with advanced MSI-H/dMMR gastric cancer, independent of PD-L1 expression. Pembrolizumab monotherapy is also a category 2A option useful in certain circumstances for MSI-H/dMMR tumors in second- and subsequent-line.

TMB-H Tumors

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. This approval was based on a prospective analysis of 102 patients enrolled in the KEYNOTE-158 trial who had tumors identified as TMB-H.[333] The ORR for these patients was 29%, with a 4% CR rate. The median duration of response was not reached, with 50% of patients having response duration for ≥24 months.[333] Based on these data, pembrolizumab may be used for the second-line or subsequent treatment of TMB-H gastroesophageal tumors. However, it should be noted that no patients with gastroesophageal cancer were included in this TMB analysis from the KEYNOTE-158 trial.

Nivolumab

HER2 Overexpression-Negative Tumors

As mentioned, nivolumab is a monoclonal PD-1 antibody. It 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. 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 mFOLFOX).[351] The 3-year follow-up was consistent with initial efficacy results. At 3 years, median OS was 14.4 months for those with PD-L1 CPS ≥5 treated with nivolumab plus chemotherapy compared to 11.1

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months with chemotherapy alone (HR, 0.70).[352] Median PFS was 8.3 months with nivolumab plus chemotherapy versus 6.1 months with chemotherapy (HR, 0.70) in the same patient population. OS and PFS benefit was maintained with nivolumab plus chemotherapy compared to chemotherapy alone in the 5-year follow-up.[353] These patients also had an ORR of 60%, and 13% achieved CR with nivolumab plus chemotherapy compared to an ORR of 45% and CR rate of 7% with chemotherapy.[352] In the PD-L1 CPS ≥1 cohort, median OS for nivolumab plus chemotherapy was 13.8 versus 11.3 months with chemotherapy (HR, 0.75) and median PFS was 7.5 versus 6.9 months (HR, 0.77), respectively.[352,353] 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 AEs, remaining consistent in the 3-year follow-up.[351,352] The most common any-grade treatment-related AEs were nausea, diarrhea, and peripheral neuropathy across both groups. Sixteen treatment-related deaths occurred in the nivolumab plus chemotherapy group compared to four in the chemotherapy alone group.[351] 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 ≥1 if no prior ICI therapy or no tumor progression while on an ICI. This combination is a category 1 preferred option when CPS is ≥5.

MSI-H/dMMR Tumors

About 3% of patients enrolled in Checkmate-649 had MSI-H tumors.[351,352] In the 3-year follow-up, the OS benefit observed with nivolumab plus chemotherapy was better for those with MSI-H tumors than chemotherapy alone. This was true in patients who had MSI-H tumors with PD-L1 CPS ≥5 (n = 34; 44.8 vs. 8.8 months; HR, 0.29) and in all randomized patients with MSI-H tumors (n = 44; 38.7 vs. 12.3 months; HR, 0.34).[352]

The Checkmate-649 trial also randomized some patients to nivolumab plus ipilimumab or chemotherapy. At a minimum 24-month follow-up, patients with tumors having PD-L1 CPS ≥5 and all randomized patients did not have improved OS, PFS, or ORR with nivolumab plus ipilimumab versus chemotherapy alone.[331] However, patients with MSI-H tumors treated with nivolumab plus ipilimumab had improved median OS versus chemotherapy (not reached vs. 10 months; HR, 0.28). ORR was also improved with the combination versus chemotherapy (70% vs. 57%) in those with an MSI-H tumor. There was no survival benefit in the microsatellite stable cohort.[331]

For MSI-H/dMMR tumors, independent of PD-L1 status, the Panel recommends nivolumab plus fluoropyrimidine and oxaliplatin as a category 2A preferred option in first-line. The Panel also recommends nivolumab plus ipilimumab as a category 2A preferred option in first-line and a category 2A option useful in certain circumstances in second- and subsequent-line for patients with MSI-H/dMMR tumors.

Tislelizumab-jsgr

Another PD-1 inhibitor, tislelizumab, was recently approved by the FDA in combination with fluoropyrimidine- and platinum-based chemotherapy for the treatment of unresectable or metastatic HER2-negative gastric or EGJ adenocarcinoma with PD-L1 CPS ≥1. The randomized, global multicenter phase III trial RATIONALE-305 investigated the use of tislelizumab plus chemotherapy (investigator's choice, capecitabine plus oxaliplatin or fluorouracil plus cisplatin) in the first-line setting for unresectable locally advanced or metastatic gastric of EGJ adenocarcinoma.[354] Patients received either tislelizumab plus chemotherapy (n = 501) or placebo plus chemotherapy (n = 496). In all randomized patients, median OS for tislelizumab was 15 months versus 12.9 months with placebo (HR, 0.80; P = .001). Median PFS was 6.9 months versus 6.2 months with tislelizumab versus placebo, respectively (HR, 0.78). In the interim analysis, in patients

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whose tumors had a PD-L1 TAP of ≥5%, median OS for tislelizumab was 17.2 months versus 12.6 months with placebo (HR, 0.74; *P* = .006) and PFS was 7.2 months versus 5.9 months, respectively (HR, 0.67; *P* < .001).[354] The authors found concordance between the TAP score and CPS and reported similar OS in each treatment arm in a post hoc analysis of PD-L1 CPS of ≥5. AEs of grade 3 or higher were observed in 54% of patients treated with tislelizumab compared to 50% with placebo. Common grade 3 or 4 AEs included decreased neutrophil and platelet counts, anemia, and neutropenia. In the tislelizumab arm, 23% experienced serious treatment-related AEs and 31% experienced immune-related AEs, compared to 15% and 12% with placebo, respectively.[354] Based on these data, the Panel recommends tislelizumab in combination with fluoropyrimidine (fluorouracil or capecitabine) and platinum (oxaliplatin or cisplatin) as a first-line treatment option for patients whose tumors are PD-L1 CPS ≥1, if no prior ICI therapy or no tumor progression while on an ICI. For tumors with PD-L1 CPS ≥5, this is a category 1, preferred option.

Zolbetuximab-clzb

The FDA recently approved zolbetuximab combined with fluoropyrimidine- and platinum-based therapy for patients with HER2-negative, CLDN18.2-positive, unresectable locally advanced or metastatic gastric or EGJ adenocarcinoma in the first-line setting. Zolbetuximab is a novel monoclonal antibody targeting the tight junction protein, CLDN18.2, that demonstrated significant survival benefit in two global, randomized, multicenter phase III trials in this setting.[169,179]

In the SPOTLIGHT trial, 565 treatment-naïve patients with HER2-negative, CLDN18.2-positive, unresectable locally advanced or metastatic gastric or EGJ tumors received either zolbetuximab plus mFOLFOX6 (n = 283) or placebo plus mFOLFOX6 (n = 282).[169] Median PFS was 10.61 months with zolbetuximab compared to 8.67 months with placebo, with the HR for disease progression or death being 0.75 (*P* = .0066). Median OS was also longer with zolbetuximab at 18.23 months versus placebo at 15.54 months (HR for risk of death, 0.75; *P* = .0053). ORR and median DOR were similar between treatment groups.[169] In the GLOW trial, 507 untreated patients with unresectable locally advanced or metastatic HER2-negative, CLDN18.2-positive gastric or EGJ adenocarcinoma received either zolbetuximab plus CAPOX (n = 254) or placebo plus CAPOX (n = 253).[179] Median PFS was longer in the zolbetuximab arm versus the placebo arm (8.21 vs. 6.8 months; HR, 0.687; *P* = .0007). Median OS was also improved with zolbetuximab compared to placebo (14.39 vs. 12.16 months; HR, 0.771; *P* = .0118). In the zolbetuximab group, ORR and DOR were 42.5% and 6.14 months versus placebo, which was 40.3% and 6.08 months, respectively.[179]

In both studies, treatment-emergent all grade AEs with a >10% difference between zolbetuximab and placebo arms were nausea and vomiting. These events were also accounted for in the most frequent AEs of grade 3 or higher. Other AEs of grade 3 or higher in the GLOW trial were anemia and neutropenia, while decreased appetite was also observed in the SPOTLIGHT trial.[169,179] Based on these data, fluoropyrimidine-based chemotherapy plus oxaliplatin and zolbetuximab is a category 1, preferred first-line therapy option for patients with unresectable locally advanced, recurrent or metastatic gastric cancer whose tumors are HER2-negative and CLDN18.2-positive.

Ramucirumab

Ramucirumab, a vascular endothelial growth factor receptor (VEGFR)-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.[324,355] 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.[324] In this study, 355 patients were randomized to receive

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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 AEs were similar.[324]

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.[355] 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.[356] 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, other recommended) 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.

Ramucirumab combined with FOLFIRI is a category 2A other recommended 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%.[327] 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 a category 2A other recommended option for second-line or subsequent therapy for patients with advanced gastric cancer.[326]

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.[357]

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.[358] 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 DOR (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 AEs (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%

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and 11%). Fam-trastuzumab deruxtecan-nxki–related interstitial lung disease (ILD) 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.[358]

The single-arm, multicenter, phase II trial, DESTINY-Gastric02 investigated fam-trastuzumab deruxtecan-nxki in patients in Western countries with unresectable or metastatic HER2-positive gastric of EGJ cancer who progressed on or after first-line therapy.[359] Based on HER2 status, the ORR was 47.1% in patients whose tumor was IHC 3+ compared to 10 months for IHC 2+/ISH+. Patients had a median DOR of 8.1 months, as well as median PFS and OS of 5.6 months and 12.1 months, respectively. The most common grade 3 or higher AEs were similar to DESTINY-Gastric01 and also included nausea. ILD/pneumonitis occurred in eight patients, and for two patients it was a grade 5 event.[359]

The FDA has approved fam-trastuzumab deruxtecan-nxki to treat patients with unresectable or metastatic HER2 overexpression-positive solid tumors in second-line or subsequent therapy. Therefore, fam-trastuzumab deruxtecan-nxki is a category 2A preferred second-line or subsequent treatment option for patients with HER2 overexpression-positive adenocarcinoma following disease progression on prior treatment with a trastuzumab-based regimen. However, careful selection of patients and close monitoring of patients for excessive toxicity is recommended.

Entrectinib, Larotrectinib, and Repotrectinib

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.[335,360] 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.[361-363]

In 2018, the FDA granted accelerated approval of the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged ≥12 years) 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. 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).[335] 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, soft tissue sarcoma, infantile fibrosarcoma, and thyroid cancer. In an updated pooled analysis of the 3 trials (n = 153), the ORR was 79%, with a CR rate of 16%.[364] At a median follow-up of 12.9 months, 23% of patients who had responses experienced a progression event. Median DOR, PFS, and OS were 35.2 months, 28.3 months, and 44.4 months, respectively. AEs were predominantly grade 1–2, the most common being fatigue, increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, vomiting, constipation, and dizziness.[364] The SCOUT (Clinical Trial ID: NCT02637687) and NAVIGATE (Clinical Trial ID: NCT02576431) trials are ongoing.

In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with

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metastatic NSCLC whose tumors are *ROS1* positive. 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 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).[334] 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 CR 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 AEs were increased weight and anemia while the most common serious treatment-related AEs were nervous system disorders. STARTRK-2 (Clinical Trial ID: NCT02568267) is ongoing.

Repotrectinib was FDA approved in 2023 for patients with locally advanced or metastatic *ROS1*-positive NSCLC. It was given accelerated approval by the FDA in 2024 for similar indications to larotrectinib and entrectinib in patients with *NTRK* gene fusion-positive solid tumors. This was based on data from the phase I/II TRIDENT-1 trial investigating repotrectinib in previously tyrosine kinase inhibitor (TKI)-treated and TKI-treatment–naïve patients with NSCLC and *NTRK*+ solid tumors (ongoing, Clinical Trial ID: NCT03093116).[336] The most common tumor types were NSCLC, salivary gland, thyroid, and soft tissue sarcoma. Confirmed ORR was 58% in the TKI-naïve group and 50% in the previously treated group. The 12-month DOR and PFS were 86% and 56% for the TKI-naïve patients, respectively, and 39% and 22%, respectively, for the previously treated patients. Dizziness was the most common treatment-emergent AE of any grade, and AEs grade 3 or higher were observed in 51% of patients.[336]

These data demonstrate that these NTRK inhibitors induce durable and clinically meaningful responses in patients with *NTRK* gene fusion-positive tumors with manageable safety profiles. Entrectinib, larotrectinib, or repotrectinib are recommended as first-line (category 2B) and second-line or subsequent treatment options (category 2A) for patients with *NTRK* gene fusion-positive gastric tumors.

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. 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 patients with dMMR solid tumors who had not received prior PD-1, PDL-1, or CTLA4 inhibitors.[365,366] The majority of patients had endometrial or GI cancers. At median follow-up of 27.7 months, the ORR was 44% and DOR was not reached.[366] Median PFS and OS were 6.9 months and not reached, respectively. The most common treatment-related AEs of any grade were fatigue, diarrhea, asthenia, pruritus, and hypothyroidism. Immune-related AEs that occurred in 34% of patients included hypothyroidism, elevated ALT, and arthralgia.[366] Based on these data, dostarlimab-gxly is a category 2A, preferred option for first-line therapy for MSI-H/dMMR tumors. It is also useful in certain circumstances for second-line therapy in patients with MSI-H/dMMR gastric tumors whose disease is progressing on or following prior treatment that does not include immuno-oncology therapy and who have no satisfactory alternatives.

Dabrafenib and Trametinib

In June 2022, the FDA granted tumor-agnostic approval for the combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK

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inhibitor, for treatment of patients with unresectable or metastatic solid tumors with *BRAF* V600E mutations who have progressed following prior treatment and have no satisfactory alternative treatment options. This approval was based in part on data from the phase II BRF117019 and NCI-MATCH trials, which enrolled a combined 131 adult patients with various *BRAF* V600E-mutated tumor types.[337] In subprotocol H (EAY131-H) of the NCI-MATCH platform trial, patients with *BRAF* V600E-mutated solid tumors (except for melanoma, thyroid cancer, or colorectal cancer) received combined dabrafenib and trametinib continuously until disease progression or intolerable toxicity. The ORR was 38% ($P < .0001$) and PFS was 11.4 months.[337] The median OS in this cohort was 29 months. For the 131 patients across both trials, the ORR was 41%. The most common treatment-related AEs included pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, and vomiting.[337] Based on these data, dabrafenib and trametinib may be used for second-line or subsequent therapy (category 2A) for patients with *BRAF* V600E-mutated gastroesophageal tumors.

Selpercatinib

In September 2022, the FDA granted tumor-agnostic approval for selpercatinib, a TKI, for treatment of patients with locally advanced or metastatic solid tumors with *RET* gene fusions who have progressed following prior treatment and have no satisfactory alternative treatment options. This approval was based on an interim analysis of data from the ongoing phase I/II LIBRETTO-001 trial, which evaluated 41 patients with *RET* fusion-positive tumors (other than NSCLC and thyroid cancer) who received selpercatinib until disease progression or unacceptable toxicity.[338] The ORR was 44% with a duration of response of 25 months. The most common treatment-related AEs included edema, diarrhea, fatigue, dry mouth, hypertension, and abdominal pain. The most common grade 3 or higher treatment-related AEs were hypertension, increased ALT, and increased AST.[338] Based on these data, selpercatinib may be used for second-line or subsequent therapy (category 2A) for patients with *RET* gene fusion-positive gastroesophageal tumors.

Leucovorin Shortage

Leucovorin is indicated with certain fluorouracil-based regimens. However, there is currently a shortage of leucovorin in the United States.[367] 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.[368-370] However, the Panel recommends use of these regimens without leucovorin in situations where leucovorin is not available.

Survivorship

In addition to survivorship care relevant to all survivors of cancer (see NCCN Guidelines for Survivorship [available at www.nccn.org]), survivors of gastric cancer 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 survivors of gastric cancer. However, due to a lack of large randomized trials, the survivorship management recommendations provided by the Panel are based on smaller studies, clinical experience, and other consensus recommendations and guidelines.[371-374] 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

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of treatment. Surveillance should be performed in conjunction with good routine medical care, including routine health maintenance, preventive care, and cancer screening. Survivors of gastric cancer 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 survivors of gastric cancer 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 who are at risk for falls.

Osteopenia/osteoporosis is another common long-term sequelae in survivors of gastric cancer, 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.[375,376] Therefore, bone density should be screened at regular intervals and low bone density should be managed as per established national guidelines.[377]

In addition to the issues discussed above, survivors of gastric cancer who underwent gastrectomy face other long-term health issues (usually lifetime) including postprandial fullness, nutritional deficiencies (including vitamins B_{12} and D, calcium, iron, and zinc), dumping syndrome, and bacterial overgrowth in the small intestine (blind loop). See *Principles of Survivorship* in the algorithm for specific management recommendations. Lifelong monitoring and management of nutritional sequelae of gastrectomy should be established with appropriate practitioners and specialists.

Survivors who undergo gastrectomy are at 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 receive partial gastrectomy.[378-380] 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.[381] Survivors of gastrectomy also have unique nutritional needs due to frequent vitamin and mineral deficiencies and other GI dysfunctions.[382] Studies have shown that long-term anemia and deficiencies in nutrients such as iron, vitamin B_{12}, vitamin D, and zinc can occur in patients treated with gastrectomy for gastric cancer.[383-386] Supplementation of nutrients such as vitamin B_{12}[387] and iron[388] is safe and effective for reversing these deficiencies. It is recommended to supplement and monitor levels of vitamin B_{12} and D, iron, and calcium. Daily multivitamin and mineral complexes that include other vitamins and nutrients, as listed in the algorithm, are recommended as clinically indicated.

Dumping syndrome, which results from rapid emptying of the stomach into the small bowel, is another concern for survivors of total gastrectomy. 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 survivors of gastrectomy reported that 67.6% and 38.4% of patients experienced early and late dumping, respectively.[389] To

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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.

Patients who undergo gastrectomy can experience small intestinal bacterial overgrowth, a shift in the microbiome of the small intestine.[390,391] Small intestinal bacterial overgrowth (blind loop) can have nonspecific symptoms and lead to maldigestion and malabsorption.[391,392] Modifications to diet[391] and use of antibiotics such as rifaximin can be effective in treating certain patients.[393,394] The Panel recommends consideration of antibiotic treatment and a diet high in protein and low in carbohydrates.

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. The 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.

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 patients with gastric cancer 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.[395] 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.[396,397] 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.[396] Interventional radiology with angiographic embolization techniques may be useful in situations where endoscopy is not helpful.[398] Additionally, external beam RT (EBRT) has been shown to effectively manage acute and chronic GI bleeding.[399,400] Palliative gastrectomy is also an option in select patients. 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[401] or gastrectomy in select patients[198]), EBRT, chemotherapy, and endoscopic placement of an enteral stent for relief of gastric outlet obstruction[401] 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.[402-405] In a systematic review, patients treated with endoscopic placement of a SEMS were more

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likely to tolerate oral intake and had shorter hospital stays than patients treated with gastrojejunostomy.[406] 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.[401] A randomized trial also reported similar findings.[199] 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.[407] 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.[408,409] Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.[410,411] 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 (available at www.nccn.org). 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 (available at www.nccn.org). Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if obstruction is present.

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. See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (available at www.nccn.org) for more information. The NCCN Panel strongly recommends multidisciplinary team management as essential for treating 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. Patients who are medically fit with resectable T1b or higher, any N tumors can receive surgery with D2 lymph node dissection. Perioperative chemotherapy is a category 1 recommendation for patients with resectable T2 or higher, any N tumors or neoadjuvant/perioperative ICI can be considered for certain patients with MSI-H/dMMR tumors (category 2A). Patients who are medically fit with surgically unresectable tumors have the option of chemoradiation or systemic therapy. Nonsurgical candidates (patients who cannot tolerate surgery or decline surgery) and patients with metastatic disease should receive palliative management.

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Following an R0 resection, observation is an option for patients with Tis or T1,N0 tumors who did not receive previous systemic therapy. 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 systemic therapy (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 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. Palliative management is also an option for certain patients following R2 resection. Options for patients who have received previous systemic therapy include systemic therapy (category 1) following R0 resection. Patients with R1 or R2 resection have the option of chemoradiation. Patients with R1 resection can also be considered for re-resection, while patients with R2 resection can receive palliative management. Palliative management is an option for patients with M1 disease, regardless of whether they received preoperative therapy.

Histologic subtype and molecular characteristics have important implications in diagnosing and treating gastric cancer. The list of biomarkers that will characterize more subsets will continue to evolve. Several targeted therapeutic agents, including HER2-directed therapies, ICIs, and various kinase inhibitors, have been approved by the FDA for advanced gastric cancer. Targeted therapies have produced encouraging results in the treatment of patients with advanced gastric cancer. The NCCN Guidelines for Gastric Cancer are based on evidence- and consensus-based treatment approaches for the comprehensive care 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 in the management of this disease.

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