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Guideline Obeservation

Updates in version 2.2018 of the NCCN guidelines for gastric cancer

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Comment

Preferred Regimen provides by expert group is adjusted: (1) Fluorouracil and cisplatin was no longer the Preferred Regimen for Preoperative Chemoradiation and Perioperative Chemotherapy (recommended as the other regimens); (2) Pembrolizumab (For second-line or subsequent therapy for MSI-H or dMMR tumors) was recommended as the Preferred Regimen for Second-Line or Subsequent Therapy; (3) Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) was no longer the Preferred Regimen for Second-Line or Subsequent Therapy. The NCCN guidelines recommend that PET/CT is used for preoperative staging due to its greater accuracy than either PET or CT alone. It helps identify M1 patients, distinguish local lesions in the early course from those in the late course of the disease, and screen appropriate candidates for surgical treatments. However, preoperative PET/CT assessment for gastric cancer has a long way to go before it can be routinely performed in our country because CT assessment remains the first choice in most cases. Nevertheless, PET/CT is worth recommending to patients with difficult staging situations. The indications for neoadjuvant treatment are still highly controversial among Eastern and Western countries. A common status quo in our country is that more aggressive surgeries are performed with a low proportion of cases receiving preoperative radiochemotherapy. Phase III MAGIC trial, compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone, established that perioperative chemotherapy improved OS and PFS in patients with non-metastatic stage II and higher gastric and EGJ adenocarcinoma. In the FNCLCC ACCORD 07 trial (n = 224 patients; 25% had gastric adenocarcinoma), Ychou *et al* reported that perioperative chemotherapy with fluorouracil and cisplatin (2 or 3 preoperative cycles and 3 or 4 postoperative cycles) significantly increased the curative resection rate, DFS, and OS in patients with resectable cancer. Phase II/III AIO-FLOT4 trial, Al-Batran et al compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen with a primary endpoint of pCR of the primary tumor. FLOT was associated with significantly higher proportions of patients achieving pCR than was ECF (16%; 95% CI, 10–23 vs. 6%; 95% CI, 3–11; P = 0.02). Additionally, FLOT was associated with a reduction in the percentage of patients experiencing at least one grade 3–4 adverse event. Although the NCCN guidelines recommend that patients with T2 stage or higher gastric cancer should prioritize perioperative chemotherapy + surgery, a treatment model of surgery + postoperative adjuvant therapy is more common in China. Therefore, the preoperative MDT discussion and a strengthened collaboration among the Departments of Surgery, Oncology, and Imaging are helpful and most important in optimizing patients' treatment plans. The recommendations of the NCCN guidelines for preoperative radiochemotherapy for gastric cancer are primarily based on the results of the CROSS study, which mainly enrolled patients with esophageal carcinoma and adenocarcinoma of the esophagogastric junction. Therefore, the recommendation level for preoperative radiochemotherapy in gastric cancer is not as high as that for perioperative chemotherapy, and more advanced evidence should be expected. In addition, special attention should be paid to the prevention and treatment of adverse reactions of the three-drug combination scheme. Even in the western population, the tolerability of the preoperative ECF/DCF/FLOT regimen remains worrisome; thus, optimization of the regimen and identification of appropriate candidates among the population should be implemented in the future.This edition of the guidelines adds a reasonable assessment on the efficacy of preoperative radiochemotherapy and emphasizes that patients who cannot achieve R0 resection after preoperative radiochemotherapy or who have undergone metastases during preoperative radiochemotherapy should be subjected to palliative supportive care.

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Comment

We believe that failure of radiochemotherapy in these patients may indicate that the disease itself is highly invasive and has a poor prognosis. To some extent, if the metastases occur during preoperative radiochemotherapy, these patients may also suffer from tumor recurrence and metastasis long before they are directly treated with surgeries without neoadjuvant therapy. Therefore, preoperative radiochemotherapy can prevent unnecessary surgeries in this group of patients. However, this point of view remains an idea because designing a controlled clinical study to confirm it is currently impractical, and patients with limited-stage gastric cancer who would present metastases immediately after the surgery cannot be identified beforehand. However, we know that, as a whole, preoperative radiochemotherapy does increase the overall survival in patients with T2 stage or higher gastric cancer. Several questions, such as the optimization of preoperative radiochemotherapy regimens, value of immunotherapy in neoadjuvant therapy, and more accurate screening methods in identifying patients who can benefit from preoperative radiochemotherapy, are still worth studying.

MSI (dMMR) and PD-L1, following HER2, have become the recommended detection markers for advanced gastric cancer and are used to guide the application of anti-PD-1/PD-L1 immune checkpoint inhibitors. Currently, the primary existing problem is that the testing standards for MSI and PD-L1 have not been established, followed by the lack of qualification standards for the testing centers. Second, in addition to patients with advanced stage gastric cancer, the therapeutic value of the drug should be explored in the perioperative population.

The strict procedures for the comprehensive management of hereditary gastric cancer in our country are lacking, and preventive total gastrectomy has not been actively recommended and accepted. In this regard, patient and family education and collection of their pedigree data are necessary. Patients who have not undergone tumor resection should be strictly and regularly monitored.

Updates in Version 2.2018 of the NCCN guidelines for Gastric Cancer from Version 1.2018

GAST-F principles of systemic therapy

The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.

The regimen and dosing schedule pages were updated to reflect the changes noted above.

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in version 1.2018 of the NCCN guidelines for gastric cancer from version 5.2017

Workup

PET/CT evaluation, from skull base to mid-thigh, if no evidence of M1 disease.

Endoscopic ultrasound (EUS) if early stage disease suspected or if early versus locally advanced disease needs to be determined (preferred).

Primary treatment

Medically fit, potentially resectable; cT2 or higher, Any N: "Perioperative chemotherapy (category 1)" changed to a preferred recommendation.

After perioperative chemotherapy and preoperative chemoradiation, a new "Response Assessment" pathway (GAST-3) was added. Previously surgery was recommended for these patients.

Surgically unresectable: Systemic therapy added as an option.

Postoperative management for patients who have not received preoperative chemotherapy or chemoradiation

R0 resection; pT3, pT4, Any N or Any pT, N+:

Revised, "Fluoropyrimidine (fluorouracil or capecitabine), then fluoropyrimidine-based chemoradiation, then fluoropyrimidine (fluorouracil or capecitabine), if less than a D2 dissection (category 1)."

"Chemotherapy for patients who have undergone primary D2 lymph node dissection" changed from a category 2A to category 1.

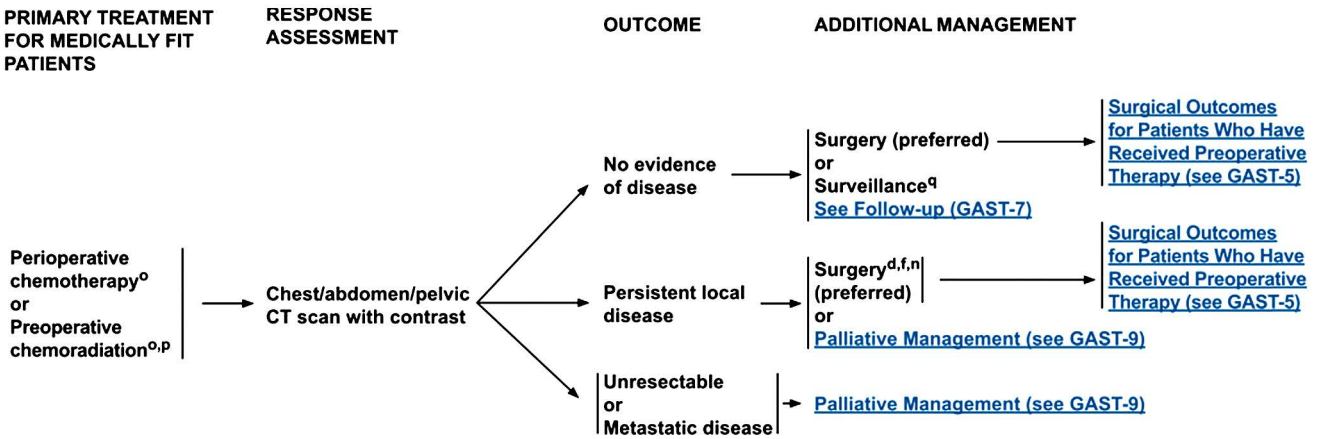
Follow-up/Surveillance

"Monitor for nutritional deficiency (eg, B12 and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated".

P stage II/III or yp stage I-III (treated with neoadjuvant ± adjuvant therapy); Fourth bullet revised: "CT chest/abdomen/pelvis with oral and IV contrast every 6–12 months for first 2 years, then annually up to 5 years and/or can consider PET/CT as clinically indicated"

Palliative management

Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2: "Chemoradiation (only if locally



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

- **MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic gastric carcinoma,[7] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.**

PD-L1 Testing

- **PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric carcinomas in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on FFPE tissue is available as an aid in identifying gastric and gastroesophageal junction adenocarcinoma patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.**
- **Assessment of PD-L1 Protein Expression in Gastric Cancers**
  - **This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in FFPE tissues from gastric adenocarcinoma. A specimen is considered to have PD-L1 expression if the Combined Positive Score (CPS) ≥1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.**

unresectable and not previously received)" added as an option.

For both pathways, revised, " Best supportive care" instead of "Palliative care".

Principles of pathologic review and biomarker testing

Title revised, "Principles of Pathologic Review and Biomarker Testing".

This section was extensively revised and includes new recommendations for "Microsatellite Instability (MSI) or Mismatch Repair (MMR)Testing" and "PD-L1 Testing".

Principles of genetic risk assessment

Surveillance recommendations

Hereditary diffuse gastric cancer: Revised, "Prophylactic total gastrectomy is recommended between ages 18 and 40 for CDH1 mutation carriers. A baseline endoscopy is indicated prior to prophylactic total gastrectomy. Intraoperative frozen sections should be..."

Lynch syndrome (LS): "Selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum). See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal for additional screening recommendations.

Principles of systemic therapy

Perioperative chemotherapy revisions

"Fluoropyrimidine and oxaliplatin" changed to a preferred option.

"Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)" added as an option with corresponding footnote, "Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit".

The following regimens were removed:

ECF (epirubicin, cisplatin, and fluorouracil) (category 2B).

ECF modifications (category 2B for all modifications)

– Epirubicin, oxaliplatin, and fluorouracil

– Epirubicin, cisplatin, and capecitabine

– Epirubicin, oxaliplatin, and capecitabine

The regimen and dosing schedule pages were updated to reflect the changes on GAST-2 of 11 and GAST-F 3 of 11.

Staging

The AJCC 7th Edition Cancer Staging Tables were updated to the 8th edition.

Definitions of Histologic Grade (G) was revised.

Definitions of histologic grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

AJCC PROGNOSTIC STAGE GROUPS were added.

Clinical staging (cTNM)

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

Pathological (pTNM)

	p T	p N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1 or N2	M0
	T4b	N0	M0
Stage IIB	T1	N3b	M0
	T2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1 or N2	M0
Stage IIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1

Pos-neoadjuvant therapy (ypTNM)

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

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