National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Gastric Cancer

V.2.2009

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines Updates

Summary of changes in the 2.2009 version of the Gastric Cancer guidelines from the 1.2009 version is the addition of the Disscussion:

Summary of changes in the 1.2009 version of the Gastric Cancer guidelines from the 1.2008 version include:

(GAST-1):
- **Workup:**
  - **Third Bullet: SMA-12 was changed to "chemistry profile". (Also for GAST-4 and GAST-5)**
  - **Fourth Bullet: Changed to "Abdominal CT *with contrast*" (Also for GAST-4)**
  - **Sixth Bullet: "Chest x-ray" changed to "Chest *imaging*".**
  - **Eighth Bullet: "PET/CT scan..." was changed to "PET/CT *(optional) or PET* scan..." (Also for GAST-4)**
  - **Added new bullet "H.pylori testing, treat if positive"**
- **Clinical Presentation: The panel added a new pathway for "Tis or T1a" (Also for GAST-2)**

(GAST-2):
- **"Discussion of patient in a multidiscplinary conference is desirable" was changed to "Multidisciplinary evaluation preferred".**
- **Medically fit, potentially resectable; M0 pathway: "T1 or less (by clinical staging)" was changed to "T1b".**

(GAST-3):
- **After "R0 resection": The panel changed "T1, N0" to "Tis or T1, N0"**
- **Footnote "j" defining R0, R1, and R2 resections is new to the page.**

(GAST-4):
- **Page title changed to "*Post Treatment Assessment*/Adjunctive Treatment".**

(GAST-5):
- **Follow-up: Fourth Bullet: Monitor or supplement for vitamin B_{12} deficiency for proximal or total gastrectomy patients" was changed to "Monitor for vitamin B_{12} deficiency *in surgically resected patients and treat as indicated*".**
- **Supportive Care Modalities box: Title was changed to "*Best* Supportive Care".**
  - **Obstruction: "Stent..." was changed to "Stent *(preferred) for initial palliation* or RT..."**

(GAST-A): Principles of Multidisciplinary Team Approach
- **Page Title: "Principles of Combined Modality Therapy" was changed to "Principles of Multidisciplinary Team Approach".**
- **First Bullet: "Frequent meetings...are useful" was changed to "Frequent meetings...are encouraged".**
- **Eighth Bullet: "...multidisciplinary meeting is a method..." was changed to "...multidisciplinary meeting is *highly encouraged*".**

(GAST-B): Principles of Gastric Cancer Surgery
- **Resectable tumors: First bullet now states "*Tis or* T1 tumors limited to mucosa (T1a) ..."**
- **Resectable tumors: Second Bullet: Changed to "T1*b*-T3..."**

(GAST-C): Principles of Systemic Therapy
- **Metastatic or Locally Advanced Cancer:**
  - **Under "Oxaliplatin plus fluoropyrimidine (5-FU or capecitabine)," the panel added a new footnote that states, "Leucovorin or levoleucovorin is indicated with certain infusional 5-FU based regimens."**
  - **"Paclitaxel-based regimen (category 2B)" was added.**

(GAST-D): Principles of Radiation Therapy
- **Blocking: "...heart (1/3 of heart < 40 GY...)" changed to "...heart (1/3 of heart < *50* GY...)"**

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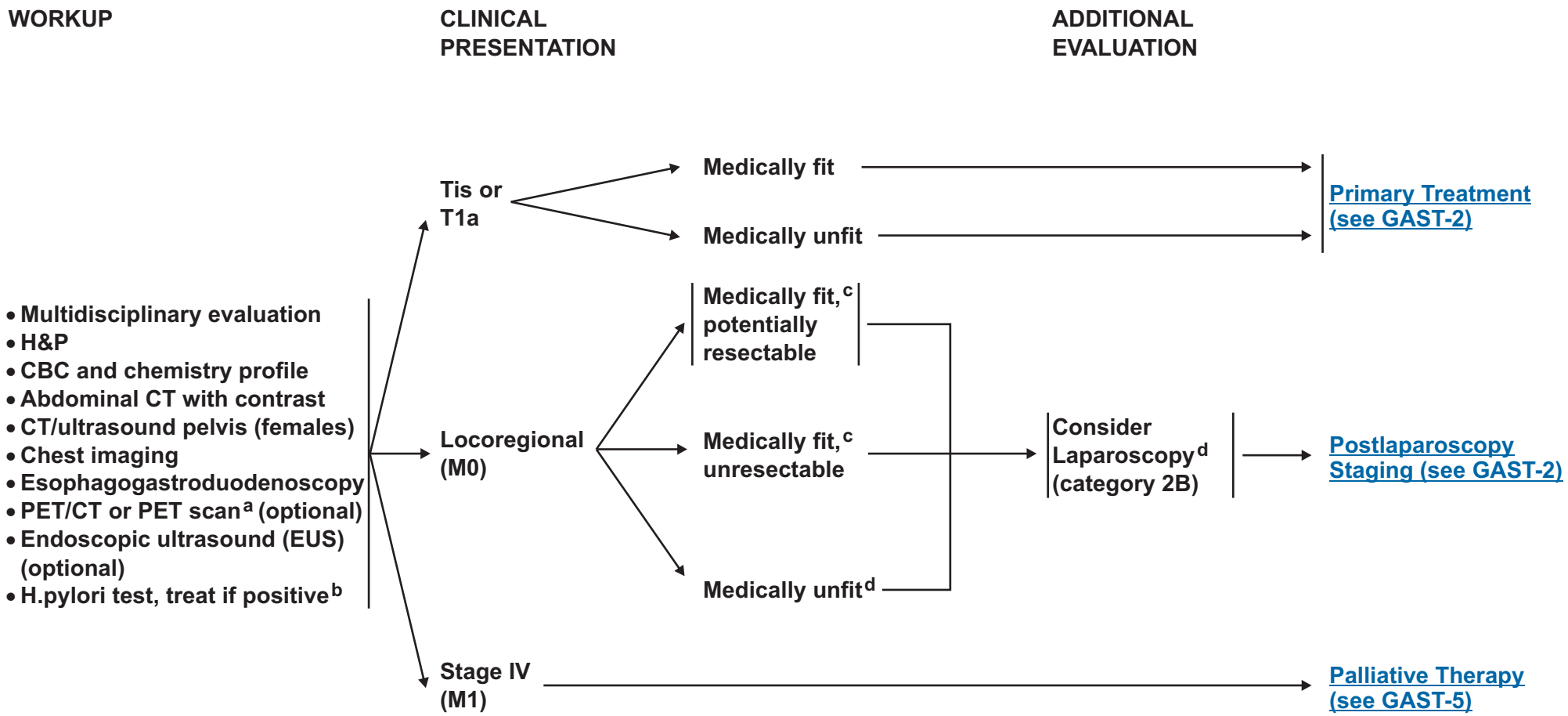
Gastric Cancer



[a] May not be appropriate for T1 or M1 patients.

[b] Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007;102(8):1808-1825.

[c] Medically able to tolerate major abdominal surgery.

[d] Laparoscopy is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy is not indicated if a palliative resection is planned.

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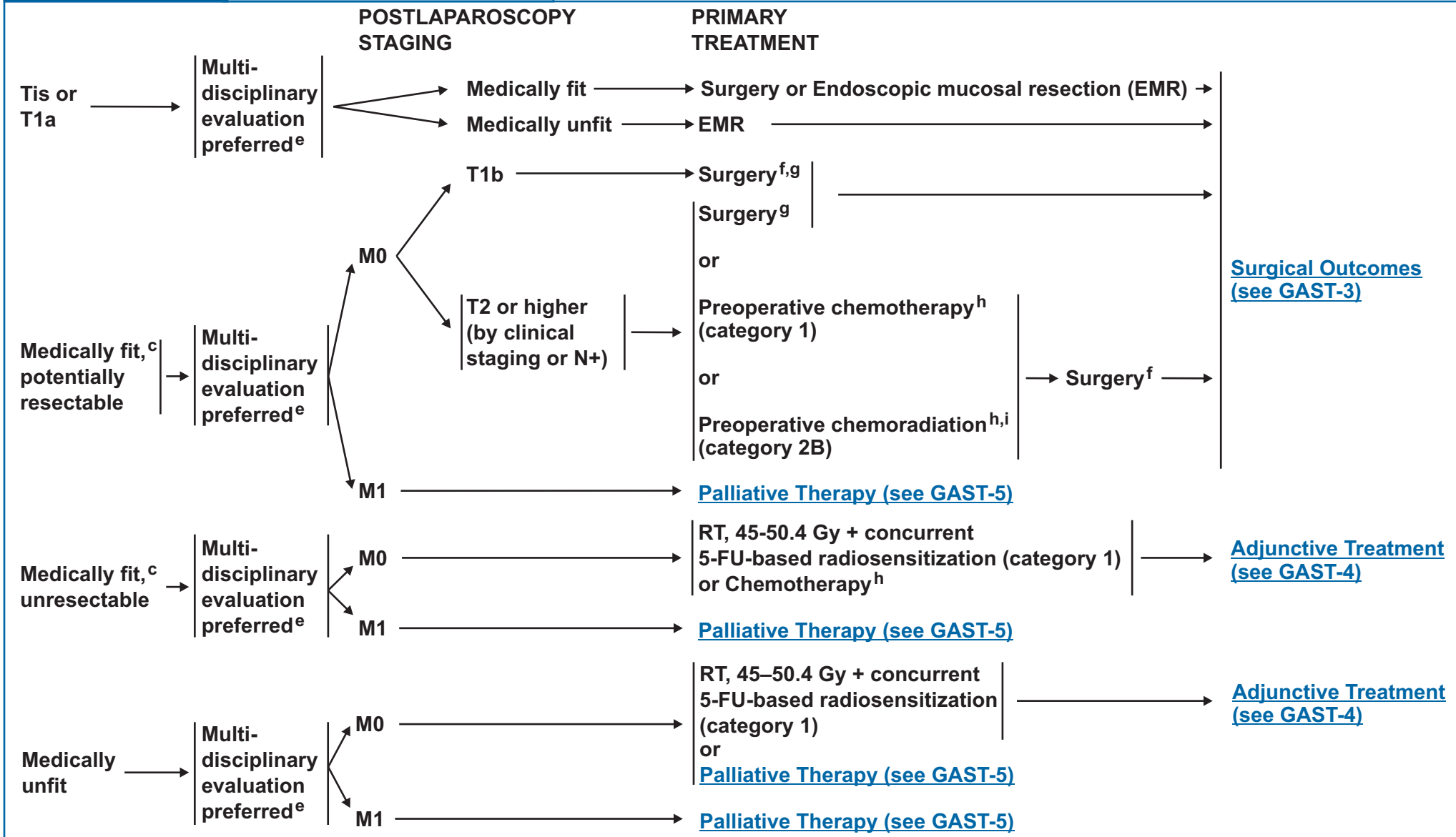
Gastric Cancer



[c]Medically able to tolerate major abdominal surgery.

[e]See Principles of Multidisciplinary Team Approach (GAST-A).

[f]Surgery as primary therapy is appropriate for T1 cancer or actively bleeding cancer, or when postoperative therapy is preferred.

[g]See Principles of Surgery (GAST-B).

[h]See Principles of Systemic Therapy (GAST-C).

[i]See Principles of Radiation Therapy (GAST-D).

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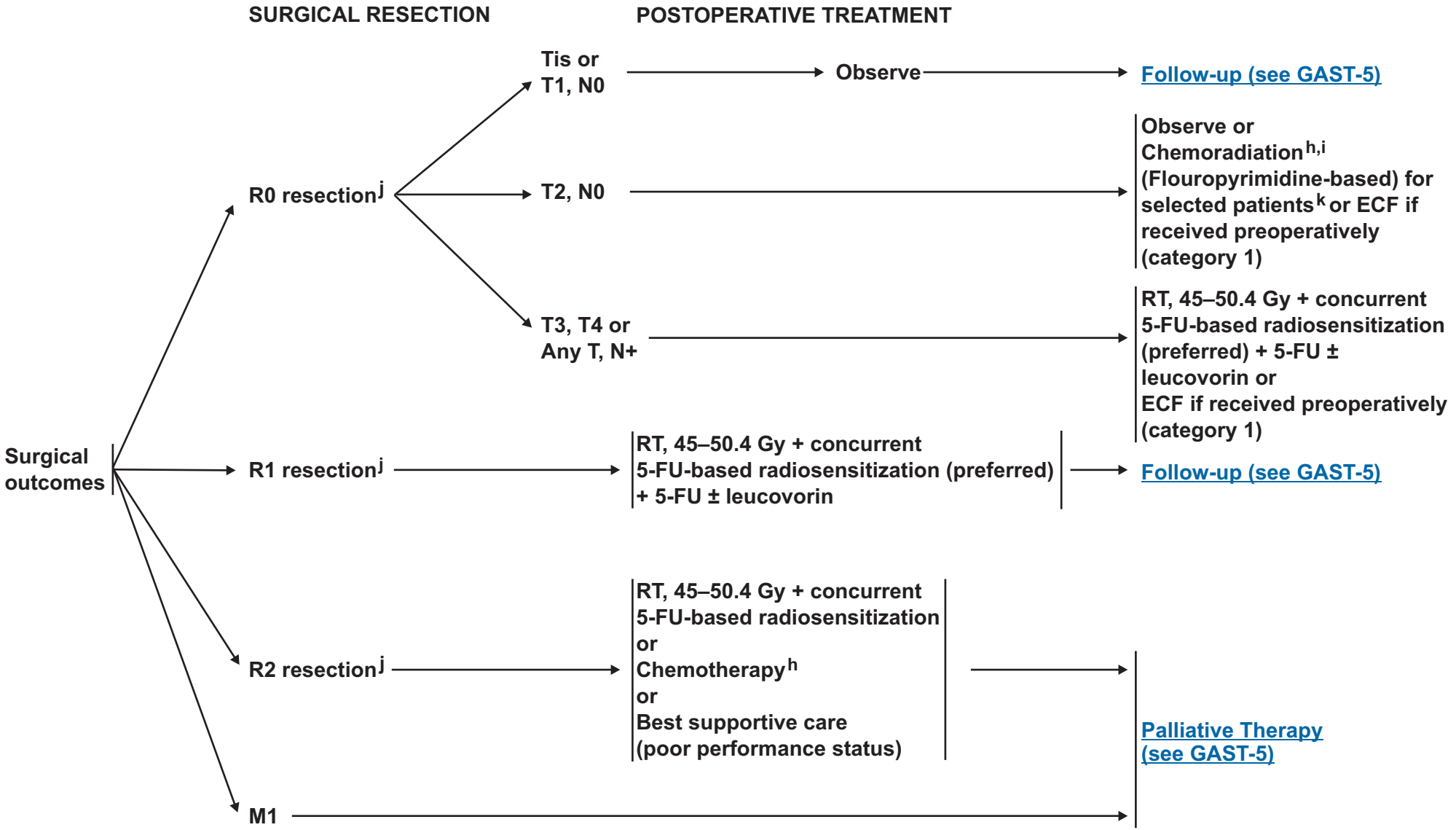
Gastric Cancer



[h] See Principles of Systemic Therapy (GAST-C).
[i] See Principles of Radiation Therapy (GAST-D).
[j] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[k] High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age.

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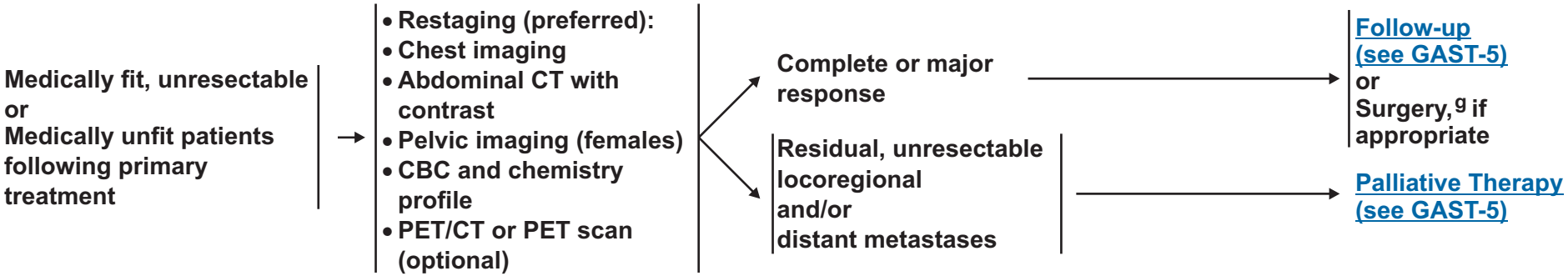
POST TREATMENT ASSESSMENT/ADJUNCTIVE TREATMENT



[g] See Principles of Surgery (GAST-B).

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Gastric Cancer

FOLLOW-UP

- H&P every 4 - 6 mo for 3 y, then annually
- CBC and chemistry profile as indicated
- Radiologic imaging or endoscopy, as clinically indicated
- Monitor for vitamin B_{12} deficiency in surgically resected patients and treat as indicated

PALLIATIVE THERAPY

Karnofsky performance score ≥ 60 % or ECOG performance score ≤ 2 → Chemotherapy[h] or Clinical trial or Best supportive care

Karnofsky performance score < 60 % or ECOG performance score ≥ 3 → Best supportive care

Best Supportive Care

- Obstruction: Stent (preferred) for initial palliation or RT (external or brachytherapy), photodynamic therapy, laser, surgery
- Nutrition: Enteral feeding, nutritional counseling
- Pain control: RT and/or medications
- Bleeding: RT, surgery or endoscopic therapy

[h] See Principles of Systemic Therapy (GAST-C).

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PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR GASTROESOPHAGEAL CANCERS

Category 1 evidence supports the notion that the combined modality therapy is effective for patients with localized gastroesophageal cancer. The NCCN panel believes in an infrastructure that discourages unilateral treatment decision-making by members of any discipline taking care of this group of patients.

The combined modality therapy for patients with localized gastroesophageal 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.**
- **At each meeting, all relevant disciplines should be encouraged to participate and these include: surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, 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 GASTRIC CANCER SURGERY (1 of 2)

Staging
- Determine extent of disease with CT scan ± EUS
- Laparoscopy[1] may be useful is select patients

Criteria of unresectablity for cure
- Locoregionally advanced
  - Level 3 or 4 lymph node highly suspicious on imaging or confirmed by biopsy
  - Invasion or encasement of major vascular structures
- Distant metastasis or peritoneal seeding (including positive peritoneal cytology)

Resectable tumors
- Tis or T1[2] tumors limited to mucosa (T1a) may be candidates for endoscopic mucosal resection (in experienced centers)[3]
- T1b-T3[4]: Adequate gastric resection to achieve negative microscopic margins (typically ≥ 4 cm from gross tumor).
  - Distal gastrectomy
  - Subtotal gastrectomy
  - Total gastrectomy
- T4 tumors require en bloc resection of involved structures
- Gastric resection should accompany the regional lymphatics (D1), with a desired goal of removing/examining 15 or greater lymph nodes[5,6]
- Routine or prophylactic splenectomy is not required.[7] Splenectomy is acceptable when the spleen or the hilum is involved.
- Consider placing feeding jejunostomy tube in select patients (especially if postoperative chemoradiation appears a likely recommendation)

Unresectable tumors (palliative procedures)
- Limited gastric resection, even with positive margins is acceptable.
- Lymph node dissection not required
- Gastric bypass with gastrojejunostomy to the proximal stomach may be useful in palliating obstructive symptoms
- Venting gastrostomy and/or jejunostomy tube

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References on next page

PRINCIPLES OF GASTRIC CANCER SURGERY (2 of 2)

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PRINCIPLES OF SYSTEMIC THERAPY FOR GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (1 of 2)

- For metastatic gastric or gastroesophageal junction adenocarcinoma, some regimens listed below represent institutional preferences and may not be superior to the category 1 regimens.
- Please refer to the original reports for specific toxicity, doses, schedule, and dose modifications.
- Please refer to the Principles of Radiation Therapy for the radiation therapy administration details (GAST-D).
- Prior to recommending chemotherapy, the requirements for the adequacy of organ function and performance status should be met.
- The schedule, toxicity, and potential benefits from chemotherapy should be thoroughly discussed with the patient and caregivers. Patient education should also include the discussion of precautions and measures to reduce the severity and duration of complications.
- During chemotherapy, patients should be observed closely, treated for any complications, and appropriate blood work should be monitored.
- Upon completion of chemotherapy, patients should be evaluated for response and any long-term complications.

Preoperative Chemotherapy
(GE junction adenocarcinoma included):
- ECF (Epirubicin, cisplatin and 5-FU) (category 1)[1]
- ECF modifications (category 1)[2]

Preoperative Chemoradiation:
- Paclitaxel or docetaxel plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[3]

Postoperative Chemotherapy (to be used only with the Preoperative Chemotherapy---see above)
- ECF (Epirubicin, cisplatin and 5-FU) (category 1)[1]
- ECF modifications (category 1)[2]

Postoperative Chemoradiation
(GE junction adenocarcinoma included)
- Fluoropyrimidine (5-FU or capecitabine) (category 1)[4]

Metastatic or Locally Advanced Cancer
(where chemoradiation is not recommended):
- DCF (Docetaxel, cisplatin and 5-FU) (category 1)[5]
- ECF (category 1)[6]
- ECF modifications (category 1)[2]
- Irinotecan plus cisplatin (category 2B)[7,8]
- Oxaliplatin plus fluoropyrimidine (5-FU† or capecitabine)[9,10]
- DCF modifications (category 2B)[11]
- Irinotecan plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[12]
- Paclitaxel-based regimen (category 2B)

†Leucovorin or levoleucovorin is indicated with certain infusional 5-FU-based regimens (category 2B).

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References on next page

PRINCIPLES OF SYSTEMIC THERAPY FOR GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (2 of 2)

[1] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.
[2] Cunningham D, Starling, N., Rao, S., Iveson, T., et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
[3] Ajani JA, Winter K, Okawara GS, Donohue JH, 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(24):3953-3958.
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PRINCIPLES OF RADIATION THERAPY (1 of 3)

General Radiation Information

- Prior to simulation, pertinent radiographs, procedure notes and pathology reports should be reviewed by a multidisciplinary team including surgical, radiation, medical oncologists, gastroenterologists, radiologists and pathologists. This will allow an informed determination of treatment volume and field borders prior to simulation.

Simulation and Treatment Planning

- Use of CT simulation and 3D treatment planning is strongly encouraged.
- The patient should be instructed to avoid intake of a heavy meal for 3 hours before simulation and treatment. When clinically appropriate, use of 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 set-up.
- All patients should be simulated and treated in the supine position.
- Although AP/PA fields can be weighted anteriorly to keep the spinal cord dose at acceptable levels using only parallel-opposed techniques, a 4-field technique (AP/PA and opposed laterals), if feasible, can spare spinal cord with improved dose homogeneity. Patients with a stomach that is sufficiently anterior to allow treatment via laterals to the target volume and draining lymph nodes with 1.5-2 cm margin while sparing spinal cord may have more liberal use of lateral beams with multiple-field techniques. The uncertainties arising from variations in stomach filling and respiratory motion should also taken into consideration.
- With the wide availability of 3D treatment-planning systems, it may be possible to target more accurately the high-risk volume and to use unconventional field arrangements to produce superior dose distributions. To accomplish this without marginal misses, it will be necessary to both carefully define and encompass the various target volumes because the use of oblique or non-coplanar beams could exclude target volumes that would be included in AP/PA fields or multiple-field techniques.

Target Volume (General Guidelines)

- Preoperative[1]
  - Pre-treatment diagnostic studies (EUS, UGI, CT scans) should be used to identify the tumor and pertinent nodal groups.[2,3] The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.
- Postoperative[4]
  - Pre-treatment diagnostic studies (EUS, UGI, 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.

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PRINCIPLES OF RADIATION THERAPY (2 of 3)

Proximal one-third/Cardia/Gastroesophageal Junction Primaries

- Preoperative and Postoperative
  - With proximal gastric lesions or lesions at the GE junction, a 3- to 5-cm margin of distal esophagus, medial left hemidiaphragm and adjacent pancreatic body should be included. Nodal areas at risk include: adjacent paraesophageal, perigastric, suprapancreatic, and celiac lymph nodes.

Middle one-third/Body Primaries

- Preoperative and Postoperative
  - Body of pancreas should be included. Nodal areas at risk include: perigastric, suprapancreatic, celiac, splenic hilar, porta hepatic, and pancreaticoduodenal lymph nodes.

Distal one-third/Antrum/Pylorus Primaries

- Preoperative
  - Head of pancreas, 1st and 2nd part of duodenum should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.
- Postoperative
  - Head of pancreas, a 3- to 5-cm margin of duodenal stump should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.

Blocking

- Custom blocking is necessary to reduce unnecessary dose to normal structures including liver (60% of liver < 30 Gy), kidneys (at least 2/3 of one kidney < 20 Gy), spinal cord (< 45 Gy), heart (1/3 of heart < 50 Gy, effort should be made to keep the left ventricle doses to a minimum) and lungs.[a]

Dose

- 45-50.4 Gy (1.8 Gy/day)

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 breaks.
- During radiation treatment course, patients should be seen for 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, enteral and/or intravenous hyperalimentation should be considered. When indicated, feeding jejunostomies (J-tube) may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.
- B_{12}, iron, and calcium level should be closely monitored, especially for postoperative patients. Monthly B_{12} shots may be needed because of loss of intrinsic factor. Iron absorption is reduced without gastric acid. Oral supplementation, given with acid such as orange juice, can often maintain adequate levels. Calcium supplementation should also be encouraged.

[a]Lung Dose Volume Histogram (DVH) parameters as predictors of pulmonary complications in gastric/gastroesophageal junction cancer patients treated with concurrent chemoradiotherapy should be strongly considered, though consensus on optimal criteria has not yet emerged. Every effort should be made to keep the lung volume and doses to a minimum. Treating physicians should be aware that the DVH reduction algorithm is hardly the only risk factor for pulmonary complications. DVH parameters as predictors of pulmonary complications in gastric/gastroesophageal junction cancer patients are an area of active development among the NCCN institutions and others.

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References on next page

PRINCIPLES OF RADIATION THERAPY (3 of 3)

[1]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. JCO 2006;24:3953-3958.
[2]Willett CG, Gunderson LL. Stomach, in: Perez and Brady's principles and practice of radiation oncology, 5th ed. Lippincott Williams & Wilkins, 2007;1318-1335.
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[4]Macdonald JS, Smalley S, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725-730, 2001.

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Staging

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach*

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria or subserosa†
T2a	Tumor invades muscularis propria
T2b	Tumor invades subserosa
T3	Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures‡
T4	Tumor invades adjacent structures‡

Regional Lymph Nodes (N)

NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis§
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2a/b	N0	M0
Stage II	T1	N2	M0
	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1-3	M0
	T1-3	N3	M0
	Any T	Any N	M1

*Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

†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 T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T3.

‡The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum. Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

§A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Upper gastrointestinal (GI) tract cancers originating in the esophagus, gastroesophageal (GE) junctions, and stomach, constitute a major health problem around the world. An estimated 37,970 new cases of and 25,160 deaths from upper GI cancers will occur in the United States in 2008.[1] A dramatic shift in the location of upper GI tumors has occurred in the United States.[2] Changes in histology and location of upper GI tumors have also been observed in some parts of Europe.[3,4] In countries in the Western Hemisphere, the most common sites of gastric cancer are the proximal lesser curvature, in the cardia, and the GE junction.[2] It is possible that in the coming decades these changing trends will also occur in South America and Asia.

Epidemiology

Gastric cancer is rampant in many countries around the world. In Japan, gastric cancer remains the most common type of cancer among men. Its incidence, however, has been declining globally since World War II. By some estimates, it is the fourth most common cancer worldwide.[5] Gastric cancer is one of the least common cancers in North America. An estimated 21,500 new cases and 10,880 deaths from gastric cancer will occur in United States in 2008.[1] In developed countries, the incidence of gastric cancer localized to the cardia follows the distribution of esophageal cancer; however, unlike the latter, the rates of gastric cancer have stabilized since 1998.[6,7,8] Non cardia gastric adenocarcinoma also shows marked geographic variation; thus, countries such as Japan, Costa Rica, Peru, Brazil, China, Korea, Chile, Taiwan, and the former Soviet Union show a high incidence of the cancer.[9,10] In contrast to the increasing incidence of proximal tumors in the West, non-proximal tumors continue to predominate in Japan and other parts of the world.[11] The cause of this shift remains elusive and may be multifactorial.

Gastric cancer is often diagnosed at an advanced stage, because screening is not performed in most of the world, except in Japan (and in a limited fashion in Korea) where early detection is often done. Thus, it continues to pose a major challenge for healthcare professionals. Risk factors for gastric cancer are Helicobacter pylori (H. pylori) infection, smoking, high salt intake, and other dietary factors.

A few gastric cancers (1% to 3%) are associated with inherited gastric cancer predisposition syndromes. E-cadherin mutations occur in approximately 25% of families with an autosomal dominant predisposition to diffuse type gastric cancers. This subset of gastric cancer has been termed hereditary diffuse gastric cancer.[12] It may be useful to provide genetic counseling and to consider prophylactic gastrectomy in young, asymptomatic carriers of germ-line truncating

CDH1 mutations who belong to families with highly penetrant hereditary diffuse gastric cancer.[13]

Staging

Two major classification systems are currently used for gastric cancer. The most elaborate of these, the Japanese classification, is based on refined anatomic involvement, particularly the lymph node stations.[14] The other staging system, developed jointly by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC), is based on a gastric cancer database and demonstrates that the prognosis of node-positive patients depends on the number of lymph nodes involved.[15,16] The modern staging of gastric cancer is based on this tumor/node/metastasis (TNM) classification, rather than on the size of the cancer. The AJCC/UICC classification is the system used in countries in the Western Hemisphere (Table 1).

Patient outcome depends on the initial stage of the cancer at diagnosis. At diagnosis, approximately 50% of patients have gastric cancer that extends beyond the locoregional confines. Nearly 70% to 80% of resected gastric cancer specimens have metastases in the regional lymph nodes. Thus, it is common to encounter patients with advanced gastric cancer at presentation. Poor performance status (2 or more), liver metastases, peritoneal metastases, and alkaline phosphatase level of 100 U/L or more are the poor prognostic factors in patients with locally advanced and metastatic esophagogastric cancer.[17]

Preoperative staging

Preoperative staging in gastric cancer is essential for the accurate diagnosis of the stage of locoregional disease and to establish the presence of metastatic disease. Although surgical pathology gives the most accurate information on preoperative staging, clinical staging has been greatly improved by advancements in imaging techniques such as endoscopic ultrasound (EUS), computed tomography (CT), positron emission tomography (PET), combined PET-CT scans, magnetic resonance imaging (MRI) and laparoscopic staging.[18,19,20]

CT scan is routinely used for preoperative staging in patients with gastric cancer and it has overall accuracy of 43% to 82% for T staging of gastric cancer. Several new modalities such as multidetector computed tomography (MDCT) and helical CT have shown better results in the preoperative staging.[21,22] CT scans are not suitable to assess the tumor depth and metastatic lymph nodes.

PET had a significantly higher specificity (92%) compared to 62% for CT and lower sensitivity (56% vs.78% for CT) in the detection of local lymph node involvement. Positron emission tomography (PET) scan is not recommended routinely for preoperative staging. However, it can be used in conjunction with CT scan to provide additional information. Combined PET-CT imaging has many advantages over PET scan or CT scan alone and it significantly improves the diagnostic accuracy and preoperative staging. [23,24,25] The accuracy of preoperative staging was significantly higher for combined PET-CT (68%) compared to PET (47%) or CT (53%) alone.[24]

EUS is useful in assessing the depth of tumor invasion and may aid in appropriate patient selection.[26] The accuracy of EUS ranges from 64.8% to 92% for T staging and 50-95% for N staging. However, evaluation of distant lymph node involvement by EUS is unsatisfactory because of the limited depth and visualization of the transducer.[27]

Laparoscopic staging is particularly useful to evaluate metastases on the peritoneum and CT-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 and was more prevalent in the cases of poorly differentiated tumors (36%), tumors of the GE junction (42%)

and whole stomach (66%). This study concluded that laparoscopic staging may be avoided if the primary tumor is not at the GE junction or whole stomach and there is no lymphadenopathy. Limitations of laparoscopic staging include two-dimensional evaluation and limited use in the identification of hepatic metastases and perigastric lymph nodes.

The use of this staging procedure differs among the NCCN institutions. Several centers prefer laparoscopic staging of the peritoneal cavity for medically fit patients with potentially resectable or unresectable disease. For medically fit patients with apparent locoregional cancer, laparoscopy is performed to evaluate peritoneal spread when considering chemoradiation therapy or surgery. In medically unfit patients, laparoscopy may still be valuable to determine if chemoradiation is a viable option. If a palliative resection is planned, laparoscopy is not indicated. If a laparoscopic examination is performed, there are two possibilities for both medically fit and unfit patients with apparent locoregional cancer. Patients will have either apparent locoregional cancer (M0) or metastatic cancer (M1). The guidelines have included laparoscopic staging with a category 2B recommendation (GAST-1).

Peritoneal cytology is another technique used for preoperative staging, which involves the cytogenetic analysis of peritoneal fluid to identify occult carcinomatosis.[29] Reports in literature have confirmed the value of positive peritoneal cytology as an independent predictor for identifying patients who are at high risk of recurrence following curative resection.[30,31] Peritoneal cytological analysis is a relatively simple technique that is feasible in the intraoperative technique. However, it is also associated with false positive results. More sensitive and specific techniques are being developed to improve the accuracy of this technique.

Surgery

Surgery is the primary treatment for gastric cancer. Complete resection with adequate margins (5 cm) is a wide agreed upon surgical principle for the management of gastric cancer, whereas the type of resection (subtotal versus total gastrectomy) and the role of extensive lymphadenectomy have been the subjects of international debate.

Principles of Surgery

The goal of surgery is to accomplish a complete resection with negative margins (R0 resection). However, approximately 50% of patients with locoregional gastric cancer cannot undergo an R0 resection.[32,33] R1 indicates microscopic residual cancer (positive margins); and R2 indicates gross (macroscopic) residual cancer (positive margins) but not distant disease.[34]

Clinical staging using CT scan and EUS should be performed before surgery to assess the extent of the disease (GAST-B). Proximal and distal margins of 4 cm or greater from the gross tumor are preferred.[35] Routine or prophylactic splenectomy should be avoided if possible. In a randomized clinical study, mortality and morbidity rates were slightly higher in patients who underwent total gastrectomy combined with splenectomy. However, survival was not significantly different when compared with the survival rates for patients who did not have splenectomy.[36] Placement of jejunostomy feeding tube may be considered for selected patients who will be receiving postoperative chemoradiation.

Subtotal gastrectomy is preferred for distal gastric cancers and has been shown to have an equivalent surgical outcome with significantly fewer complications when compared with total gastrectomy.[37] The surgical procedure of choice for proximal gastric cancers is more controversial, because both proximal gastrectomy and total gastrectomy are associated with postoperative nutritional impairment.

The guidelines recommend either one of these procedures as clinically indicated for proximal (cardia) tumors. It is recommended that at least 15 lymph nodes be removed and examined.

Carcinomas are unresectable if there is evidence of peritoneal involvement, distant metastases, or locoregional advancement with the involvement of 3 or 4 lymph nodes and invasion or encasement of major blood vessels. Limited gastric resection, even with positive margins is acceptable for unresectable tumors only for symptomatic palliation of bleeding. Gastric bypass with gastrojejunostomy to the proximal stomach may be useful for the palliation of obstructive symptoms. Placement of venting gastronomy and/or jejunostomy tube is recommended.

Lymph Node Dissection

The extent of lymph node dissection remains controversial. The Japanese Research Society for the Study of Gastric Cancer has established guidelines for pathologic examination and evaluation of lymph node stations that surround the stomach. [38] The perigastric lymph node stations along the lesser curvature (stations 1, 3, and 5) and greater curvature (stations 2, 4, and 6) of the stomach are grouped together as N1. The nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), and splenic artery (stations 10 and 11) are grouped together as N2. More distant nodes, including para-aortic (N3 and N4), are regarded as distant metastases. A recent retrospective analysis has shown that more extensive lymph node dissection and analysis influences survival in patients with advanced gastric cancer. This analysis included 1,377 patients diagnosed with advanced gastric cancer in the Surveillance Epidemiology and End Results (SEER) database. Patients who had more than15 N2 nodes and more than 20 N3 nodes examined had the best long-term survival outcomes.[39]

D0 dissection reflects failure to remove N1 lymph nodes. D1 dissection involves the removal of the involved proximal or distal part of the stomach or the entire stomach (distal or total resection), including the greater and lesser omental lymph nodes. The omental bursa along with the front leaf of the transverse mesocolon is removed and the corresponding arteries are cleared completely in a D2 dissection. A splenectomy (to remove stations 10 and 11) is required for a D2 dissection for proximal gastric tumors. The technical aspects of performing a D2 dissection require a significant degree of training and expertise. Japanese investigators comparing D2 versus extended D2 (including para-aortic lymph nodes) have recently reported a postoperative morality rate of 0.8% in each arm.[40] Survival data from this study are currently not available. Japanese investigators have often emphasized the value of extensive lymphadenectomy (D2 and above). However, Western investigators have not found a survival advantage when extensive lymphadenectomy is compared with a D1 resection.[41-44]

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 lymphadenectomy.[42] Both the morbidity (25% vs. 43%, $P < .001$) and mortality (4% vs. 10%, $P = .004$) were higher for patients who underwent D2 dissection, with no difference in overall survival (30% vs. 35%, $P = .53$) between the two groups. In a subset analysis, patients with N2 cancer undergoing a D2 lymphadenectomy showed a trend towards improved survival. Unfortunately, N2 cancer can only be detected after microscopic examination of the surgical specimen.

The British Cooperative trial conducted by the Medical Research Council also failed to demonstrate a survival benefit for D2 over D1 lymphadenectomy.[43] The 5-year survival rates were 35% for D1 dissection and 33% for D2 dissection. No difference was seen in overall survival between the two groups. In addition, the D2 dissection was

associated with increased morbidity and mortality. Both these trials found that splenectomy and pancreatectomy performed along with the D2 dissection significantly increased the mortality and morbidity.

Despite these results, interest in extended lymph node dissections (D2 and greater) has not waned.[45] Investigators have argued that if the complication rate after a D2 dissection could be decreased then there may be a benefit in selected patients. A surgical option that may decrease morbidity and mortality is a modified D2 lymphadenectomy without pancreatectomy and splenectomy.[46-49]

The phase II study conducted by the Italian Gastric Cancer Study Group (IGCSG) reported a survival benefit of pancreas-preserving D2 lymphadenectomy when performed in experienced cancer centers. Pancreatectomy was performed only in patients with proximal gastric tumors with direct invasion. The overall 5-year morbidity rate was 20.9% and a postoperative mortality rate was 3.1% for D2 dissection without pancreatectomy.[50] These rates are comparable to the rates for D1 dissections in the Dutch and United Kingdom trial. The inclusion of pancreatectomy and splenectomy in D2 dissection resulted in increased morbidity and mortality.

Other reports from Western countries have also shown better outcomes for D2 lymphadenectomy when performed according to the recommendations of Japanese Research Society of Gastric cancer. In an Austrian study, overall 5-year and 10-year survival rates were 45.7% and 34.3% respectively.[51] For patients who underwent curative surgery, 5-year and 10-year survival rates were 57.7% and 44.3% respectively, which are comparable to those reported in Japanese trials. Postoperative mortality rates were 4.9% for R0 resection, 9% for R1-R2 resection and 13.4% for palliative resection. We recognize that cross-trial comparisons result in weak evidence and conclusions.

Sierra and colleagues from Spain reported longer 5-year survival rates in the D2 group (50.6%) than the D1 group (41.4%).[52] No significant differences were seen in morbidity (48.2% for D1 and 53.5% for D2).Operative mortality was 2.3% for D1 and 0% for D2 dissection. Pancreatectomy, hepatic wedge resection or partial colectomy was performed only for macroscopic invasion.

In a recent analysis involving patients from the Intergroup 0116 adjuvant chemoradiation trial, Enzinger and colleagues assessed the impact of hospital volume on the outcome of patients who underwent lymphadenectomy.[53] Patients were stratified into two groups: those who underwent D0 dissection (54%) and those who underwent D1 or D2 resection (46%). For patients who underwent D0 dissection, high-volume centers did not have any effect on overall or disease-free survival. However, there was a trend toward improved overall survival among patients who underwent D1 or D2 dissection at moderate to high volume cancer centers.

In the West, D2 dissection is considered a recommended but not required operation. We recommend that gastric cancer surgery should be performed by experienced surgeons in high volume cancer centers.

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) and minimally invasive surgery (laparoscopic wedge resection) have been used for patients with early gastric cancer (Tis or T1a tumors limited to mucosa). Node-negative T1 tumors require limited resection since the 5-year survival rate is more than 90%.[54] Proper patient selection is essential when employing endoscopic or limited gastric resections (wedge). The probability of lymph node metastasis in early gastric cancer is influenced by tumor factors and is increased with increasing tumor size, submucosal invasion, poorly differentiated tumors, and lymphatic and vascular invasion.[55]

EMR represents a major advance in minimally invasive surgery for gastric neoplasms.[56,57] Most of the experience with EMR for early gastric cancer has been gained by countries with a high incidence of gastric cancer and an active screening program.[58] The applicability of these techniques in the United States is limited because of the low incidence of early gastric cancer. Indications for EMR include well-differentiated or moderately differentiated histology, tumors less than 30 mm in size, absence of ulceration and no evidence of invasive findings.[59] No randomized studies have compared EMR with other surgical techniques for GI cancers. Nevertheless, EMR continues to evolve as a promising technology in the diagnosis and treatment of early esophageal and gastric cancers. Since long-term follow-up and survival data are lacking, the routine use of endoscopic techniques is not recommended outside a clinical trial and should be limited to medical centers with extensive experience.

Laparoscopic Resection

Laparoscopic resection is an emerging surgical approach which offers important advantages (less blood loss, reduced postoperative pain, accelerated recovery, early return to normal bowel function and reduced hospital stay) when compared with open surgical procedures for patients with gastric cancer.[60] A prospective randomized study conducted by Huscher and colleagues compared early and 5-year clinical outcomes of laparoscopic and open subtotal gastrectomy in 59 patients with distal gastric cancer.[61] Operative mortality rates (3.3% vs. 6.7% respectively), 5-year overall survival rates (58.9% vs. 55.7% respectively) and disease-free survival rates (57.3% vs. 54.8% respectively) were better (though not significant) for the laparoscopic group. However, the role of this approach in the treatment of gastric cancer requires further investigation in larger randomized clinical trials.

Radiation Therapy

Radiation therapy (RT) has been assessed in randomized trials in both preoperative and postoperative setting in patients with resectable gastric cancer. Smalley and colleagues have reviewed clinical and anatomic issues related RT and offer detailed recommendation for the application of RT for the management of patients with resected gastric cancer.[62]

In a randomized trial conducted by Zhang and colleagues, there was a significant improvement in survival with preoperative radiation (30% vs. 20%, $P = .0094$).[63] Resection rates were higher in the preoperative radiation arm (89.5%) compared to surgery alone (79%), suggesting that preoperative radiation improves local control and survival. These data suggest that preoperative radiation improves local control and survival. However, randomized trials are needed to confirm these results in patients from the Western Hemisphere.

In the trial conducted by the British Cancer Stomach Group, 432 patients were randomized to undergo surgery alone or surgery followed by RT or chemotherapy.[64] At 5-year follow-up, no survival benefit was seen for patients receiving postoperative RT or chemotherapy compared with those who underwent surgery alone. This trial also showed a significant reduction in locoregional relapse with the addition of RT to surgery (27% with surgery vs. 10% for adjuvant RT and 19% for adjuvant chemotherapy).

External-beam RT (45-50.4 Gy) as a single modality has minimal value in palliating locally unresectable gastric cancer and does not improve survival.[65] However, when used concurrently with 5-fluorouracil (5-FU), external-beam RT improves survival. Moertel and colleagues assessed 5-FU plus RT compared with RT alone in the treatment of locally unresectable gastric cancer.[66] Patients receiving combined modality

treatment had a significantly better median survival (13 vs. 6 months) and 5-year overall survival (12% vs. none).

In another study by the Gastrointestinal Tumor Study Group (GITSG), 90 patients with locally advanced gastric cancer were randomized to receive either combination chemotherapy with 5-FU and methyl-CCNU (lomustine) or split-course RT with a concurrent intravenous bolus of 5-FU followed by maintenance 5-FU and methyl-CCNU.[67] In the first 12 months mortality was higher in the combined modality group. At 3 years the survival curve reached a plateau in the combined modality arm, but tumor-related deaths continued to occur in the chemotherapy-alone arm, suggesting that a small fraction of patients can be cured with combined modality treatment. In most of the randomized trials, combined modality treatment showed advantage over RT alone in relatively few patients with unresectable cancer, as reviewed by Hazard and colleagues.[68]

Intensity modulated radiation therapy (IMRT) has a great potential to reduce radiation-related toxicity by delivering large doses of radiation to target tissues.[69] The use of this technique in gastric cancer remains investigational.

Principles of Radiation Therapy

RT (preoperative, postoperative or palliative) can be an integral part of treatment for gastric cancer. All patients should be simulated and treated in the supine position. The panel encourages the use of CT simulation and 3D treatment planning. Intravenous and /or oral contrast may be used when appropriate for CT simulation to aid target localization. Use of immobilization device is strongly recommended for reproducibility.

The panel recommends involvement of a multidisciplinary team, which should include medical, radiation and surgical oncologist, radiologists, gastroenterologists and pathologists to determine optimal diagnostic, staging and treatment modalities. Pretreatment diagnostic studies such as EUS, upper GI endoscopy and CT scans should be used to identify tumor and pertinent nodal groups. The relative risk of nodal metastases at a specific location is dependent on the location of the primary tumor and the extent of invasion of the gastric wall. It may be possible to accurately target high-risk areas and to produce superior dose distributions with the use of 3D treatment planning systems and unconventional field arrangements. To accomplish this, itis necessary to carefully define and encompass various target volumes. General guidelines for defining target volumes for preoperative and postoperative RT for different locations of the tumor are described in detail in GAST-D.

The panel recommends a dose range of 45-50.4 Gy delivered in fractions of 1.8 Gy per day. Every effort should be made to reduce unnecessary radiation doses to vital organs such as liver, kidneys, spinal cord, heart (especially the left ventricle) and lungs. Optimal dose ranges for these vital organs are included in GAST-D. Lung dose volume histogram (DVH) parameters should be considered as predictors of pulmonary complications in patients with gastric and GE junction cancers treated with concurrent chemoradiation. Optimal criteria for DVH parameters are being actively developed in NCCN institutions.

Close patient monitoring and aggressive supportive care are essential during radiation treatment. Management of acute toxicities is necessary to avoid treatment interruptions or dose reductions. Antiemetics should be given on a prophylactic basis when appropriate. Antacid and antidiarrheal medications may be prescribed when needed. If the caloric intake is inadequate, oral, enteral and /or intravenous hyperalimentation should be considered. Feeding jejunostomies may be placed if clinically indicated. It is essential to monitor levels of B12,

iron and calcium in postoperative patients. Oral supplementation is recommended to maintain adequate levels.

Combined Modality Treatment: Concomitant Chemotherapy and Radiation Therapy

Preoperative Chemoradiation Therapy

In a pilot study, Lowy and colleagues assessed the feasibility of preoperative chemoradiation (45 Gy of external beam RT with concurrent continuous infusion of 5-FU) followed by surgery and IORT (10 Gy) in the treatment of patients with potentially resectable gastric cancer.[70] Significant pathologic responses were seen in 63% of patients and complete pathologic response was seen in 11% of patients who received preoperative chemoradiation. Eighty three percent of patients who received chemoradiation therapy underwent D2 lymphadenectomy.

Recent studies have also shown that preoperative induction chemotherapy followed by chemoradiotherapy yields a substantial pathologic response that results in durable survival time.[71,72,73] In the RTOG study, pathologic complete response was achieved in 26% of patients. D2 lymphadenectomy and R0 resection were achieved in 50% and 77% of patients respectively.[73] However, the value of preoperative chemoradiation therapy needs to be determined in randomized trials.

Postoperative Chemoradiation Therapy

Nonrandomized trials from Baeza and colleagues have reported encouraging results for patients with R0 resections who receive adjunctive treatment.[74] Limited reports from randomized trials of postoperative RT with or without chemotherapy after a complete resection with negative margins did not reveal a clear survival advantage.[75,76]

The landmark trial is the Intergroup trial SWOG 9008/INT-0116.[77,78] Patients with T3, T4 and/or node positive adenocarcinoma of the stomach or GE junction were eligible for participation. After a resection with negative margins, 603 patients were randomized to either observation alone or postoperative combined modality treatment consisting of five monthly cycles of bolus chemotherapy (5-fluorouracil and leucovorin) with RT (45 Gy) concurrent with cycles 2 and 3. There was a significant decrease in local failure as the first site of failure (19% vs. 29%) as well as an increase in median survival (36 vs. 27 months), 3-year relapse-free survival (48% vs. 31%), and overall survival (50% vs. 41%, P = .005) with combined modality treatment. Although gastric resection with extended lymph node dissection (D2) was recommended for all patients, only 10% of patients had the recommended D2 lymphadenectomy. D1 dissection was performed in 36% of the patients and 54% underwent D0 dissection. It should be noted that surgery was not part of this protocol and patients were eligible for the study only after recovery from surgery. Nevertheless, the result of this study has established postoperative chemoradiation therapy as a standard of care in patients with resected gastric cancer.

Chemotherapy

Perioperative Chemotherapy

The British Medical Research Council performed the first well-powered phase III trial (MAGIC trial) for perioperative chemotherapy.[79] In this trial, 503 patients were randomized to receive either perioperative chemotherapy [preoperative and postoperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF)] and surgery or surgery alone. In each group, 74% of patients had stomach cancer, 14% had lower esophageal cancer and 11% had cancer of esophagogastric junction. The perioperative chemotherapy group had a greater proportion of pathologic T1 and T2 tumors (51.7%) than the surgery group (36.8%). Five-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

Perioperative chemotherapy with the ECF regimen significantly improved progression free survival and overall survival in patients with operable gastric and lower esophageal adenocarcinomas. The result of this study has established perioperative chemotherapy as an added option to the standard of care of patients with resectable gastric cancer.

Postoperative chemotherapy

S-1 is a novel oral fluoropyrimidine which is a combination of tegafur (prodrug of 5-fluorouracil), 5-chloro-2,4-dihydropyridine (CDHP) and oxonic acid.[80]

A large randomized phase III study (ACTS GC) in Japan evaluated the efficacy of adjuvant chemotherapy with S-1 in patients with stage II (excluding T1) or stage III gastric cancer who underwent gastric surgery (R0 resection) with extensive lymph-node dissection (D2).[81] This study randomized 1,059 patients to undergo surgery followed by adjuvant treatment with S-1 or undergo surgery alone. Overall survival at 3 years was 80.1% for S-1 group and 70.1% for surgery alone. Hazard ratio of death for S-1 was 0.68. Additional follow-up and impact of adjuvant chemotherapy with S-1 needs to be assessed in patients with stage III gastric cancer.

This is the first time adjuvant chemotherapy has been shown to be beneficial after D2 resection in the Japanese population. In an earlier randomized trial (579 patients) conducted by Japan Clinical Oncology Group (JCOG 8801), no significant survival benefit with adjuvant chemotherapy was seen after D2 resection.[82] Although adjuvant treatment with S-1 following D2 dissection was effective in patients with locally advanced gastric cancer, the investigators of the ACTS-GC trial acknowledge that the results of their trial may not be valid if D2 dissection is not considered as the standard surgical procedure. The impact of these results in the treatment of western patients is limited.

Chemotherapy for Advanced or Metastatic Disease

Advanced gastric cancer is incurable, but chemotherapy can have a palliative effect in symptomatic patients. Single agents which are active in patients with advanced gastric cancer include 5-FU, mitomycin, etoposide, and cisplatin, with pooled response rate of 10 % to 20%.[83, 84] Several newer agents and their combinations including paclitaxel, docetaxel, irinotecan, epirubicin, oxaliplatin, oral etoposide, and UFT (a combination of uracil and tegafur) have shown activity against gastric cancer.[85-103] A number of oral agents also hold promise in the treatment of gastric cancer.[104,105]

Combination chemotherapy resulted in better quality of life and overall survival when compared with best supportive care in patients with advanced gastric cancer.[106,107,108] However, all these studies only had a small number of patients. In the early 1980s, the FAM (5-FU, doxorubicin, and mitomycin) regimen was the gold standard for patients with advanced gastric cancer.[109] The pivotal study performed by the North Central Cancer Treatment Group (NCCTG), compared the FAM regimen with 5-FU as a single agent and 5-FU plus doxorubicin. [110] No significant survival difference was seen among patients treated with these regimens. However, higher response rates were seen in patients who received combination chemotherapy compared with 5-FU alone. Thus, combination chemotherapy is preferable to single-agent chemotherapy for palliation.

In the past several years, several randomized studies have compared FAM vs. FAMTX (5-FU, adriamycin, and methotrexate),[111] FAMTX vs. ECF (epirubicin, cisplatin, 5-fluorouracil),[112] FAMTX vs. ELF (etoposide, leucovorin, and 5-FU) vs. 5-FU plus cisplatin,[113] and ECF vs. MCF (mitomycin, cisplatin, 5-flourouracil).[114] ECF regimen demonstrated improved median survival and quality of life benefits compared to FAMTX and MCF regimens. However, no standard treatment has emerged from these trials.

In a randomized multinational phase III study (V325), 445 untreated patients with advanced gastric cancer were randomized to receive either the combination of docetaxel, cisplatin and 5-fluorouracil (DCF) every 3 weeks or the combination of cisplatin and fluorouracil (CF).[115] Time to progression was significantly longer for DCF compared with CF (5.6 vs. 3.7 months; 95% CI). Two-year survival rate was 18% with DCF and 9% with CF. Median overall survival was significantly longer with the DCF regimen (9.2 vs. 8.6 months, p = 0.02). In 2006, based on the results of this study, FDA (Food and Drug Administration) approved docetaxel in combination with cisplatin and 5-fluorouracil (DCF) for the treatment of advanced gastric cancer, including cancer of the GE junction, in patients who have not received prior chemotherapy for advanced disease.

Recently published results from the phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) was associated with significantly less toxicity than fluorouracil, leucovorin and cisplatin (FLP) in patients with metastatic gastroesophageal cancer.[116] There was a trend toward improved median progression free survival with FLO (5.8 v 3.9 months). However, there were no significant differences in median overall survival (10.7 vs. 8.8 months, respectively) between the FLO and FLP. In patients older than 65 years, FLO resulted in significantly superior response rates (41.3% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), and progression free survival (6.0 vs. 3.1 months), and an improved overall survival (13.9 vs. 7.2 months) compared with FLP, respectively.

Capecitabine is an orally administered fluoropyrimidine which is converted to 5-flurouracil preferentially in the tumor tissue. Several studies have evaluated capecitabine in combination with other agents in patients with advanced esophagogastric cancers.[117] Two phase III trials (REAL-2 and ML 17032) have assessed the efficacy and safety of capecitabine in gastric cancer. [118,119]

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.[118] Patients with histologically confirmed adenocarcinoma, squamous or undifferentiated cancer of the esophagus, GE junction or stomach were randomized to receive one of the four epirubicin-based regimens [ECF, epirubicin, oxaliplatin, 5-FU (EOF), epirubicin, cisplatin and capecitabine (ECX) and epirubicin, oxaliplatin and capecitabine (EOX)]. Median follow-up was 17.1 months. No significant differences in response rates were seen among the ECF (41%) and EOF, ECX, and EOX regimens (42%, 46% and 48% respectively). Overall survival at one year was 37.7% for ECF compared with 40.4%, 40.8%, and 46.8% for EOF, ECX and EOX regimens, respectively. Overall survival and response rates were better for EOX than ECF. Capecitabine clearly provides convenience to patients who can swallow but provides no recognizable safety advantage when replacing 5-FU.

ML 17032, a phase III randomized trial, evaluated the combination of capecitabine and cisplatin (XP) versus the combination of 5-fluorouracil and cisplatin (FP) as first-line treatment in patients with previously untreated advanced gastric cancer.[119] Overall response rate (41% vs. 29%) and overall survival (10.5 months vs. 9.3 months) were superior for patients who received XP regimen. No difference in median progression free survival was seen for both regimens (5.6 months for XP and 5.0 months for FP).

The results of these studies concluded that capecitabine is non-inferior to 5-FU in the treatment of patients with advanced gastroesophageal cancers. In addition, REAL-2 trial also concluded that oxaliplatin is

non-inferior to cisplatin in the treatment of patients with advanced gastroesophageal cancers.

Phase I and II studies have shown that another novel oral fluoropyrimidine S-1 is effective for advanced gastric cancer, as a single agent and in combination with cisplatin.[120-123] 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 overall survival (13 vs. 11 months respectively) and progression free survival (6.0 vs. 4 months respectively) were significantly longer for the combination of S-1 and cisplatin compared with S-1 alone.[124] The safety and efficacy of S-1 and cisplatin in patients with untreated advanced gastric and GE junction adenocarcinoma was also confirmed in a multicenter phase II trial conducted in the United States.[125,126] The ongoing phase III trials [First-Line Advanced Gastric Cancer Study (FLAGS)] are comparing the combination of S-1 and cisplatin with 5-fluorouracil and cisplatin.

In a multicenter phase II study, bevacizumab (anti VEGF antibody) in combination with irinotecan and cisplatin was active for the treatment of advanced gastric or GE junction adenocarcinoma (time to progression was 8.3 months and median survival was 12.3 months). However, safety concerns such as the rate of bowel perforation, hypertension, and thromboembolic phenomenon remain.[127] An ongoing phase III trial will answer the value of adding of bevacizumab to chemotherapy.

In a recent phase II study, the combination of sorafenib with docetaxel and cisplatin showed encouraging results in the treatment of metastatic or advanced unresectable gastric and GE junction adenocarcinoma.[128] Median overall and progression free survival were 14.9 and 5.8 months respectively. Phase III trials with this combination are needed confirm these preliminary results.

Many other combination chemotherapy regimens are currently in phase III trials, and we anticipate that, although a global standard is not likely, broad consensus on front-line therapy for patients with advanced gastric cancer might emerge.

Treatment Guidelines

The management of gastric cancer requires the expertise of several disciplines (radiation oncology, surgical oncology, medical oncology, nutritional support, and endoscopic expertise). Hence, the panel believes that multidisciplinary evaluation is preferred for the treatment of patients with esophagogastric cancer. The guidelines have now included a section on Principles of Multidisciplinary Team Approach for Gastroesophageal Cancers (GAST-A).

Workup

In patients with gastric cancer, symptoms can include anemia, early satiety, weight loss, nausea/vomiting, and/or bleeding. Newly diagnosed patients should undergo a complete history & physical examination (H&P), chest imaging, and endoscopy of the entire upper GI tract. A complete blood count (CBC), chemistry profile and abdominal CT with contrast should be performed. A pelvic CT scan or ultrasound is also recommended for women. EUS is recommended in patients with potentially resectable cancer. The panel also recommends H. pylori testing and appropriate treatment when clinically indicated.[129]

PET-CT or PET scan is optional. PET scans are useful for predicting response to preoperative chemotherapy as well as in the evaluation of recurrent gastric cancer.[130,131] PET scan may also be useful if there is no evidence of metastatic disease, although there may be false-positive results with PET.[132] Additional studies are needed to assess the efficacy of combined PET-CT scan in gastric cancer.

Initial workup enables patients to be classified into three groups with the following characteristics (GAST-1):

- Localized (Tis or T1a) cancer
- Locoregional cancer (stages I-III or M0)
- Metastatic cancer (stage IV or M1)

Patients with apparent locoregional cancer are further classified into the following groups:

- Medically fit patients (who are able to tolerate major abdominal surgery) with potentially resectable disease
- Medically fit patients with unresectable disease
- Medically unfit patients

Primary Treatment

Surgery or EMR is the primary treatment option for medically fit patients with Tis or T1a tumors. EMR is the treatment of choice in medically unfit patients with these early cancers (Tis and T1a).

Surgery is the primary treatment option for medically fit patients with potentially resectable locoregional cancer (T1b). For more advanced tumors, based on the results of the MAGIC trial,[79] the guidelines have included perioperative chemotherapy with ECF regimen or its modifications with a category 1 recommendation for patients (with T2 or higher tumors), before and after surgery (GAST-2 and GAST-3). This strategy is feasible in the institutions where a multi-disciplinary approach to localized gastric cancer is already in place. The panel has also included preoperative chemoradiation (paclitaxel or docetaxel in combination with 5-fluorouracil or capecitabine) [73] as an alternate treatment option with a category 2B recommendation (GAST-2).

RT (45-50.4 Gy) with concurrent 5-FU-based radiosensitization (category 1) is recommended for medically fit patients with unresectable locoregional cancer as well as medically unfit patients with locoregional cancer (GAST-2).[66,67] Palliative chemotherapy with any one of the regimens listed in GAST-C for metastatic or locally advanced cancer is an alternate option for this group of patients.

All patients diagnosed with metastatic cancer after laparoscopic staging should be treated with any one of the regimens listed in GAST-C for metastatic or locally advanced cancer.

Medically unfit patients as well as medically fit patients with unresectable disease should undergo restaging (including CBC and chemistry profile, chest imaging, abdominal CT with contrast, pelvic imaging for women and PET-CT or PET scan) after completion of primary treatment (GAST-4). If there is a complete response, patients should be observed or they can undergo surgery if it is deemed appropriate. If there is evidence of residual, unresectable, locoregional and/or distant metastases, patients may be offered palliative treatment.

Postoperative Treatment

Postoperative treatment is based on the surgical margins and nodal status (GAST-3). Based on the results of the Intergroup trial (INT-0116), selected patients with no residual disease at surgical margins (R0 resection) and no evidence of metastases after gastrectomy may receive postoperative chemoradiation.[77,78] However, after R0 resection, patients with Tis or T1, N0 or T2, N0 tumors may be observed. Fluoropyrimidine-based postoperative chemoradiation is recommended after R0 resection for selected patients with T2, N0 tumors along with high-risk features such as poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or age younger than 50 years. INT-0116 trial also included patients (20%) with GE junction adenocarcinoma. Therefore, fluoropyrimidine (5-fluorouracil or capecitabine)-based postoperative chemoradiation may also be

recommended (category 1) for patients with GE junction adenocarcinoma.

The panel recommends that all patients with T3, T4, or any node positive tumors with no residual disease at surgical margins (R0 resection) and all patients with microscopic residual disease at surgical margins (R1 resection) should be treated with RT (45-50.4 Gy) plus concurrent 5-FU-based radiosensitization (preferred) plus 5-FU with or without leucovorin (GAST-3). In the absence of metastases (M1), patients with macroscopic residual disease at surgical margins (R2 resections) may be treated with RT (45-50.4Gy) and concurrent 5-FU-based radiosensitization or palliative chemotherapy. Best supportive care may be offered for patients with poor performance status (GAST-3).

Follow-up and Surveillance

All patients should be followed up systematically. This follow-up should include a complete history and physical examination every 4 to 6 months for 3 years and annually thereafter (GAST-5). CBC, chemistry profile, imaging studies or endoscopy should be done if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B12 and iron deficiency.

Palliative Treatment

Palliative treatment options include best supportive care, chemotherapy, or clinical trial. In a randomized comparison between chemotherapy and best supportive care vs. best supportive care alone for advanced gastric cancer, overall survival (8 months vs. 5 months, though not statistically significant) and time to progression (5 months vs. 2 months) were longer in patients receiving chemotherapy.[133] More patients in the chemotherapy group (45%) had an improved or prolonged high quality of life for minimum of 4 months compared to those who received only best supportive care (20%). Recent meta-analysis of randomized trials that compared chemotherapy and supportive care in patients with advanced gastric cancer also showed that chemotherapy increased one year survival rate and improved in quality of life.[134] Whenever possible, patients should be enrolled in clinical trials.

Best supportive care is always indicated for patients with advanced gastric cancer. The decision to offer best supportive care alone or with chemotherapy is dependent on the patient's performance status. Several scales are available to measure performance status in patients with cancer. Karnofsky scale of Performance Status (KPS) and Eastern Cooperative Group Performance Status (ECOG PS) are the two commonly used scales.[135,136,137] KPS is an ordered scale with 11 levels (0 to 100) and the general functioning and survival of a patient is assessed based on their health status (activity, work and self-care). Low Karnofsky scores are associated with poor survival and serious illnesses (http://www.hospicepatients.org/karnofsky.html). ECOG PS is a 5-point scale (0-4) based on the level of symptom interference with normal activity. Patients with higher levels are considered to have poor performance status (http://www.ecog.org/general/perf_stat.html).

Patients with a Karnofsky performance score of 60 or less or an ECOG performance score of 3 or more should probably be offered best supportive care only. Patients with better performance status (Karnofsky performance score of 60 or more, or an ECOG performance score of 2 or less) may be offered best supportive care with or without chemotherapy, or a clinical trial.

For metastatic gastric cancer, there have been only a few phase III trials, which have assessed ECF, DCF, and FOLFIRI regimens. However, participating institutions have developed chemotherapy regimens in the context of phase II studies. The regimens that have not been studied in the phase III setting may not be superior to DCF or ECF. There is no established second-line treatment for advanced

gastric cancer. The following regimens are listed in the guidelines for metastatic or locally advanced cancer when chemoradiation is not an option (GAST-C):

- DCF or its modifications
- ECF or its modifications
- Irinotecan in combination with cisplatin or fluoropyrimidine (5-fluorouracil or capecitabine)
- Oxaliplatin in combination with fluoropyrimidine (5-fluorouracil or capecitabine)
- Paclitaxel-based regimens

The ECF regimen or its modifications and the DCF regimen have a category 1 recommendation. DCF modifications and all other regimens have a category 2B recommendation. Leucovorin or levoleucovorin can be used with certain infusional 5-fluorouracil-based regimens.

Best Supportive Care

The goal of best supportive care is to prevent, reduce, and relieve suffering and improve quality of life for patients and their caregivers, regardless of disease stage. In patients with unresectable or locally advanced cancer, palliative interventions provide symptomatic relief and may result in significant improvement in nutritional status, the sensation of well-being, and overall quality of life.

The options for best supportive care depend on the patient's symptoms. Endoscopic placement of self-expanding metal stents (SEMS) is a safe, effective and minimally invasive palliative treatment for patients with luminal obstruction due to advanced gastric cancer.[138,139,140] Other palliative procedures such as RT may be used to alleviate symptoms of luminal obstruction.

Surgery or external beam RT and/or endoscopic treatment may be indicated in patients experiencing bleeding. Placement of a percutaneous endoscopic gastronomy tube may be necessary to provide adequate nutritional support. Nutritional counseling may also be valuable. Pain control may be achieved with the use of RT and pain medications. See NCCN Adult Cancer Pain guidelines.

Summary

Gastric cancer is rampant in several countries around the world. Its incidence in the Western Hemisphere has been on the decline for more than 40 years. In the past 15 years, the incidence of proximal gastric cancer has increased in Western countries compared to non-proximal gastric cancer, which is more prevalent in Japan and other parts of the world. Diffuse histology is also more common now than intestinal type of histology. H. pylori infection, smoking, and high salt intake are the risk factors for gastric cancer. Few gastric cancers are associated with inherited gastric cancer predisposition syndromes.

Several advances have been made in therapeutic approaches, imaging techniques and staging procedures. Multidisciplinary team management is essential for treating patients with gastric cancer. Patients with locoregional gastric cancer should also be referred to high-volume treatment centers.

Surgery is the primary treatment option for medically fit patients with localized resectable gastric cancer. However in the West, surgery alone is an insufficient therapy for most patients. Subtotal gastrectomy is preferred for distal gastric cancers whereas proximal or total gastrectomy is recommended for proximal tumors. Based on the results of recent clinical trials, perioperative chemotherapy with ECF regimen or its modifications is recommended for medically fit patients with resectable locoregional distal esophageal, GE junction adenocarcinoma

(category 1). Preoperative chemoradiation may also be considered for these patients (category 2B).

Postoperative treatment is based on surgical margins and nodal status. If there is no residual disease at surgical margins (R0 resection), fluoropyrimidine-based chemoradiation is recommended for selected high risk patients with T2, N0 tumors, whereas 5-fluorouracil-based radiosensitization is used for patients with T3, T4 and/or any node positive tumors. Fluoropyrimidine-based postoperative chemoradiation is also recommended for patients with GE junction adenocarcinoma. All patients with residual disease at surgical margins (R1 and R2 resections) and patients with unresectable disease may be treated with 5-fluorouracil-based radiosensitization.

Best supportive care is an integral part of treatment, especially in patients with metastatic and advanced gastric cancer. Assessment of severity of the disease and related symptoms is essential to initiate appropriate palliative interventions that will prevent and relieve suffering and improve quality of life for patients and their caregivers. Patients with good performance status can be treated with chemotherapy or best supportive care, whereas best supportive care alone is the appropriate treatment for patients with poor performance status. Treatment options used for palliation of symptoms in patients with advanced gastric cancer include endoscopic placement of SEMS, laser surgery or RT.

The NCCN Gastric Cancer Guidelines provide an evidence-based systematic approach to gastric cancer in the United States. Many new chemotherapeutic agents, including targeted therapies, vaccines, gene therapy, and antiangiogenic agents are being studied in clinical trials. The panel encourages patients with gastric cancer to participate in well-designed clinical trials to enable further advances.

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