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Clinical Practice Guidelines in Oncology

Jaffer A. Ajani, MD; Thomas A. D'Amico, MD; Khaldoun Almhanna, MD, MPH; David J. Bentrem, MD, MS; Joseph Chao, MD; Prajnan Das, MD, MPH, MS; Crystal S. Denlinger, MD; Paul Fanta, MD; Farhood Farjah, MD; Charles S. Fuchs, MD, MPH; Hans Gerdes, MD; Michael Gibson, MD, PhD; Robert E. Glasgow, MD; James A. Hayman, MD, MBA; Steven Hochwald, MD; Wayne L. Hofstetter, MD; David H. Ilson, MD, PhD; Dawn Jaroszewski, MD; Kimberly L. Johung, MD, PhD; Rajesh N. Keswani, MD; Lawrence R. Kleinberg, MD; W. Michael Korn, MD; Stephen Leong, MD; Catherine Linn, MD; A. Craig Lockhart, MD, MHS; Quan P. Ly, MD; Mary F. Mulcahy, MD; Mark B. Orringer, MD; Kyle A. Perry, MD; George A. Poultsides, MD, MS; Walter J. Scott, MD; Vivian E. Strong, MD; Mary Kay Washington, MD, PhD; Benny Weksler, MD, MBA; Christopher G. Willett, MD; Cameron D. Wright, MD; Debra Zelman, JD; Nicole McMillian, MS; and Hema Sundar, PhD

Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, esophagogastric junction (EGJ), and stomach constitute a major health problem around the world. A dramatic shift in the location of upper GI tract tumors has occurred in the United

Abstract

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer in the world. Several advances have been made in the staging procedures, imaging techniques, and treatment approaches. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer provide an evidence- and consensus-based treatment approach for the management of patients with gastric cancer. This manuscript discusses the recommendations outlined in the NCCN Guidelines for staging, assessment of HER2 overexpression, systemic therapy for locally advanced or metastatic disease, and best supportive care for the prevention and management of symptoms due to advanced disease.

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NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Gastric Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

Disclosures for the NCCN Gastric Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN NCCN Gastric Cancer Panel members can be found on page 1312. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

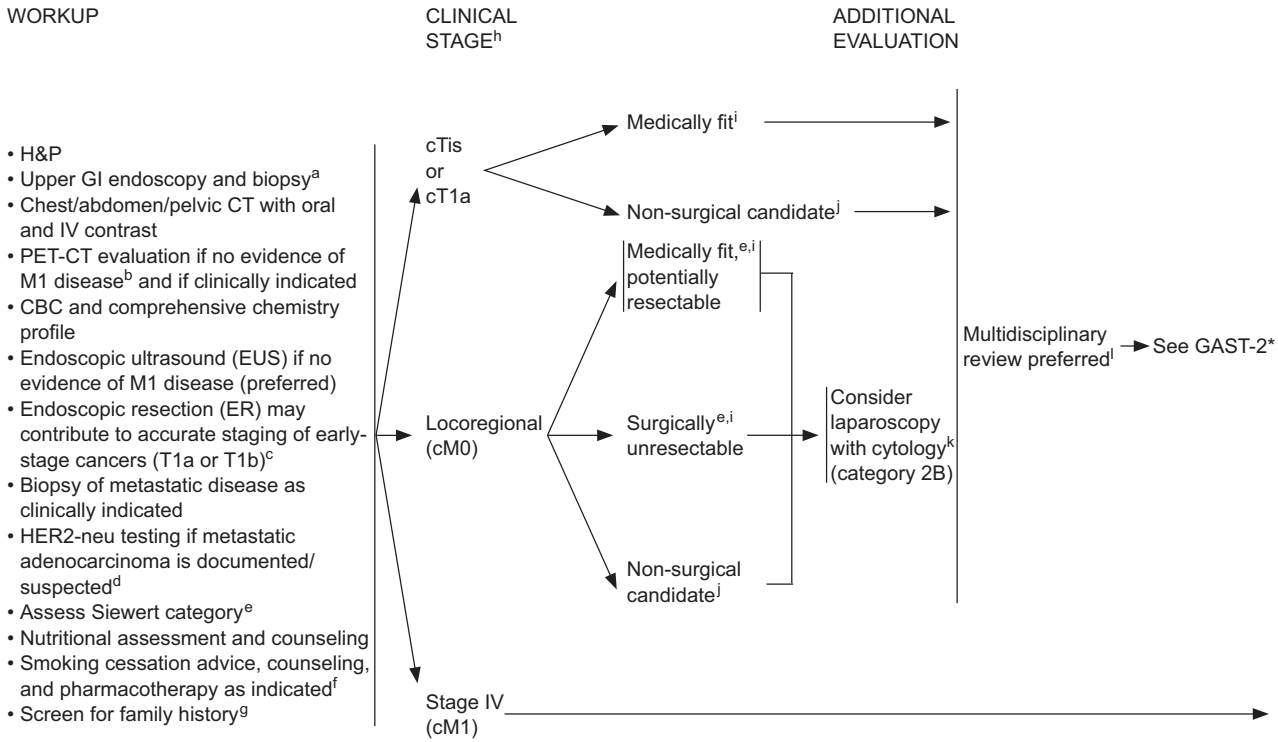
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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

Gastric cancer is rampant in many countries around the world. The incidence of gastric cancer is much higher in China than in any other country. In Japan, it remains the most common type of cancer among men. The incidence of gastric cancer, however, has been declining globally since World War II, and it is one of the least common cancers in North America. By some estimates, it is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer worldwide.[4] In 2016, an estimated 26,370 people will be diagnosed and 10,730 people will eventually die of the disease in the United States.[5] In developed countries, the incidence of gastric cancer originating from the cardia follows the distribution of esophageal cancer.[6–8] Non-cardia gastric cancer shows marked geographic variation, with countries such as Japan, Korea, China, Taiwan, Costa Rica, Peru, Brazil, Chile, and the former Soviet Union.[9] In contrast to the incidence trends in the West, nonproximal tumors continue to predominate in Japan and other parts of the world.[10] The etiology of this shift remains elusive and may be multifactorial.

Gastric cancer is often diagnosed at an advanced stage. In Japan (and in a limited fashion in Korea), where screening is performed widely, early detection is often possible. In other parts of the world, it

Text cont. on page 1300.



*Available online, in these guidelines, at NCCN.org.

†To view the most recent version of these guidelines, visit NCCN.org.

[a]See Principles of Endoscopic Staging (GAST-A).

[b]May not be appropriate for T1.

[c]EMR may also be therapeutic for early-stage disease/lesions.

[d]See Principles of Pathologic Review and HER2-neu Testing (GAST-B).

[e]See Principles of Surgery (GAST-C*).

[f]See NCCN Guidelines for Smoking Cessation.†

[g]See Principles of Genetic Risk Assessment for Gastric Cancer (GAST-D*). Also see NCCN Guidelines for Colorectal Cancer Screening and for Genetic/Familial High-Risk Assessment: Breast and Ovarian.†

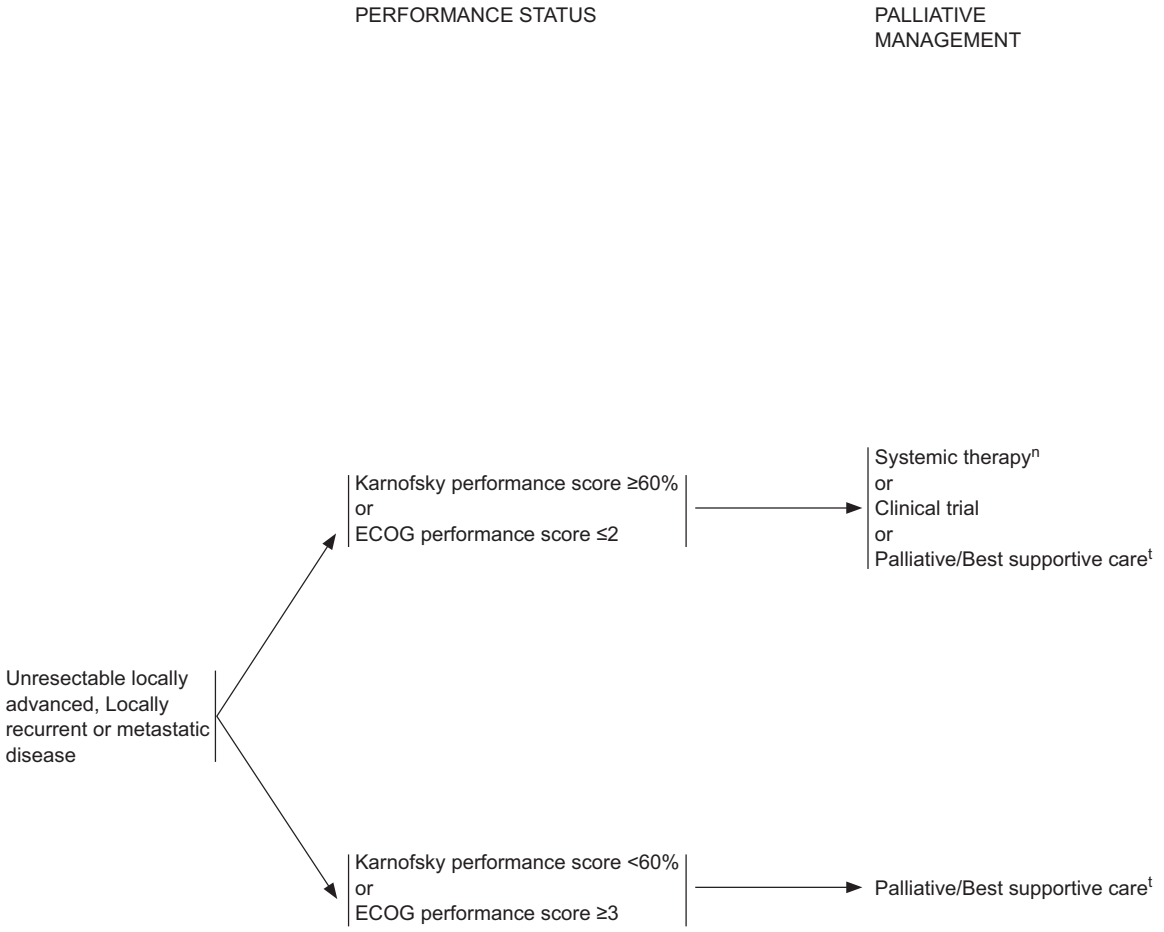
[h]See Staging (ST-1*) for tumor classification.

[i]Medically able to tolerate major surgery.

[j]Medically unable to tolerate major surgery or medically fit patients who decline surgery.

[k]Laparoscopy with cytology is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy with cytology is not indicated if a palliative resection is planned. Laparoscopy with cytology is indicated for clinical stage T1b or higher.

[l]See Principles of Multidisciplinary Team Approach (GAST-E).



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

PRINCIPLES OF ENDOSCOPIC STAGING

Endoscopy has become an important tool in the diagnosis, staging, treatment, and palliation of patients with gastric cancer. Although some endoscopy procedures can be performed without anesthesia, most are performed with conscious sedation administered by the endoscopist or assisting nurse or deeper anesthesia (monitored anesthesia care) provided by the endoscopist and nurse, a nurse anesthetist, or an anesthesiologist. Some patients who are at risk for aspiration during endoscopy may require general anesthesia.

DIAGNOSIS

- Diagnostic and surveillance endoscopies are performed with the goal of determining the presence and location of neoplastic disease and to biopsy any suspicious lesion. Thus, an adequate endoscopic exam addresses both of these components. The location of the tumor in the stomach (cardia, fundus, body, antrum, and pylorus) and relative to the esophagogastric junction (EGJ) for proximal tumors should be carefully recorded to assist with treatment planning and follow-up examinations.
- Multiple (6–8) biopsies using standard size endoscopy forceps should be performed to provide adequate sized material for histologic interpretation, especially in the setting of an ulcerated lesion.[1,2] Larger forceps may improve the yield.
- Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can be performed in the evaluation of small lesions. EMR or ESD of focal nodules ≤2 cm can be safely performed to provide a larger specimen that can be better assessed by the pathologist, providing greater information on degree of differentiation, the presence of lymphovascular invasion (LVI), and the depth of infiltration, thereby providing accurate T-staging.[3] Such excisional biopsies have the potential of being therapeutic.[4]
- Cytologic brushings or washings are rarely adequate in the initial diagnosis, but can be useful in confirming the presence of cancer when biopsies are not diagnostic.

STAGING

- EUS performed prior to any treatment is important in the initial clinical staging of gastric cancer.[5] Careful attention to ultrasound images provides evidence of depth of tumor invasion (T-category), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N-assessment), and occasionally signs of distant spread, such as lesions in surrounding organs (M-category) or the presence of ascites.[6] This is especially important in patients who are being considered for endoscopic resection (EMR or ESD).[7]
- Hypoechoic (dark) expansion of the gastric wall layers identifies the location of tumor, with gradual loss of the layered pattern of the normal stomach wall corresponding with greater depths of tumor penetration, correlating with higher T-categories. A dark expansion of layers 1–3 correspond with infiltration of the superficial and deep mucosa plus the submucosal, T1 disease. A dark expansion of layers 1–4 correlates with penetration into the muscularis propria, T2 disease, and expansion beyond the muscularis propria resulting in an irregular outer border that correlates with invasion of the subserosa, T3 disease. Loss of the bright line recognized as the serosa is now staged as pT4a, and extension of the mass into surrounding organs such as the liver, pancreas, and spleen is staged as pT4b disease.
- Perigastric lymph nodes are readily seen by EUS, and the identification of enlarged, hypoechoic (dark), homogeneous, well circumscribed, rounded structures around the stomach correlates with the presence of malignant or inflammatory lymph nodes. The accuracy of this diagnosis is significantly increased with the combination of features, but also may be confirmed with the use of fine-needle aspiration (FNA) biopsy for cytology assessment.[8] FNA of suspicious lymph nodes should be performed if it can be achieved without traversing an area of primary tumor or major blood vessels, and if it will impact on treatment decisions. Furthermore, an attempt should be made to identify the presence of ascites and FNA should be considered to rule out peritoneal spread of disease.

PRINCIPLES OF ENDOSCOPIC STAGING
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PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of Overexpression of HER2-neu in Gastric Cancer

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

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

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

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

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

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

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

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

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

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PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- Trastuzumab should be added to chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.[1]
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.[2]
- Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.
- Perioperative chemotherapy,[3,4] or postoperative chemotherapy plus chemoradiation[5] is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.[6,7] (See Principles of Surgery [GAST-C*])
- Induction chemotherapy may be appropriate as clinically indicated.
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

*Available online, in these guidelines, at NCCN.org.

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PRINCIPLES OF SYSTEMIC THERAPY

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

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

First-Line Therapy

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

- Preferred Regimens:
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[2-5] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[3,6,7]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[8-10]
  - Docetaxel with cisplatin[11,12]
  - Fluoropyrimidine[4,13,14] (fluorouracil† or capecitabine)
  - Docetaxel[15,16]
  - Paclitaxel[17,18]
  - Fluorouracil† and irinotecan (category 1)[19]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil†,[20]
    - Docetaxel, oxaliplatin, and fluorouracil[21]
    - Docetaxel, carboplatin, and fluorouracil (category 2B)[22]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[23]
  - ECF modifications (category 1)[24,25]
    - Epirubicin, oxaliplatin, and fluorouracil
    - Epirubicin, cisplatin, and capecitabine
    - Epirubicin, oxaliplatin, and capecitabine

Second-Line Therapy

Dependent on prior therapy and PS:

- Preferred Regimens:
  - Ramucirumab and paclitaxel (category 1)[26]
  - Docetaxel (category 1)[15,16]
  - Paclitaxel (category 1)[17,18,27]
  - Irinotecan (category 1)[27-30]
  - Ramucirumab (category 1)[31]
- Other Regimens:
  - Irinotecan and cisplatin[6,32]
  - Fluoropyrimidine (fluorouracil† or capecitabine) and irinotecan[33] (category 2B)
  - Docetaxel and irinotecan[34] (category 2B)

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

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PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE[a]

The goal of best supportive care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. For gastric cancer, interventions undertaken to relieve major symptoms may result in prolongation of life. This appears to be particularly true when a multimodality interdisciplinary approach is pursued, and, therefore, a multimodality interdisciplinary approach to palliative care of the gastric cancer patient is encouraged.

Bleeding

- Acute bleeding is common in patients with gastric cancer and may directly arise from the tumor or as a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment.[1]
  - Endoscopic Treatment
    - The efficacy of endoscopic therapy for bleeding in patients with gastric cancer is not well studied.[2] The limited data suggest that while endoscopic therapies may initially be effective, the rate of recurrent bleeding is very high.[3]
    - Widely available treatment options include injection therapy, mechanical therapy (eg, endoscopic clips), ablative therapy (eg, argon plasma coagulation), or a combination of methods.
  - Interventional Radiology
    - Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful or bleeding occurs.
  - External beam radiation therapy has been shown to effectively manage acute and chronic gastrointestinal bleeding in multiple small series.[4,5]
- Chronic blood loss from gastric cancer
  - Although proton pump inhibitors can be prescribed to reduce bleeding risk from gastric cancer, there are no definite data supporting its use at this time.
  - External beam radiation therapy may be used for chronic blood loss due to gastric cancer.[4,5]

Obstruction

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

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

Pain

- External beam radiation therapy
- Chemotherapy[b]
- If patient is experiencing tumor-related pain, then the pain should be assessed and treated in accordance with the NCCN Guidelines for Adult Cancer Pain, available at NCCN.org.

Nausea/Vomiting

- If patient is experiencing nausea and vomiting, then the patient should be treated in accordance with the NCCN Guidelines for Antiemesis, available at 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.

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

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE
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continues to pose a major challenge for health care professionals. Environmental risk factors include *Helicobacter pylori* (*H. pylori*) infection, smoking, high salt intake, and other dietary factors. In a recent meta-analysis, no appreciable association was seen between moderate alcohol drinking and gastric cancer risk; however, a positive association was seen with heavy alcohol drinking, particularly for non-cardia gastric cancers.[11]

Several advances have been made in clinical staging procedures, imaging techniques, and treatment approaches. Targeted therapies have produced encouraging results in the treatment of patients with advanced gastric cancer. The NCCN Clinical Practice in Oncology (NCCN Guidelines) for Gastric Cancer provide an evidence- and consensus-based treatment approach for the management of patients with gastric cancer. This manuscript discusses the recommendations outlined in the NCCN Guidelines for staging, assessment of HER2 overexpression, systemic therapy for locally advanced or metastatic disease, and best supportive care for the prevention and management of symptoms due to advanced disease.

Staging

Two major classifications are currently being used. The Japanese classification is more elaborate and is based on anatomic involvement, particularly the lymph node stations.[12] The other staging system, developed jointly by the AJCC and the Union for International Cancer Control (UICC), is the system used in countries in the Western Hemisphere.[13] A minimum of 15 examined lymph nodes is recommended for adequate staging. The 7th Edition of the AJCC Staging Manual does not include the proximal 5 cm of the stomach, which has created debates, confusion, and disagreements. In addition, the new classification has a number of other drawbacks, as it is based on primary surgery and is not reliable when considering clinical baseline staging or after preoperative therapy.

Clinical baseline stage provides useful information for the development of an initial treatment strategy. Approximately 50% of patients will present with advanced disease at diagnosis and will have a poor outcome. Other measures of poor outcome include poor performance status (PS), presence of metastases, and alkaline phosphatase level of 100 U/L or more.[14] In patients with localized resectable disease, outcome depends on the surgical stage of the disease. Nearly 70% to 80% of patients have involvement of the regional lymph nodes. The number of positive lymph nodes has a profound influence on survival.[15] Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), CT, PET/CT, MRI, and laparoscopic staging.[16–18]

EUS is indicated for assessing the depth of tumor invasion.[19] However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30% to 90% for N staging.[20] In a more recent large multi-institutional study that evaluated the use and accuracy of EUS in patients undergoing curative intent resection for gastric adenocarcinoma, the overall accuracy of EUS was 46.2% for T classification and 66.7% for N classification.[21] Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.[22] EUS may be useful for differentiating T3 and T4 tumors, and it should be used in combination with other staging modalities.[20,21] EUS is also helpful for identifying T1 tumors for potential endoscopic approaches.

CT scanning is routinely used for preoperative staging. It has an overall accuracy of 43% to 82% for T staging. PET/CT has a low detection rate because of the low tracer accumulation in diffuse and mucinous tumor types, which are frequent in gastric cancer.[23] It has a significantly lower sensitivity compared with CT in the detection of local lymph node involvement (56% vs 78%), although it has an improved specificity (92% vs 62%).[24] Combined PET/CT imaging, conversely, has several potential advantages over PET scan alone.[25] PET/CT has a significantly higher accuracy in preoperative staging (68%) than PET (47%) or CT (53%) alone. Recent reports have confirmed that PET alone is not an adequate diagnostic procedure in the detection and preoperative staging of gastric cancer but it could be helpful when used in conjunction with CT.[26,27]

Laparoscopic staging can detect occult metastases. In a study conducted by Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a period of 10 years.[28] Distant metastatic disease (M1) was detected in 31% of the patients. Limitations of laparoscopic staging include

2-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.[16] Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer.[29–31] A positive peritoneal cytology is an independent predictor for identifying patients who are at higher risk for recurrence following curative resection.[29] Clearing of cytology-positive disease, by chemotherapy is associated with a statistically significant improvement in disease-specific survival, but cures are rare and the role of surgery is uncertain in patients with positive peritoneal cytology.[30] Therefore, positive peritoneal cytology in the absence of visible peritoneal implants should be considered as M1 disease, and surgery as initial treatment is not recommended for patients with positive peritoneal cytology. In patients being considered for surgical resection without preoperative therapy, laparoscopy may be useful for the detection of radiographically occult metastatic disease in patients with T3 and/or N+ tumors identified on preoperative imaging.

Assessment of HER2 Overexpression

Human epidermal growth factor receptor 2 (*HER2*) gene and/or HER2 protein expression has been implicated in the development of gastric and EGJ adenocarcinomas.[32] The reported rates of *HER2* amplification and HER2 overexpression in patients with gastric cancer range from 12% to 27% and 9% to 23%, respectively.[33–38] HER2 positivity also varies with the histologic subtype (intestinal more than diffuse) and tumor grade (moderately differentiated more than poorly differentiated).[33,36–38] HER2 positivity is reported in 20% or less of Western patients with metastatic gastric cancer, with significantly higher rates of HER2 positivity in patients with intestinal histology (33% vs 8% for diffuse/mixed histology; P=.001).[38] In the United States population, the reported HER2 positive rate is 12%, and HER2 positivity is more often identified in the intestinal subtype than the diffuse subtype (19% and 6%, respectively).[37] In the Trastuzumab for Gastric Cancer (ToGA) trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2–positive advanced gastric cancer, HER2 neu–positivity rates were 33%, 21%, 32%, and 6%, respectively, in patients with EGJ adenocarcinoma, gastric adenocarcinoma, intestinal and diffuse cancer, and mixed type cancer.[39] Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

However, unlike in breast cancer, the prognostic significance of HER2 status in patients with gastric cancer remains unclear, with some studies suggesting that HER2 positivity is associated with poor prognosis.[35,36,40,41] 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.[37,38,42] Although further studies are needed to assess the prognostic significance of HER2 positivity, the most important clinical application of HER2 status in patients with gastric cancer concerns the management of advanced or metastatic disease.

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

According to the HER2 scoring system for breast cancer proposed by the ASCO/College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, due to 2 major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many patients with gastric cancer who could otherwise be candidates for anti-HER2 therapy.[43,44] Results from 2 separate series also showed that the HER2 scoring system for breast cancer identified a significantly lower percentage of patients with gastric cancer meeting the criteria for HER2 positivity by IHC (5.4% vs 11% in the ToGA trial).[45,46]

In 2008, Hoffmann et al[43] developed a modified 4-tier HER2 scoring system specific for gastric cancer by using the assessment area cut off of at least 10% stained tumor cells for resection specimens and omitting this area cut off for biopsy specimens.[43] In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.[44] This modified HER2 scoring system was also used in the ToGA trial.[45]

HER2 testing is now recommended for all patients with metastatic disease at the time of diagnosis. The guidelines recommend that assessment for HER2 status should be performed first using IHC following the modified scoring system used in the ToGA trial.[43,45] A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in situ hybridization techniques. The panel recommends FISH only for patients with a score of IHC 2+, although some institutions routinely perform both IHC and FISH on all patients. See the Principles of Pathologic Review and HER2 Testing Assessment of Treatment Response in the guidelines (available in these guidelines at NCCN.org).

Chemotherapy for Locally Advanced or Metastatic Disease

Chemotherapy can provide palliation of symptoms and improved survival and quality of life compared with best supportive care in patients with advanced and metastatic disease.[47,48]

Various fluorouracil-based combination regimens have been evaluated in randomized studies for the treatment of advanced or metastatic gastric cancer.[49–53] In the pivotal study performed by the North Central Cancer Treatment Group (NCCTG) that evaluated FAM (fluorouracil, doxorubicin and mitomycin) versus fluorouracil and doxorubicin versus fluorouracil alone, combination chemotherapy was associated with higher response rates than fluorouracil alone, although no significant survival differences were seen between the 3 arms.[49]

Other randomized studies have shown improvements in median survival and quality of life for epirubicin, cisplatin and fluorouracil (ECF) compared with FAMTX (fluorouracil, doxorubicin, and methotrexate) or MCF (mitomycin, cisplatin, and fluorouracil).[51,53] The combination of fluorouracil, leucovorin, and oxaliplatin (FLO) was evaluated as an alternative to fluorouracil and cisplatin for advanced or metastatic gastric cancer.[54–56] A phase III trial conducted by the German Study Group showed that the combination of FLO had a trend toward improved median progression-free survival (PFS) compared with fluorouracil, leucovorin, and cisplatin (FLP; 5.8 vs 3.9 months).[56] However, no significant differences were seen in median overall survival (OS) (10.7 vs 8.8 months, respectively) between the 2 groups. FLO was associated with significantly less toxicity than FLP. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs16.7%), time to treatment failure (5.4 vs 2.3 months), PFS (6.0 vs 3.1 months), and OS (13.9 vs 7.2 months) compared with FLP.

The REAL 2 (with 30% of patients having an esophageal cancer) trial was a randomized multicenter phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in 1003 patients with advanced esophagogastric cancer.[57] Patients with histologically confirmed adenocarcinoma, or squamous cell or undifferentiated carcinoma of the esophagus, EGJ, or stomach were randomized to receive one of the 4 epirubicin-based regimens (ECF; epirubicin, oxaliplatin, fluorouracil [EOF]; epirubicin, cisplatin, and capecitabine [ECX]; and epirubicin, oxaliplatin, and capecitabine [EOX]). Median follow up was 17.1 months. Results from this study suggest that capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy. The toxic effects from fluorouracil and capecitabine were not different.

ML 17032, another phase III randomized trial, evaluated the combination of capecitabine and cisplatin (XP) versus the combination of fluorouracil and cisplatin (FP) as first-line treatment in patients with previously untreated advanced gastric cancer.[58] Overall response rate (ORR; 41% vs 29%) and OS (10.5 vs 9.3 months) were superior for patients who received the XP regimen. No difference in median PFS was seen for both regimens (5.6 months for XP and 5.0 months for FP). The results of this study sug-

gest that capecitabine is as effective as fluorouracil in the treatment of patients with advanced gastroesophageal cancers. A meta-analysis of the REAL 2 and ML17032 trials suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared with the 664 patients treated with fluorouracil-based combinations, although no significant difference in PFS was seen between treatment groups.[59]

The combination of docetaxel, cisplatin, and fluorouracil (DCF) has also been evaluated in randomized clinical trials for patients with advanced gastric cancer.[60,61] In a randomized multinational phase III study (V325), 445 untreated patients with advanced gastric cancer were randomized to receive either DCF every 3 weeks or cisplatin and fluorouracil (CF).[60] Most patients had advanced gastric cancer, and 19% to 25% of patients had EGJ cancer. At a median follow up of 13.6 months, time to progression (TTP) was significantly longer with DCF compared with CF (5.6 vs 3.7 months; $P<.001$). The median OS was significantly longer for DCF compared with CF (9.2 vs 8.6 months; $P=.02$) at a median follow up of 23.4 months; the confirmed ORR was also significantly higher with DCF than CF (37% and 25%, respectively; $P=.01$).[60] The 2-year survival rates for DCF and CF were 18% and 9%, respectively. In 2006, based on the results of this study, the FDA approved the DCF regimen for the treatment of patients with advanced gastric cancer, including EGJ cancers, who have not received prior chemotherapy. However, DCF was associated with increased myelosuppression and infectious complications.

In the phase III study (V325), grade 3 adverse events occurred in 69% of patients in the DCF arm versus 59% of patients in the CF arm. The most frequent grade 3 or 4 toxicities reported in both treatment arms (DCF vs CF) were neutropenia (82% vs 57%), stomatitis (21% vs 27%), diarrhea (19% vs 8%), and lethargy (19% vs 14%), and complicated neutropenia was more frequent with DCF than CF (29% vs 12%).

In recent clinical trials, various modifications of the DCF regimen have shown efficacy and an improved safety profile in patients with advanced gastric cancer compared with the DCF regimen evaluated in the phase III study (V325).[62–67] In a randomized phase II trial that evaluated the efficacy and tolerability of docetaxel plus oxaliplatin with or without infusional 5-FU or capecitabine in patients with metastatic or locally recurrent gastric adenocarcinoma (including adenocarcinoma of the EGJ), docetaxel, oxaliplatin, and fluorouracil had a better safety profile and was also associated with a higher response rate and longer median PFS and OS (47%, 7.7 and 14.6 months, respectively) compared with docetaxel and oxaliplatin (23%, 4.5 and 9 months, respectively) and docetaxel, oxaliplatin, and capecitabine (26%, 5.6, and 11.3 months, respectively).[66] The frequency of grade 3 or 4 adverse events was lower among patients treated with docetaxel, oxaliplatin, and fluorouracil (25%) compared with those treated with docetaxel and oxaliplatin (37%) or docetaxel, oxaliplatin, and capecitabine (38%). Febrile neutropenia was reported in only 2% of patients treated with docetaxel, oxaliplatin, and fluorouracil (compared with 14% and 9% for docetaxel/oxaliplatin and docetaxel, oxaliplatin, and capecitabine, respectively), which is also much lower than the 16.4% reported with DCF in the V325 trial. Docetaxel, oxaliplatin, and capecitabine was also effective and well tolerated as first-line treatment in patients with metastatic gastric cancer resulting in an ORR of 52.1% with a PFS and OS of 6.9 and 12.6 months, respectively.[65]

In another recent randomized, multicenter phase II study, a dose-modified DCF regimen (docetaxel 40 mg/m^2, cisplatin 40 mg/m^2, and fluorouracil 2,000 mg/m^2) was less toxic than parent DCF (even when the parent regimen was given with growth factors) and is also associated with improved efficacy in previously untreated patients with metastatic gastric or EGJ adenocarcinoma.[67] In this study, 85 evaluable patients were randomized to receive dose-modified DCF (n=54) or the parent DCF regimen (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and fluorouracil 750 mg/m^2 with growth factor support). The DCF arm (n=31) closed early because of toxicity (71% grade 3 to 4 toxicity within 3 months and 90% grade 3 to 4 toxicity over the course of treatment). In the dose-modified DCF arm, the grade 3 or 4 toxicity rates were 54% within the first 3 months and 76% over the course of treatment. The 6-month PFS rate was 63% for dose-modified DCF and 53% for DCF. Dose-modified DCF was also associated with improved median OS (18.8 vs 12.6 months; $P=.007$).

Due to concerns regarding toxicity, the panel does not recommend the doses or the schedule of the DCF regimen as used in the phase III trial (V325).[60] Dose-modified DCF or other DCF modifications (docetaxel,

oxaliplatin or carboplatin and fluorouracil) are included as alternative options for first-line therapy.[63,66,67]

Irinotecan as a single agent or in combination has been explored extensively in single-arm and randomized clinical trials The results of a randomized phase III study comparing irinotecan in combination with fluorouracil and folinic acid (IF) to CF in patients with advanced gastric or EGJ adenocarcinoma (337 patients) showed that IF was noninferior to CF for PFS (the estimated probabilities of PFS at 6 and 9 months were 38% and 20% for IF compared with 31% and 12%, respectively, for CF) but not for OS (9 vs 8.7 months) and TTP (5 vs 4.2 months; *P*=.018).[68] However, IF was associated with a more favorable toxicity profile. Thus, IF can be an alternative option for patients who are unable to tolerate platinum-based chemotherapy.

In another randomized, multicenter phase II study, Moehler et al[69] compared capecitabine combined with irinotecan or cisplatin in metastatic gastric or EGJ adenocarcinoma. No significant differences were seen in ORR (37.7% and 42.0%, respectively) and median PFS (4.2 and 4.8 months, respectively), although there was a trend toward better median OS in the irinotecan arm (10.2 vs 7.9 months). The results of this study need to be validated further in larger studies.

A more recent randomized phase III study (French Intergroup Study) compared fluorouracil, leucovorin, and irinotecan (FOLFIRI) with ECF as first-line treatment in patients with advanced or metastatic gastric or EGJ adenocarcinoma.[70] In this study, 416 patients (65% of patients had gastric adenocarcinoma and 33% had EGJ adenocarcinoma) were randomized to receive either FOLFIRI or ECF. After a median follow up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECX (5.1 vs 4.2 months; *P*=.008).[70] 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%). FOLFIRI was less toxic and better tolerated than ECF. The panel felt that FOLFIRI is an acceptable option for first-line therapy for patients with advanced gastric cancer.

Irinotecan (single agent or in combination with other cytotoxic agents) has also been evaluated in the second line setting.[71–76] In a randomized phase III study that compared irinotecan with paclitaxel in 223 patients with advanced gastric cancer after failure of fluoropyrimidine-based chemotherapy; OS was not significantly different between the 2 groups.[74] The median OS was 9.5 and 8.4 months, respectively, for patients treated with paclitaxel and irinotecan (*P*=.38); the median PFS was 3.6 and 2.3 months, respectively (*P*=.33). Second-line chemotherapy with irinotecan, fluorouracil, and leucovorin was active and well tolerated in patients with metastatic gastric cancer with disease progression on docetaxel-based chemotherapy.[75] The ORR was 22.8% and stable disease was recorded in 30% of patients. Median PFS and OS were 3.8 and 6.2 months, respectively. Irinotecan (studied as a single agent or in combination with other cytotoxic agents in phase II and phase III trials) has not produced high-level evidence (category 1) for prolongation of survival in patients with advanced gastric cancer; therefore, its use is preferred in the second- or third-line setting.

The novel oral fluoropyrimidine S-1 has shown promise in advanced gastric cancer, both as a single agent and in combination with cisplatin in early phase studies. In a randomized phase III trial (SPIRITS trial), 298 patients with advanced gastric cancer were randomized to S-1 plus cisplatin and S-1 alone. Median OS (13 vs 11 months, respectively) and PFS (6.0 vs 4 months, respectively) was significantly longer for the combination of S-1 and cisplatin compared with S-1 alone.[77] The combination of S-1 and cisplatin in patients with untreated advanced gastric and EGJ adenocarcinoma was shown to be safe and active in multicenter phase II/III trials conducted in the United States.[78–80] In the phase III randomized trial (First Line Advanced Gastric Cancer Study [FLAGS]), 1053 patients with advanced gastric or EGJ adenocarcinoma were randomized to either cisplatin and S-1 (CS) or CF. CS and CF resulted in similar median OS (8.6 and 7.9 months, respectively; *P*=.20), but CS was associated with a significantly improved safety profile.[80,81] Additional studies are needed to confirm the activity of S-1 in the United States and Western Hemisphere. S-1 remains an investigational agent in North America.

Targeted Therapies

Trastuzumab

The ToGA study is the first randomized, prospective, multicenter phase III trial to evaluate the ef-

ficacy and safety of trastuzumab in patients with HER2-positive gastric and EGJ adenocarcinoma in combination with cisplatin and a fluoropyrimidine.[45] In this trial, 594 patients with HER2-positive (3+ on IHC or FISH-positive [HER2:CEP17 ≥2]), locally advanced, recurrent, or metastatic gastric and EGJ adenocarcinoma were randomized to trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone.[45] Most patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow up was 19 and 17 months, respectively, in the 2 groups. There was a significant improvement in the median OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in patients with HER2 neu overexpression or amplification (13.8 vs 11 months, respectively; *P*=.046).

This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with HER2-positive advanced or metastatic gastric and EGJ adenocarcinoma. However, the benefit of trastuzumab was limited only to patients with a tumor score of IHC 3+ or IHC 2+ and FISH positive. No significant survival benefit was seen for patients whose tumors were IHC 0 or 1+ and FISH positive results.[45] In the post hoc subgroup analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n=446; 16 vs 11.8 months; hazard ratio [HR] =.65) compared with those with tumors that were IHC 0 or 1+ and FISH positive (n=131; 10 vs 8.7 months; HR=1.07).

Ramucirumab

Ramucirumab, a vascular endothelial growth factor receptor (VEGFR) 2 antibody, has shown promising results in the treatment of patients with previously treated advanced or metastatic gastric or EGJ cancers in phase III clinical trials.[82,83] An international, randomized, placebo-controlled, multicenter phase III trial (REGARD trial) showed a survival benefit for ramucirumab for patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[82] In this study, 355 patients were randomized to receive ramucirumab (n=238; 178 patients with gastric cancer; 60 patients with EGJ adenocarcinoma) or placebo (n=117; 87 patients with gastric cancer; 30 patients with EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared with 3.8 months for those in the placebo group (*P*=.047). Ramucirumab was associated with higher rates of hypertension than the placebo group (16% vs 8%), whereas rates of other adverse events were mostly similar between the 2 groups.

In a more recent international phase III randomized trial (RAINBOW trial) that evaluated paclitaxel with or without ramucirumab in patients with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy, the combination of paclitaxel with ramucirumab resulted in significantly higher OS, PFS, and objective response rate than paclitaxel alone.[83] In this study, 665 patients were randomized to ramucirumab plus paclitaxel (n=330) and paclitaxel alone (n=335). The median OS was significantly longer for the ramucirumab plus paclitaxel group compared with paclitaxel alone (9.63 vs 7.36 months; *P*<.0001). The median PFS times were 4.4 and 2.86 months, respectively, for the 2 treatment groups. The objective response rate was 28% for ramucirumab plus paclitaxel compared with 16% for paclitaxel alone (*P*=.0001). Neutropenia and hypertension were more common in the ramucirumab plus paclitaxel arm. Based on the results of these 2 studies, ramucirumab as a single agent or in combination with paclitaxel was recently approved by the FDA for the treatment for patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive after first-line therapy with platinum- or fluoropyrimidine-based chemotherapy.

Treatment Guidelines

The management of patients with gastric cancer requires the expertise of several disciplines, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines are also desirable.[84] Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of any discipline taking care of patients with esophagogastric cancer. Optimally at each meeting, the panel encourages all relevant disciplines to participate. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient. See the section on Principles of Multidisci-

plinary Team Approach for Esophagogastric Cancers in the guidelines (GAST-E, page 1293).

Workup

Newly diagnosed patients should undergo a complete history, physical examination, and upper GI endoscopy with biopsy of the primary tumor. Biopsy to confirm metastatic disease should be done as clinically indicated and is not mandated in all patients, as long as biopsy of the primary tumor has established a diagnosis. A complete blood count, comprehensive chemistry profile, and CT scan (with oral and intravenous contrast) of the chest, abdomen, and pelvis should also be performed. EUS and PET/CT evaluation are recommended, if metastatic cancer is not evident. PET/CT scans are useful for predicting response to preoperative chemotherapy as well as in the evaluation of recurrent gastric cancer.[85–88] They may also be useful in showing occult metastatic disease, although false-positive results may be seen. Therefore, histologic confirmation of occult PET-avid metastasis is recommended.[89] PET is also not sensitive to detect peritoneal disease and does not obviate laparoscopy. Additional studies are needed to assess the efficacy of combined PET/CT scan in gastric cancer.

HER2 testing is recommended if metastatic disease is documented or suspected. See the section on Principles of Pathology for assessment of HER2 overexpression (GAST-B 3 of 4, page 1292).

Although most gastric cancers are considered sporadic, experts estimate that 5% to 10% have a familial component and 3% to 5% are associated with inherited cancer predisposition syndromes. The guidelines recommend screening for family history of gastric cancers, and referral to a cancer genetics professional is recommended for affected individuals who are at a higher risk of developing hereditary cancer syndromes associated with gastric cancer risk. See the Principles of Genetic Risk Assessment for Patients with Gastric Cancers (available in these guidelines at NCCN.org).

Management of Unresectable Locally Advanced, Recurrent or Metastatic Disease

Palliative therapy (systemic therapy, clinical trial, or best supportive care) is recommended for patients with unresectable locally advanced, recurrent, or metastatic gastric cancer. Surgery should be considered as an option for resectable locoregional recurrence in patients who are medically fit. The survival benefit of second-line chemotherapy compared with best supportive care for patients with metastatic or advanced gastric cancer has been shown in randomized controlled studies.[90–93]

In a randomized comparison between chemotherapy and best supportive care versus best supportive care alone, OS (8 vs 5 months, though not statistically significant) and TTP (5 vs 2 months) were longer in patients receiving chemotherapy for advanced gastric cancer.[90] More patients in the chemotherapy group (45%) had an improved or prolonged high quality of life for a minimum of 4 months compared with those who received only best supportive care (20%).

In another randomized phase III study, second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n=40).[91] The study was closed prematurely due to poor accrual. Median survival was 4 months in the irinotecan arm compared with 2.4 months in the best supportive care only arm. In another larger randomized trial (n=193), second-line chemotherapy with irinotecan or docetaxel significantly improved OS (5.1 vs 3.8 months) compared with best supportive care in patients with advanced gastric cancer.[92] However, both studies have limitations, and larger studies are now underway.

In an open-label multicenter, phase III, randomized trial, the addition of docetaxel to active symptom control was associated with a survival benefit for patients with advanced, histologically confirmed adenocarcinoma of the esophagus, EGJ junction, or stomach who experienced progression on or within 6 months of treatment with platinum fluoropyrimidine–based combination chemotherapy.[93] In this study, patients (n=168) with an ECOG Performance Status Scale (ECOG PS) score of 0 to 2 were randomly assigned to receive docetaxel plus active symptom control or active symptom control alone. After a median follow up of 12 months, the median OS was 5.2 months for patients in the docetaxel group compared with 3.6 months for those in the active symptom control group (P=.01). Docetaxel was associated with higher incidence of grade 3/4 neutropenia, infection, and febrile neutropenia. However, disease-specific, health-related quality-of-life mea-

sures also showed benefits for docetaxel in reducing dysphagia and abdominal pain.

First-line therapy with 2-drug chemotherapy regimens is preferred for patients with unresectable locally advanced, recurrent, or metastatic disease. Three-drug regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation. Based on the results of the ToGA trial, the guidelines recommend the addition of trastuzumab to first-line chemotherapy (category 1 for combination with cisplatin and fluoropyrimidine; category 2B for combination with other chemotherapy agents) for patients with HER2-positive metastatic gastric cancer (a tumor score of IHC 3+ and IHC 2+ with the evidence of HER2 amplification by FISH [HER2:CEP17 ratio ≥2]).[45] Trastuzumab is not recommended for patients with a tumor score of IHC 0 or 1+. The use of trastuzumab in combination with an anthracycline is not recommended.

The selection of a second-line therapy regimen for patients with unresectable locally advanced, recurrent or metastatic gastric cancer is dependent on prior therapy and PS. Based on the recent FDA approvals, the guidelines have included ramucirumab, single agent or in combination with paclitaxel (category 1) as options for second-line therapy.[82,83] Irinotecan and docetaxel are also included as options for second-line therapy.[74,91,93]

Best supportive care is always indicated for patients with unresectable locally advanced, recurrent, or metastatic gastric cancer. The decision to offer best supportive care alone or with chemotherapy depends on the patient's PS. The ECOG PS and the Karnofsky Performance Status Scale (KPS) are commonly used to assess PS in patients with cancer.[94–96] ECOG PS is a 5 point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher scores are considered to have poor PS (more information is available at http://www.ecog.org/general/perf_stat.html). KPS is an ordered scale with 11 levels (0 to 10). The general functioning and survival of a patient is assessed based on his or her health status (activity, work, and self-care). Low Karnofsky scores are associated with poor survival and serious illnesses (more information is available at http://www.hospicepatients.org/karnofsky.html).

Patients with a KPS score of less than 60 or an ECOG PS score of 3 or more should be offered best supportive care only. Best supportive care with or without systemic therapy, or a clinical trial is recommended for patients with better PS (KPS score of 60 or more or an ECOG PS score of 2 or less). See the Principles of Systemic Therapy section of the guidelines for a list of specific regimens (GAST-F, pages 1294–1297; additional information available in these guidelines, at NCCN.org).

Best Supportive Care

The goal of best supportive care is to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of disease stage. In patients with unresectable or locally advanced cancer, palliative interventions undertaken to relieve major symptoms may result in prolongation of life.

Bleeding: Acute bleeding is common in patients with gastric cancer and may be secondary to tumor or tumor-related phenomenon, or as a consequence of therapy.[97] A multidisciplinary approach is required for the proper diagnosis and management of GI bleeding in patients with cancer. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment. The efficacy of endoscopic therapy for bleeding in patients with gastric cancer is not well studied.[98] Limited available data suggest that although endoscopic therapies may be as effective as initial treatment, the rate of recurrent bleeding is very high.[99] Widely available options for endoscopic therapies include injection therapy, mechanical therapy (eg, endoscopic clip placement), ablative therapy (eg, argon plasma coagulation), or a combination of different modalities.[98] Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful. External beam RT and endoscopic treatment have been shown to effectively manage acute and chronic blood loss from GI bleeding.[100,101] Proton pump inhibitors can be prescribed to reduce the risk of bleeding from gastric cancer; however, no definite data are available supporting their use at this time.

Obstruction: The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet. Surgery (gastrojejunostomy or gastrectomy in selected patients), external beam RT, chemotherapy, and placement of enteral stent for relief of gastric outlet obstruction, or esophageal stent for EGJ/cardia obstruction are used

to alleviate or bypass obstruction. Management of malignant gastric outlet obstruction should be individualized, and treatment options should be selected as clinically appropriate. A multimodality interdisciplinary approach is strongly encouraged.

Endoscopic placement of self-expandable metal stents is a safe and effective, minimally invasive palliative treatment for patients with luminal obstruction due to advanced gastric cancer.[102–105] In a systematic review, patients treated with endoscopic placement of stents were more likely to tolerate oral intake and they also had shorter hospital stays than patients treated with gastrojejunostomy.[106] The results of a systematic review suggest that stent placement may be associated with more favorable results in patients with a relatively short life expectancy, whereas gastrojejunostomy is preferable in patients with a more prolonged prognosis.[107] A recent randomized trial also reported similar findings.[108] However, these results need to be confirmed in a larger cohort of patients. Percutaneous decompressive gastrostomy either by endoscopic or radiologic gastrostomy has also been associated with palliative benefit for patients with gastric outlet obstruction.[109,110]

When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy.[111] If endoscopic lumen restoration is not undertaken or successful, percutaneous endoscopic or interventional radiology gastrostomy tube placement for gastric decompression may be performed, if tumor location permits. Ascites, if present, should be drained before venting gastrostomy tube placement to reduce the risk of infectious complications.[112,113] Feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or a jejunal feeding tube for patients with mild and distal gastric obstruction may be necessary to provide adequate hydration and nutritional support for patients who cannot tolerate an oral diet. Nutritional counseling may also be valuable.

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

Nausea and Vomiting: Patients experiencing nausea and vomiting should be treated according to the NCCN Guidelines for Antiemesis (available at NCCN.org). Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if luminal enhancement is indicated.

Summary

Multidisciplinary team management is essential for the management of patients with gastric cancer. Best supportive care is an integral part of treatment, especially in patients with metastatic and locally advanced gastric cancer. Treatment should be individualized based on the patient's PS, comorbidities, and HER2 status, and the toxicity profile of each drug. The addition of trastuzumab to first-line chemotherapy is recommended for patients with HER2-positive metastatic gastric cancer. Ramucirumab, single agent or in combination with paclitaxel, is included as an option for second-line therapy for patients with unresectable locally advanced, recurrent, or metastatic gastric cancer. The panel encourages patients with gastric cancer to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

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Individual Disclosures of the Gastric Cancer Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Jaffer A. Ajani, MD	Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; ImClone Systems Incorporated; Novartis Pharmaceuticals Corporation; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	Bristol-Myers Squibb Company; Eli Lilly and Company; Five Prime Therapeutics, Inc.; Genentech, Inc.; Roche Laboratories, Inc.; and sanofi-aventis U.S.	None	7/11/16
Khaldoun Almhanna, MD, MPH	None	Bayer HealthCare; and Eli Lilly and Company	Genentech, Inc.	4/21/16
David J. Bentrem, MD, MS	None	None	None	4/19/16
Joseph Chao, MD	Merck & Co., Inc.	Five Prime Therapeutics, Inc.	Bayer HealthCare	4/20/16
Thomas A. D'Amico, MD	None	Scanlan	None	6/9/16
Prajnan Das, MD, MPH, MS	None	None	None	4/4/16
Crystal S. Denlinger, MD	Astex Pharmaceuticals, Inc.; Bayer HealthCare; Eli Lilly and Company; Genentech, Inc.; Incyte Corporation; MedImmune Inc.; Merrimack Pharmaceuticals, Inc.; OncoMed Pharmaceuticals, Inc.; and Pfizer Inc.	Eli Lilly and Company; and Merrimack Pharmaceuticals, Inc.	None	4/10/16
Paul Fanta, MD	None	None	None	5/7/16
Farhood Farjah, MD	None	None	None	7/21/16
Charles S. Fuchs, MD, MPH	None	Amgen Inc.; Celgene Corporation; Eli Lilly and Company; Genentech, Inc.; Merck & Co., Inc.; Entrinsic Health Solutions, LLC; Gilead Sciences, Inc.; MacroGenics, Inc.; Pfizer Inc.; and Sanofi-aventis U.S.	None	4/20/16
Hans Gerdes, MD	None	None	None	7/9/16
Michael Gibson, MD, PhD	None	None	Bristol-Myers Squibb Company; and Eli Lilly and Company	8/22/16
Robert E. Glasgow, MD	Domain Surgical	Domain Surgical	None	3/30/16
James A. Hayman, MD, MBA	None	None	None	4/19/16
Steven Hochwald, MD	None	None	Ethicon, Inc.	4/19/16
Wayne L. Hofstetter, MD	None	None	None	3/18/16
David H. Ilson, MD, PhD	Amgen Inc.; Bayer HealthCare; and Bristol-Myers Squibb Company	Amgen Inc.; Bayer HealthCare; Eli Lilly and Company; and MacroGenics, Inc.	Genentech, Inc.	6/24/16
Dawn Jaroszewski, MD	None	Zimmer BioMet	None	4/19/16
Kimberly L. Johung, MD, PhD	None	None	None	7/29/16
Rajesh H. Keswani, MD	None	None	Boston Scientific; and Cook Medical	4/19/16
Lawrence R. Kleinberg, MD	None	None	None	4/21/16
W. Michael Korn, MD	ARMO BioSciences, Inc.; Five Prime Therapeutics, Inc.; and Merck & Co., Inc.	Foundation Medicine, Inc.; Merrimack Pharmaceuticals, Inc.	None	4/19/16
Stephen Leong, MD	Deciphera Pharmaceuticals, LLC; Eli Lilly and Company; and Pfizer Inc.	None	None	4/19/16
Catherine Linn, MD	None	None	None	4/19/16
A. Craig Lockhart, MD, MHS	Bayer HealthCare; Daiichi Sankyo, Inc.; EMD Serono, Inc.; Genentech, Inc.; MacroGenics, Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Taiho Parmaceuticals Co., Ltd.; and Vertex Pharmaceuticals Incorporated	None	None	3/30/16
Quan P. Ly, MD	Pacira Pharmaceuticals, Inc	None	None	8/1/16
Mary F. Mulcahy, MD	BTG International Ltd.; and Roche Laboratories, Inc.	None	None	6/9/16
Mark B. Orringer, MD	None	None	None	4/19/16
Kyle A. Perry, MD	Medigus Ltd.; and Torax Medical, Inc.	None	None	4/22/16
George A. Poultsides, MD, MS	Medtronic, Inc.; and Stanford University	Medtronic, Inc.	None	4/30/16
Walter J. Scott, MD[a]	None	None	None	4/4/16
Vivian E. Strong, MD	None	None	None	6/9/16
Mary Kay Washington, MD, PhD	None	Chiampoulis, Hunter & Lynn Law Firm	None	3/25/16
Benny Weksler, MD, MBA	None	None	None	7/8/16
Christopher G. Willett, MD	None	None	None	6/16/16
Cameron D. Wright, MD	None	None	None	4/20/16
Debbie Zelman, JD	None	None	Debbie`s Dream Foundation: Curing Stomach Cancer	7/20/16

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Walter J. Scott, MD: Celgene Corporation; and Johnson & Johnson

The NCCN Guidelines staff have no conflicts to disclose.