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NCCN Clinical Practice Guidelines in Oncology™

Gastric Cancer

V.2.2010

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¶ Surgery/Surgical oncology
Þ Internal medicine
§ Radiotherapy/Radiation oncology
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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

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these 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 makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010.

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Summary of the Guidelines Updates

Summary of changes in the 2.2010 version of the Gastric Cancer guidelines from the 1.2010 version include:

- The Staging tables were updated to reflect the 7th edition (2010) of the AJCC Staging Manual (ST-1) and (ST-2).
- The Gastric Cancer Discussion section was updated correspondent to the changes in the algorithm (MS-1).

Summary of changes in the 1.2010 version of the Gastric Cancer guidelines from the 2.2009 version include:

(GAST-1):
- Workup;
  - Fourth bullet: Clarified "Abdominal CT with IV contrast".
  - Last bullet: "H.pylori test, treat if positive," changed to "H.pylori test, if patient symptomatic from H.pylori, then treat".

(GAST-3):
- After R1 resection: Removed the phrase "preferred" after "...+ concurrent fluoropyrimidine-based radiosensitization".

(GAST-5):
- Follow-up: H&P changed from "every 4 - 6 mo for 3 y, then annually" to "every 3-6 mo for 1-3 y, every 6 mo for 3-5 y, then annually".

(GAST-A): Principles of Multidisciplinary Team Approach
- Sentence that states, "The NCCN panel believes in an infrastructure that discourages unilateral treatment decision-making..." changed to "The NCCN panel believes in an infrastructure that *encourages multidisciplinary* treatment decision-making."

(GAST-B): Principles of Gastric Cancer Surgery
- The entire Principles of Surgery page was revised.

(GAST-C): Principles of Systemic Therapy
- There is no longer a separate category for "Postoperative Chemotherapy". The agents are now listed under "Preoperative and Postoperative chemotherapy".
- Preoperative Chemoradiation: "Cisplatin plus fluoropyrimidine (category 2B)" was added.

(GAST-C): Principles of Systemic Therapy (continued)
- Metastatic or Locally advanced cancer: "Trastuzumab" with corresponding footnote that states "Used in combination with systemic chemotherapy for the treatment of patients with advanced gastric cancer or GE junction adenocarcinoma that is HER-2-positive as determined by a standardized method" was added.
- Footnote that states "Leucovorin or levoleucovorin is indicated with certain infusional 5-FU-based regimens" changed to "Leucovorin is indicated with..."

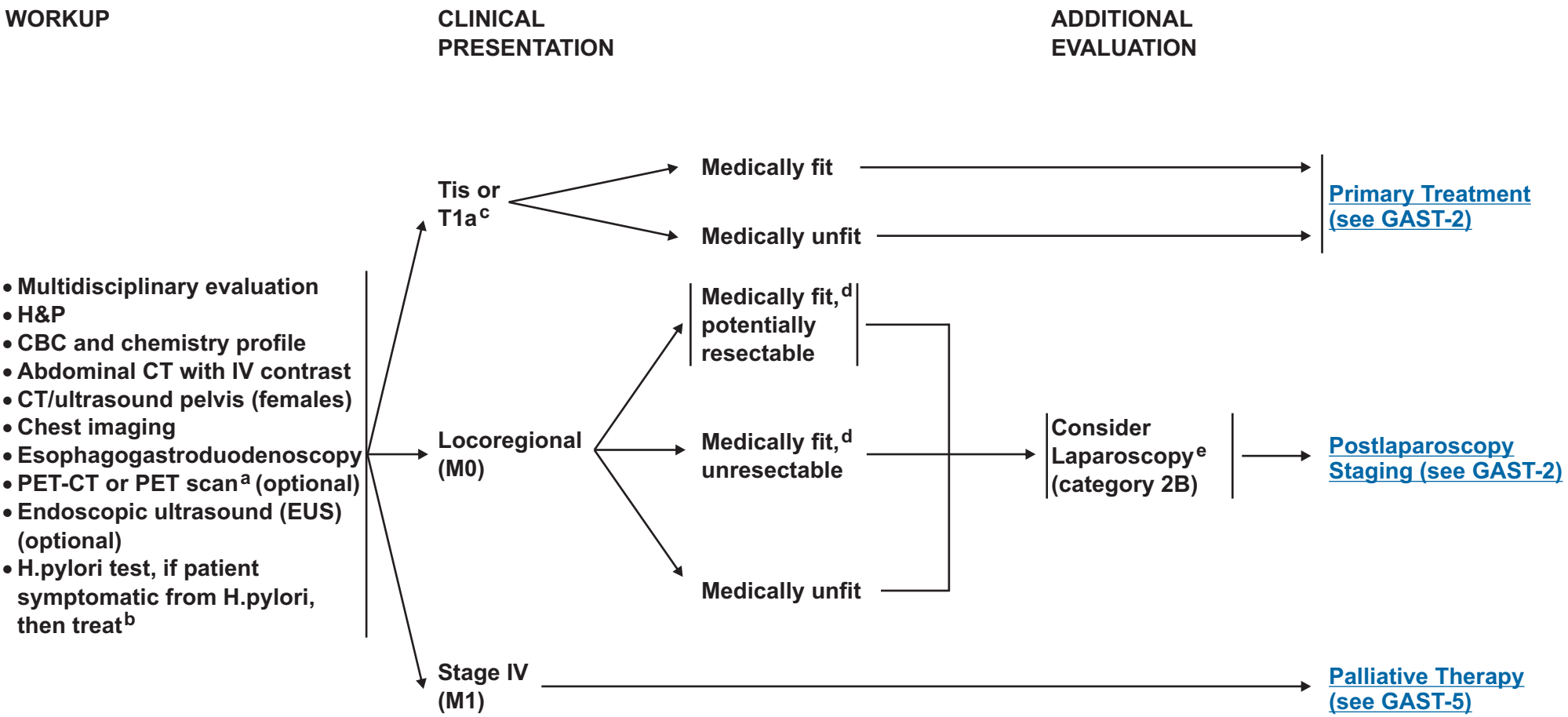
(GAST-D): Principles of Radiation Therapy
- Target Volume; Preoperative and Postoperative: "EGD" was added as an example of Pre-treatment diagnostic studies.
- Supportive Therapy; Fourth bullet: "Intravenous hyperalimentation" was removed from the first sentence. "Nasogastric feeding tube" was added to the second sentence.
- New bullet added that states "Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery".

(GAST-E): Principles of Best Supportive Care for Gastric Cancer
- Principles of Best Supportive Care for Gastric Cancer is a new page that provides specific recommendations for gastric cancer best supportive care throughout the guidelines. The new page replaces the "Best Supportive Care" table that was on page GAST-5.

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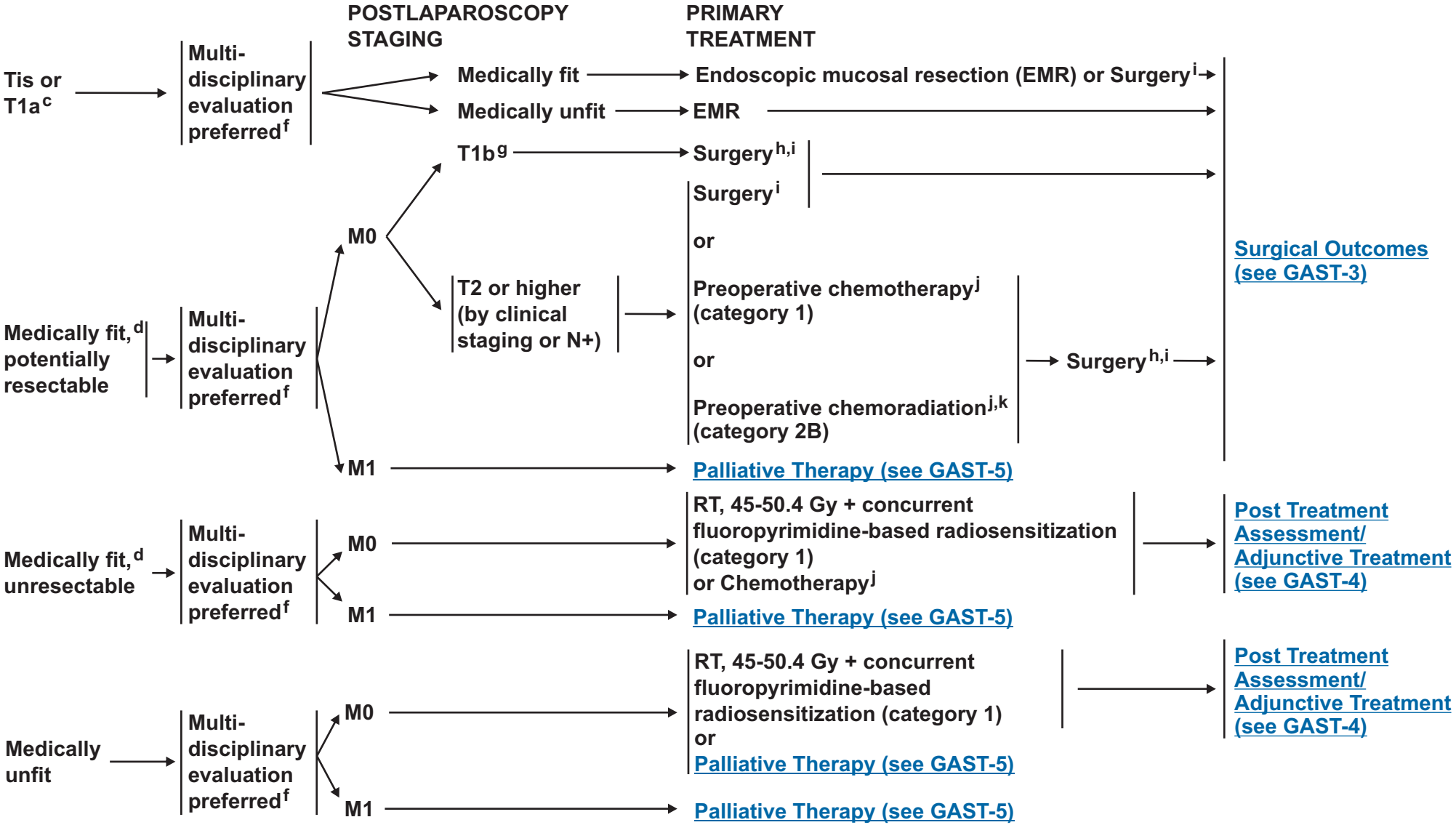


[a] May not be appropriate for T1 or M1 patients.
[b] Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007;102(8):1808-1825
[c] Tis or T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[d] Medically able to tolerate major abdominal surgery.
[e] 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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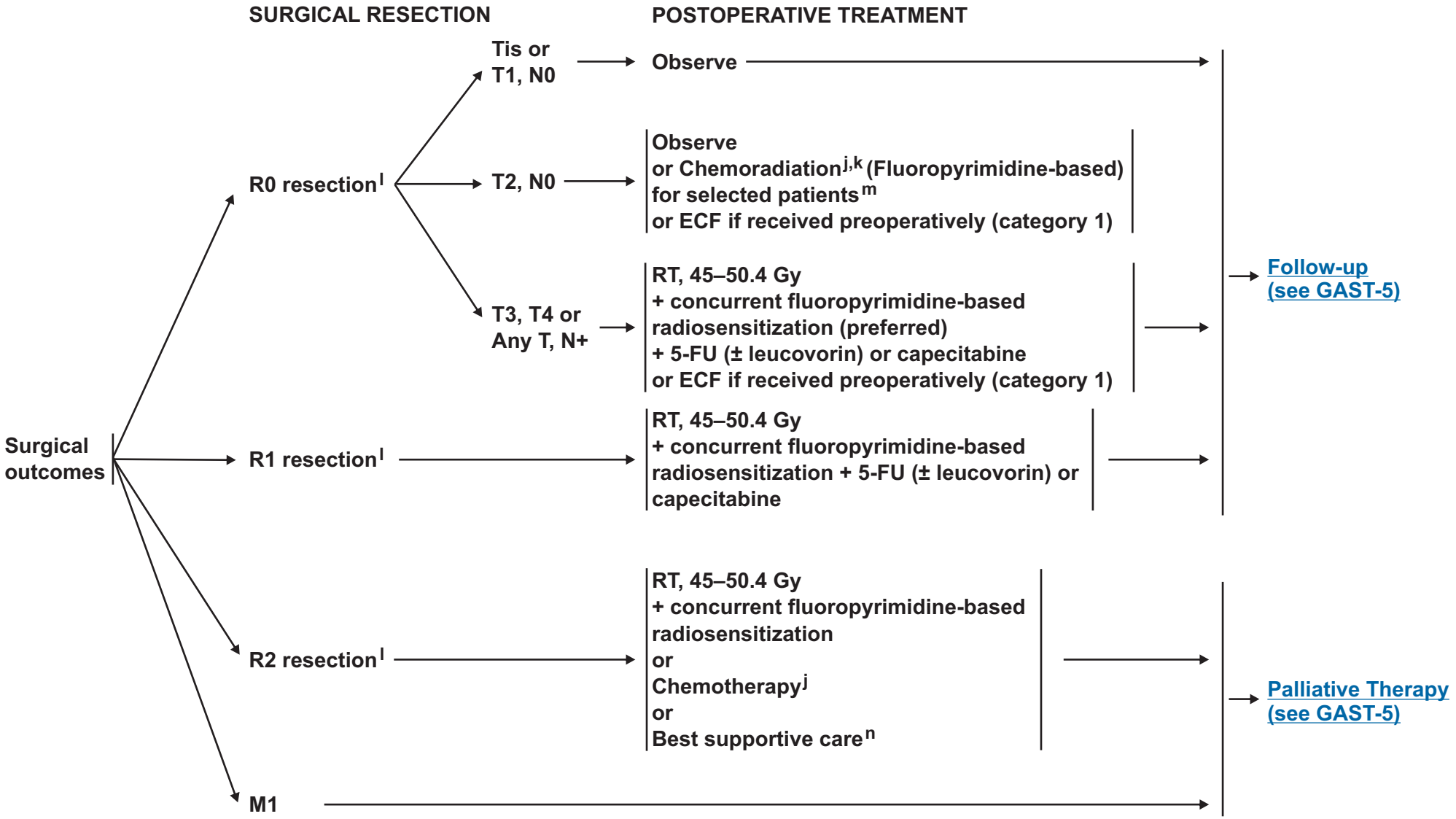
[c] Tis or T1a: Defined as tumors involving the mucosa, but not invading the submucosa.
[d] Medically able to tolerate major abdominal surgery.
[f] See Principles of Multidisciplinary Team Approach (GAST-A).
[g] T1b: Tumors invading the submucosa.
[h] Surgery as primary therapy is appropriate for T1 cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[i] See Principles of Surgery (GAST-B).
[j] See Principles of Systemic Therapy (GAST-C).
[k] See Principles of Radiation Therapy (GAST-D).

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Gastric Cancer

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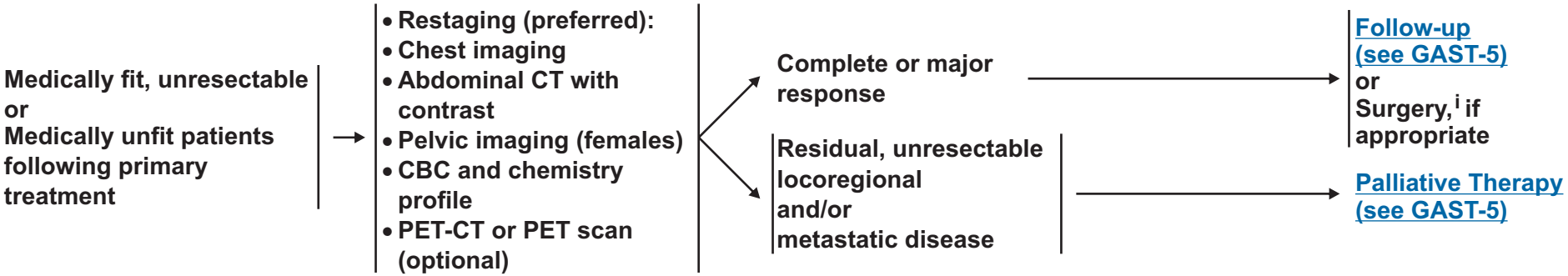
[j] See Principles of Systemic Therapy (GAST-C).
[k] See Principles of Radiation Therapy (GAST-D).
[l] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[m] High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age.
[n] See Principles of Best Supportive Care for Gastric Cancer (GAST-E).

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POST TREATMENT ASSESSMENT/ADJUNCTIVE TREATMENT

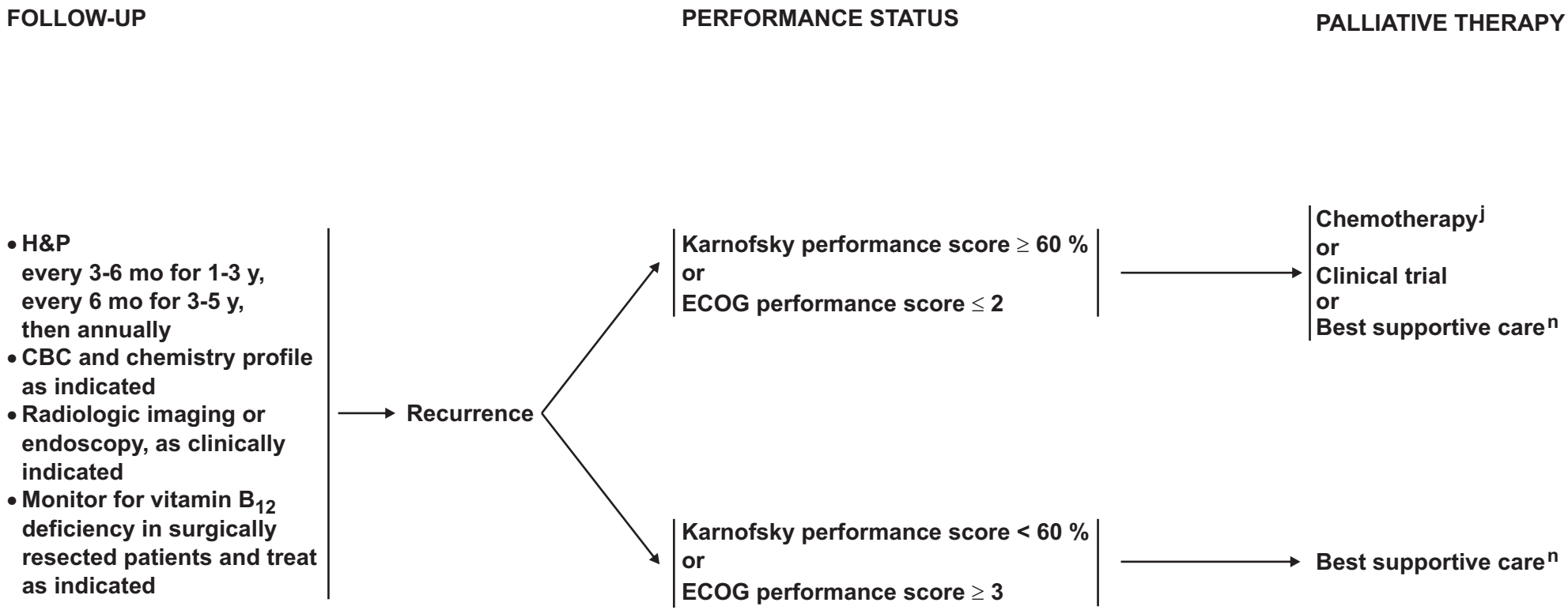


[i] See Principles of Surgery (GAST-B).

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[j] See Principles of Systemic Therapy (GAST-C).
[n] See Principles of Best Supportive Care for Gastric Cancer (GAST-E).

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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.[1,2,3] The NCCN panel believes in an infrastructure that encourages multidisciplinary 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.**

[1] Cunningham D, Allum WH, Stenning SP, Thompson JN, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.
[2] Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Jr., Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281(17):1623-1627.
[3] Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730.

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PRINCIPLES OF GASTRIC CANCER SURGERY (1 of 2)

Staging

- Determine extent of disease with CT scan ± EUS
- Laparoscopy[1] may be useful in select patients in detecting radiographically occult metastatic disease

Criteria of unresectability 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 include the regional lymphatics-- perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining 15 or greater lymph nodes[5,6,7]
- Routine or prophylactic splenectomy is not required.[8] 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)

- Palliative gastric resection should not be performed unless patient is symptomatic.
- Lymph node dissection not required
- Gastric bypass with gastrojejunostomy to the proximal stomach may be useful in palliating obstructive symptoms in symptomatic patients
- Venting gastrostomy and/or jejunostomy tube may be considered

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PRINCIPLES OF GASTRIC CANCER SURGERY (2 of 2)

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[2]Soetikno R, Kaltenbac T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005;23(20):4490-4498.
[3]Ono H, Kondo H, Gotoda T, Shirao K, et al,. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225-229.
[4]Ito H, Clancy TE, Osteen RT, Swanson RS, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg. 2004;199(6):880-886.
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[8]Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg. 2006;93(5):559-563.

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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 and Postoperative Chemotherapy

(GE junction adenocarcinoma included):

- ECF (Epirubicin, cisplatin and 5-FU) (category 1)[1]
- ECF modifications (category 1)[1,2]

Preoperative Chemoradiation:

- Docetaxel or paclitaxel plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[3]
- Cisplatin plus fluoropyrimidine (category 2B)[4]

Postoperative Chemoradiation

(GE junction adenocarcinoma included)

- Fluoropyrimidine (5-FU or capecitabine) (category 1)[5]

Metastatic or Locally Advanced Cancer

(where chemoradiation is not recommended):

- DCF (Docetaxel, cisplatin and 5-FU) (category 1)[6]
- ECF (category 1)[7]
- ECF modifications (category 1)[2,8,9]
- Irinotecan plus cisplatin (category 2B)[10,11]
- Oxaliplatin plus fluoropyrimidine (5-FU† or capecitabine) (category 2B)[8,12]
- DCF modifications (category 2B)[2,13,14,15]
- Irinotecan plus fluoropyrimidine (5-FU or capecitabine) (category 2B)[16,17]
- Paclitaxel-based regimen (category 2B)
- Trastuzumab††[,18]

†Leucovorin is indicated with certain infusional 5-FU-based regimens.

††Used in combination with systemic chemotherapy for the treatment of patients with advanced gastric cancer or GE junction adenocarcinoma that is HER-2-positive as determined by a standardized method.

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PRINCIPLES OF SYSTEMIC THERAPY FOR GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

[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] Okines AFC, Norman AR, McCloud P, Kang Y-K, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009;20:1529-1534.
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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 be 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, EGD, and CT scans) should be used to identify the tumor and pertinent nodal groups.[2,3] The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.
- Postoperative[4]
  - Pre-treatment diagnostic studies (EUS, UGI, EGD, and CT scans) and clip placement should be used to identify the tumor/gastric bed, the anastomosis or stumps, and pertinent nodal groups.[2,3] Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach. The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall.[5]

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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 and/or enteral nutrition should be considered. When indicated, feeding jejunostomies (J-tube) or nasogastric feeding tubes may be placed to ensure adequate caloric intake. During surgery, a J-tube may be placed for postoperative nutritional support.
- 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.
- Adequate enteral and/or IV hydration is necessary throughout chemoradiation and early recovery.

[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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PRINCIPLES OF RADIATION THERAPY (3 of 3)

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PRINCIPLES OF BEST SUPPORTIVE CARE FOR GASTRIC CANCER

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

- Bleeding is common in patients with gastric cancer and may directly from the tumor, from tumor related phenomenon, or as a consequence of therapy. Patients with acute bleeding (hematemesis or melena) should undergo prompt endoscopic assessment.[1]
  - Endoscopic hemostatic interventions appropriate to the findings should be carried out
  - Interventional radiology angiographic embolization techniques may be useful in those situations where endoscopy is not helpful
  - External beam radiation therapy[2]
- Chronic blood loss from gastric cancer
  - External beam radiation therapy[2]

Obstruction

- Endoscopic relief of obstruction
  - Balloon dilation
  - Placement of enteral stent[3]
- Surgery
  - Gastrojejunal bypass[3]
  - Gastrectomy in select patients[4]
- Establish enteral access for purposes of hydration and nutrition if endoscopic lumen restoration is not undertaken or is unsuccessful
  - Percutaneous endoscopic gastroscopy for gastric decompression if tumor location permits
  - Surgical placement of jejunal feeding tube for hydration and nutritional purposes
- External beam radiation therapy
  - Chemotherapy[a]

Pain

- External beam radiation therapy[2]
- Chemotherapy[a]
- If patient is experiencing tumor related pain, then the pain should be assessed and treated in accordance with the PAIN-1 section of the NCCN Adult Cancer Pain Guidelines.
- Severe uncontrolled pain following gastric stent placement should be treated emergently with endoscopic removal of the stent once uncontrollable nature of pain is established.

Nausea/Vomiting

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

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

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PRINCIPLES OF BEST SUPPORTIVE CARE FOR GASTRIC CANCER

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Staging

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Stomach
(7th ed., 2010)

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, muscularis mucosae or submucosa
T1a Tumor invades lamina propria or muscularis mucosae
T1b Tumor invades submucosa
T2 Tumor invades muscularis propria*
T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures**,***
T4 Tumor invades serosa (visceral peritoneum) or adjacent structures**,***
T4a Tumor invades serosa (visceral peritoneum)
T4b 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 - 2 regional lymph nodes
N2 Metastasis in 3 - 6 regional lymph nodes
N3 Metastasis in seven or more regional lymph nodes
N3a Metastasis in 7 - 15 regional lymph nodes
N3b Metastasis in 16 or more regional lymph nodes

Distant Metastasis (M)
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

* Note: 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 T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4.

**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Intramural extension to the duodenum or esophagus is 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.

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Staging

Table 1 - Continued

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Carcinoma of the Stomach

(7th ed., 2010)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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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

Cancers originating in the esophagus, gastroesophageal (GE) junctions, and stomach, constitute a major health problem around the world. An estimated 37,600 new cases of and 25,150 deaths from upper gastrointestinal (GI) cancers will occur in the United States in 2009.[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, it remains the most common type of cancer among men. More new cases of gastric cancer are diagnosed in China each year than any other country. 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 fourth most common cancer worldwide.[5] In 2009, an estimated 21,130 new cases will be diagnosed and 10,620 cases will eventually die of their disease in United States.[1] In developed countries, the incidence of gastric cancer originating from the cardia follows the distribution of esophageal cancer.[6-8] Non-cardia gastric adenocarcinoma shows marked geographic variation with countries such as Japan, Korea, China, Taiwan, Costa Rica, Peru, Brazil, Chile and the former Soviet Union show a high incidence of the cancer.[9] In contrast to the incidence trends in the West, non-proximal 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 continues to pose a major challenge for healthcare professionals. Environmental risk factors include Helicobacter pylori (H. pylori) infection, smoking, high salt intake, and other dietary factors. Patients with a family history of non-hereditary gastric cancer have a higher risk of developing gastric cancer. In a limited number of patients (1% to 3%), its diagnosis is associated with inherited syndromes. E-cadherin mutations occur in approximately 25% of families with an autosomal dominant of a hereditary form of diffuse gastric cancer.[11] Genetic counseling is recommended and a consideration should be given to prophylactic gastrectomy in young, asymptomatic carriers of germ-line truncating

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CDH1 mutations who belong to families with highly penetrant hereditary diffuse gastric cancer.[12]

Staging

Two major classifications are currently used. The Japanese classification is more elaborate and is based on anatomic involvement, particularly the lymph node stations.[13] The other staging system developed jointly by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC), is the system used in countries in the Western Hemisphere (Table 1).[14] A minimum of 15 examined lymph nodes is recommended for adequate staging.

Clinical baseline stage provides useful information for the development of an initial therapeutic strategy. Approximately 50% of patients will present with advanced disease at diagnosis and have a poor outcome. Other measures of poor outcome include poor performance status, presence of metastases, and alkaline phosphatase level of 100 U/L or more.[15] In patients with localized resectable disease, outcome depends on the surgical stage of the disease. Nearly 70-80% of have involvement of the regional lymph nodes. The number of positive lymph nodes has a profound influence on survival.[16]

Preoperative Staging

Clinical staging has greatly improved with the availability of diagnostic modalities such as endoscopic ultrasound (EUS), computed tomography (CT), combined positron emission tomography PET-CT, magnetic resonance imaging (MRI) and laparoscopic staging.[17-19]

CT scan 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.[20] It has a significantly lower sensitivity compared to CT in the detection of local lymph node involvement (56% vs.78%), although it has an improved specificity (92% vs. 62%).[21] Combined PET-CT imaging, on the other hand, has several potential advantages over PET scan alone.[22] 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.[23,24]

EUS is indicated for assessing the depth of tumor invasion.[25] The accuracy of EUS for T-staging ranges from 65% to 92% and 50% to 95% for N staging and is operator dependent. Distant lymph node evaluation by EUS is suboptimal given the limited depth and visualization of the transducer.[26]

Laparoscopic staging can detect occult metastases (GAST-B). 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.[27] Distant metastatic disease (M1) was detected in 31% of the patients. Limitations of laparoscopic staging include two-dimensional evaluation and limited use in the identification of hepatic metastases and perigastric lymph nodes.

Indications for the use of laparoscopic staging differ among various NCCN institutions. In some, laparoscopic staging is reserved for medically fit patients with potentially resectable disease, specifically when consideration is made for chemoradiotherapy or surgery. In medically unfit patients, laparoscopy may still be considered especially if there is consideration for adding radiation to chemotherapy. The guidelines have included laparoscopic staging with a category 2B recommendation (GAST-1).

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Cytogenetic analysis of peritoneal fluid can help improve staging through identification of occult carcinomatosis.[17] Reports in literature suggest that positive findings on peritoneal cytology is an independent predictor for identifying patients who are at higher risk for recurrence following curative resection.[28,29]

Surgery

Surgery is the primary treatment for early stage gastric cancer. Complete resection with adequate margins (4 cm or greater) is widely considered as a standard goal, whereas the type of resection (subtotal versus total gastrectomy) along with extent of lymphadenectomy remains a subject of controversy.

Principles of Surgery

The primary goal of surgery is to accomplish a complete resection with negative margins (R0 resection). Only 50% of patients will end up with an R0 resection of their primary.[30,31] As a reminder, R1 indicates microscopic residual disease (positive margins); and R2 indicates gross (macroscopic) residual disease in the absence of distant metastasis.[32]

Subtotal gastrectomy is the preferred approach for distal gastric cancers. This procedure has a similar surgical outcome compared to total gastrectomy although with significantly fewer complications.[33] Proximal gastrectomy and total gastrectomy are both indicated for proximal gastric cancers and are typically associated with postoperative nutritional impairment.

Clinical staging using CT scan with or without 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.[34] The guidelines recommend distal, subtotal or total gastrectomy for T1b-T3 tumors. T4 tumors require en bloc resection of involved structures. Routine or prophylactic splenectomy should be avoided if possible. In a randomized clinical study, postoperative mortality and morbidity rates were slightly higher in patients who underwent total gastrectomy combined with splenectomy, and marginally better survival, but there were no statistically significant differences between the groups.[35] The results of this study do not support the use of prophylactic splenectomy to remove macroscopically negative lymph nodes near the spleen in patients undergoing total gastrectomy for proximal gastric cancer. Placement of a jejunostomy feeding tube may be considered for selected patients who will be receiving postoperative chemoradiation.

Carcinomas are considered unresectable if there is evidence of peritoneal involvement, distant metastases, or locally advanced disease such as (invasion or encasement of major blood vessels). Limited gastric resection, even with positive margins is acceptable for unresectable tumors for symptomatic palliation of bleeding. Palliative gastric resection should not be performed unless the patient is symptomatic and lymph node dissection is not required (GAST-B). Gastric bypass with gastrojejunostomy to the proximal stomach may be useful for the palliation of obstructive symptoms in symptomatic patients. Placement of venting gastrotomy and/or a feeding jejunostomy tube may be considered.

Lymph Node Dissection

Gastric resection may be classified by the extent of lymph node dissection at surgery. 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.[36] 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

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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. D0 dissection refers to incomplete resection of 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.

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 than 15 N2 nodes and more than 20 N3 nodes examined had the best long-term survival outcomes.[37]

Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. In a randomized controlled trial (JCOG9501), Japanese investigators comparing D2 lymphadenectomy alone with D2 lymphadenectomy with para-aortic nodal dissection (PAND) in patients undergoing gastrectomy for curable (T2b, T3 or T4) gastric cancer reported a postoperative mortality rate of 0.8% in each arm.[38] The final results of this study showed that D2 lymphadenectomy with PAND does not improve survival rate in curable gastric cancer, compared to D2 lymphadenectomy alone. The 5-year overall survival (OS) rates were 70.3% and 69.2% respectively. There were also no significant differences in the relapse-free survival (RFS) rates between the two groups.[39] In a post hoc subgroup analysis, the survival rates were better among patients with pathologically negative nodes assigned to D2 lymphadenectomy plus PAND than those who were assigned to D2 lymphadenectomy alone, whereas in patients with metastatic nodes, the survival rates were worse for those assigned to D2 lymphadenectomy plus PAND. However, the investigators of this study caution that these results from post hoc analysis could be false positive due to multiple testing and the survival benefit of D2 lymphadenectomy plus PAND in node-negative patients need to be clarified in further studies. The investigators concluded that D2 lymphadenectomy plus PAND should not be used to treat patients with curable (T2b, T3 or T4) gastric cancer.

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.[40-43]

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 postoperative 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 OS (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.[41] The 5-year OS rates were 35% for D1 dissection and 33% for D2 dissection. In addition, the D2 dissection was associated with increased postoperative morbidity and mortality. Both these trials found that splenectomy and pancreatectomy performed

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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.[44] 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.[45-48]

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.[49,50] The 5-year OS rate among all eligible patients was 55%. The overall 5-year morbidity rate was 20.9% and a postoperative in-hospital 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, 5-year and 10-year OS 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 for R0, R1-R2 and palliative resections were 4.9%, 9% and 13.4% respectively. We recognize that cross-trial comparisons result in weak evidence and conclusions.

Sierra and colleagues from a single institution in 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 OS or disease-free survival (DFS). However, there was a trend toward improved OS 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. Modified D2 lymphadenectomy (without pancreatectomy and splenectomy) is associated with low mortality and reasonable survival times when performed in institutions that have sufficient experience with the operation and postoperative management.

The panel recommends that gastric cancer surgery should be performed by experienced surgeons in high volume cancer centers and should include removal of perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining 15 or greater lymph nodes (GAST-B).

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) represents a major advance in minimally invasive surgery for gastric cancer. EMR has been used for patients with early gastric cancer (Tis or T1a tumors limited to mucosa).[54,55] Node-negative T1 tumors require limited resection since

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the 5-year survival rate is more than 90%.[56] 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.[57] 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.[58] 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.

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.[59] Tis or T1 tumors limited to mucosa (T1a) may be candidates for EMR in experienced centers.

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 Hulscher 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 OS rates (58.9% vs. 55.7% respectively) and DFS 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 recommendations 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. 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). The results from a recent systematic review and meta-analysis showed a statistically significant 5-year survival benefit with the addition of radiotherapy in patients with resectable gastric cancer.[65]

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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.[66] However, when used concurrently with 5-fluorouracil, external-beam RT improves survival. Moertel and colleagues assessed 5-fluorouracil plus RT compared with RT alone in the treatment of locally unresectable gastric cancer.[67] Patients receiving combined modality treatment had a significantly better median survival (13 vs. 6 months) and 5-year OS (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-fluorouracil and methyl-CCNU (lomustine) or split-course RT with a concurrent intravenous bolus of 5-fluorouracil followed by maintenance 5-fluorouracil and methyl-CCNU.[68] 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.[66]

Intensity modulated radiation therapy (IMRT) has 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 and the impact of new conformal radiotherapy technologies needs to be assessed in randomized clinical trials.

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 an immobilization device is strongly recommended for reproducibility.

The panel recommends involvement of a multidisciplinary team, which should include medical, radiation and surgical oncologists, radiologists, gastroenterologists and pathologists to determine optimal diagnostic, staging and treatment modalities. 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 (GAST-D). 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, though optimal criteria have not yet emerged. 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

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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, enteral and/or parenteral nutrition should be considered. Oral and/or intravenous hydration is often necessary throughout chemoradiation and early recovery. Feeding jejunostomies may be placed if clinically indicated. It is essential to monitor levels of B_{12}, 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-fluorouracil) 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.[71-74] 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] In a recent phase III study, Stahl et al. compared preoperative chemotherapy (cisplatin, fluorouracil and leucovorin) with chemoradiation therapy using the same regimen in 119 patients with locally advanced adenocarcinoma of the GE junction.[74] Patients with locally advanced adenocarcinoma of the lower esophagus or GE junction were randomized between two treatment groups: chemotherapy followed by surgery (arm A) or chemotherapy followed by chemoradiotherapy followed by surgery (arm B). Patients in arm B had a significantly higher probability of showing pathologic complete response (15.6% vs. 2.0%) or tumor-free lymph nodes (64.4% vs. 37.7%) at resection. Preoperative chemoradiation therapy improved 3-year survival rate from 27.7% to 47.4%. Although the study was closed prematurely due to low accrual and statistical significance was not achieved, there was a trend towards survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the GE junction. The value of preoperative chemoradiation therapy remains uncertain and needs to be determined in larger prospective randomized trials.

Postoperative Chemoradiation Therapy

Nonrandomized trials from Baeza and colleagues have reported encouraging results for patients with R0 resections who receive adjunctive treatment.[75] 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.[67,76,77]

The landmark trial is the Intergroup trial SWOG 9008/INT-0116.[78] In this trial 556 patients with adenocarcinoma of the stomach or GE junction [stage IB through stage IV (M0)] were randomly assigned to surgery only (n=275) or surgery plus chemoradiation (n=281). Patients were at high risk for relapse; more than two thirds of them had T3 or T4 tumors and 85% of patients had node positive disease. 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

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well as an increase in median survival (36 vs. 27 months), 3-year RFS (48% vs. 31%), and OS (50% vs. 41%, P = .005) with combined modality treatment. With more than 10 years of median follow-up, survival remains improved in patients with stage IB-IV (M0) gastric cancer treated with postoperative chemoradiation. No increases in late toxic effects were noted.[79] 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 results of this study have established postoperative chemoradiation therapy as a standard of care in patients with resected gastric cancer who have not received preoperative therapy.

An ongoing large phase III trial (ARTIST) is comparing the effects of adjuvant chemoradiation (capecitabine and cisplatin plus RT) compared to adjuvant chemotherapy (capecitabine and cisplatin) after D2 resection of gastric cancer. The primary endpoint is 3-year DFS.[80]

Chemotherapy

Perioperative Chemotherapy

The British Medical Research Council performed the first well-powered phase III trial (MAGIC trial) for perioperative chemotherapy.[81] 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 GE 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 PFS and OS in patients with operable gastric and lower esophageal adenocarcinomas. The results of this study have established perioperative chemotherapy as another added option to the standard of care of for 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) and oxonic acid.[82] 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 R0 gastric resection with extensive lymph-node dissection (D2).[83] This study randomized 1,059 patients to surgery followed by adjuvant treatment with S-1 or surgery alone. OS rate at 3 years was 80.1% and 70.1% for S-1 group and surgery alone respectively. Hazard ratio for death in the S-1 group was 0.68.

This is the first time adjuvant chemotherapy has been shown to be beneficial after D2 resection in the Japanese patient 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 with UFT (a combination of uracil and tegafur) after D2 resection.[84] There are no data available with S-1 in Western patients in this setting.

Chemotherapy for Advanced or Metastatic Disease

Chemotherapy can provide both palliation and improved survival in patients with advanced and metastatic disease. Single agents with activity in patients with advanced gastric cancer include 5-fluorouracil, mitomycin, etoposide, and cisplatin, with reported response rate ranging between 10% and 20%.[85,86] Other agents including irinotecan,

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paclitaxel, docetaxel, oral etoposide, oxaliplatin, UFT have shown activity as single agents and in combination in patients with advanced gastric cancer.[87-98]

Irinotecan as a single agent or in combination has been explored extensively in single arm and randomized clinical trials.[99-108] The results of a randomized phase III study comparing irinotecan in combination with 5-fluorouracil and folinic acid to cisplatin combined with infusional 5-fluorouracil in patients with advanced adenocarcinoma of the stomach or GE junction showed non-inferiority for progression-free survival and improved tolerance of the irinotecan containing regimen, thus it can be alternative when platinum-based therapy cannot be delivered.[102] Irinotecan, however, is best suited after front- line therapy.

In another randomized multicenter phase II study, Moheler et al. compared capecitabine combined with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or GE junction.[105] There were no significant differences in overall response rates (37.7% and 42.0% respectively), and median PFS (4.2 months and 4.8 months respectively), although there was a trend towards 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.

Chemotherapy resulted in an improved quality of life and OS compared to best supportive care in patients with advanced gastric cancer.[109,110] In the early 1980s, FAM (5-fluorouracil, doxorubicin, and mitomycin) was considered the gold standard for patients with advanced gastric cancer.[111] The pivotal study performed by the North Central Cancer Treatment Group (NCCTG) comparing FAM to 5-fluorouracil alone and 5-fluorouracil plus doxorubicin showed no significant survival difference between all 3 arms.[112] Higher response rates were observed in patients who received combination chemotherapy versus 5-fluorouracil alone.

In the past 3 decades, several randomized studies have compared FAM vs. FAMTX (5-fluorouracil, adriamycin, and methotrexate),[113] FAMTX vs. ECF (epirubicin, cisplatin, and 5-fluorouracil),[114] FAMTX vs. ELF (etoposide, leucovorin, and 5-fluorouracil) vs. 5-fluorouracil plus cisplatin,[115] and ECF vs. MCF (mitomycin, cisplatin, 5-flourouracil).[116] ECF demonstrated improvements in median survival and quality of life when compared to FAMTX or MCF regimens. Recently, a phase III trial conducted by the German Study Group showed that the combination of fluorouracil, leucovorin and oxaliplatin (FLO) had a trend toward improved median PFS compared to fluorouracil, leucovorin and cisplatin (FLP) (5.8 vs. 3.9 months).[117] However, there were no significant differences in median OS (10.7 vs. 8.8 months, respectively) between the two 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% vs.16.7%), time to treatment failure (5.4 vs. 2.3 months), PFS (6.0 vs. 3.1 months), and an improved OS (13.9 vs. 7.2 months) compared with FLP, respectively.

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).[118] Time to progression was significantly longer with DCF compared with CF (5.6 vs. 3.7 months). In 2006, based on the results of this study, FDA (Food and Drug Administration) approved DCF regimen for the treatment of advanced gastric cancer, including cancer of the GE junction, in patients who have not received prior chemotherapy for advanced disease. Various modifications of DCF regimen with the intent to improve tolerability are being evaluated in clinical trials for patients with advanced gastric cancer.[119,120]

Capecitabine is an orally administered fluoropyrimidine which is converted to 5-flurouracil intracellularly. Several studies have evaluated

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capecitabine in combination with other agents in patients with advanced esophagogastric cancers.[121] Two phase III trials (REAL-2 and ML 17032) have assessed the efficacy and safety of capecitabine in gastric cancer.[122,123]

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.[122] 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-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 5-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 5-fluorouracil and cisplatin (FP) as first-line treatment in patients with previously untreated advanced gastric cancer.[123] Overall response rate (41% vs. 29%) and OS (10.5 months vs. 9.3 months) were superior for patients who received 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 suggest that capecitabine is as effective as 5-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 5-fluorouracil-based combinations although no significant difference in PFS between treatment groups was seen.[124]

Another 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.[125-127] 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) were significantly longer for the combination of S-1 and cisplatin compared with S-1 alone.[128] The combination of S-1 and cisplatin in patients with untreated advanced gastric cancer and GE junction adenocarcinoma was shown to be safe and active in a multicenter phase II trial conducted in the United States.[129,130]

The results of First Line Advanced Gastric Cancer Study (FLAGS) comparing the combination of cisplatin and S-1 (CS) with cisplatin and 5-fluorouracil (CF) in patients with advanced gastric/gastroesophageal adenocarcinoma was recently presented. In this study 1053 patients were randomized to either CS or CF.[131] CS had similar efficacy compared to CF with improved safety. In a subset analysis, CS produced statistically superior OS for patients with diffuse type histology. Additional studies are needed to confirm the activity of S-1 in the US and western hemisphere.

Targeted Therapies

The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and HER2 has been associated with poor prognosis in patients with gastric and esophageal cancers.[132,133] In clinical trials, trastuzumab (anti-HER2

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antibody), bevacizumab (an anti-VEGFR antibody) and cetuximab (anti-EGFR antibody) have been evaluated in combination with chemotherapy in the treatment of patients with advanced gastric and GE junction adenocarcinoma.

The ToGA study is the first randomized, prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in HER2-positive gastric cancer in combination with cisplatin and a fluoropyrimidine.[134] The results of this study confirmed that trastuzumab plus standard chemotherapy is superior to chemotherapy alone in patients with HER2-positive advanced gastric cancer. Five hundred and ninety four patients with HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent, or metastatic) were randomized to receive trastuzumab plus chemotherapy (5-fluorouracil or capecitabine and cisplatin) or chemotherapy alone. There was a significant improvement in the median OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone (13.5 vs. 11.1 months, respectively). Safety profiles were similar with no unexpected adverse events in the trastuzumab. There was also no difference in symptomatic congestive heart failure between arms. This establishes that trastuzumab plus chemotherapy as a new standard of care for the treatment of patients with a HER2-expressing advanced gastric and GE cancers.

The safety and efficacy of bevacizumab,[135-137], sorafenib,[138] and cetuximab,[139-144] has been evaluated in multiple phase II studies. Ongoing phase III trials are underway to confirm the efficacy and safety of the above mentioned agents in combination with standard chemotherapy in patients with advanced gastric and GE junction cancers.

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 particularly for loco-regionally confined tumors. 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.[145]

The use of PET-CT scans is optional. PET-CT scans are useful for predicting response to preoperative chemotherapy as well as in the evaluation of recurrent gastric cancer.[146,147] They may also be useful in demonstrating occult metastatic disease, although there may be false positive results. Therefore, histologic confirmation of occult PET-avid metastasis is recommended.[148] 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

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- 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

EMR or surgery is the primary treatment option for medically fit patients with Tis or T1a tumors. 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, the guidelines have included perioperative chemotherapy with ECF regimen or its modifications with a category 1 recommendation for patients with T2 or higher tumors (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 (cisplatin or paclitaxel or docetaxel in combination with 5-fluorouracil or capecitabine) [73,74] as an alternate treatment option with a category 2B recommendation (GAST-2).

RT (45-50.4 Gy) with concurrent fluoropyrimidine-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).[67,68] 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 disease 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 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.[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-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) and

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concurrent fluoropyrimidine-based radiosensitization plus 5-fluorouracil (with or without leucovorin) or capecitabine (GAST-3). In the absence of metastases (M1), patients with macroscopic residual disease at surgical margins (R2 resections) may be treated with RT (45-50.4 Gy) and concurrent fluoropyrimidine-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. Follow-up should include a complete history and physical examination every 3-6 months for 1-3 years, every 6 months for 3-5 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 B_{12} and iron deficiency.

Palliative Treatment for Recurrent or Metastatic disease

In a randomized comparison between chemotherapy and best supportive care vs. best supportive care alone for advanced gastric cancer, OS (8 months vs. 5 months, though not statistically significant) and time to progression (5 months vs. 2 months) were longer in patients receiving chemotherapy.[149] More patients in the chemotherapy group (45%) had an improved or prolonged high quality of life for a 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.[150] A randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO) comparing irinotecan to best supportive care in the second-line setting showed that irinotecan significantly prolonged OS compared to best supportive care.[151] Median survival was 123 days in the irinotecan arm compared to 72.5 days in the best supportive care only arm.

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.[152-154] 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).

Palliative treatment options include chemotherapy, or clinical trial or best supportive care. 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 a number of phase III trials that assessed combinations such as ECF, DCF, and FOLFIRI. There is no established second-line treatment for advanced gastric cancer. Some of the regimens listed in the guidelines are based on institutional preferences that have support only from phase II studies. The following regimens are listed in the guidelines for metastatic or locally advanced cancer (GAST-C):

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- 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
- Trastuzumab in combination with chemotherapy for patients with advanced gastric cancer or GE junction adenocarcinoma that is HER-2 –positive as determined by a standardized method.[134]

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 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 undertaken to relieve major symptoms may result in prolongation of life. Palliative interventions for the management of bleeding, obstruction, pain, nausea and vomiting are described in detail in GAST-E.

Bleeding

Bleeding is common in patients with gastric cancer and may be secondary to tumor or tumor related phenomenon, or as a consequence of therapy. A multidisciplinary approach is required for the proper diagnosis and management of gastrointestinal bleeding in patients with cancer.[155] Patients with acute bleeding (hematemesis or melena) should undergo prompt endoscopic assessment. Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful. External beam RT and/or endoscopic treatment may be indicated in patients experiencing bleeding.[156]

Obstruction

Gastrojejunostomy is the most commonly used palliative treatment modality for malignant gastric outlet obstruction. 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.[157-159] 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.[160] Other palliative procedures such as external beam RT or balloon dilation may be used to alleviate symptoms of obstruction. The optimal palliative treatment for patients with malignant gastric outlet obstruction needs to be determined in large randomized clinical trials.

If endoscopic lumen restoration is not undertaken or unsuccessful, percutaneous endoscopic gastrotomy for gastric decompression may be performed if tumor location permits. Surgical placement of jejunal feeding tube may be necessary to provide adequate hydration and nutritional support. 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 Adult Cancer Pain guidelines. Severe uncontrolled pain following gastric stent placement should be treated emergently with endoscopic removal of the stent once uncontrollable nature of pain is established.

Nausea/Vomiting

Patients experiencing nausea and vomiting should be treated according to the NCCN Antiemesis guidelines.

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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 disease should be referred to high volume treatment centers.

Surgery is the primary treatment option for medically fit patients with 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 the ECF regimen or its modifications is recommended for medically fit patients with resectable locoregional distal esophageal, GE junction and gastric adenocarcinoma (category 1). Preoperative chemoradiation may also be considered for these patients (category 2B). Postoperative treatment is based on surgical margins and nodal status. All patients with unresectable disease may be treated with 5-fluorouracil-based chemoradiation.

Targeted therapies in combination with chemotherapy have produced encouraging results in the treatment of patients with advanced gastric, esophageal and gastroesophageal junction cancers. Based on the results of the ToGA trial, the NCCN panel included trastuzumab plus chemotherapy in the guidelines as a new treatment option for patients with HER2-positive advanced gastric cancer or GE junction adenocarcinoma. The efficacy vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) inhibitors in combination with chemotherapy for patients with advanced gastric and GE junction cancers are being evaluated in ongoing randomized phase III trials.

Best supportive care is an integral part of treatment, especially in patients with metastatic and advanced gastric cancer. 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.

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. 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 the management of gastric cancer in the United States. Many new chemotherapeutic agents, targeted therapies, vaccines, gene therapy, and antiangiogenic agents are being studied in clinical trials. The panel encourages patients to participate in well-designed clinical trials to enable further advances.

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