NCCN Guidelines® Insights

Gastric Cancer, Version 2.2013

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer provide evidence- and consensus-based recommendations for a multidisciplinary approach for the management of patients with gastric cancer. For patients with resectable locoregional cancer, the guidelines recommend gastrectomy with a D1+ or a modified D2 lymph node dissection (performed by experienced surgeons in high-volume centers). Postoperative chemoradiation is the preferred option after complete gastric resection for patients with T3–T4 tumors and node-positive T1–T2 tumors. Postoperative chemotherapy is included as an option after a modified D2 lymph node dissection for this group of patients. Trastuzumab with chemotherapy is recommended as first-line therapy for patients with HER2-positive advanced or metastatic cancer, confirmed by immunohistochemistry and, if needed, by fluorescence in situ hybridization for IHC 2+. (*JNCCN* 2013;11:531–546)

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Disclosures for the NCCN Gastric Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Gastric Cancer Panel members can be found on page 532.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.**

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Describe the postoperative treatment options for patients with resectable gastric cancer.
- Discuss the role of HER-2 testing and trastuzumab for patients with metastatic cancer.

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Disclosure of Affiliations and Significant Relationships

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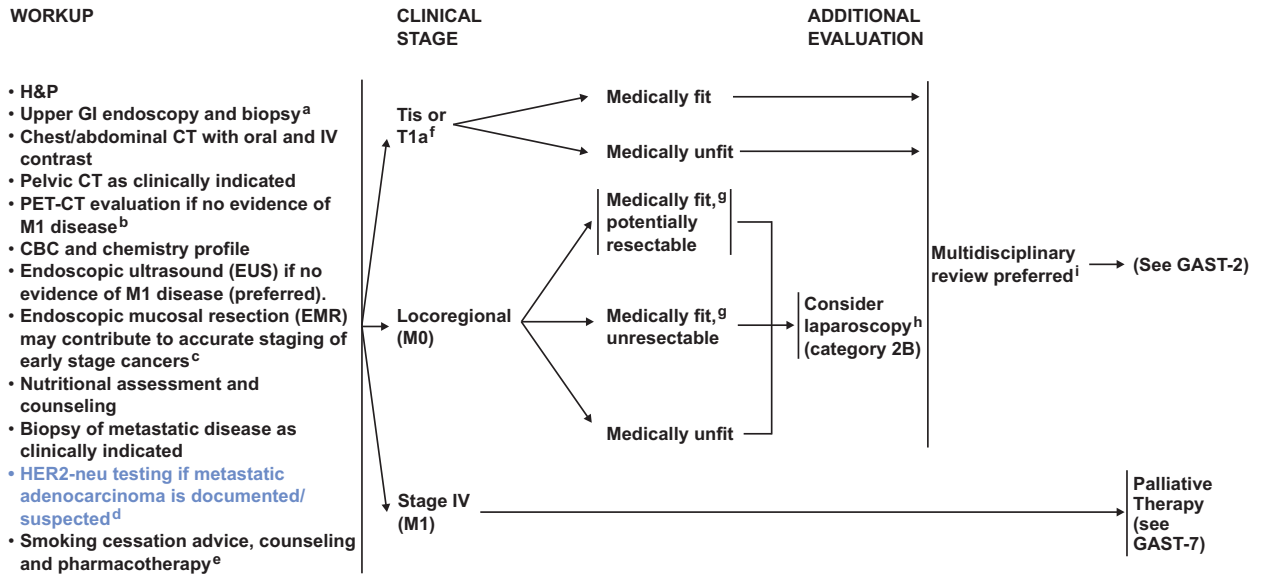


[a]See Principles of Endoscopic Surgery and Therapy (GAST-A).
[b]May not be appropriate for T1 patients.
[c]EMR may also be therapeutic for early stage disease/lesions.
[d]See Principles of Pathologic Review and HER2-neu Testing (GAST-B).
[e]Smoking cessation guidelines are available from the Public Health Service at: www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf or http://guideline.gov/content.aspx?id=12520

[f]Tis or T1a: Defined as carcinoma in situ (Tis) or invasion of mucosa without submucosal invasion (T1a).
[g]Medically able to tolerate major abdominal surgery.
[h]Laparoscopy is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy is not indicated if a palliative resection is planned.
[i]See Principles of Multidisciplinary Team Approach (GAST-C).

GAST-1

NCCN Categories of Evidence and Consensus

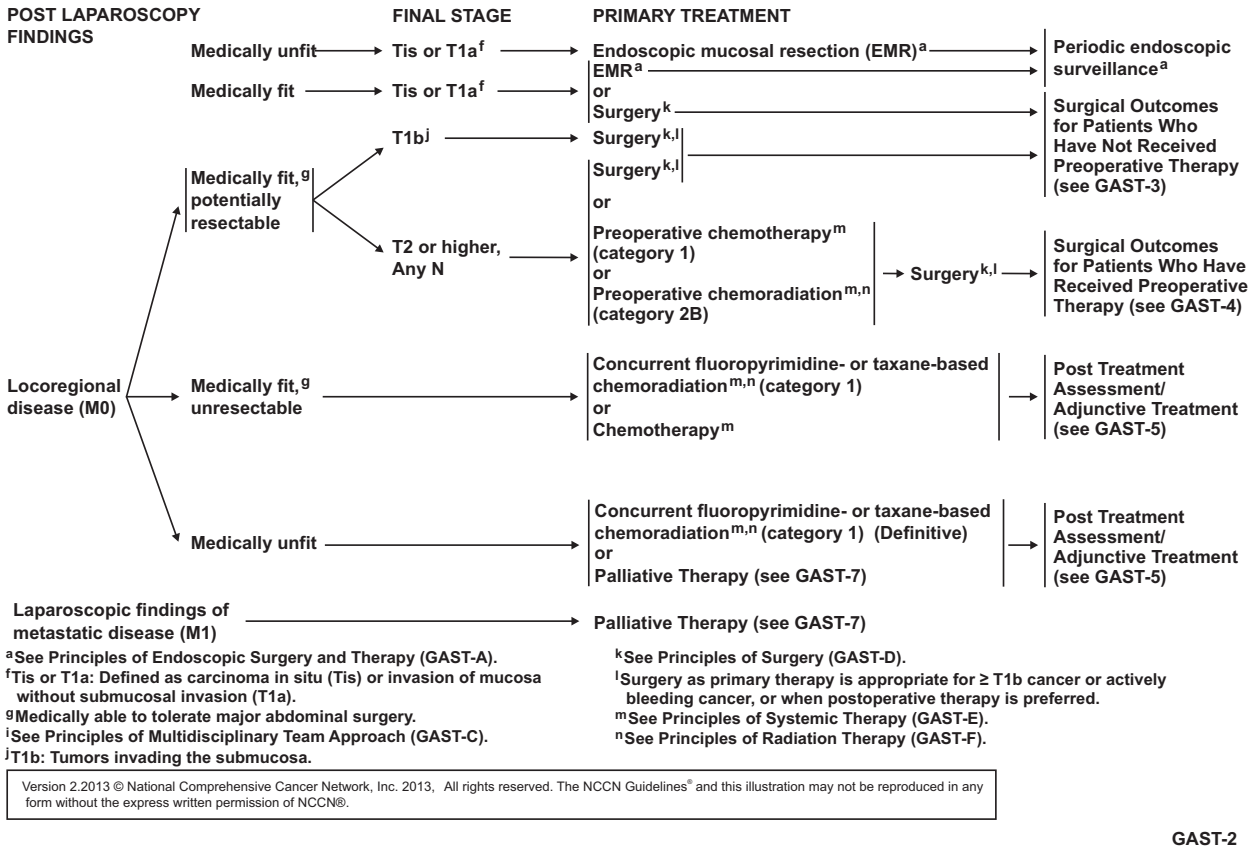
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death worldwide. In 2013, an estimated 21,600 new cases will be diagnosed and 10,990 people will die of the disease in United States.[1] Surgery with lymph node dissection is the primary treatment for patients with resectable cancer; however, for most patients, surgery alone is not sufficient and adjunctive therapy must be considered. Recent studies have demonstrated that a modified D2 lymph node dissection when performed in high-volume cancer centers is associated with low morbidity/mortality and a survival benefit.[2,3] In recent years, combined modality therapy has been used as an adjunct to surgery to improve survival rates in patients with localized resectable cancer.[4–7] The Trastuzumab for Gastric Cancer (ToGA) trial showed that the addition of trastuzumab to chemotherapy significantly improves survival in patients with HER2-expressing



advanced or metastatic cancer, underscoring the importance of accurate HER2 testing for identifying patients eligible for this treatment.[8,9]

These NCCN Guidelines Insights include the major discussion points regarding the recommendations for the extent of lymph node dissection and postoperative therapy in the management of patients with localized resectable cancer and the role of HER2 testing in patients with advanced or metastatic cancer.

Lymph Node Dissection

Lymph node dissection is classified as D0, D1, or D2, depending on the extent of lymph nodes removed at the time of gastrectomy (GAST-D, 1 of 2, page 539). Gastrectomy with D2 lymph node dissection is the standard treatment for curable gastric cancer in eastern Asia. In Western countries, extended lymph node dissection of distant lymph nodes contributes to accurate staging of the disease, but its contribution to the prolongation of survival is unclear and much of the survival benefit associated with an extensive lymph node dissection may be from the effect of stage migration.[10–12] In the West, D2 lymph node dissection is considered a recommended but not a required procedure. However, there is uniform consensus that removal of an adequate number of nodes (≥15) is beneficial for staging purposes.

Although initial results from 2 large randomized trials performed in Western countries failed to demonstrate a significant survival benefit for D2 lymph node dissection over D1,[13–15] long-term follow-up data from the Dutch Gastric Cancer Group trial have confirmed a survival benefit for D2 lymph node dissection. The 15-year overall survival (OS) rates were 21% and 29%, respectively, for the D1 and D2 groups (P=.34). D2 lymph node dissection was also associated with lower rates of local (12% vs 22%)

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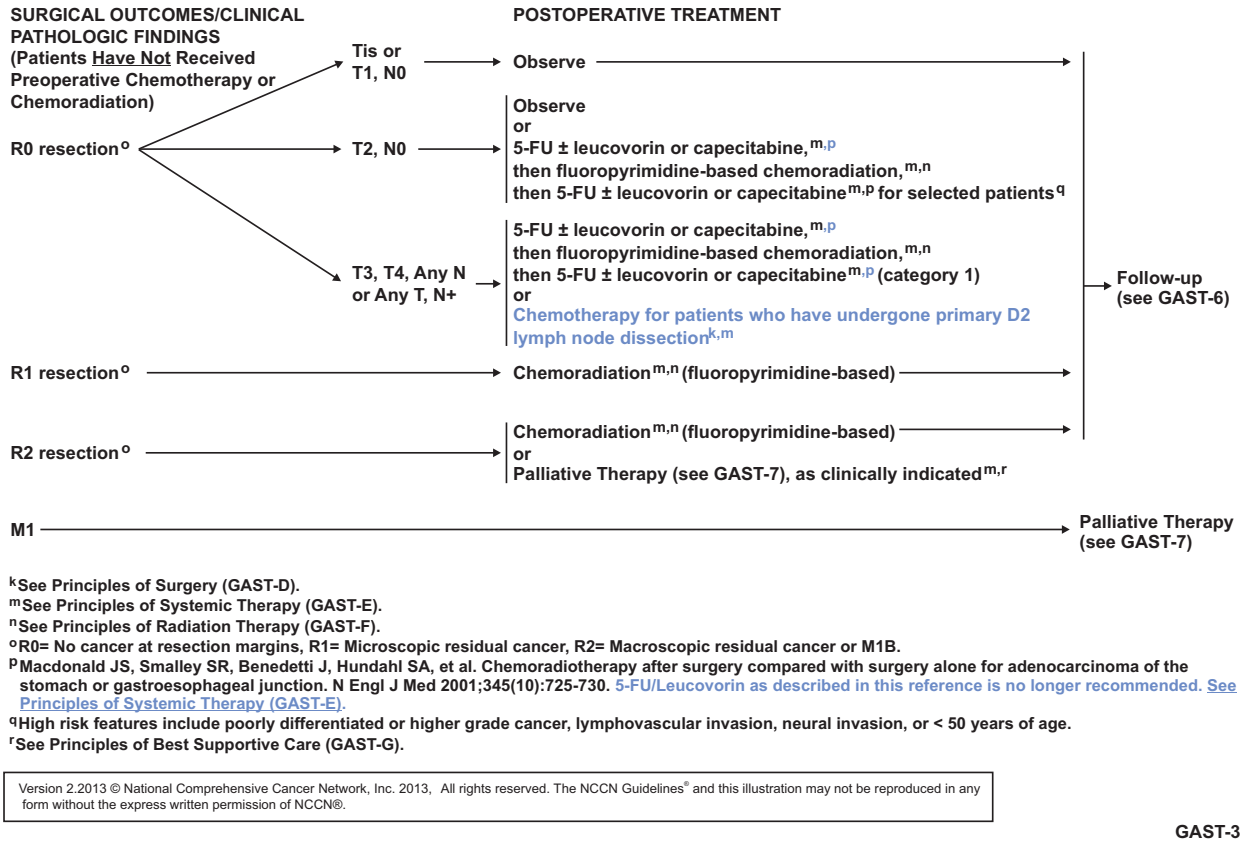


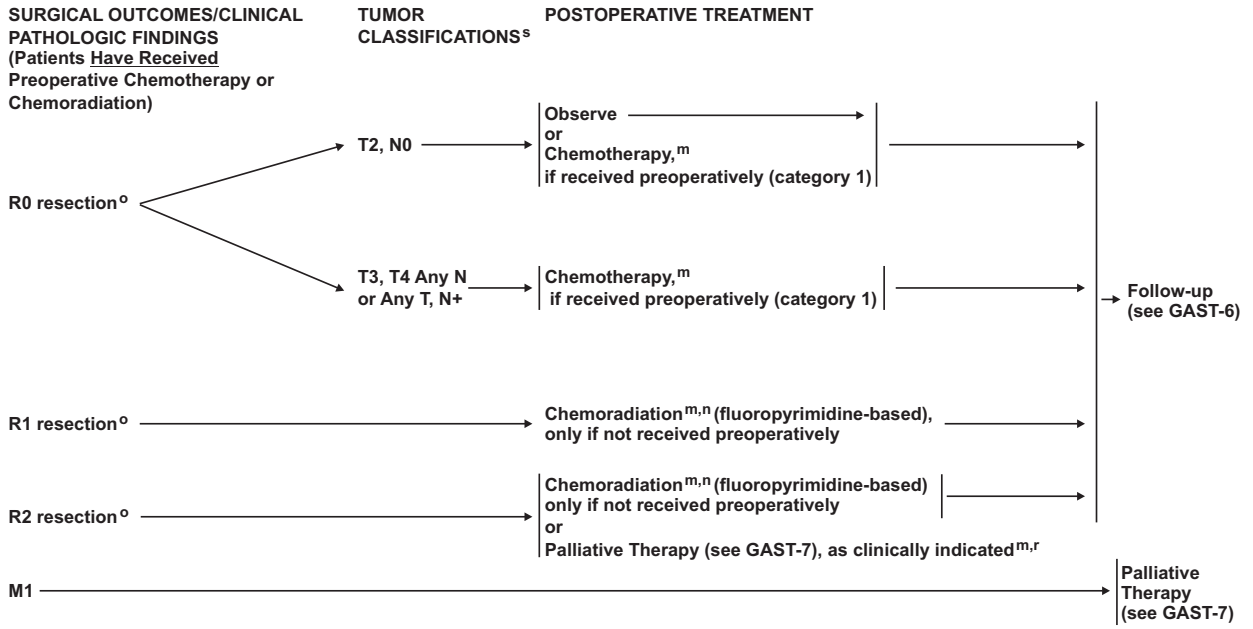
[k]See Principles of Surgery (GAST-D).
[m]See Principles of Systemic Therapy (GAST-E).
[n]See Principles of Radiation Therapy (GAST-F).
[o]R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[p]Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, 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. 5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy (GAST-E).
[q]High risk features include poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age.
[r]See Principles of Best Supportive Care (GAST-G).

GAST-3

and regional recurrences (13% vs 19%).[3] More importantly, gastric cancer–related death rate was significantly lower in the D2 group compared with the D1 group (37% and 48%, respectively).[3] Two other reports from Western countries have also reported better outcomes for D2 lymph node dissection when performed according to the recommendations of Japanese Research Society of Gastric Cancer.[16,17]

Investigators have long been arguing that if the complication rate after a D2 lymph node dissection could be decreased, then this procedure may have a benefit in selected patients. Although pancreatectomy and splenectomy have been widely performed with D2 lymph node dissection in Japan, both of these procedures have been shown to increase postoperative mortality and morbidity.[14,15,18,19] In a prospective randomized phase II study conducted by the Italian Gastric Cancer Study Group, pancreas-preserving D2 lymph node dissection was associated with a survival benefit and lower complication rate.[18,19] Pancreatectomy was performed only when T4 tumor involvement was suspected. Postoperative complications were higher after D2 gastrectomy (16.3% vs 10.5% after D1), but the difference was not statistically significant ($P<.29$). Postoperative mortality rates were 0% and 1.3% for D2 and D1 lymph node dissections, respectively. The 5-year OS rate among all eligible patients was 55%. The overall 5-year morbidity and postoperative in-hospital mortality rates for pancreas-preserving D2 lymph node dissections were 3% and 21%, respectively. These were comparable to the rates for D1 lymph node dissections in the Dutch and United Kingdom trial.[19]

Recent reports also suggest that D2 lymph node dissection is associated with lower postoperative complications and a trend toward improved OS when performed in high-volume centers that have



[m] See Principles of Systemic Therapy (GAST-E).
[n] See Principles of Radiation Therapy (GAST-F).
[o] R0= No cancer at resection margins, R1= Microscopic residual cancer, R2= Macroscopic residual cancer or M1B.
[r] See Principles of Best Supportive Care (GAST-G).
[s] See Staging (ST-1).

GAST-4

sufficient experience with the operation and postoperative management.[2,20]

NCCN Recommendation

The panel agreed that updated data from trials performed in Western countries suggest that a modified D2 lymph node dissection (without pancreatectomy and splenectomy) is associated with low mortality and reasonable survival times. The guidelines recommend gastrectomy with D1 or a modified D2 lymph node dissection, with a goal of examining at least 15 if not more lymph nodes, for patients with localized resectable cancer (GAST-D, 1 of 2, page 539).[3,11,18,19] The panel members also acknowledge that the technical aspects of performing a D2 dissection require a significant degree of training and expertise. Therefore, the guidelines emphasize that D2 dissection should be performed by experienced surgeons in high-volume centers.

Prophylactic pancreatectomy and splenectomy is no longer recommended with D2 lymph node dissection.[21,22] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer recommend splenectomy only when spleen or hilum is involved (to view the most recent version of these guidelines, visit NCCN.org).

Postoperative Treatment

Two large randomized trials have established the benefit of postoperative chemoradiation and perioperative chemotherapy (preoperative and postoperative chemotherapy) after curative gastrectomy in patients with resectable cancer.[4,5]

In the landmark Intergroup trial (SWOG 9008/INT-0116), 556 patients with completely resected gastric cancer or esophagogastric junction (EGJ) adenocarcinoma (stage IB–IV, M0) were randomized to surgery alone (n=275) or surgery plus postoperative chemoradiation (n=281).[4] Most patients

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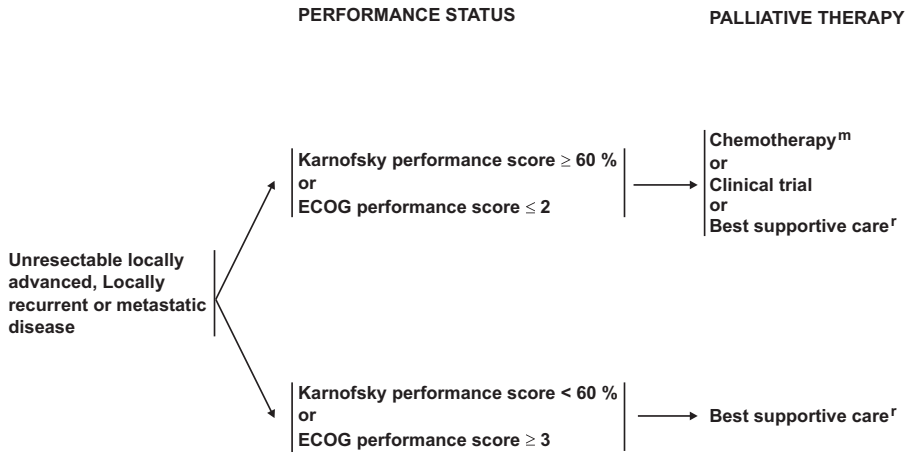

[m]See Principles of Systemic Therapy (GAST-E).
[r]See Principles of Best Supportive Care (GAST-G).

GAST-7

had T3 or T4 tumors (69%) and node-positive disease (85%); only 31% of the patients had T1–T2 tumors and 14% of patients had node-negative tumors. Surgery was not part of the trial protocol, but resection of all detectable disease (R0 resection) was required for participation in the trial. Postoperative chemoradiation (offered to all patients with tumors T1 or higher, with or without lymph node metastases) significantly improved OS and relapse-free survival (RFS). Median OS was 27 months in the surgery-only group and 36 months in the chemoradiation group (P=.005). The chemoradiation group had better 3-year OS (50% vs 41%) and RFS rates (48% vs 31%) than the surgery-only group. A significant decrease was also seen in local failure as the first site of failure (19% vs 29%) in the chemoradiation group. With more than 10 years of follow-up, survival remains improved with no increases in late toxic effects.[23]

Although the results of this trial demonstrated a significant survival benefit for postoperative chemoradiation in patients with T3–T4, N0, and any T node-positive tumors, the effectiveness of this approach in patients with T2,N0 tumors remains unclear because of the smaller number of such patients enrolled in this trial.

Furthermore, the regimen used in the INT-0116 trial (bolus fluorouracil and leucovorin before and after chemoradiation with the same combination) was associated with high rates of grade 3 or 4 hematologic and gastrointestinal toxicities (54% and 33%, respectively). Among the 281 patients assigned to the chemoradiation group, only 64% completed treatment and 17% discontinued because of toxicity. Three patients (1%) died as a result of chemoradiation-related toxic effects, including pulmonary fibrosis, a cardiac event, and myelosuppression. Subsequent reports from other investigators

PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING

Assessment of Overexpression of HER2-neu in Gastric Cancer

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

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

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

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

***Reprinted and adapted from The Lancet, 376(9742), Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-neu-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. pages 687-697, 2010, with permission from Elsevier.**

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have demonstrated the feasibility of postoperative chemoradiation with regimens containing infusional fluorouracil or capecitabine in patients with gastric cancer.[24–26] The better tolerance and efficacy of postoperative chemoradiation with infusional fluorouracil and leucovorin was also demonstrated in a trial including 905 patients with stage II or III colorectal cancer.[27]

In the MAGIC trial, 503 patients (stage II or higher, M0) were randomized to receive either perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) and surgery, or surgery alone.[5] Patients were randomized before surgical intervention (74% of patients had gastric cancer; 69% in the surgery-plus-chemotherapy group and 66% in the surgery-only group had undergone R0 resection). Most patients had T2 or higher tumors (12% had T1 tumors, 32% of patients had T2 tumors, and 56% of patients had T3–T4 tumors) and 71% of patients had node-positive disease. The perioperative chemotherapy group had a greater proportion of T1 and T2 tumors (51.7%) and less-advanced nodal disease (N0 or N1; 84%) than the surgery group (36.8% and 70.5%, respectively). Perioperative chemotherapy significantly improved progression-free survival ($P<.001$) and OS ($P=.009$). Five-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

In a more recent FNLCC/FFCD trial (n=224; 75% of patients had adenocarcinoma of the lower esophagus or EGJ and 25% had gastric cancer), Ychou et al[6] reported that perioperative chemotherapy with fluorouracil and cisplatin significantly increased the curative resection rate, disease-free survival (DFS), and OS in patients with resectable cancer. The 5-year OS rate was 38% for patients in the surgery-plus-perioperative chemotherapy group and 24% in the surgery-only group ($P=.02$). The

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PRINCIPLES OF SURGERY

Resectable tumors

- **Tis or T1[1] tumors limited to mucosa (T1a) may be candidates for endoscopic mucosal resection (in experienced centers)[2]**
- **T1b-T3:[3] 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 at least 15 or greater lymph nodes[4-6]**
  - **Definition of D1 and D2 lymph node dissections**
    - **D1 dissection entails gastrectomy and the resection of both the greater and lesser omenta (which would include the lymph nodes along right and left cardiac, along lesser and greater curvature, suprapyloric along the right gastric artery, and infrapyloric area);**
    - **D2 dissection is a D1 plus all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery.**
- **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)**

Palliative procedures

- **Gastric resections should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease.**
- **Lymph node dissection not required**
- **In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) is preferable to endoluminal stenting in patients with gastric outlet obstruction.[8]**
- **Venting gastrostomy and/or jejunostomy tube may be considered**

[1] Soetikno R, Kaltenbac T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005;23:4490-4498.
[2] Ono H, Kondo H, Gotoda T, Shirao K, et al,. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-229.
[3] 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;199:880-886.
[4] Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomized nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-449.
[5] Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. Ann Surg Oncol. 2007;14:317-328.
[6] Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. Ann Surg. 2000;232:362-571.
[7] Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. Br J Surg. 2006;93:559-563.
[8] Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18-27.

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GAST-D 1 of 2

corresponding 5-year DFS rate was 34% and 19%, respectively. This trial was prematurely terminated even after allowing enrollment of patients with gastric cancer because of the lack of accrual.

These 3 trials support the benefit of preoperative or postoperative treatment as an adjunct to curative surgery with limited lymph node dissection (D0 or D1) and were not powered to evaluate the role of preoperative or postoperative treatment when a D2 lymph node dissection is performed. In the INT-0116 trial, D2 lymph node dissection was not commonly performed and patients were not excluded based on the extent of lymph node dissection (D0, D1, and D2 dissections were performed in 54%, 36%, and 10% of patients, respectively).[4] In the MAGIC trial, the extent of lymph node dissection was determined by the surgeon's discretion; the reported rates of D2 dissection were 28% in the perioperative chemotherapy group and 30% in the surgery-only group.[5] In the FNLCC/FFCD trial, D2 dissection was recommended and the surgical procedure was decided by the surgeon according to the tumor site and local practice.[6]

The benefit of postoperative treatment after D2 lymph node dissection was evaluated in 3 recently completed phase III trials.[7,28,29]

The results of the ARTIST trial showed that postoperative chemoradiation with capecitabine and cisplatin did not significantly reduce recurrence after D2 lymph node dissection in patients with curatively resected gastric cancer (n=458; stage IB–IV, M0).[28] At a median follow-up of 53 months, the estimated 3-year DFS rates were 78% and 74%, respectively, for postoperative chemoradiation and chemotherapy (P=.0862). However, this study demonstrated that postoperative treatment with capecitabine and cisplatin is feasible after a D2 lymph node dissection.

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PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation (EGJ and gastric cardia):
- Preferred Regimens:
  - Paclitaxel and carboplatin (category 1)[1]
  - Cisplatin and fluorouracil† (category 1)[2,3]
  - Oxaliplatin and fluorouracil† (category 1)[4,5]
  - Cisplatin and capecitabine[6]
  - Oxaliplatin and capecitabine[7]
- Other Regimens:
  - Irinotecan and cisplatin (category 2B)[8]
  - Docetaxel or paclitaxel and fluoropyrimidine (Fluorouracil† or capecitabine) (category 2B)[9,10]

Perioperative Chemotherapy (including EGJ adenocarcinoma) (3 cycles preoperative and 3 cycles postoperative):
- ECF (epirubicin, cisplatin and fluorouracil) (category 1)[11]
- ECF modifications (category 1)[12]
  - Epirubicin, oxaliplatin and fluorouracil
  - Epirubicin, cisplatin and capecitabine
  - Epirubicin, oxaliplatin and capecitabine
- Fluorouracil and cisplatin (category 1)[13]

Postoperative Chemoradiation (including EGJ):*
- Fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation[14-19]

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection) (See Principles of Surgery [GAST-D])
- Capecitabine and oxaliplatin[20]
- Capecitabine and cisplatin[21]

Chemotherapy for Metastatic or Locally Advanced Cancer [where local therapy is not indicated]π
- Trastuzumab can be added to chemotherapy for HER2-neu overexpressing adenocarcinoma [See Principles of Pathologic Review and HER2-neu Testing (GAST-B)]
  - Combination with cisplatin and fluoropyrimidine (category 1 for first-line therapy)[22]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

*5-FU/Leucovorin as described in this reference is no longer recommended. See Principles of Systemic Therapy: Regimens and Dosing Schedules (GAST E).

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

πSee the NCCN Guidelines for Gastric Cancer (www.nccn.org) for a complete list of chemotherapy regimens recommended for metastatic or locally advanced cancer.

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

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In the CLASSIC trial (conducted in South Korea, China, and Taiwan), 1035 patients with stage II–IIIB gastric cancer who underwent curative gastrectomy with D2 dissection were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin.[7] More than 30 lymph nodes were examined to ensure adequate disease classification. Most patients had T2 and T3 tumors (55% and 44%, respectively) and less advanced nodal disease (60% of patients had N1 tumors and 29% had N2 tumors). The planned interim analysis (after a median follow-up of 34 months) showed that postoperative chemotherapy significantly improved DFS compared with surgery alone for all disease stages (II, IIIA, and IIIB). The 3-year DFS rates were 74% and 59%, respectively ($P<.0001$). The lack of difference in OS is most likely from inadequate length of follow-up, but the OS is expected to become significant at a later date.

ACTS GC trial showed a survival benefit for postoperative chemotherapy with an oral fluoropyrimidine S-1 in patients with stage II or III gastric cancer who had undergone D2 gastrectomy. S-1 remains an investigational agent in North America.[29]

These results confirm that postoperative chemotherapy is associated with a survival benefit after D2 lymph node dissection, and postoperative chemoradiation remains an effective and preferred treatment after D0 or D1 dissection but not after D2 dissection.

NCCN Recommendations

Postoperative Chemoradiation: The benefit of postoperative chemoradiation after complete resection (R0) has been established only in patients who have not received any preoperative therapy. The guidelines recommend postoperative chemoradiation for this group of patients based on tumor stage, nodal status, surgical margins, and the extent of lymph node dissection.

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PRINCIPLES OF SYSTEMIC THERAPY--REGIMENS AND DOSING SCHEDULES††

POSTOPERATIVE CHEMORADIATION (INCLUDING EG JUNCTION)

5-FU (bolus) and leucovorin (category 1)[14]
Cycles 1, 3, and 4 (before and after radiation)
Leucovorin 20 mg/m^2 IVP on Days 1-5
5-FU 425 mg/m^2 IVP daily on Days 1-5
Cycled every 28 days

Cycle 2 (with radiation)
Leucovorin 20 mg/m^2 IVP on Days 1-4 and 31-33
5-FU 400 mg/m^2 IVP daily on Days 1-4
Cycled every 35-day cycle

With radiation
Fluorouracil 200-250 mg/m^2 IV continuous infusion
over 24 hours daily on Days 1-5 or 1-7
Weekly for 5 weeks[18]

With radiation
Capecitabine 625-825 mg/m^2 PO BID on Days 1-5 or 1-7
Weekly for 5 weeks[19]

THE PANEL ACKNOWLEDGES THAT THE INTERGROUP 0116 TRIAL[14] FORMED THE BASIS FOR POSTOPERATIVE ADJUVANT CHEMORADIATION STRATEGY. HOWEVER, THE PANEL DOES NOT RECOMMEND THE ABOVE SPECIFIED DOSES OR SCHEDULE OF CYTOTOXIC AGENTS BECAUSE OF CONCERNS REGARDING TOXICITY. THE PANEL RECOMMENDS ONE OF THE FOLLOWING MODIFICATIONS INSTEAD:

- 1 cycle before and 2 cycles after chemoradiation
  Capecitabine 750-1000 mg/m^2 PO BID on Days 1-14
  Cycled every 28 days [15,16]

- 1 cycle before and 2 cycles after chemoradiation
  Leucovorin 400 mg/m^2 IV on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 400 mg/m^2 IVP on Days 1 and 15 or Days 1, 2, 15, and 16
  Fluorouracil 1200 mg/m^2 IV continuous infusion
  over 24 hours daily on Days 1, 2, 15, and 16
  Cycled every 28 days[17]

††Chemotherapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

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

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The panel acknowledges that the INT-0116 trial formed the basis for the recommendation of postoperative chemoradiation in patients with completely resected gastric cancer.[4,23] However, the panel does not recommend the doses or the schedule of chemotherapy agents used in the INT-0116 trial because of concerns regarding toxicity. Instead, the panel recommends the use of fluoropyrimidine (infusional fluorouracil or capecitabine) before and after fluoropyrimidine-based chemoradiation (GAST-E, 6 of 13, this page).[24,25,27]

T3–T4 Tumors and Node-Positive T1–T2 Tumors: Based on the results of the INT-0116 trial, postoperative chemoradiation is included with a category 1 recommendation (GAST-3, page 535).[4]

T2,N0 Tumors: The guidelines recommend observation or postoperative chemoradiation only for patients with high-risk features (poorly differentiated or higher-grade cancer, lymphovascular invasion, neural invasion, or age <50 years; GAST-3, page 535).[30] Given the relatively good prognosis combined with the lack of evidence from randomized clinical trials showing any survival benefit for postoperative chemoradiation for patients with T2,N0 tumors, some of the panel members felt that chemoradiation is not necessary for this group of patients. Therefore, observation is included as an option.

Postoperative Chemoradiation After R1 or R2 Resections (Only if Not Received Preoperatively): Although this approach has not been evaluated in a prospective study, given the significantly worse prognosis associated with margin positive resections, the panel members believe that this could be a reasonable treatment option, especially in patients who have not received preoperative chemoradiation (GAST-3, page 535). Data from a recent retrospective analysis suggest that postoperative chemoradiation may be associated with a significant improvement in 2-year

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OS (66% vs 29%; *P*=.002) and a significant decrease in the local recurrence rate (6% vs 26%; *P*=.02) after an R1 resection compared with the surgery alone.[31]

Perioperative Chemotherapy

Based on the results of the MAGIC trial and FNLCC/FFCD trial, perioperative chemotherapy (ECF or its modifications, and fluorouracil and cisplatin) is included with a category 1 recommendation after R0 resection for all patients with T2 or higher, any N tumors (GAST-4, page 536).[5,6]

Postoperative Chemotherapy

The 2 large randomized trials that demonstrated a survival benefit for postoperative chemotherapy after a D2 lymph dissection were both conducted in Japan/Korea/Taiwan.[7,29] The radiation oncologists on the panel thought that it may be difficult to apply these results to patients in the United States, because D2 dissection is not a recommended procedure in many US cancer centers, and more importantly, this approach has not been evaluated in patients undergoing D0 or D1 dissection. However, the medical oncologists were of the opinion that the data from the CLASSIC trial using a regimen available in the United States offer stronger support for the use of postoperative chemotherapy than for a postoperative chemoradiation in patients undergoing a modified D2 resection.

In the end, the consensus of the panel was to include postoperative chemotherapy (capecitabine with oxaliplatin or cisplatin) as an option for patients with T3–T4 tumors and node-positive T1–T2 tumors after R0 resection and a modified D2 lymph node dissection (GAST-3, page 535). The panel emphasizes that postoperative chemoradiation is the preferred option (category 1) for patients undergoing less than a D2 lymph node dissection.[28] The guidelines have also included a general definition for D1 and D2 lymph node dissections in the "Principles of Surgery" section that would be helpful in the appropriate patient selection for postoperative chemotherapy (GAST-D, 1 of 2, page 539).

HER2 Testing in Gastric Cancer

HER2 gene and/or HER2 protein expression has been implicated in the development of gastric and EGJ adenocarcinomas.[32] The reported rates of *HER2* amplification and HER2 overexpression in patients with gastric cancer range from 12% to 27% and 9% to 23%, respectively.[33–38] HER2 positivity also varies with histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated > poorly differentiated).[33,36–38] HER2 positivity is seen in 20% or fewer of Western patients with metastatic gastric cancer, with significantly higher rates of HER2 positivity in patients with liver metastasis (31% vs 11% for those with no liver metastases; *P*=.025) and intestinal histology (33% vs 8% for diffuse/mixed histology; *P*=.001).[38] In the U.S. population, the reported HER2-positive rate is 12% and is more often identified in the intestinal subtype rather than the diffuse subtype (19% and 6%, respectively).[37]

However, unlike in breast cancer, the prognostic significance of HER2 status in patients with gastric cancer remains unclear, with some studies suggesting that HER2 positivity is associated with poor prognosis[35,36,39,40] and others showing that it is not an independent prognostic factor of patient outcome, except in a very small subgroup of patients with intestinal histology.[37,38,41] Although further studies are needed to assess the prognostic significance of HER2 positivity, the most important clinical application of HER2 status in patients with gastric cancer concerns the management of patients with advanced or metastatic disease.

Assessment of HER2 Expression

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

According to the HER2 scoring system for breast cancer proposed by ASCO/College of American Pathologists, uniform intense membrane staining in more than 30% of invasive tumor cells is considered positive for HER2 overexpression. However, because of 2 major differences in HER2 staining patterns between the breast and gastric cancer cells (incomplete membrane staining in a basolateral pattern and greater tumor heterogeneity, both of which are more frequent in gastric cancer), it has been reported that application of this scoring system would not identify many patients with gastric cancer who could otherwise be candidates for anti-HER2 therapy.[9,42] Results from 2 separate series also demonstrated that the HER2 scoring system for breast cancer identified a significantly lower percentage of cases with gastric cancer meeting the criteria for HER2 positivity according to immunohistochemistry (5.4% vs 11% in the ToGA trial).[8,43]

In 2008, Hofmann et al[9] developed a modified 4-tier HER2 scoring system specific for gastric cancer by using the assessment area cutoff of at least 10% stained tumor cells for resection specimens and omitting this area cutoff for biopsy specimens. In a subsequent validation study (447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible among different pathologists.[42] This modified HER2 scoring system was also used in the ToGA trial (GAST-B, 3 of 4, page 8).[8]

ToGA Trial

In this trial, 594 patients with HER2-positive (3+ on immunohistochemistry or FISH-positive [HER2:CEP17 ≥2]), locally advanced, recurrent, or metastatic gastric and EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) or chemotherapy alone.[8] Most patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 and 17 months, respectively, in the 2 groups. A significant improvement was seen in the median OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in patients with HER2 overexpression or amplification (13.8 vs 11 months, respectively; *P*=.046). This study established trastuzumab in combination with chemotherapy as a new standard of care for patients with HER2-positive advanced gastric and EGJ adenocarcinoma.

However, the benefit of trastuzumab was limited only to patients with a score of IHC 3+ or 2+ and FISH-positive. No significant survival benefit was seen for patients who were IHC 0 or 1+ and FISH-positive.[8]

NCCN Recommendations

Given that gastric cancer is often diagnosed at an advanced stage, HER2 testing is now recommended for all patients with metastatic disease at the time of diagnosis (GAST-1, page 533). Subclassification of gastric adenocarcinomas as intestinal- or diffuse-type may have implications for therapy, because intestinal-type cancers are more likely to overexpress HER2. In the ToGA trial, HER2 positivity rates were 32%, 6%, and 20.4%, respectively, for patients with intestinal- and diffuse- or mixed-type cancer.[44]

The guidelines recommend that assessment for HER2 status should be performed first using immunohistochemistry following the modified scoring system used in the ToGA trial.[8,9] A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in situ hybridization techniques. The panel recommends FISH only for cases with IHC 2+, although some institutions routinely perform both IHC and FISH on all cases (GAST-B, 3 of 4, page 538).

In the post hoc subgroup analysis of the ToGA trial, the addition of trastuzumab to chemotherapy substantially improved OS in patients with high HER2 expression (IHC 2+ and FISH-positive or IHC 3+; n=446; 16 vs 11.8 months; hazard ratio [HR] =.65) compared with those with low HER2 expression (IHC 0 or 1+ and FISH-positive; n=131; 10 vs 8.7 months; HR =1.07).[8] Therefore, the guidelines recommend trastuzumab with chemotherapy only for patients with IHC 3+ and IHC 2+ with an evidence of *HER2* amplification by FISH (HER2:CEP17 ratio ≥2). Trastuzumab is not recommended if the IHC score is 0 or 1+.

Summary

Combined modality therapy plays an important role in the management of patients with localized gastric cancer because of higher rates of recurrence and poor overall survival rates associated with surgery alone. The choice of appropriate postoperative therapy depends on the stage, surgical margins, and extent of lymph node dissection. In patients with advanced or metastatic disease, the selection of appropriate systemic therapy should be based on the patient's performance status and HER2 status. Multidisciplinary team management and meticulous selection of patients are critical to achieve the best possible outcomes associated with a particular treatment modality.

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Gastric Cancer, Version 2.2013

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 70% minimum passing score and complete the evaluation at **http://education.nccn.org/node/19849;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. Modified D2 lymph node dissection is associated with a low mortality and reasonable survival times.
   a. True
   b. False
2. Which of the following are appropriate postoperative treatment options for patients with locally advanced and completely resected gastric cancer?
   a. Fluoropyrimidine before and after fluoropyrimidine-based chemoradiation
   b. Perioperative chemotherapy
   c. Postoperative chemotherapy following a modified D2 lymph node dissection
   d. All of the above
3. NCCN Guidelines recommend assessment of HER2 expression with IHC and FISH for all patients with metastatic gastric cancer.
   a. True
   b. False