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CANCER COMMUNICATIONS Open Access

GUIDELINES

# The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2023

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**Abbreviations:** CSCO, Chinese Society of Clinical Oncology; MMR/MSI, mismatch repair/microsatellite instability; MSS, microsatellite stability; PD-L1, programmed death ligand-l; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; ISH, in situ hybridization; DSISH, double signal in situ hybridization; ADCs, antibody-drug conjugates; dMMR, deficient DNA MMR; MSI-H/L, MSI-high/low; TNM, tumor-node-metastasis; AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer; D, type of lymphadenectomy; NCCN, National Comprehensive Cancer Network; EUS, endoscopic ultrasound; CT, computed tomography; MRI, Magnetic resonance imaging; PET, positron emission tomography; c/p/ypTNM, clinical/pathological/post-neoadjuvant classification of the TNM staging system; EGJ, esophagogastric junction; MSI, microsatellite instability; PCR, polymerase chain reaction; NGS, next-generation sequencing; iRECIST, immune Response Evaluation Criteria in Solid Tumors; DW-MRI, diffusion-weighted MRI; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; WHO, World Health Organization; TRG, tumor regression grade; ctDNA, circulating tumor DNA; double signal in situ hybridization, double signal in situ hybridization; CFDA, China Food and Drug Administration; PD-1, programmed death protein-1; TMB, tumor mutational burden; EBV, Epstein-Barr virus; pMMR, proficient MMR; MLH1, MutL Homolog 1; PMS2, Postmeiotic Segregation Increased Homolog 2; NCI, National Cancer Institute; CPS, Combined Positive Score; TAP, Tumor Area Positivity; TRK, tropomyosin receptor kinase; *NTRK*, *neurotrophic tyrosine receptor kinase*; c-MET, cellular-mesenchymal-epithelial transition; UL0/1, ulceration present/absent; SM1, submucosal infiltration depth <500$\mu$m VM, vertical margin; Ly, lymphatic invasion; V0, venous invasion absent; HM0, horizontal margin negative; OS, overall survival; HR, hazard ratio; CI, confidence interval; LATG/LAPG/LADG, laparoscopy-assisted total gastrectomy/proximal/distal gastrectomy; RADG, robot-assisted distal gastrectomy; XELOX, capecitabine (Xeloda) and oxaliplatin (Eloxatin); SOX, S-1 and oxaliplatin; XP, capecitabine (Xeloda) and cisplatin; FOLFOX, folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; DS, S-1 plus docetaxel; PF, cisplatin plus 5-FU; MDT, Multidisciplinary Team; DT, radiation dose of tumor; DOS, docetaxel, oxaliplatin and S-1; FLOT4, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel-4; RFS, recurrence-free survival; SOXRT, SOX plus radiotherapy; DFS, disease-free survival; F-OX, fluoropyrimidine plus oxaliplatin; pCR, pathologic complete response; ECC, epirubicin, cisplatin and capecitabine; ECX, epirubicin plus cisplatin plus capecitabine; ECOG, Eastern Cooperative Oncology Group; PS, performance score; D, three dimension; MPR, major pathological response rates; ICIs, immune checkpoint inhibitors; IMRT, intensity-modulated radiation therapy; mOS, median OS; DPD, dihydropyrimidine dehydrogenase deficiency; PFS, progression free survival; ORR, overall response rate; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; ITT, intention to treat; DCR, disease control rate; DoR, duration of response; PR, progressive response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CAR, Chimeric antigen receptor; IPC, Intraoperative peritoneal chemotherapy; EIPL, extensive intraoperative peritoneal lavage; RR, risk ratio; OR, odds ratio; HIPEC, hyperthermic intraperitoneal perfusion chemotherapy; CEA, carcinoembryonic antigen; CA199, cancer antigen 199; RFA, radiofrequency ablation; MWA, microwave ablation; HAIC, epatic artery infusion chemotherapy; TACE, transarterial chemoembolization; SBRT, stereotactic body radiotherapy; ERAS, enhanced recovery after surgery; ONS, nutritional supplements; TEN, total enteral nutrition; PEN+PPN, partial enteral nutrition combined with partial

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parenteral nutrition; TPN, total parenteral nutrition; NSAIDs, non-steroidal anti-inflammatory drugs; APC, argon plasma coagulation; PPIs, proton pump inhibitors; CTCAE, Common Terminology Criteria for Adverse Events; EPO, erythropoietin; rhG-CSF, recombinant human granulocyte colony-stimulating factor; TPO, thrombopoietin; IL, interleukin; HDGC, hereditary diffuse gastric cancer; FIGC, family internal gastric cancer; GAPPS, gastric proximal polyposis of the stomach; FAP, familial adenomatous dysplasia; *CTNNA1*, alpha-E-catenin 1; JP, Juvenile polyposis; IGCLC, International Gastric Cancer Linkage Consortium; AFAP, attenuated FAP; *EPCAM*, *Epithelial Cell Adhesion Molecule*; *SMAD4*, *SMAD family member 4*; *BMPR1A*, *Bone Morphogenetic Protein Receptor Type 1A*; *STK11*, *Serine/Threonine Kinase 11*; *APC*, *Adenomatous Polyposis Coli*;.

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**Abstract**

The 2023 update of the Chinese Society of Clinical Oncology (CSCO) Clinical Guidelines for Gastric Cancer focuses on standardizing cancer diagnosis and treatment in China, reflecting the latest advancements in evidence-based medicine, healthcare resource availability, and precision medicine. These updates address the differences in epidemiological characteristics, clinicopathological features, tumor biology, treatment patterns, and drug selections between Eastern and Western gastric cancer patients. Key revisions include a structured template for imaging diagnosis reports, updated standards for molecular marker testing in pathological diagnosis, and an elevated recommendation for neoadjuvant chemotherapy in stage III gastric cancer. For advanced metastatic gastric cancer, the guidelines introduce new recommendations for immunotherapy, anti-angiogenic therapy and targeted drugs, along with updated management strategies for human epidermal growth factor receptor 2 (HER2)-positive and deficient DNA mismatch repair (dMMR)/microsatellite instability-high (MSI-H) patients. Additionally, the guidelines offer detailed screening recommendations for hereditary gastric cancer and an appendix listing drug treatment regimens for various stages of gastric cancer. The 2023 CSCO Clinical Guidelines for Gastric Cancer updates are based on both Chinese and international clinical research and expert consensus to enhance their applicability and relevance in clinical practice, particularly in the heterogeneous healthcare landscape of China, while maintaining a commitment to scientific rigor, impartiality, and timely revisions.

**KEYWORDS**
Chinese Society of Clinical Oncology (CSCO), gastric cancer, diagnosis, surgery, neoadjuvant, adjuvant, radiotherapy, chemotherapy, targeted therapy, immunotherapy

## BACKGROUND

There exist differences in the epidemiological characteristics, clinicopathological features, tumor biological characteristics, treatment patterns and drug selections between gastric cancer patients from Eastern and Western countries. The Chinese Society of Clinical Oncology (CSCO) has organized a panel of senior experts specializing in all sub-specialties of gastric cancer to compile a clinical guideline for the diagnosis and treatment of gastric cancer since 2016 and renews it annually for standardizing cancer treatment in China. These guidelines are designed in line with evidence-based medicine principles while also accounting for the accessibility of healthcare resources and the latest advancements in precision medicine.

In recent years, there has been a shift in the approach to developing clinical practice guidelines, with a focus on healthcare resource availability, particularly for developing countries and regions where there are significant differences in healthcare resources. China, given its vast geographic expanse and disparities in economic and academic development across regions, requires CSCO guidelines to comprehensively address three important aspects: regional disparities, availability of drugs and diagnostic/treatment modalities, and societal value of cancer treatments. Therefore, CSCO guidelines categorize recommendations for each clinical question based on the strength of evidence from evidence-based medicine and expert consensus while also considering the accessibility and cost-effectiveness of available therapies. Recommendations backed by robust evidence and characterized by high accessibility are categorized as Grade I, while those supported by relatively strong evidence but marked by lower expert consensus or limited accessibility are designated as Grade II and recommendations that are clinically practical but lack substantial evidence are classified as Grade III.

The 2023 CSCO Clinical Guidelines for Gastric Cancer covers the diagnosis, treatment, follow-up and screening of gastric cancer. Based on the 2021 version of the CSCO Clinical Guidelines for Gastric Cancer, the 2023 version has updated the following:

1. Gastric cancer diagnosis:

(i) Imaging diagnosis: To enhance the standardization and applicability of imaging reports, a structured template content is now provided for imaging reference reports in the appendix.
(ii) Pathological diagnosis: Due to emerging evidence in the last two years related to targeted therapy and immunotherapy, recommendations and standards for molecular marker testing, such as mismatch repair/microsatellite instability (MMR/MSI), programmed death ligand-l (PD-L1) and Claudin18.2, have been revised.

2. Treatment of non-metastatic gastric cancer:

(i) Comprehensive treatment strategy for resectable gastric cancer: The recommendation for neoadjuvant chemotherapy in stage III gastric cancer has been upgraded from level III to level I.
(ii) Surgical treatment for resectable gastric cancer: Updates have been made regarding surgical techniques, the extent of lymph node dissection, and standards for reconstructing the digestive tract.
(iii) Perioperative treatment for resectable gastric cancer: New information regarding perioperative immunotherapy/targeted therapy has been included with explanatory notes.

3. Treatment of advanced/metastatic gastric cancer:

(i) Choice of anti-cancer drugs:
   a. Immunotherapy: Based on recent clinical evidences and the release of phase III study results, anti-PD-L1 monoclonal antibody has been moved from third-line monotherapy to first-line combination chemotherapy. Recommendations and explanations for selecting different anti-PD-L1 monoclonal antibodies and suitable patient groups are provided.
   b. Anti-angiogenic therapy: The combination of ramucirumab with paclitaxel as a second-line treatment option is given priority.
   c. Claudin18.2 targeted drugs: Annotations have been added to provide information on Claudin18.2 monoclonal antibodies and clinical research data.
(ii) Management of HER2-positive gastric cancer:
   a. For HER2-positive (immunohistochemistry [IHC] 3+ or 2+ with fluorescent in situ hybridization [FISH]+) gastric cancer patients, pembrolizumab combined with first-line trastuzumab and chemotherapy is recommended.
   b. For HER2-positive (IHC 3+ or 2+) gastric cancer patients, targeted HER2 antibody-drug conjugates (ADCs) are added as third-line and above and are given priority.
(iii) Management of deficient DNA MMR (dMMR)/MSI-high (MSI-H) population: This is now independently categorized, with recommendations provided for immunotherapy alone, along with evidence-based drugs provided in the annotations.

4. Screening for hereditary gastric cancer: Detailed recommendations for screening assessments are outlined.

CSCO guidelines are based on both Chinese and international clinical research findings, supplemented by insights and opinions of CSCO experts, to establish recommendation grades. This methodological approach aims to facilitate their referencing and application in clinical settings. The CSCO Guidelines Expert Committee firmly asserts that guidelines founded on robust evidence while concurrently taking into consideration accessibility and incorporating expert perspectives are better suited for addressing the intricacies of clinical practice, particularly in China, and are committed to a thorough evaluation and active incorporation of suggestions during guideline updates, with a commitment to maintaining the scientific rigor, impartiality, and timeliness of CSCO guidelines.

## 1 | GASTRIC CANCER DIAGNOSIS

### 1.1 | Basic principles

The tumor-node-metastasis (TNM) staging system released by the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) is the internationally accepted standard for gastric cancer staging, and the 8th edition is used throughout this guideline. Initial evaluation of gastric cancer mainly includes imaging and pathological examinations for diagnosis. Other examinations include complete physical examination, blood chemistry tests, endoscopy (endoscopic ultrasound [EUS] and fine-needle biopsy), metastatic lesion biopsy, diagnostic laparoscopy, and diagnostic intraperitoneal fluid examination.

Chest, abdominal and pelvic computed tomography (CT) is the primary diagnostic modality for pre-treatment clinical staging. Magnetic resonance imaging (MRI), laparoscopic exploration and positron emission tomography (PET) scan are alternatives to CT for the diagnosis of liver, peritoneal, and systemic metastases, respectively. The imaging reports should clearly describe observations

to support the clinical classification and stage (cTNM) evaluation of the disease.

Histopathological examination is the gold standard for gastric cancer diagnosis and is the basic prerequisite for treatment initiation. The postoperative histopathological staging (pTNM) and diagnosis provide information for a complete assessment of the tumor to predict and plan personalized treatment strategies. Currently, the molecular classification of gastric cancer is based on the HER2 expression in tumor tissues, and it is the basis for selecting anti-HER2 targeted therapy. All cases pathologically diagnosed as gastric or esophagogastric junction (EGJ) adenocarcinoma should undergo HER2 assessment. It is recommended to also evaluate the MSI) by polymerase chain reaction (PCR) or dMMR status by IHC in gastric cancer tissues for all newly diagnosed gastric cancer cases. The use of next-generation sequencing (NGS) and liquid biopsy in gastric cancer remains in an investigational phase.

## 1.2 | Imaging and endoscopy

| Purpose (diagnosis/evaluation) | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Definitive diagnosis | Gastroscopy + biopsy (Evidence 1A) | Cytological examination[a] (Evidence 2A) | |
| Location evaluation | • Gastroscopy (Evidence 1A)<br>• Abdominal enhanced CT (Evidence 1A) | Abdominal MRI (Evidence 2A) | X-ray barium double contrast radiography (Evidence 2B) |
| Staging evaluation | • Abdominal and pelvic enhanced CT[b] (Evidence 1B)<br>• Chest CT[c] (Evidence 1B)<br>• EUS[d] (Evidence 1A) | • Abdominal MRI[e] (Evidence 2A)<br>• PET/CT (Evidence 2A)<br>• Diagnostic laparoscopy and examination of intraperitoneal washings[f] (Evidence 1B) | |
| Treatment efficacy evaluation | Abdominal and pelvic enhanced CT[g] (Evidence 1A) | • Gastroscopy (Evidence 2A)<br>• PET/CT (Evidence 1B)<br>• Abdominal MRI (Evidence 2A) | Functional imaging examination[h] (Evidence 3) |

Abbreviations: CT, computed tomography; MRI, Magnetic resonance imaging; PET, positron emission tomography.

**Notes**

[a]If it is not possible to obtain a pathological diagnosis of gastric cancer despite repeated gastroscopic biopsies, cytological examination of ascites/pleural effusion or pathological examination of metastatic lesions can be used as the basis for qualitative diagnosis.

[b]Ensure that the gastric cavity is fully dilated through the gas or water under effective hypotonic procedures before examination [1, 2]. Multiphase contrast-enhanced scans combined with multi-planar reconstruction are recommended for diagnosis [3]. Plain abdominal CT scans are not recommended. If patients have contraindications to the contrast agent for enhanced CT, MRI or EUS is recommended. The staging accuracy of the radiologist might be potentially increased with the assistance of radiomics [4, 5].

[c]Chest CT can detect lung metastasis more effectively than X-ray plain film [3]. For EGJ carcinoma, enhanced CT scan of the chest is recommended to assess the extent of esophageal infiltration and status of mediastinal lymph nodes.

[d]EUS should be performed in qualified centers. In the 8th edition of the AJCC/UICC staging system for gastric cancer and EGJ cancer, EUS is recommended as the preferred modality for the clinical evaluation of tumor invasion depth (cT) [2]. EUS cT staging not only enables direct observation of the lesions but can also provide visual descriptions regarding the different anatomical layers of the gastric wall and non-homogeneous hypoechoic regions of the cancers, which could suggest the destruction of corresponding layers of the gastric wall. Simultaneously, EUS can detect enlarged perigastric lymph nodes, EGJ area and nearby metastatic lesions in the liver and peritoneal cavity. EUS is helpful for the diagnosis and clinical staging of gastric cancer and assessment of response to neoadjuvant therapy. A systematic meta-analysis reported that the overall sensitivity and specificity of EUS for distinguishing T1 to T2 (superficial) versus T3 to T4 (advanced) gastric cancer was 0.86 and 0.90, respectively [6]. Further, the diagnostic ability of EUS to distinguish T1 (early gastric cancer) versus T2 (muscle-infiltrating) tumor was 0.85 and 0.90, and T1a (mucosal) versus T1b (submucosal) cancer was 0.87 and 0.75, respectively [6].

[e]Liver contrast MRI is recommended for further confirmation of CT undetermined liver metastasis. Hepatocyte-specific contrast agent can be used based on clinical conditions [7].

[f]Diagnostic laparoscopic exploration and examination of intraperitoneal washings are recommended for detecting occult metastasis when peritoneal metastasis is suspected [2]. For intraperitoneal lavage, 200 mL of normal saline can be infused into the different quadrants of the abdominal cavity and collect ≥50 mL of the lavage fluid for cytological examinations.

[g]According to the response evaluation criteria in solid tumors (Response Evaluation Criteria in Solid Tumors [RECIST]) criteria (version 1.1) [8], metastasis nodules of the liver, lung, or peritoneum with a long diameter ≥1 cm or lymph nodes with a short diameter ≥1.5 cm could be enrolled as target lesions for treatment evaluation. The thickness of primary lesions in the stomach can be used as a reference for therapeutic assessment but could not be considered as a target lesion. In regard to immunotherapy, treatment efficacy can be evaluated by referring to the immune RECIST (iRECIST) criteria [9].

[h]Small sample-sized studies have shown that volume measurement [10] and functional imaging parameters such as the apparent diffusion coefficient value of diffusion-weighted MRI (DW-MRI) [11] and iodine concentration of spectral CT examinations [12] can assist in the evaluation of treatment efficacy of gastric cancer and can be used as a reference for evaluating treatment of atypical cases. Further, deep learning technology for CT has also shown potential in assisting the response evaluation of gastric cancer efficacy [13].

## 1.3 | Pathological diagnosis

### 1.3.1 | Histopathological diagnosis

| Sample type | Grade I recommendations | | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|
| Gross examination | Microscopic assessment | | | |
| Biopsy specimen* | Evaluation of the size and number of samples | Confirm the histopathology of the lesion:<br>• Cancerous/non-cancerous<br>• Benign/malignant<br>• Histological subtype<br>• Depth of invasion (if possible) | Immunohistochemical examination for diagnosis if needed[j] | Evaluate the status of *Helicobacter pylori* infection[m] (Evidence 1B) |
| Endoscopic resection specimen[a] (EMR/ESD) | • Tumor site[b]<br>• Tumor size ($cm^3$) | Intra-epithelial neoplasm/adenoma (low grade/high grade)Invasive carcinoma:<br>• Histological subtype[d]/ Lauren classification[e]<br>• Histological grade<br>• The depth of penetration into the gastric wall<br>• The proximal/distal margin and the deep margin<br>• Vascular and lymphatic invasion | • Immunohistochemical examination for diagnosis if needed[j]<br>• Early-stage gastric cancer<br>• Macroscopic appearance[k] | Evaluate the status of *Helicobacter pylori* infection[m] (Evidence 1B) |
| Surgical resection specimens for those without neoadjuvant therapy[#] | • Type of the surgical specimen<br>• Tumor site<br>• Tumor size ($cm^3$)<br>• Distance of tumor from the proximal and distal margin<br>• The stations and number and of lymph nodes retrieved (at least 16 lymph nodes and/or preferentially >30 lymph nodes to be retrieved) [c] | • Histological subtype/ Lauren classification/ Histological grade (G1, G2, G3)<br>• The depth of penetration into the gastric wall (pT classification)<br>• Vascular, lymphatic, and perineural invasion<br>• Proximal/distal margin[f]<br>• Involvement of the esophagus/duodenum (if resected)<br>• Number of positive lymph nodes and total number of lymph nodes examined (pN classification)<br>• Number of lesions[g]<br>• Distant metastasis (pM stage)[h]<br>• pTNM stage ($8^{th}$ AJCC/UICC edition) | • Immunohistochemical examination for diagnosis if needed[j]<br>• Advanced stage gastric cancer<br>• Macroscopic appearance[l] | Evaluate the status of *Helicobacter pylori* infection[m] (Evidence 1B) |
| Surgical resection specimens for those who had neoadjuvant therapy[#] | • Type of the surgical specimen<br>• Tumor site<br>• Tumor size ($cm^3$)<br>• Distance of tumor from the proximal and distal margin | • Histological subtype/Lauren classification/Histological grade (G1, G2, G3)<br>• The depth of penetration into the gastric wall (pT classification) | • Immunohistochemical examination for diagnosis if needed[j] Gastric cancer with the advanced stage[l] | Evaluate the status of *Helicobacter pylori* infection[m] (Evidence 1B) |

| Sample type | Grade I recommendations | | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|
| Gross examination | Microscopic assessment | | | |
| | • The stations and number and of lymph nodes retrieved (at least 16 lymph nodes and/or preferentially >30 lymph nodes to be retrieved) (If lesion is not evident, careful examination and multipoint sampling should be made to avoid misdiagnosis or down staging) | • Vascular, lymphatic, and perineural invasion<br>• Proximal/distal margin[f]<br>• Involvement of the esophagus/duodenum (if resected)<br>• Number of positive lymph nodes and total number of lymph nodes examined (pN classification)<br>• Number of lesions[g]<br>• Distant metastasis (pM stage) [h]<br>• pTNM stage (8th AJCC/UICC edition)<br>• TRG[i]<br>• ypTNM stage (8th AJCC/UICC edition) | | |

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; pT, pathological tumor depth invasion classification; pN, pathological nodal classification; pM, pathological distant metastasis classification; ypTNM, post neoadjuvant pathological tumor-node-metastasis classification; AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer.

*When a diagnosis cannot be established through biopsy, cytological brushings or lavage fluid may serve to confirm the presence of a tumor. In cases of unresectable advanced gastric cancer, an exfoliative cytological examination of their peritoneal ascites or pleural effusion, along with biopsies from distant metastases, can aid in pathological diagnosis.

#Institutions are encouraged to adopt a standardized pathological report template, as it streamlines diagnosis and enables consistent clinical analysis. A reference template is provided in section 5.3.

**Notes**:

[a]Endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) have emerged as the new alternative treatment for early-stage gastric cancer [14, 15]. EMR/ESD specimens should be meticulously resected, collected and prepared according to standardized protocols by the endoscopists or surgeons. It is advised that all samples be sectioned at intervals of 2-3 mm, perpendicular to the mucosal surface [16–18].

[b]As per the 8th edition of the AJCC/UICC staging system for gastric cancer, esophageal cancer, and EGJ carcinoma [19], the staging criteria for EGJ carcinoma or gastric-cardia carcinoma are specified as follows: 1) When the tumor infiltrates the gastroesophageal boundary and its epicenter is <2 cm proximal from the EGJ (Siewert I and II), staging criteria for esophageal cancer should be applied; 2) In cases where the tumor invades the gastroesophageal boundary but its epicenter is located ≥2 cm distal from the EGJ (Siewert III), the staging criteria for gastric cancer should be utilized. Thus, accurately determining the location of the gastroesophageal boundary and assessing whether it has been invaded by the tumor are crucial considerations.

[c]In patients who have undergone radical gastrectomy without neoadjuvant therapy, it is advisable to pathologically evaluate at least ≥16 lymph nodes for proper staging. However, for a more precise staging evaluation, the ideal number of evaluated lymph nodes should exceed 30. To facilitate an accurate assessment of lymph node metastasis extent, surgeons and pathologists are recommended to systematically collect and categorize peri-gastric lymph nodes based on their respective stations. These details should be included in the postoperative pathological report along with the total number of metastatic lymph nodes and the total number of lymph nodes examined by clinicians for comprehensive evaluation.

[d]The histopathological classification of gastric cancer follows the guidelines outlined in the "World Health Organization (WHO) classification of tumours of the digestive system (2019 edition)" [20]. In instances where achieving a pathological diagnosis poses challenges in lower-tier hospitals, it is advisable to forward the specimen samples to a specialized center/hospital for further evaluation.

[e]As per the Lauren classification [21], gastric adenocarcinoma is classified into intestinal type, diffuse type and mixed type based on its histological growth patterns. The intestinal type typically presents as intestinal metaplasia, predominantly comprising highly to moderately differentiated atypical glands. Occasionally, proximal regions of tumor invasion may exhibit poor differentiation. In contrast, the diffuse type is characterized by loosely adherent cells that extensively infiltrate gastric walls, displaying minimal to no glandular formation. These cells typically appear small, scattered, or clustered, with noticeable interstitial fiber proliferation. The mixed type consists of an approximately equal distribution of intestinal and diffuse type cells.

[f]This guideline specifies a positive surgical margin as the detection of cancer cells within a 1 mm distance from the resected margin.

[g]The identification of carcinomatous nodules within sub-serous adipose tissues neighboring the primary tumor site should be considered as regional lymph node metastasis, regardless of the absence of residual lymph node tissues [19]. It is advisable to distinctly document both metastatic lymph nodes and carcinomatous nodules for proper record-keeping.

[h]Tissues confirmed as metastatic and obtained from areas distant to the stomach should be classified as distant metastasis (pM1). This classification encompasses metastatic tissues from remote lymph node stations and cancerous cells identified in other organs, including instances of intraperitoneal washings or peritoneal seedings [19].

[i]Assessment of the tumor regression grade (TRG) involves evaluating residual tumor cells and the extent of fibrosis following anti-cancer treatment, as outlined in the 8th AJCC TNM staging system [19] or the guidelines from National Comprehensive Cancer Network (NCCN) [22]. The 8th edition of the AJCC staging

system introduced the post-neoadjuvant pathological tumor-node-metastasis classification (ypTNM) to depict the postoperative pathological staging subsequent to neoadjuvant therapy.

[j]In cases where establishing a pathological diagnosis poses challenges, gastric cancer-related markers can serve for differential diagnosis, prognostic assessment, and guiding treatment or follow-up [23].

[k]Early-stage gastric cancer is characterized by its confinement within the mucosa and submucosa, regardless of evidence of regional lymph node metastasis.

[l]Advanced gastric cancer is delineated by infiltration into the muscularis propria or the deeper layer of the gastric wall. The Borrmann classification consists of four subtypes: Type I represents a nodular polypoid tumor; Type II indicates a local central, bowl-shaped ulcer with distinct elevated margins; Type III suggests an infiltrating ulcerative tumor with indistinct boundaries; and Type IV depicts a diffuse tumor characterized by poorly demarcated, infiltrative growth (local Borrmann Type IV, diffuse tumor infiltration of the gastric wall [linitis plastica]).

[m]The 8th edition of the AJCC/UICC staging system for gastric cancer mandates the documentation of the *Helicobacter pylori* infection status [19].

## 1.3.2 | Molecular examination

| Molecular classification | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Following a pathological diagnosis of gastric cancer, molecular profiling[a] should be undertaken, directing treatment based on the molecular classification. | HER2 assessment is recommended for all cases of gastric adenocarcinoma[b-d] (Evidence 1A);<br>Evaluation of MSI/dMMR status in all new gastric cancer cases is recommended[e-g] (Evidence 1B) | The assessment of PD-L1 expression status is advised for patients scheduled to undergo treatment with PD-1/PD-L1 inhibitors[h] (Evidence 2A) | Detection of the NTRK fusion gene[i]<br>Detection of the Claudin18.2 expression[j] (Evidence 2B) |

Abbreviations: HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; dMMR, deficient DNA mismatch repair; PD-L1, programmed death-ligand 1; *NTRK*, neurotrophic tyrosine receptor kinase.

**Notes**:

[a]In cases of treatment failure following standard therapy for advanced gastric cancer, NGS can aid in identifying potential therapeutic targets. It is crucial to prioritize certified platforms and products that adhere to stringent quality control and standardized operational processes are recommended to ensure the reliability of the obtained results.

[b]HER2 status has shown correlation with the response and prediction of survival in patients with advanced gastric cancer receiving trastuzumab treatment. Therefore, it is advisable to conduct HER2 status testing for all gastric cancer [24–27].

[c]According to studies [28, 29], high-throughput sequencing-based serial circulating tumor DNA (ctDNA) genotyping emerges as an efficient approach for tracking resistance to trastuzumab, relying on variations in HER2 copy numbers in HER2-positive gastric cancer. In cases where tissue biopsy is unattainable, evaluating HER2 amplification through liquid biopsy stands as a promising alternative. Additionally, *HER2* amplification detected from ctDNA may serve as a means to monitor the response for gastric cancer patients to trastuzumab.

[d]IHC and in situ hybridization (ISH) techniques utilized for HER2 assessment must strictly adhere to the "Guidelines for HER2 detection in gastric cancer (2016)" [30]. All associated tests (IHC, FISH/double signal in situ hybridization [DSISH]) should utilize kits approved by the China Food and Drug Administration (CFDA).

[e]In recent years, immune checkpoint inhibitors targeting programmed death protein-1 (PD-1) and its ligand-1 (PD-L1) have gained significant attention in the field of tumor immunotherapy. For patients planned for immunotherapy, it is advisable to assess MSI/MMR status and explore the link between PD-L1 expression and tumor mutational burden (TMB). The correlation of Epstein-Barr virus (EBV) status with immunotherapy is still undergoing comprehensive elucidation.

[f]MMR protein detection involves the immunohistochemical assessment of MutL homolog 1 (MLH1), postmeiotic segregation increased homolog 2 (PMS2), MSH2, and MSH6 proteins within the nucleus. The absence of any of these four proteins categorizes the patient as dMMR, whereas the presence of all four proteins classifies the patient as proficient MMR (pMMR).

[g]MSI detection is recommended using the 5 microsatellite loci (BAT25, BAT26, D5S346, D2S123, D17S250) proposed by the US National Cancer Institute (NCI). Grading criteria are defined as follows: microsatellite stability (MSS) indicates stability across all 5 loci, MSI-L is identified when 1 locus displays instability, and MSI-H is diagnosed when ≥2 loci exhibit instability. MSI typically arises due to mutations or function defects in MMR genes, reflected in MMR protein analysis. Consequently, dMMR can be equated to MSI-H, while pMMR corresponds to MSI-L or MSS.

[h]It is advisable to utilize certified antibodies and platforms for PD-L1 testing to ensure the reliability of test results. For a sample to be deemed suitable for PD-L1 assessment, a minimum of 100 tumor cells should be present within the sample. The testing report is recommended to use either the Combined Positive Score (CPS) or Tumor Area Positivity (TAP) scoring. CPS is calculated as follows: CPS = (the total number of PD-L1-stained cells [including tumor cells, macrophages, and lymphocytes] / total number of tumor cells under the microscope) × 100 [31]. TAP is calculated as follows: TAP = (percentage of PD-L1-positive tumor cells and tumor-associated immune cells [including macrophages and lymphocytes] / total tumor area) × 100 [32, 33].

[i]The U.S. FDA has approved the use of tropomyosin receptor kinase (TRK) inhibitors (i.e., larotrectinib or entrectinib) for patients with solid tumors displaying neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion. In gastric cancer patients unresponsive to standard treatment, the detection of *NTRK* gene fusion can be accomplished through various methods. While immunohistochemistry serves as a fast and convenient preliminary screening method, its accuracy requires validation through FISH or NGS techniques.

[j]For advanced or recurrent gastric cancer cases unresponsive to standard treatment, conducting tests to detect markers such as Claudin 18.2, fibroblast growth factor receptor 2 (FGFR2), and cellular-mesenchymal-epithelial transition (c-MET) [34] can help identify potential therapeutic targets.

# 2 | COMPREHENSIVE TREATMENT OF GASTRIC CANCER

## 2.1 | Treatment of non-metastatic gastric cancer

### 2.1.1 | Treatment of resectable gastric cancer

The treatment of resectable gastric cancer is based on the evaluated clinical stage. For early gastric cancer patients meeting the indications, the primary choice of treatment is endoscopic treatment, which includes EMR and ESD. For patients unsuitable for endoscopic treatment, abdominal laparotomy or laparoscopy can be performed. For non-EGJ gastric cancer patients, the current standard treatment is D2 gastrectomy followed by adjuvant chemotherapy. For advanced resectable gastric cancer patients (stage cIII or above), neoadjuvant therapy can be considered, and for advanced EGJ gastric cancer patients, neoadjuvant chemoradiotherapy therapy or neoadjuvant chemotherapy can be considered. However, for patients with progressive disease and unable to undergo R0 resection after neoadjuvant treatment, till present, there is no adequate evidence-based data to support remedial therapy. For cases without distant metastasis and did not undergo neoadjuvant radiotherapy, radiotherapy can be considered. It is recommended to formulate a treatment plan through a multidisciplinary team (MDT) discussion based on the individual's condition. For patients with resectable tumors but unsuitable for surgery, chemoradiotherapy can be considered as an alternative choice. However, for each such patient, based on the individualized characteristics and conditions, a personalized optimal treatment strategy must be proposed (refer to section "2.1.2 Comprehensive Treatment for Unresectable Gastric Cancer").

*Endoscopic treatment for early-stage gastric cancer*

| Stage | Stratification | Grade I recommendations | Grade II recommendations |
|---|---|---|---|
| cT1aN0M0, Stage I | Patients suitable for EMR/ESD[a] | • EMR/ESD (Evidence 1B)<br>• Patients who had non-radical resection with EMR/ESD must be re-operated (Evidence 1A)[b] | Patients with non-radical resection must receive additional ESD, electrotomy or close follow-up upon providing informed consent (Evidence 2A) |

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic sub-mucosal dissection; cTNM, clinical tumor-node-metastasis.

**Notes**

[a]Principles of EMR/ESD for early gastric cancer

Endoscopic resection of early gastric cancer mainly includes EMR and ESD. In principle, endoscopic therapy is suitable for tumors with the least risk of lymph node metastasis [35]. The initial absolute indications for endoscopic resection were previously identified as well-differentiated tumors limited to mucosa invasion (T1a) with a diameter <2 cm and without ulceration. Following the publication of the results of a Japanese multicenter prospective single-arm study (JCOG0607) [36], the 5th edition of the Japanese Gastric Cancer Guidelines [37] expanded the indications for EMR and ESD to differentiated cancers invading the mucosal layer with diameter <2 cm (cT1a) and without ulcerations; and expanded indications for ESD to differentiated cancers of diameter >2 cm without ulceration invading the intramucosal layer (cT1a), and differentiated cancers of diameter <3 cm with ulceration and invading the intramucosal layer (cT1a). The expanded indications for ESD include undifferentiated non-ulcerated intramucosal carcinoma (cT1a) with diameter <2 cm, patients with lesions classified as C1 (eCura evaluation system) following initial ESD or EMR, or cT1a following endoscopic evaluation after local recurrence, and for early gastric cancer patients aged >75 years or on anticoagulant therapy. For the Chinese gastric cancer population, the clinical implications of the expanded indications are still being investigated in many centers across China.

[b]Evaluation and curative strategies for endoscopic radical resection.

The radicality of endoscopic resection is based on the extent of local resection and the possibility of lymph node metastasis. Results of large-scale case studies and systematic analyses showed that for cases with absolute indications and negative margins, the rate of lymph node metastasis was <1% and had a long-term prognosis similar to surgical resection. For cases satisfying the expanded criteria, the rate of lymph node metastasis was <3%, but long-term follow-up data are awaited [36, 38, 39].

The radicality of endoscopic resection should be confirmed using the resected specimen on the postoperative pathological report, based on which the necessity of further treatment and follow-up are to be determined.

To determine the curative extent of endoscopic resection for diagnostic purposes, which will guide subsequent follow-up and treatment strategies, the eCura evaluation system can be used, as shown below.

eCura evaluation system

| Tumor depth | Ulcer | Differentiated | | Undifferentiated | |
|---|---|---|---|---|---|
| $pT_{1a}$ (M) | 0 | <2cm*,† | >2cm*,† | <2cm*,‡ | >2cm※ |
| | 1 | <3cm*,† | >3cm※ | | |
| $pT_{1b}$ (SM 1) | | <3cm*,‡ | >3cm※ | | |

Abbreviations: eCura, endoscopic curative resection; SM1, submucosal infiltration depth <500$\mu$m.

*Complete resection, negative margins, and no lymphovascular invasion.

†eCura A; ‡, eCura B, ※, eCura C-2.

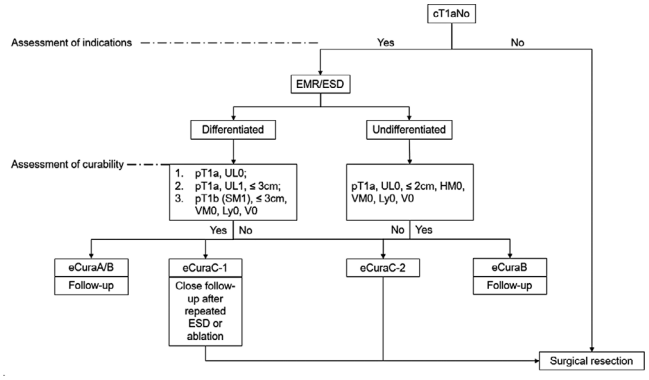
eCura C-1 refers to either eCura A or B but with positive lateral margins or block resection.

Of note, when the tumor is limited to the mucosa (T1a), it can be represented as M. When the tumor involves the submucosal shallow layer, it is represented as T1b - SM1, with submucosal infiltration depth <500$\mu$m.

Post-endoscopic resection follow-up and management strategies:

1. Curative resection A (eCura A) and Curative Resection B (eCura B): Following endoscopic resection, the recommended follow-up protocol consists of quarterly endoscopic exams in the first year, followed by semi-annual exams in the second year, and subsequent annual examinations. Concurrently, it is recommended to regularly monitor serum markers, conduct abdominal ultrasound, and perform CT scans to detect any potential metastasis. For individuals positive for *Helicobacter pylori* infection, it is strongly advised to undergo eradication therapy as part of the follow-up and treatment strategy [40, 41].
2. Curative resection C (eCura C):
   (i) When eCura C-1 has been achieved, the risk of lymph node metastasis is notably low. Based on the specific clinical circumstances and after thorough consultation with the patient, repeating ESD or invasive surgical resection can be considered. In cases characterized by partial submucosal infiltration and positive margin involvement and when the pathological diagnosis remains uncertain, invasive surgical resection is recommended.
   (ii) When eCura C-2 has been achieved, surgical resection is recommended. However, if gastric resection is unsuitable due to advanced age or the presence of comorbidities, comprehensive discussions with the patient are required regarding the following treatment, especially to emphasize the potential lymph node metastasis, local recurrence, and distant metastasis risks. Furthermore, challenges associated with curative treatment in case of recurrence and the potentially unfavorable prognosis should be clarified to the patient.

The flow chart for endoscopic treatment is shown below:




Abbreviations: e Cura, endoscopic curative resection; cTNM, clinical tumor-node-metastasis; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; UL0/1, ulceration present/absent; SM1, submucosal infiltration depth <500$\mu$m VM, vertical margin; Ly, lymphatic invasion; V0, venous invasion absent; HM0, horizontal margin negative.

*Surgical treatment of resectable gastric cancer*
*Overall treatment strategy.*

| Clinical staging* | | Stratification | Grade I recommendations** | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|---|
| I | cT1aN0M0 | Patients not suitable for EMR/ESD | D1 gastrectomy (Evidence 1A) | | |
| | cT1bN0M0 | Patients suitable for surgery | D1 gastrectomy (differentiated type, <1.5 cm) or D1+ gastrectomy (other indications) (Evidence 1A) | | |
| | cT2N0M0 | Patients suitable for surgery | D2 gastrectomy (Evidence 1A) | | |
| II | cT1-2N1-3M0 cT3-4N0M0 | Non-EGJ cancer and patients suitable for surgery | D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy (Evidence 1A) | | |
| | | EGJ cancer and patients suitable for surgery | • Neoadjuvant chemotherapy + D2 gastrectomy + adjuvant chemotherapy, (Evidence 1B)<br>• Neoadjuvant chemoradiotherapy + D2 gastrectomy + adjuvant chemotherapy, (Evidence 1B) | D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy (Evidence 1B) | |
| III | cT3-4aN1-3M0 | Non-EGJ cancer and patients suitable for surgery | • D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy, (Evidence 1A)<br>• Laparoscopic exploration, (Evidence 1B)<br>• Neoadjuvant chemotherapy + D2 gastrectomy + adjuvant chemotherapy (Evidence 1A) | | |
| | | EGJ cancer and patients suitable for surgery | • Laparoscopic exploration, (Evidence 1B)<br>• Neoadjuvant chemotherapy + D2 gastrectomy + adjuvant chemotherapy (Evidence 1A)<br>• Neoadjuvant chemoradiotherapy + D2 gastrectomy + adjuvant chemotherapy (Evidence 1B) | D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy (Evidence 1B) | |
| IVA | cT4bN0-3M0 | Cases with no unresectable factors | MDT discussion for the optimal personalized management | • Laparoscopic exploration (Evidence 1B)<br>• Neoadjuvant chemotherapy + gastrectomy (combined organ resection) + adjuvant chemotherapy (Evidence 2A)<br>• Neoadjuvant chemoradiotherapy + gastrectomy (combined organ resection) + adjuvant chemotherapy (Evidence 2B) | Encourage participation in clinical trials |

Abbreviations: cTNM, clinical tumor-node-metastasis; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EGJ, esophagogastric junction.
*The 8th edition of the AJCC/UICC clinical staging system (cTNM).
**Laparoscopic surgery may serve as an alternative to open surgery for distal gastrectomy in early and advanced gastric cancer, as well as for total gastrectomy in early gastric cancer.

*Principles of surgery.*

| Technical requirement | Stratification | | | Grade I recommendations* | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|---|---|
| Lymphadenectomy recommendations[a] | Non-EGJ tumors | Distal gastrectomy | D1 | Stations: 1, 3, 4sb, 4d, 5, 6, 7[a,b] (Evidence 1A) | | |
| | | | D1+ | Stations: D1 + 8a, 9[a,b] (Evidence 1A) | | |
| | | | D2 | Stations: D1 + 8a, 9, 11p, 12a[a,b] (Evidence 1A) | D2 stations and station 14v[a,b], * (Evidence 2A) | If tumor invaded duodenum: D2 stations + station 13[a,b] (Evidence 2B) |
| | | Pylorus-preserving gastrectomy** | D1 | Stations: 1, 3, 4sb, 4d, 6, 7[a,b] (Evidence 1A) | | |
| | | | D1+ | Stations: D1 + 8a, 9[a,b] (Evidence 1A) | | |
| | | Total gastrectomy | D1 | Stations: 1-7[a,b] (Evidence 1A) | | |
| | | | D1+ | Stations: D1 + 8a, 9, 11p[a,b] (Evidence 1A) | | |
| | | | D2 | Stations: 1-7, 8a, 9, 11, 12a[a,b] (Evidence 1A) | D2 stations and station 10[a,b], *** (Evidence 2A) | |
| | EGJ tumors | Proximal gastrectomy | D1 | Stations: 1, 2, 3a, 4sa, 4sb, 7[a,b] (Evidence 1A | | |
| | | | D1+ | Stations: D1 + 8a, 9, 11p, 19[a,b] (Evidence 1A) | | |
| | | | D2 | Stations: D1 + 8a, 9, 11, 19 (If tumor invaded esophagus >2 cm: + station 110; if tumor invaded esophagus >4cm: stations 106recR, 107, 108, 109, 111, 112)[a,b] (Evidence 2A | | |
| | | Total gastrectomy | D1 | Stations: 1-7[a,b] (Evidence 1A) | | |
| | | | D1+ | Stations: D1 + 8a, 9, 11p[a,b] (Evidence 1A) | | |
| | | | D2 | Stations: 1-7, 8a, 9, 11, 19 (If tumor invaded esophagus >2 cm: station 110; if tumor invaded esophagus >4cm: stations 106recR, 107, 108, 109, 111, 112)[a,b] (Evidence 2A) | | |
| Digestive tract reconstruction[c] | Distal gastrectomy | | | • Billroth I[c] (Evidence 1A)<br>• Billroth II[c] (Evidence 1A) | | Roux-en-Y anastomosis[c] (Evidence 2B) |
| | Pylorus-preserving gastrectomy | | | | Remnant gastrogastrostomy[c] (Evidence 2A) | - |
| | Proximal gastrectomy | | | | • Double-tract reconstruction[c] (Evidence 2A)<br>• Tubular gastroesophageal anastomosis[c] (Evidence 2A) | • Esophagogastric side-to-side anastomosis[c] (Evidence 2B)<br>• Esophago-remnant gastrostomy[c] (Evidence 2B)<br>• Jejunal interposition for gastric replacement[c] (Evidence 2B) |
| Digestive tract reconstruction[c] | Total gastrectomy | | | Roux-en-Y anastomosis[c] (Evidence 1A) | | • Roux-en-Y anastomoses with jejunal pouch reconstruction[c] (Evidence 2B)<br>• Jejunal interposition for gastric replacement[c] (Evidence 2B) |

Abbreviations: cTNM, clinical tumor-node-metastasis; EGJ, esophagogastric junction.
*For stage III patients in the middle and lower part of the stomach with positive subpyloric lymph nodes.
**For early gastric cancer (clinical stage cT1N0M0) involving the middle 1/3 of the stomach and lesion located >4 cm from the pylorus (tumor distal margin is at least 2 cm from the distal resection margin and at least 2 cm from the pylorus)
***For patients preoperatively staged as cT3 or cT4, primary tumor >6 cm, and located along the greater curvature
****The lymphadenectomy procedure and extent are selected based on TNM staging and overall treatment strategy

**Notes**

[a]**Resection extent and lymphadenectomy**

The extent of gastrectomy is based on the location of the tumor, with the aim to ensure adequate surgical resection margin. For T1 early gastric cancer, the gross margin should be >2 cm. Based on data from recent studies [42, 43], the recommendations for an adequate distance of resection margin for >T2 Borrmann I-II gastric cancers is ≥3 cm, and for Borrmann III-IV is ≥5 cm. If the tumor has invaded the esophagus or pylorus, a resection margin of 5 cm is not obligatory as long as R0 resection and negative margins on frozen pathological examinations can be assured.

Based on the findings of the JCOG9502 study [44], for EGJ adenocarcinoma, which has invaded <3 cm into the esophagus or the body of the stomach, abdominal (non-endoscopic) surgery is recommended. Transthoracic surgery is not recommended. For EGJ tumors, the choice between total gastrectomy and proximal gastrectomy primarily depends on the lesion extent, lymph node metastasis at stations 4, 5 and 6, and the patient's survival outcomes. A prospective study [45] by the Japan Gastric Cancer Association and the Japan Esophageal Society across 42 centers on patients with cT2-cT4 adenocarcinoma or squamous cell carcinoma of the EGJ for assessing lymph node metastasis rates found that for tumors with a diameter ≤4 cm, the rates of metastasis at station 4d, 5 and 6 were 2.2%, 1.1% and 1.7%, respectively, and for tumors with a diameter ≥6 cm, the rates of metastasis at station 4d, 5 and 6 ranged from 6% to 10.7%. However, no long-term survival data for these cases were reported [45]. Therefore,

the CSCO Expert Committee considered that for EGJ cancer of ≤ 4 cm diameter, with no station 4d, 5 or 6 lymph node metastasis by imaging assessments, proximal gastrectomy may be considered, with the stipulation that at least half of the distal stomach should be preserved.

The resection of perigastric lymph nodes and those alongside accompanying vessels of the celiac trunk should be performed according to the type of gastrectomy [42, 43]. D1 gastrectomy includes the resection of the required part of the stomach (with adequate resection margin), greater and lesser omentum, and the following perigastric lymph nodes: the right and left para-cardiac lymph nodes, lesser and greater curvature lymph nodes, lymph nodes along the left gastric artery, suprapyloric, and infrapyloric lymph nodes along the right gastric artery. D2 gastrectomy includes the structures resected in D1 gastrectomy and the resection of the lymph nodes along the common hepatic artery, gastroduodenal ligament and splenic artery. Based on the Dutch study [46], for resectable cT2-4 and cT1N+ cases, D2 lymphadenectomy is recommended as it has been shown to be superior in decreasing the risk of recurrence and gastric-related death compared to D1 lymphadenectomy. It is recommended that ≥16 lymph nodes should be pathologically examined to ensure accurate staging and prognostication.

Currently, there is still controversy regarding the necessity for splenic hilar lymph node dissection. A phase III clinical study conducted at a single center in China revealed that for tumors located in the proximal stomach without involvement of the greater curvature, the addition of laparoscopic splenic hilar lymphadenectomy to D2 lymphadenectomy does not result in a survival benefit [47]. However, for tumors with advanced TNM stage, size >6 cm, and located at the greater curvature of the stomach, the probability of splenic hilar lymph node metastasis is high [48]. The Expert Committee recommends that splenic hilar lymph node dissection should be performed in the following cases: the primary tumor is >6 cm, the tumor is located at the middle-upper part of the stomach along the greater curvature and preoperatively staged as cT3-4 [49, 50]. Splenectomy for lymph node dissection is not recommended.

Whether it is necessary to dissect lymph nodes at the root of the superior mesenteric vein (station 14v) in advanced gastric cancer remains controversial. Although station 14v is not within the routine extent of D2 lymphadenectomy in the 3rd edition of the Japanese Gastric Cancer Treatment Guidelines [51], it has been observed that D2 lymphadenectomy with station 14v lymph node dissection may improve overall survival (OS) in patients with clinically staged III/IV middle- and lower-third gastric cancer. Retrospective studies showed that the rate of metastasis to station 14v in distal gastric cancer was 18.3%-19.7%, while the metastasis rate of stage I distal gastric cancer patients was 0, and that of stage II distal gastric cancer patients was 1.6% [52, 53]. D2 lymphadenectomy with resection of station 14v lymph nodes may improve the OS of stage cIII/IV middle and lower gastric cancer patients [54]. Therefore, the Expert Committee recommends the following indications for the dissection of station 14v lymph nodes: clinically staged III patients with tumors located at the middle and lower parts of the stomach, especially for those with metastasis to the infra-pyloric lymph nodes.

Although the station 13 (retro-pancreatic) lymph nodes are not within the routine extent of D2 dissection, studies have found that for advanced lower gastric cancer, the metastasis rate to station 13 was 2.5%-9.0%, and if the tumor has invaded the duodenum, the metastasis rate is even higher, at 26.7% [55–57]. In terms of survival outcome, for patients with stage cI/II disease, the dissection of station 13 does not improve OS, while for stage cIII/IV patients, it can improve OS. For patients with duodenal invasion and stage cIII disease, dissection of station 13 can be considered, but this population is often accompanied by a low R0 resection rate. Therefore, neoadjuvant therapy combined with D2 lymphadenectomy and station 13 dissection can be considered for such patients.

In EGJ tumors, particularly in regard to mediastinal lymphadenectomy, a consensus on the optimal extent of lymphadenectomy remains unclear. A multicenter prospective study in Japan assessing the lymph node metastasis rates of cT2c-T4 patients with EJC adenocarcinoma and squamous cell carcinoma revealed that different lengths of esophageal infiltration were associated with varying lymph node metastasis rates [45]. When esophageal infiltration was ≤2 cm, mediastinal lymph node metastasis was less frequent. However, for esophageal infiltrations >2 cm but ≤4 cm, lower mediastinal lymph nodes (station 110) exhibited higher metastasis rates, whereas upper and middle mediastinal lymph nodes had lower metastatic rates. Comparatively, in cases where the tumor had esophageal infiltrated >4 cm of the EGJ, upper and middle mediastinal lymph node metastasis rates were increased. Based on these findings, the CSCO Expert Committee recommends dissecting station 110 in lymph nodes when esophageal infiltration exceeds 2 cm. Furthermore, if infiltration exceeds 4 cm, dissection should extend to encompass the 106recR, 107, 108, 109, 111 and 112 stations lymph nodes.

For patients with resectable advanced gastric cancer, it has been reported that preventive para-aortic lymph node dissection was not associated with improved long-term survival of these patients [58], and the value of therapeutic para-aortic lymph node dissection is still controversial. Suitable patients should be encouraged to participate in clinical trials.

Regarding the utility of postoperative abdominal lavage in curative surgery for gastric cancer, findings from the 2021 EXPEL study indicate that postoperative abdominal lavage following standard D2 surgery did not reduce the risk of peritoneal recurrence (7.9% vs. 6.6%, hazard ratio [HR]: 1.33; 95% confidence interval [CI]: 0.73-2.42; $P = 0.347$) but instead increased the risks of adverse events (relative risk: 1.58; 95% CI: 1.07-2.33; $P = 0.019$) [59]. Consequently, the Expert Committee does not recommend the use of extensive abdominal lavage following radical gastrectomy.

**[b]Laparoscopic and robotic surgery**

For distal gastrectomy of gastric cancer classified as cT1N0 and cT1N1, large-scale prospective studies from Japan and Korea, JCOG0912 [60] and KLASS-01 [61], have shown that laparoscopic surgery was equivalent to open surgery in terms of safety and long-term prognosis. Therefore, laparoscopic surgery is recommended as a routine surgical technique.

There is no large prospective study for laparoscopy-assisted total and proximal gastrectomy (LATG and LAPG) of early gastric cancer. Although preliminary evidence from China's CLASS02 [64], South Korea's KLASS-03 [62] and Japan's JCOG1401 [63] studies confirmed the safety of LATG/LAPG, there is currently no long-term efficacy data available. Therefore, the Expert Committee recommends further investigations of such cases in experienced medical centers.

For advanced gastric cancer, the CLASS-01 [65] and KLASS-02 [66] phase III randomized controlled trials confirmed that LADG combined with D2 lymph node dissection was safe when performed by experienced surgeons in high-volume medical centers. It was associated with reduced blood loss, faster gastrointestinal recovery, shorter hospital stays, and similar long-term survival compared to open surgery.

Whether laparoscopic gastrectomy is feasible for patients with advanced gastric cancer after neoadjuvant therapy is still controversial. Currently, there is a lack of large cohort prospective studies. The recent results of a Chinese randomized controlled study comparing the safety of LADG with D2 lymphadenectomy against open distal gastrectomy (ODG) with D2 lymphadenectomy in locally advanced gastric cancer (cT2-4aN+M0) patients who received neoadjuvant chemotherapy, showed that LADG was associated with better postoperative safety and adjuvant chemotherapy tolerance compared than ODG [67].

Therefore, the Expert Committee suggests that for patients with stage I-III gastric cancer who are suitable for distal subtotal gastrectomy, laparoscopic surgery can be routinely performed. LATG for early gastric cancer can be performed in experienced medical centers as clinical investigations. However, there is no evidence for the benefit or superiority of proximal and LATG for advanced gastric cancer, and the results of clinical studies are awaited. Further, whether laparoscopic surgery can be performed for advanced gastric cancer after neoadjuvant therapy still urges more prospective clinical confirmations.

Further, robotic gastric cancer surgery has attracted much attention in recent years. Although there is no large prospective study to confirm its efficacy in the treatment of gastric cancer, a retrospective study from Korea that compared robotic gastric cancer surgery ($n = 421$) with open/laparoscopic surgery ($n = 1663$) [68] showed that although there was no difference in long-term survival between the study groups, patients from the robotic group had a lower risk of intra-operative bleeding. A retrospective analysis from 7 major centers in China showed that robot-assisted surgery was associated with lower complication rates, lesser bleeding, a more extensive lymph node dissection, and equivalent long-term survival compared to laparoscopic surgery [69]. Furthermore, two randomized controlled clinical studies in China comparing robot-assisted distal gastrectomy (RADG) with LADG demonstrated that RADG resulted in fewer postoperative complications and led to more extensive resection of perigastric lymph nodes [70, 71]. Currently, the Expert Committee considers that the advantages and significance of robotic gastric cancer surgery still need further confirmatory evidence before wide clinical application.

According to the Expert Committee, for stage cIII patients, laparoscopic exploration should be performed, and the 3-incision method should be applied. Peritoneal metastasis should be evaluated. For complete exploration, it is recommended to open the gastrocolic ligament and observe whether there is occult metastasis in the omentum. If peritoneal metastasis is detected, HER2 and MMR status detection in the metastatic lesion should be performed to guide the treatment. If no obvious peritoneal metastasis is found, cytological examination of peritoneal lavage fluid should be performed.

**[c]Digestive tract reconstruction**

The type of digestive tract reconstruction performed depends on the patient's physical condition and the surgeon's experience as far as it does not affect the radicality of the gastrectomy.

Billroth I and Billroth II reconstructions are mostly adopted for distal gastrectomy. The postoperative complication rates for both reconstructions are similar. However, Billroth I is easier to perform and better suits the normal physiological gastrointestinal pathway. For tumors located in the lower third of the stomach, especially those invading the pylorus and the duodenum, Billroth II reconstruction is recommended because these patients can have a second chance for surgery in case of tumor recurrence [72]. Compared with Billroth type I and II, Roux-en-Y anastomosis can effectively reduce bile reflux and prevent the occurrence of remnant gastritis. However, this operation is relatively complex, and the risk of postoperative retention syndrome may be increased [73].

Although proximal gastrectomy preserves some functions of the stomach, it disrupts the cardia's anti-reflux mechanism and delays gastric emptying. Therefore, digestive tract reconstruction after proximal gastrectomy should aim to minimize the occurrence of reflux esophagitis. While esophagogastrostomy can be considered a simpler and quicker procedure with fewer anastomoses and lower risks of short-term complication rates, it can be associated with common and severe gastroesophageal reflux [74]. Researchers indicated that the likelihood of severe gastroesophageal reflux after surgery significantly decreases with double-tract reconstruction, modified tubular stomach-esophagus anastomosis, and modified esophagogastrostomy [75–77]. Compared with gastroesophageal anastomosis, the Jejunal interposition procedure can reduce the occurrence of moderate or severe esophageal reflux, but this operation is complex and abdominal discomfort, upper abdominal fullness, and hiccups are commonly observed in these cases [78]. Therefore, its advantages remain to be confirmed, and if required, it is suggested that the Jejunal interposition method is recommended to be performed in large experienced medical centers. Therefore, there is no recognized optimal digestive tract reconstruction, and the Expert Committee recommends large medical centers to conduct randomized controlled trials to explore the optimal digestive tract reconstruction.

Roux-en-Y is the preferred reconstruction procedure for total gastrectomy [43]. It has been reported that, in addition to Roux-en-Y anastomosis, the reconstruction of the Jejunal pouch digestive tract may improve the patients' postoperative quality of life, which is mainly reflected in the increase of food intake and the decrease of digestive tract symptoms [79]. However, the Jejunal interposition technique is complicated and may be associated with a high risk of postoperative complications, and controversies concerning its efficacy in improving the patients' quality of life exist. Therefore, if required, it is suggested that this procedure should be carried out in large experienced medical centers.

*Perioperative treatment of resectable gastric cancer.*

## Adjuvant therapy[d]

| Stratification* | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Stage II:<br>• pT1N2-3aM0<br>• pT2N1-2M0<br>• pT3N0-1M0<br>• pT4aN0M0<br>with R0 resection and D2 dissection | Adjuvant chemotherapy:<br>• XELOX (Evidence 1A)<br>• S-1 alone (Evidence 1A) | Adjuvant chemotherapy:<br>• XP (Evidence 1B)<br>• SOX (Evidence 1B) | Adjuvant chemotherapy: FOLFOX (Evidence 2B) |
| Stage III:<br>• pT1N3bM0<br>• pT2N3M0<br>• pT3N2-3M0<br>• pT4aN1-3M0<br>• pT4bN0-3M0<br>with R0 resection and D2 dissection | Adjuvant chemotherapy:<br>• XELOX (Evidence 1A)<br>• SOX (Evidence 1A) | Adjuvant chemotherapy: S-1 × 1-DS × 7-S1 for up to 1 year*** (Evidence 1A) | Adjuvant chemotherapy: FOLFOX (Evidence 2B) |
| • pT2-4NanyM0 with R0 resection but did not reach D2 dissection | Adjuvant chemoradiotherapy: DT 45-50.4 Gy (concurrent fluoropyrimidine) (Evidence 1A) | MDT discussion for optimal treatment regimen | - |
| pT2-4NanyM0 and R1/R2 resection | Adjuvant chemoradiotherapy**: DT 45-50.4 Gy (concurrent fluoropyrimidine) (Evidence 2A) | MDT discussion for optimal treatment regimen | - |

Abbreviations: pTNM, pathological tumor-node-metastasis; XELOX, capecitabine (Xeloda) and oxaliplatin (Eloxatin); SOX, S-1 and oxaliplatin; XP, capecitabine (Xeloda) and cisplatin; FOLFOX, folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; DS, S-1 plus docetaxel MDT, Multidisciplinary Team; DT, radiation dose of tumor; AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer.

*According to the 8th AJCC/UICC pathological staging system (pTNM) for gastric cancer;

**For cases with positive margin or residual tumor, an additional dose can be given according to the specific clinical condition;

***For patients with poor postoperative physical fitness, consider using S1 × 1-DS1 × 7-S1 for up to 1 year

## Neoadjuvant therapy

| Treatment | Stratification* | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|
| Neoadjuvant therapy[e, f] | Non-EGJ gastric cancer: cT3-4aN+M0, stage cIII | Neoadjuvant chemotherapy: SOX regimen (Evidence 1A) | Neoadjuvant chemotherapy:<br>• DOS (Evidence 1B)<br>• FLOT4 (Evidence 1B) | Neoadjuvant chemotherapy:<br>• XELOX (Evidence 2A)<br>• FOLFOX (Evidence 2A) |
| | Gastric cancer invading the EGJ: cT3-4aN+M0, stage cIII | Neoadjuvant chemoradiotherapy: DT 45-50.4 Gy (concurrent 5-fluorouracil, platinum or taxanes) (Evidence 1B) | Neoadjuvant chemotherapy:<br>• XELOX (Evidence 2A)<br>• FOLFOX (Evidence 2A)<br>• SOX (Evidence 1B)<br>• DOS (Evidence 1B)<br>• FLOT4 (Evidence 1B) | Neoadjuvant Radiotherapy (patients unsuitable for chemotherapy) (Evidence 2B) |

Continued.

| Treatment | Stratification* | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|
| Neoadjuvant therapy[e] | cT4bNanyM0, stage cIVA (without non-resectable factors) | MDT discussion for optimal personalized treatment | • Laparoscopic exploration[e] (Evidence 1B)<br>• Neoadjuvant chemoradiotherapy + gastrectomy (with adjacent organ resection) + adjuvant chemotherapy (Evidence 2B)<br>• Neoadjuvant chemotherapy: SOX (Evidence 1B)<br>• Neoadjuvant chemotherapy: DOS (Evidence 1B) | Encourage participation in clinical trials |
| | R1/R2 resection after neoadjuvant therapy | MDT discussion for optimal personalized treatment | Encourage participation in clinical trials | |
| | Localized disease progression after neoadjuvant therapy | MDT discussion for optimal personalized treatment | Encourage participation in clinical trials | |

Abbreviations: AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer; cTNM, clinical tumor-node-metastasis; EGJ, esophagogastric junction; DT, dose of therapy; SOX, S-1 and oxaliplatin; MDT, Multidisciplinary Team; FOLFOX, folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin; XELOX, capecitabine (Xeloda) and oxaliplatin (Eloxatin); DOS, docetaxel, oxaliplatin and S-1; FLOT4, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel-4.

*According to the 8th AJCC/UICC clinical staging system (cTNM) for gastric cancer

**Notes**

[d]**Adjuvant treatment for resectable gastric cancer**

There are several large phase III clinical trials supporting the use of adjuvant chemotherapy for patients who have undergone D2 radical gastrectomy [80–83]. The indications of adjuvant chemotherapy for resectable gastric cancer are D2 radical gastrectomy and no prior neoadjuvant therapy for stage pII/III patients. For stage II patients, the recommended regimen is S-1 (oral till 1 year after operation) or capecitabine combined with oxaliplatin [80, 81]. In the JACCRO GC-07 study [82, 84], the investigators found that S-1+docetaxel (oral S-1 on days 1-14 with 7 days of rest followed by 6 cycles of S-1 combined with docetaxel on day 1 of each cycle, then 4 further cycles of S-1 on days 1-28 every 42 days) was associated with improved survival of patients with stage III gastric cancer compared to S-1 monotherapy (3-year recurrence-free survival [RFS] rate: 65.9% vs. 49.6%, $P = 0.0007$) and suppressed all types of recurrences, including hematogenous, lymphatic and peritoneal recurrences. The RESOLVE trial [85] showed that for locally advanced cT4a/N+M0 or cT4b/NxM0 gastric cancer, adjuvant S-1 plus oxaliplatin (SOX) was not inferior to adjuvant capecitabine plus oxaliplatin (XELOX) (3-year disease-free survival [DFS] rate: 60.3% vs. 54.8%, $P = 0.162$). The ARTIST-II trial [86] enrolled 900 stage II/III gastric cancer patients with positive lymph nodes who underwent D2 radical gastrectomy and investigated the curative effects of 1-year S-1 monotherapy versus 6-month SOX chemotherapy versus SOX chemotherapy plus radiotherapy (SOXRT). The results showed that compared to S-1 monotherapy, adjuvant SOX or SOXRT could significantly prolong DFS, but compared to adjuvant SOX regimen, adjuvant SOXRT had no additional survival benefit. In recent years, there have been studies investigating the applicability of survival prediction models, such as nomograms, based on tumor and patient characteristics to evaluate the survival benefits of individualized adjuvant chemotherapy for stage II/III gastric cancer. Wang et al. [87] reviewed the data of 1,464 pT3-4 or N+ gastric cancer patients who received adjuvant fluoropyrimidine plus oxaliplatin (F-OX) after D2 gastrectomy at three major centers across China. The results showed that, compared to the 7th AJCC gastric cancer classification, the nomogram was superior in stratifying patients for predicting benefit from F-OX. Using the nomogram, patients in the low-risk group had no improvement in survival with F-OX, while for those classified in the intermediate- and high-risk groups, F-OX could reduce the risk of death by over 20%; thereby, the nomogram could more accurately guide the selection of gastric cancer patients who would benefit from F-OX adjuvant chemotherapy.

At present, it is not clear whether patients with stage pI gastric cancer would benefit from adjuvant chemotherapy. It is suggested for stage pI patients with high-risk factors, such as younger age (<40 years old), high histological grade or low differentiation, and nervous plexus, vascular or lymphatic invasion, investigational treatment can be offered.

For resectable gastric cancer, the results of phase III clinical studies investigating the efficacy of chemoradiotherapy after radical surgery were different in the East and the West. The INT0116 study [88], from the US, confirmed that concurrent radiotherapy and 5-fluorouracil (5-FU) chemotherapy after surgery improved OS compared to surgery alone, but the surgery performed was mainly D0/D1 gastrectomy, while in countries such as China, Korea and Japan, mostly D2 gastrectomy is performed. The ARTIST study [89] from South Korea, which compared 6 cycles of adjuvant capecitabine plus cisplatin (XP) versus 2 cycles of XP followed by concurrent capecitabine combined with RT (XP/XRT/XP) plus 2 additional cycles of XP in gastric cancer patients after D2 R0 gastrectomy, found no significant reduction in recurrence between the two therapies in the overall population (3-year DFS rates, XP/XRT/XP arm: 78.2% vs. XP arm: 74.2%; $P = 0.0862$), but in subgroup analysis of patients with positive pathologic lymph nodes, patients from the XP/XRT/XP arm had superior DFS than the XP arm (3-year DFS rate:

77.5% vs. 72.3%, $P = 0.0365$). However, the ARTIST-II study [86], performed in patients with D2-resected, stage II/III, node-positive gastric cancer, did not confirm that the combination of the SOX regimen with radiotherapy improves survival. Thus, for resectable patients who can undergo R0 and D2 resection, adjuvant chemoradiotherapy is not recommended unless they are diagnosed with advanced pathological stage and associated with high-risk factors, including insufficient dissection distance from tumor margin (<2 cm), vascular tumor thrombus, perineural invasion, N3 or metastatic lymph node ratio >25%, then, after systemic therapy adjuvant radiotherapy could be considered. For those who did not achieve R0 resection (without distant metastasis), adjuvant chemoradiotherapy [90] or MDT discussion is recommended.

At present, adjuvant chemotherapy for gastric cancer invading the EGJ is mostly based on the findings of studies from Asia. Among four large-scale phase III clinical studies, the rate of EGJ-gastric cancer was 23.4% in the JACCOR GC-07 study [82, 84], 4.8% in the ARTIST study [81], 2.3% in the CLASSIC study [80], and 1.4% in the ACTS-GC study [91]. However, there is still a lack of randomized controlled trials investigating the significance of adjuvant chemotherapy or chemoradiotherapy for EGJ carcinoma.

**[e]Preoperative and perioperative chemotherapy for advanced gastric cancer**

Perioperative therapy (neoadjuvant chemoradiotherapy + surgery + adjuvant chemotherapy/chemoradiotherapy) for gastric cancer has been proven to be superior to surgery alone in Western countries as it could downstage the tumor, increase the rate of radical resection, and improve survival whilst not increasing the risks of postoperative complications and deaths [92, 93]. Also, neoadjuvant chemotherapy prior to radical gastrectomy in Asian studies has been associated with significantly improved tumor remission rates, R0 resection rates, and treatment safety [94, 95]. The survival benefits of perioperative chemo-/radiotherapy, as compared with postoperative chemotherapy after radical D2 gastrectomy, remain to be determined in large phase III clinical trials. The RESOLVE study [85], a large-cohort randomized controlled phase III clinical study led by Chinese investigators aiming at comparing the efficacy and safety of adjuvant XELOX (arm A) or adjuvant SOX (arm B) after D2 radical gastrectomy against perioperative SOX (neoadjuvant SOX followed by 5 cycles of adjuvant SOX and 3 cycles of S-1; arm C) in locally advanced gastric cancer patients, found that perioperative SOX was superior to adjuvant XELOX (3-year DFS rate: 62.0% vs. 54.8%, $P = 0.045$) for locally advanced gastric cancer at stage cT4a/N+M0 or cT4a/NxM0 while adjuvant SOX was non-inferior to adjuvant XELOX (3-year DFS rate: 60.3% vs. 54.8%, $P = 0.162$). Therefore, 3 cycles of neoadjuvant SOX chemotherapy and 5 cycles of adjuvant SOX followed by 3 cycles of S-1 monotherapy is recommended as the perioperative treatment for locally advanced gastric cancer. In addition, during the same period, the PRODIGY study [96] reported that for locally advanced gastric cancer staged as cT2/3N+M0 or cT4/NxM0, 3 cycles of neoadjuvant docetaxel plus oxaliplatin plus S-1 (DOS) chemotherapy plus 8 cycles of postoperative S-1 monotherapy, compared to surgery followed by 8 cycles of S-1 monotherapy, was associated with tumor downstaging and significant improvement in 3-year DFS. The 2022 MATCH study demonstrated that in preoperative neoadjuvant treatment, the major pathologic response (MPR) rates for the DOS group and SOX group were 25.45% and 11.8%, respectively, and the corresponding R0 resection rates were 78.9% and 61.8%, with 3-year progression-free survival (PFS) rates of 52.3% and 35%, respectively [97]. Thus, the DOS regimen can be recommended for preoperative chemotherapy in gastric cancer.

Currently, the recommended neoadjuvant chemotherapy regimens for gastric cancer include XELOX [98], FOLFOX [99], cisplatin combined with S-1 (SP) [100], and SOX [101]. Results of the large prospective phase III FLOT4-AIO study [102] showed that compared with epirubicin plus cisplatin (ECF)/epirubicin plus cisplatin and capecitabine (ECX) regimen, the docetaxel combined with oxaliplatin, leucovorin and 5-FU (FLOT) regimen was associated with improved 3-year OS and DFS and had higher pathological response rate and R0 resection rate. Therefore, the FLOT regimen can also be used as the recommended regimen for preoperative chemotherapy of gastric cancer. In recent years, there have been studies on neoadjuvant anti-HER2 treatment for HER2-positive gastric cancer and chemotherapy plus immunotherapy for HER2-negative gastric cancer. However, the sample sizes in these studies are small, and the evidence level is low. Thus, there is no sufficient evidence for standard recommendations. Therefore, we prioritize recommending these patients to participate in clinical trials. For patients with dMMR status, the use of immunotherapy in the neoadjuvant and adjuvant settings is an emerging trend. Both the GERCOR NEONIPIGA study [103] and the INFINITY study [104] have reported promising results, showing pathologic complete response (pCR) rates of 59% and 60%, respectively, when PD-1/PD-L1 antibodies were combined with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies in neoadjuvant treatment. There is also ongoing research on neoadjuvant immunotherapy in combination with chemotherapy and radiotherapy for pMMR gastric cancer. However, data from these studies is currently insufficient for drawing definitive conclusions. The DANTE study [105], which has the largest sample size, confirmed that the addition of atezolizumab to FLOT chemotherapy can improve tumor regression compared to FLOT alone, with pCR rates of 24% and 15%, respectively. Notably, the pCR rate for MSI-H patients was promising, at 63%. Therefore, it is advisable to prioritize the inclusion of these patients in clinical trials to further explore and optimize treatment options.

Results of the international multicenter CRITICS study [106] showed that compared with adjuvant chemotherapy alone, adjuvant chemoradiotherapy did not improve survival for stage IB-IVA resectable gastric cancer or EGJ cancer patients who received neoadjuvant epirubicin, cisplatin or oxaliplatin, and capecitabine (ECC/EOC) chemotherapy followed by curative intent gastrectomy with adequate lymph node dissection (D1+ accounted for 86% of the study population). However, the completion rate of the study was only 50%, and 60% of the investigated cohort were stage I-II patients. As such, the local control rate of radiotherapy could not be fully determined and decreased its clinical referential value.

For gastric cancer patients with T4b disease and without unresectable factors, based on current research evidence [107–109], the following points could be considered as treatment options: 1) R0 resection is an independent prognostic factor for survival; 2) the rate of complications after combined organ resection is very high, close to 40%, among which pancreatoduodenectomy is the highest risk procedure; 3) surgery for peripheral organ involvement is very complex, and it is difficult to formulate a standard treatment principle. Therefore, it is suggested that such cases should undergo MDT discussion for an individualized treatment plan. Further, neoadjuvant therapy could improve the R0 resection rate and can be used as a treatment option. For patients who can achieve R0 resection, combined organ resection is acceptable, but combined pancreatoduodenectomy should be carefully assessed for risk and benefits.

A multinational individual patient data meta-analysis [110] explored the associations of MSI status with postoperative prognosis and perioperative chemotherapy efficacy in patients with resectable gastric cancer enrolled in the CLASSIC [80], ARTIST [81], MAGIC [92] and ITACA-S trials [111]. The results showed that for resectable dMMR/MSI-H gastric cancer patients, the prognosis of patients who underwent only surgery was better than those who underwent surgery plus adjuvant chemotherapy. Currently, small sample size retrospective studies have shown that the prognosis of dMMR and MSI-H patients was good but had conflicting results regarding the benefits of adjuvant chemotherapy [112]. Overall, considering the small proportion of the population in these studies, there is still some controversy to implement it in clinical practice. Taking adverse reactions related to chemotherapy and patients' financial implications into account, it is suggested that for dMMR/MSI-H patients, (neo)adjuvant treatments such as immunotherapy in clinical trial settings could be first considered, unless unwillingness from the patient's side, after detailed discussion with the patient and families about the risk and benefits of different treatment strategies, postoperative observation or chemotherapy can be considered.

For gastric cancer located in the middle to distal part of the stomach, the efficacy of preoperative chemoradiotherapy, especially the comparison of perioperative modes of chemotherapy, still needs to be verified by the ongoing phase III clinical trials. Several clinical trials are actively exploring the regimens of preoperative chemoradiotherapy for gastric cancer, such as the international multicenter TOPGEAR trial (NCT01924819) [113], Netherlandish CRITICS-II study (NCT02931890)

[114], the multicentral trial from Sun Yat-sen University (NCT01815853) and the trial from the Cancer Hospital of the Chinese Academy of Medical Sciences (NCT04062058).

The efficacy of neoadjuvant therapy should be evaluated in a timely manner using EUS, CT, or PET/CT imaging modalities. Compared with CT and other non-invasive imaging examinations, laparoscopic laparotomy can improve the diagnostic rates of occult metastasis within the abdominal cavity, including radiologically undetected small liver metastases. It can be carried out alongside a cytological examination of intraperitoneal washings [115]. As such, prior to neoadjuvant therapy (for T3-4 or N+ cases), explorative laparoscopic staging and cytological examination of intraperitoneal washings are recommended.

For surgically resected specimens diagnosed as pCR after neoadjuvant therapy, it is recommended that the same neoadjuvant regimen be continued postoperatively. Till present, there is no sufficient evidence attributing to the survival differences between those who undergo different adjuvant regimens as to their initial neoadjuvant regimens or abstain from adjuvant therapies.

For patients who underwent neoadjuvant therapy and achieved R0 resection, if the preoperative imaging or pathological assessments showed improvement in shrinking the cancerous lesion, it is recommended that the same neoadjuvant regimen be continued postoperatively.

In case of disease progression following neoadjuvant therapy, surgery should be considered if R0 resection can be achieved. If not, the treatment protocol should be discussed via an MDT panel.

For patients who could not achieve R0 gastrectomy despite the absence of distant metastasis after neoadjuvant chemotherapy, either adjuvant chemoradiotherapy or MDT discussion is recommended. If neoadjuvant chemoradiotherapy was performed, the subsequent treatment should be discussed via an MDT panel, else palliative treatment is recommended.

**[f]Neoadjuvant treatment for EGJ cancer**

The choice of perioperative treatment for EGJ cancer has some particularity because of the differences in clinical research designs and results between Eastern and Western countries. In clinical studies of postoperative adjuvant chemotherapy with positive results in multiple Asian countries, the proportion of patients with EGJ cancer included in the studies was very low, and although the overall population benefited from postoperative adjuvant chemotherapy in terms of survival, it is still uncertain whether patients with esophagogastric junction cancer in Asian countries can benefit from such treatment. Comparatively, in European clinical trials that investigated perioperative treatment for gastric cancer, the proportion of patients with EGJ cancer was higher, e.g., 60% in the FFCD study [116] and 56% in the FLOT4-AIO study [102], suggesting that perioperative chemotherapy was indeed an effective treatment for patients with EGJ cancer in Western countries. In the RESOLVE study [85], EGJ cancer patients comprised 36.5% of the study population, suggesting that perioperative chemotherapy could also be an effective treatment in the Asian population.

For adenocarcinomas of the EGJ or squamous cell carcinoma in the middle to lower esophagus, clinical research supports neoadjuvant chemoradiotherapy followed by surgery and adjuvant chemotherapy to effectively achieve tumor downstaging, improve R0 resection rate and prolong OS, without increasing post-operative complications or mortality rates [117, 118], and it is considered the standard treatment. Long-term follow-up results from the German POET study [119], which involved neoadjuvant chemoradiotherapy combined with adjuvant chemoradiotherapy versus neoadjuvant chemotherapy for esophagogastric adenocarcinomas (Siewert I-III), suggest a tendency towards reduced recurrence and prolonged survival compared to neoadjuvant chemotherapy alone, with no significant increase in treatment toxicity or perioperative complications. Multiple multicenter phase II clinical studies, including the US RTOG-9904 trial [120], have demonstrated the favorable efficacy of preoperative chemoradiotherapy for locally advanced gastric cancer. As a result, the currently recommended indication for the treatment approach involving preoperative chemoradiotherapy followed by D2 surgery is stage III EGJ cancer. Synchronous chemotherapy regimens may include combinations of paclitaxel with fluoropyrimidines or platinum agents, as well as fluoropyrimidines with platinum agents.

Research on neoadjuvant chemotherapy and perioperative chemotherapy for esophageal or gastric adenocarcinoma (including EGJ) has been increasing and has yielded definitive results, categorizing it as Class I evidence. Similar to previously published studies like MAGIC [92], FLOT4-AIO [102], EORTC40954 [121] and FFCD9703, recent Asian studies such as RESOLVE [85], PRODIGY [96] and RESONANCE [122] have included subsets of EGJ cancer patients. In the PRODIGY study [96], which included 5.6% EGJ cancer cases, neoadjuvant chemotherapy using the DOS regimen showed tumor-shrinking effects, improved R0 resection rates and extended PFS. In the RESOLVE study [85], where EGJ cancer accounted for 36.5%, the neoadjuvant SOX regimen outperformed adjuvant XELOX chemotherapy by increasing R0 resection rates and prolonging DFS. A propensity score-matched study conducted at the Zhongshan Hospital of Fudan University [123] indicated that the DOS regimen was more effective than the XELOX regimen in terms of both PFS and OS, with EGJ cancer accounting for 32% of cases. Based on these studies, the DOS and SOX regimens can also be considered for neoadjuvant chemotherapy in EGJ cancer. Moreover, there has been research comparing preoperative neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for EGJ cancer. The POET study [119] demonstrated the potential advantages of preoperative chemoradiotherapy for EGJ cancer. However, a meta-analysis suggested that compared to neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy increased the pCR rate and reduced local recurrence but did not prolong OS, which differs from the findings of the POET study [124]. In 2021, the NEO AEGIES study [125] conducted a comparison between intensified three-drug perioperative chemotherapy and preoperative chemoradiotherapy using the CROSS regimen for the treatment of EGJ cancer. The findings indicated that intensified perioperative chemotherapy did not result in worse OS compared to the CROSS regimen, with a 3-year estimated survival probability of 57% and 56%, respectively, and that the preoperative chemoradiotherapy demonstrated superior tumor regression without additional negative effects.

In summary, based on the current research evidence for EGJ cancer, perioperative chemoradiotherapy or intensified three-drug perioperative chemotherapy may be more suitable than adjuvant chemotherapy, although further data on Chinese patients are needed.

## 2.1.2 | Comprehensive treatment for unresectable locally advanced gastric cancer

| Stratification | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| ECOG PS = 0-1 | • Concurrent chemoradiotherapy[a-c,e,f ①③] (Evidence 1A)<br>• Referral to MDT to assess the possibility of surgery after concurrent chemoradiotherapy. If complete resection can be achieved, surgery is recommended | • Chemotherapy[b,c,g ②] (Evidence 2B)<br>• Radiotherapy[b,c,e-h ③] (Evidence 2B)<br>• Referral to MDT to assess the possibility of surgery after concurrent chemoradiotherapy. If complete resection can be achieved, surgery is recommended | • Chemotherapy ② + radiotherapy[b-h] or concurrent chemoradiotherapy[a-f, ①③] (Evidence 3)<br>• Referral to MDT to assess the possibility of surgery after concurrent chemoradiotherapy. If complete resection can be achieved, surgery is recommended |
| ECOG PS = 2 | • Best supportive care or symptomatic treatment (Evidence 1A)<br>• Bypass surgery, endoscopic treatment, stenting, and/or palliative radiotherapy are recommended if they may improve nutritional status, alleviate cancer-related complications such as bleeding, pain, or obstruction. | • Best supportive care or symptomatic treatment + chemotherapy ± radiotherapy[b-h] (Evidence 2A)<br>• After nutritional support, if the patient conditions are suitable, can consider chemotherapy[②] alone or in combination with palliative radiotherapy | - |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance score; MDT, multidisciplinary team; 3D, three dimension; 5-FU, 5-fluorouracil.

① Concurrent chemoradiotherapy regimen:

Carboplatin + paclitaxel [126] (Evidence 1A)

Cisplatin + 5-FU or capecitabine or tegafur [127] (Evidence 1A)

Oxaliplatin + 5-FU or capecitabine or tegafur [128] (Evidence 2B)

Paclitaxel + 5-FU or capecitabine or tegafur [129, 130] (Evidence 2B)

Capecitabine [131] (Evidence 2B)

S-1 [132–134] (Evidence 2B)

5-FU [135] (Evidence 1A)

② Systemic regimen: refer to section "2.2 Treatment of advanced or metastatic gastric cancer"

③ Radiotherapy: 3D conformal radiotherapy/intensity-modulated radiotherapy

**Notes**

Gastric adenocarcinomas are considered unresectable if: (1) presence of tumor-related factors: the primary tumor shows extensive invasion to adjacent structures and cannot be separated from the surrounding normal tissues or have encased major vascular structures; the regional lymph nodes are fixed and fused into clusters, or presence of metastatic lymph nodes outside the scope of surgery; presence of distant metastasis or intraperitoneal implantation (including positive peritoneal lavage fluid cytology), etc.; (2) contraindications to surgery or refusal of surgical intervention due to poor general condition, malnutrition, and severe hypoproteinemia, anemia or other underlying causes.

[a]For patients with an unresectable tumor and good general conditions, if the tumor is localized and radiotherapy can be provided, concurrent chemoradiotherapy is recommended. Studies have confirmed that concurrent chemoradiotherapy was superior to chemotherapy alone or radiotherapy alone in terms of tumor downstaging and pathological remission rate [136, 137]. If the tumor responds well after treatment, the possibility of radical resection should be evaluated. Some studies have shown that if a patient is suitable for surgery, radical or palliative resection could both provide survival benefits [136, 137]. Retrospective studies have shown that even in patients who cannot undergo surgical resection, chemoradiotherapy can provide survival benefits compared to chemotherapy alone, with a few patients able to achieve long-term DFS [138, 139].

[b]For patients with locally advanced tumors or extensive lymph node involvement, radiation oncologists should evaluate the treatment approach based on MDT recommendations to assess the feasibility of irradiation target volumes. When the irradiation target volume is deemed excessively large and could potentially make patients intolerant to concurrent chemoradiotherapy, options such as chemotherapy alone or radiotherapy alone may be considered [140]. Following chemotherapy or radiotherapy, patients are presented to the MDT for further evaluation. Surgery may be an option for a selected group of patients who are sensitive to chemotherapy, aiming for curative resection. If complete tumor removal is not achievable, a sequential approach of chemotherapy followed by radiotherapy or concurrent chemoradiotherapy may be considered, with the possibility of reevaluating the feasibility of surgery after completing radiotherapy.

[c]For concurrent chemoradiotherapy, the choice between sequential chemotherapy plus chemoradiotherapy or primary concurrent chemoradiotherapy should be based on the comprehensive assessment by radiation oncologists in conjunction with the MDT consultation recommendations, taking into account the patient's physical condition and the required extent of irradiation. In general, concurrent chemoradiotherapy is preferred over radiotherapy alone [141], except in cases where patients cannot tolerate concurrent chemoradiotherapy. The selection of chemotherapy regimens during concurrent chemoradiotherapy depends on the tumor's location (the EGJ or stomach) and specific clinical trial protocols. Limited courses of induction chemotherapy may also be considered to screen for chemosensitivity. Patients who have undergone chemotherapy may have reduced tolerance to radiotherapy, and strategies to enhance tolerability, such as acid suppression,

nutritional support, dose reduction or consideration of single-agent fluoropyrimidine-based chemotherapy regimens during concurrent chemoradiotherapy, may be considered [131–134].

[d]Combining immune checkpoint inhibitors (ICIs) with chemotherapy is becoming more common in advanced or recurrent gastric cancer. There is a growing body of research exploring concurrent chemoradiotherapy with immunotherapy for locally advanced gastric cancer. Published phase II clinical trials [142–145] have shown promise for this approach, both in salvage therapy for unresectable advanced or recurrent gastric cancer after standard chemotherapy failure and in neoadjuvant treatment for locally advanced EGJ and/or gastric adenocarcinoma. These trials reported favorable tumor response rates, with MPR rates ranging from 48.7% to 73.7% and pCR ranging from 22.6% to 42.1%. Treatment-related toxicities were manageable. Additional data on optimal chemotherapeutic agents, irradiation target volumes and dose fractionation in combination therapy are still needed.

[e]Radiotherapy is recommended to employ precise techniques such as three-dimensional conformal and intensity-modulated radiotherapy (IMRT). Several studies have reported that compared to conventional two-dimensional radiotherapy techniques, three-dimensional conformal or IMRT techniques offer superior advantages in terms of target dose distribution and the protection of normal tissues and organs, which is particularly evident in protecting the gastrointestinal, renal or hepatic structures, leading to a reduction in radiation-related adverse reactions [146, 147].

[f]Consideration for radiotherapy planning. For patients with potentially resectable tumors, in addition to the visible lesions (primary/metastatic tumors or lymph nodes) confirmed by imaging examinations, expansion of the irradiation field to include high-risk regions of lymphatic drainage can be considered. The recommended radiation dose of tumor (DT) is 45-50.4 Gy. After treatment, the tumor should be re-assessed to judge whether the patient can undergo surgery or continue the systemic treatment. For unresectable tumors at pretreatment evaluation, radical radiotherapy at a dose of DT 50-60 Gy can be considered. For frail patients or those with extensive non-resectable cancer, the irradiation field should only include the visible tumor and avoid the inclusion of the regional lymph nodes. The recommended dose for palliative radiotherapy is DT 30-40 Gy for 10-20 cycles. The dosage and scope of irradiation should be based on the patient's general condition, the irradiation target volume, expected lifespan, and possible irradiation damage to surrounding normal tissues and organs.

[g]Compared to best supportive care, effective systemic therapy can prolong the survival of patients with advanced or metastatic gastric cancer [148]. As such, for patients presenting with severe gastrointestinal obstruction, bleeding, or obstructive jaundice, it is recommended to first provide feeding gastrostomy tube, stent implantation, gastrointestinal bypass surgery, local palliative radiotherapy, proton pump inhibitors, and analgesia, based on the patient's condition, preferentially within the first 2-4 weeks of presentation as longer waiting time could result in tumor progression. After amelioration of the patient's general condition, chemotherapy, targeted therapy and immunotherapy can then be considered. If not, best supportive care can be continued. The main chemotherapy regimens could be 5-FU-based, platinum-based, taxanes-based, and irinotecan regimens. Combination chemotherapy is recommended as it has been associated with a response rate of 30%-54% and a median OS (mOS) of 8-13 months [149]. For those who cannot tolerate combined chemotherapy, single-drug chemotherapy, such as 5-FU alone, can be considered.

[h]Radiotherapy can significantly alleviate some clinical symptoms of late-stage gastric cancer, such as hemorrhage, severe cancer pain, dysphagia and obstruction, and can improve the patients' general condition and quality of life [150–152]. Palliative radiotherapy may be considered for patients of old age, with advanced disease, decreased cardiopulmonary functions, multiple underlying diseases, and difficulty sustaining surgical intervention.

## 2.2 | Treatment of advanced or metastatic gastric cancer

For unresectable/metastatic GC, it is currently recognized that systemic therapies of antitumor drugs are the mainstay of comprehensive treatment. Local therapies such as palliative surgery, radiotherapy, radiofrequency ablation, intraperitoneal infusion or arterial embolization can help to prolong survival and improve the quality of life if the patient population is properly selected..Therefore, it is necessary to emphasize the concept of multidisciplinary comprehensive treatment throughout the whole management process of metastatic gastric cancer treatment.

In China, the current anti-tumor drugs for gastric cancer include chemotherapy, targeted therapy and immune checkpoint inhibitors. Chemotherapeutic agents have sufficient evidence-based medical evidence and rich clinical experience. There have been many clinical studies on targeted drugs for gastric cancer. Currently, the approved drugs for gastric cancer in China are limited to the anti-HER2 drugs, trastuzumab and disitamab vedotin, and the anti-angiogenic pathway drugs, ramucirumab and apatinib. There is still a lack of molecular targeted drugs approved for other targets based on their efficacy. Breakthroughs have been made in the field of immunotherapy in the treatment of advanced gastric cancer. PD-1 monoclonal antibody was approved for third-line treatment of advanced gastric cancer. However, the efficacy of immune checkpoint inhibitors alone is limited. The combination of PD-1 monoclonal antibody and chemotherapy has now become the new standard for first-line treatment of advanced metastatic gastric cancer. Gastric cancer is characterized by spatiotemporal heterogeneity and complex tumor microenvironment. There are differences in epidemiological characteristics, clinicopathological features, biological behavior, therapeutic modes and drug selections between Eastern and Western populations of gastric cancer. The patients should be encouraged to actively participate in clinical trials.

The stomach is an important digestive organ, and the primary lesion or tumor metastases may directly or indirectly affect a patient's nutritional status. Patients often suffer from tumor-related malnutrition and may face various complications such as massive bleeding, perforation, gastrointestinal tract obstruction or obstructive jaundice, and so on. Therefore, it is emphasized that supportive treatment should include the entire anti-tumor treatment process of gastric cancer. Supportive care aims to prevent or alleviate cancer-related symptoms or treatment-related side effects as early as possible, with special attention paid to maintaining the patient's nutritional status, actively preventing and treating while striving to maintain the patient's quality of life.

## 2.2.1 | Choice of antitumor drug treatment for metastatic gastric cancer[a]

### First-line treatment

| Line of treatment and tumor types | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| **First-line treatment** | | | |
| HER2 positive (IHC 3+ or IHC 2+ and FISH +) | Trastuzumab combined with oxaliplatin/cisplatin + 5-FU/capecitabine[h] (Evidence 1A) | Trastuzumab combined with oxaliplatin/cisplatin + S-1[h] (Evidence 2B) | • Trastuzumab + pembrolizumab + XELOX/PF[h] (Evidence 1B)<br>• Trastuzumab combined with other first-line chemotherapy regimens (excluding anthracyclines) (Evidence 3) |
| HER2 negative | PD-L1 CPS ≥ 5, FOLFOX/XELOX combined with nivolumab[k] (Evidence 1A) | • PD-L1 CPS < 5 or undetectable, FOLFOX/XELOX combined with nivolumab[k] (Evidence 1B)<br>• PD-L1 CPS < 5 or undetectable, XELOX combined with sintilimab[k] (Evidence 1B) | SOX combined with nivolumab |
| | • PD-L1 CPS ≥ 5, XELOX combined with sintilimab[k] (Evidence 1A)<br>• PD-L1 TAP ≥ 5%, XELOX combined with tislelizumab[k] (Evidence 1A) | PD-L1 CPS < 5 or undetectable, FOLFOX/XELOX combined with nivolumab[k] (Evidence 1B) | Single-agent fluoropyrimidines (5-FU/capecitabine/S-1) or paclitaxel/docetaxel[b, c] (Evidence 2B) for patients with poor physical conditions and other clinical situations. |
| | Oxaliplatin/cisplatin + fluoropyrimidines (5-FU/capecitabine/S-1)[b-e] (Evidence 1A)<br><br>Paclitaxel/docetaxel + fluoropyrimidines (5-FU/capecitabine/S-1)[b-d] (Evidence 2A) | Three-drug combination regimens, i.e., DCF and mDCF (Evidence 1B) for patients in good physical conditions and with large tumor burden[b] | PD-L1 CPS ≥ 1, pembrolizumab monotherapy[l] (Evidence 2B). |
| MSI-H/dMMR, regardless of HER2 status | | Pembrolizumab[m] (Evidence 2B) | Nivolumab + ipilimumab[m] (Evidence 2B)<br>Nivolumab combined with FOLFOX/XELOX[m] (Evidence 2B)<br>Pembrolizumab combined with PF[m] (Evidence 2B)<br>Other immune checkpoint inhibitors[m] (Evidence 3)<br>Chemotherapy alone[m] (Evidence 3) |

Continued.

| Line of treatment and tumor types | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| **Second-line treatment** | | | |
| HER2 positive (IHC 3+ or IHC 2+ and FISH +) | If trastuzumab has been previously used:<br>• Paclitaxel + ramucirumab (Evidence 1A)<br>• Single-agent chemotherapy (paclitaxel/docetaxel/irinotecan)[f] (Evidence 1A). | For those who failed with platinum therapy and did not receive trastuzumab, trastuzumab in combination with paclitaxel is recommended[h] (Evidence 2a) | If trastuzumab has not been previously used, trastuzumab in combination with second-line chemotherapy regimens other than anthracycline is recommended. (Evidence 3)<br>Refer to the second-line chemotherapy drug selection for HER2-negative gastric cancer.<br>Encourage participation in clinical trial. |
| HER2 negative | • Paclitaxel + ramucirumab (Evidence 1A)<br>• Single-agent chemotherapy (paclitaxel/docetaxel/irinotecan)[f] (Evidence 1A). | Two-drug chemotherapy, according to the previous regimens:<br>• Irinotecan + 5-FU, paclitaxel/docetaxel + fluoropyrimidines (5-FU/capecitabine/S-1) (Evidence 2B)[f]<br>• Albumin-bound paclitaxel[f] (Evidence 1B) | If there is no previous platinum treatment failure, oxaliplatin- or cisplatin-based regimens can be considered (Evidence 3). |
| MSI-H/dMMR, regardless of HER2 status | Envafolimab (Evidence 2A)*<br>Tislelizumab (Evidence 2A)* | Pembrolizumab (Evidence 2B)* | If previously used PD-1/PD-L1 monotherapy, select second-line treatment based on HER2 status[n] (Evidence 3) |
| **Third-line treatment** | | | |
| HER2 positive (IHC 3+ or 2+) | Disitamab vedotin[i] (Evidence 2A)<br>Apatinib[j] (Evidence 1A)<br>Nivolumab monotherapy[o] (Evidence 1A)* | | Select monotherapy chemotherapy based on past anti-tumor drug use and referring to second-line Recommended regimens[g] (Evidence 3) |
| HER2 negative | Afatinib[j] (Evidence 1A)<br>Nivolumab monotherapy[o] (Evidence 1A)* | Encourage participation in clinical trials. | |

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; dMMR, deficient DNA MMR; MSI-H, microsatellite instability-high; 5FU, 5-fluorouracil; PD-L1, programmed death ligand-l; PD-1, programmed death protein-1; CPS, Combined Positive Score; ELOX, capecitabine (Xeloda) and oxaliplatin (Eloxatin); FOLFOX, folinic acid (leucovorin), 5-FU, and oxaliplatin; mDCF, modified docetaxel, cisplatin and 5-FU; PF, cisplatin plus 5-FU;

*PD-1/PD-L1 monoclonal antibodies have not been previously used.

**Notes**

[a]The overall prognosis of advanced gastric cancer remains poor. The development of chemotherapeutic drugs stepped into a bottleneck period. The selection of targeted drugs remains limited. The current efficacy of immunotherapy alone was unsatisfactory. In the era of precision medicine, considering the high heterogeneity of gastric cancer, the dilemma of precision therapy and the exploration of new anti-tumor drugs, patients with advanced gastric cancer should be encouraged to participate in clinical trials.

[b]Fluoropyrimidines, platinums and taxanes are the main chemotherapeutic drugs for gastric cancer. First-line chemotherapeutic regimens are generally dual- or triple-drugs regimen which is based on fluoropyrimidines in combination with platinum and/or taxanes [153–162]. In China, the dual-drug regimen consisting of fluoropyrimidine and platinum is recommended, and oxaliplatin is preferred over cisplatin, based on Chinese real-world data and better tolerability [157, 161]. In the phase III SOX-GC clinical trial [161], the efficacy of SOX and SP as first-line treatment in diffuse or mixed advanced gastric/EGJ adenocarcinoma was compared. The results showed that compared with the SP regimen, the SOX regimen was associated with improved efficacy, survival and tolerance, and was then recommended as the first choice of treatment for non-intestinal type gastric cancer. Paclitaxel combined with fluorouracil has shown sufficient efficacy and safety in clinical research and practice [158]. Although the three-drug DCF regimen has attained its endpoint in phase III clinical trials, its high toxicity limits its clinical application [159]. The modified docetaxel plus cisplatin plus 5-FU (mDCF) [160] and paclitaxel plus oxaliplatin and 5-FU (POF) regimens [163] were shown to

be more effective and tolerable than the two-drug regimens in randomized trials. However, a phase III study found that the addition of docetaxel to cisplatin and S-1 did not improve the OS in chemotherapy-naïve, unresectable or recurrent gastric cancer [164]. The choice of chemotherapy regimen should be based on the patient's age, physical condition, accompanying diseases, previous treatment, patient's willingness, economic status, possible clinical practice bias, and drug accessibility.

[c]There is no sufficient evidence to recommend chemotherapeutic drugs based on the prediction of chemotherapeutic response according to the Lauren classification, molecular classification, in vitro drug susceptibility test, xenograft transplantation model, xenobiotic metabolism, or metabolomics. Patients suspected of fluoropyrimidine-associated metabolic disorders are advised to undergo a dihydropyrimidine dehydrogenase deficiency (DPD) test [165], and those suspected of irinotecan-associated metabolic disorders can undergo the *UGT1A1* gene polymorphism testing [166].

[d]The standard treatment for late-stage gastric cancer usually lasts 4-6 months, and these patients should be regularly followed-up after disease control. A phase III randomized controlled trial revealed that sequential therapy, involving the combination of paclitaxel and capecitabine for 4 cycles followed by single-agent capecitabine, did not result in an extension of overall survival compared to six cycles of cisplatin combined with capecitabine but significantly improved quality of life and decreased treatment-related adverse events [158]. This study marked a milestone as the first large-scale prospective clinical investigation into maintenance therapy for gastric cancer. Findings from the phase III JAVELIN G100 study showed that in first-line treatment, continuing avelumab monotherapy maintenance after achieving disease control with chemotherapy extended OS in the PD-L1 CPS $\geq 1$ subgroup but did not yield the same benefit in the overall population [167]. With the advent of immunotherapy and targeted therapy in first-line treatment, sequential maintenance therapy following chemotherapy has become a common choice in clinical practice. Studies such as KEYNOTE-062, CheckMate 649 and various Chinese phase III clinical trials have explored various maintenance therapy patterns, with the most common being single-agent immunotherapy/targeted therapy, followed by combinations of these agents with capecitabine or combinations of targeted and immune agents. Presently, the optimal maintenance therapy approach for first-line treatment of advanced gastric cancer remains undetermined.

[e]Studies have shown that two-drug regimens for reducing dosage were better than single-drug regimens for elderly or frail patients [168, 169]. In the GO2 study [156], elderly or frail patients were randomly assigned to the following three dose levels: A: oxaliplatin 130 mg/m$^2$ + capecitabine 625 mg/m$^2$ (twice daily on days 1-21, every 3 weeks); B: 80% dosage of Level A; C: 60% dosage of Level A. The results showed that, compared to Level A and B doses, patients with Level C doses not only had non-inferior outcomes in terms of PFS but also had better overall treatment utility (overall therapeutic efficacy, toxicity, and quality of life).

[f]Currently, the second-line chemotherapy in phase III clinical trials is based on single-drug treatment, but there are small-sample phase II studies that show that for patients with PS = 0-1, two-drug chemotherapy regimens are safe and can bring improved tumor control [170, 171]. Therefore, for patients with good physical condition, after fully weighing the pros and cons of treatment, combined chemotherapy can be considered. The Japanese ABSOLUTE phase III clinical trial showed that weekly nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was not inferior to weekly solvent-based paclitaxel in terms of OS [172]. Neutropenia and loss of appetite were more common in the nab-paclitaxel group, but the rate of hypersensitivity was lower.

[g]Clinical studies regarding third-line treatment for advanced gastric cancer, although comprised of a limited number of patients, did not find significant benefit from chemotherapy in this group of patients. Although the phase III TAGS study showed that trifluridine/tipiracil (TAS-102) provided a survival benefit in third-line treatment, no Chinese patients were included in the study [173]. The risks and benefits of treatment should be carefully weighed depending on the patients' physical condition, underlying diseases, tumor-related symptoms, and risk of complications.

[h]ToGA trial [174] showed that, compared with chemotherapy alone, trastuzumab combined with first-line chemotherapy was associated with improved efficacy and survival in HER2-overexpressed, treatment-naïve, advanced or metastatic gastric cancer patients. Several phase II clinical studies have evaluated the combination of trastuzumab and other chemotherapeutic regimens and shown good efficacy and safety [175, 176]. The EVIDENCE study was designed to evaluate the efficacy, safety, treatment model, and clinical outcomes of trastuzumab in Chinese HER2-positive metastatic gastric cancer patients. It included 1,600 patients and further confirmed the efficacy and good safety of trastuzumab in the Chinese population. Among the first-line combined chemotherapeutic regimens, XELOX had the best outcome with an OS of 34.6 months [177]. For HER2-positive advanced gastric cancer patients without prior use of trastuzumab, paclitaxel combined with trastuzumab was found to be effective and safe in a phase II clinical study [175]. However, for HER2-positive advanced gastric cancer patients who have previously failed to receive first-line treatment with trastuzumab, recent Chinese or international phase II and retrospective studies showed controversy over the value of trastuzumab as cross-line therapy, lacking high-level evidence-based medical evidence [175]. The 2020 "Chinese expert consensus on drug analogues" approved the clinical substitution of drug analogues. In August 2020, the National Medical Products Administration (NMPA) of China approved the indications of trastuzumab analog HLX02 for HER2-positive breast cancer and the combination of capecitabine/5-FU and cisplatin for newly diagnosed, metastatic, HER2-positive gastric cancer. Immunotherapy has become an important exploration direction for the combined treatment of HER2 positive advanced gastric cancer. Several Phase II studies have shown that for HER2-positive advanced gastric cancer patients, first-line treatment with chemotherapy, trastuzumab and PD-1 monoclonal antibody achieved a high overall response rate (ORR) and significantly prolonged PFS than previous survival data [178]. Phase III KEYNOTE-811 clinical trial [179] involved 434 previously untreated patients with advanced HER2-positive gastric cancer. A mid-term analysis of 264 enrolled patients showed that compared to the control group treated with trastuzumab and chemotherapy, the further combination of pembrolizumab resulted in a significantly higher response rate (74.4% vs 51.9%; $P = 0.00006$). In May 2021, the FDA accelerated the approval of pembrolizumab combined with trastuzumab and fluoropyrimidine and platinum chemotherapy as first-line treatment for unresectable locally advanced or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma patients.

[i]Other HER2-targeted drugs included pertuzumab (anti-HER2 monoclonal antibody (mAb), JACOB study) [180], lapatinib (small molecule tyrosine kinase inhibitor; LOGIC study and TyTAN study) [181, 182], Disitamab vedotin (ADC and C008 studies [183]) and trastuzumab deruxtecan (T-DXd) (ADC, DESTINY-Gastric01 and 02 studies [184, 185]). The phase III study of trastuzumab emtansine (T-DM1) in second-line treatment of gastric cancer showed negative results [186]. The phase II multicenter C008 study showed that Disitamab vedotin used in advanced gastric cancer patients with HER2 positive expression (IHC 2+ or 3+) who had previously received ≥2 lines of therapy achieved an ORR of 24.4% and a median OS of 7.6 months [183] . In June 2021, China NMPA conditionally approved Disitamab vedotin for HER2-positive expressing advanced or metastatic gastric cancer (including EGJ adenocarcinoma) patients who had previously received ≥2 lines of therapy. Phase II study DESTINY-Gastric01 compared the efficacy of T-DXd with chemotherapy in HER2-positive advanced gastric cancer patients who had previously failed trastuzumab-based treatment and revealed that T-DXd group had a higher ORR (51% vs. 14%, $P < 0.001$) and a longer median OS (12.5 months vs. 8.4 months; HR: 0.59) compared with chemotherapy [184]. T-DXd has also shown good results in the second-line treatment of gastric cancer. The DESTINY-Gastric02 study included 79 HER2-positive gastric cancer patients who had failed first-line trastuzumab-containing regimens. T-DXd monotherapy, achieving a response rate of 41.8% and a PFS of 5.6 months [185]. However, this study did not include the Asian population. In January 2021, the U.S. FDA approved T-DXd for use in advanced or metastatic HER2-positive gastric or EGJ adenocarcinoma patients who had previously received trastuzumab-based treatment.

[j]Anti-angiogenic drugs for advanced gastric cancer included ramucirumab (anti-VEGFR2 monoclonal antibody) and methanesulfonic acid apatinib (VEGFR-2 small-molecule tyrosine kinase inhibitor). For metastatic EGJ/gastric adenocarcinoma that progressed after first-line platinum and/or fluorouracil-based chemotherapy, REGARD study [187] showed that ramucirumab monotherapyas second-line treatment, compared with placebo, could prolong mOS (5.2 vs. 3.8 months, $P = 0.047$). RAINBOW study [188] showed that compared with paclitaxel alone, ramucirumab combined with paclitaxel as second-line could prolong

mOS (9.63 vs. 7.36 months, $P = 0.0169$) and had tolerable adverse reactions. Moreover, this combination therapy was associated with manageable adverse reactions. RAINBOW-Asia phase III study [189] (90% of patients from China) showed that the PFS of patients in the combination of ramoxizumab and paclitaxel group was significantly longer than that of the paclitaxel group (4.14 months vs 3.15 months) and showed a median OS benefit consistent with results from the global key registered clinical trial RAINBOW (HR: 0.963). The patients generally tolerated the treatment well, and no new safety concerns were observed. A phase III clinical study [190] enrolled 273 patients who had failed second-line or above treatment. The results showed that the apatinib group, compared with the placebo group, could prolong the mPFS (2.6 vs. 1.8 months, $P < 0.001$) and increase the disease control rate (42.05% vs. 8.79%, $P < 0.001$). Apatinib was approved for third-line or above treatment in patients with advanced gastric or EGJ adenocarcinoma.

[k]In the phase III clinical trial ORIENT-16 [191], 650 patients with treatment naïve advanced gastric cancer were enrolled, and the study compared sintilimab plus XELOX chemotherapy with a placebo plus XELOX chemotherapy. For patients with PD-L1 CPS $\geq 5$, the combination of sintilimab with XELOX significantly improved both PFS (7.7 months vs. 5.8 months, HR: 0.628, $P = 0.0002$) and OS (18.4 months vs. 12.9 months, HR: 0.660, $P = 0.0023$). The ORR also increased from 48.4% to 58.2%. In the intention to treat (ITT) population, PFS and OS were improved by 1.4 months and 2.9 months, respectively. However, no survival benefits were observed for patients with PD-L1 CPS $< 5$. The CheckMate 649 study demonstrated statistically significant survival benefits in the ITT population, including 626 patients with a PD-L1 CPS score $< 5$ [192]. Two meta-analyses also supported the lack of survival improvement in advanced gastric cancer patients with PD-L1 negative or low expression [193, 194]. Considering the clinical practice in China, it is recommended that for patients with PD-L1 CPS $< 5$ or when PD-L1 testing is not available, the combination of XELOX/FOLFOX with nivolumab or XELOX with sintilimab may be considered, especially in cases whose tumor burden is substantial, the patient's performance status is good, there's a need to quickly reduce tumor burden and alleviate symptoms, or when second-line treatment options are limited, and there are no contraindications to immune checkpoint inhibitors. The RATIONALE 305 study is a global phase III clinical trial that compared the effectiveness and safety of trastuzumab deruxtecan in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy as a first-line treatment for locally advanced, unresectable or metastatic gastric or EGJ adenocarcinoma patients [195]. The study's results demonstrated a substantial improvement in median OS among patients who were PD-L1 positive (TAP score $\geq 5\%$) in the combination group compared to the control group (17.2 months vs. 12.6 months, HR: 0.74, 95% CI: 0.59-0.94), which represents a significant 26% reduction in the risk of death. Remarkably, the survival benefit of trastuzumab deruxtecan in combination with chemotherapy was consistent across various patient subgroups, including different age groups, ECOG performance status, gender, race, chemotherapy regimen selection, and the presence of peritoneal metastasis. The combination group also exhibited a marked extension in PFS (7.2 months vs. 5.9 months, HR: 0.67; 95% CI: 0.55-0.83), indicating a 33% reduction in the risk of disease progression. As a result, trastuzumab deruxtecan in combination with chemotherapy may become a standard first-line treatment option for advanced gastric cancer patients who are PD-L1 positive. The ATTRACTION-4 study enrolled 724 patients and compared SOX/XELOX plus nivolumab with SOX/XELOX plus a placebo using primary endpoints PFS and OS [196]. The findings revealed that the combination of chemotherapy and immunotherapy significantly prolonged PFS (10.45 months vs. 8.34 months, HR: 0.68, $P = 0.0007$) and elevated the ORR from 47.8% to 57.5%. While the difference in OS (17.45 months vs. 17.15 months, HR: 0.9, $P = 0.26$) did not reach statistical significance, this may be attributed to the influence of subsequent treatments. Nevertheless, considering that SOX is a widely accepted first-line chemotherapy regimen in China with established efficacy and safety, SOX in combination with nivolumab, has been included as a Grade III recommendation.

[l]In the phase III KEYNOTE-062 study [197], among patients with gastric/EGJ cancer with a PD-L1 CPS score of $\geq 1$, pembrolizumab was found to be non-inferior to chemotherapy, demonstrating median overall survivals of 10.6 months vs. 11.1 months. Additionally, in the CPS $\geq 10$ subgroup, the pembrolizumab group demonstrated a significant advantage over the chemotherapy group (HR: 0.69). Data from the Asian subgroup revealed that pembrolizumab monotherapy led to a longer OS benefit compared to chemotherapy, with OS of 22.7 months vs. 13.8 months for patients with CPS $\geq 1$ and 28.5 months vs. 14.8 months for patients with CPS $\geq 10$. Pembrolizumab monotherapy also showed superior PFS and ORR in Asian patients compared to the overall population. Therefore, in patients with gastric cancer and a CPS score of $\geq 1$, pembrolizumab monotherapy may be considered when first-line chemotherapy combined with immunotherapy is not suitable.

[m]dMMR/MSI-H gastric cancer accounts for approximately 6% of advanced gastric cancer cases [198]. It exhibits significant differences in molecular subtyping characteristics, biological behavior, drug sensitivity, tumor microenvironment, treatment modalities and prognosis compared to pMMR/MSS patients [199]. Its main features include a favorable prognosis, insensitivity to chemotherapy and good response to immunotherapy. Therefore, in this update, it is classified separately for comprehensive management. However, due to the low incidence, there is a lack of large-sample high-level evidence in evidence-based medicine for dMMR/MSI-H gastric cancer patients, who are often included as non-predefined subgroups in prospective studies. For example, the KEYNOTE-062 and CheckMate-649 studies included 50 and 55 patients with dMMR/MSI-H gastric cancer, respectively. Hence, there is currently no Grade I recommendation for first-line treatment for this patient group. Participation in clinical research is encouraged [192, 197]. In the dMMR/MSI-H gastric cancer subgroup of the KEYNOTE-062 study, 14, 17, and 19 patients received pembrolizumab monotherapy, pembrolizumab combined with chemotherapy, and chemotherapy alone, respectively. The ORRs and 24-month survival rates were as follows: pembrolizumab monotherapy 57.1%/71%, pembrolizumab combined with chemotherapy 36.8%/26%, and chemotherapy alone 64.7%/65% [197]. These findings suggest that in first-line treatment, immunotherapy as monotherapy and immunotherapy combined with chemotherapy are superior to chemotherapy alone. The long-term survival benefits of immunotherapy monotherapy are more evident and can be considered as Grade II recommendations. Based on clinical practice in China and considering patient affordability, other immune checkpoint inhibitors that are already approved in China can also be considered as Grade III recommendations. Immune combination therapy (pembrolizumab combined with FP or nivolumab combined with FOLFOX/XELOX) is recommended as Grade III, but only when there are contraindications or unavailability of immune checkpoint inhibitors, should chemotherapy alone be considered. In the MSI-H subgroup of the CheckMate 649 study, dual immunotherapy (nivolumab combined with ipilimumab) compared to chemotherapy had ORRs of 70% and 57%, respectively. OS was significantly extended (not reached vs. 10 months, HR: 0.28), with a 72% reduction in the risk of death in the dual immunotherapy group. The combination therapy group had ORR and OS of 55% and 38.7 months, respectively. Although the dual immunotherapy group was prematurely terminated due to safety concerns, subsequent studies such as CheckMate 142 confirmed the good safety profile of adjusted doses (nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg) [192, 200]. Therefore, adjusted-dose dual immunotherapy can be considered as Grade III recommendation for first-line treatment of dMMR/MSI-H gastric cancer.

[n]In a prospective multicenter phase II clinical study that included patients with advanced solid tumors, including gastric cancer, who had failed standard treatment, a total of 18 patients with gastric cancer were enrolled. Among them, 33.3% had undergone third or higher line of treatments. These patients were given envafolimab, and the ORR, disease control rate (DCR), duration of response (DoR) for $\geq 12$ months, 12-month PFS, and 12-month OS were 44.4%, 83.3%, 100.0%, 58.0%, and 83.3%, respectively. However, the PFS and OS were not reached. Compared to the KEYNOTE-016 study, this study was conducted in a larger sample of Chinese patients and demonstrated good safety. Envolizumab has received conditional approval for the indication of advanced dMMR/MSI-H solid tumors through a priority review process. Therefore, in the second-line treatment population who have not previously received PD-1/PD-L1 monoclonal antibody inhibitors, it can be considered as a Grade I recommendation [201]. In a phase II study, RATIONALE-209 [202], which included 80 patients with locally advanced unresectable or metastatic MSI-H/dMMR solid tumors, monotherapy with toripalimab was used. Among the 9 patients with gastric cancer/EGJ), 1 achieved CR and 4 achieved

progressive response (PR), resulting in an ORR of 55.6%, with good safety. On March 11, 2022, the China NMPA approved the use of toripalimab for locally advanced unresectable or metastatic MSI-H/dMMR solid tumors after failing previous treatments [202]. For patients who have received ICI therapy as first-line treatment, second-line treatment is recommended based on HER2 status. A prospective clinical study comprising 68 patients with MSI-H/dMMR advanced malignancies who had failed standard treatment gave them serplulimab, and the patients demonstrated an ORR of 39.7%, a 12-month DoR of 92.1%, and a 12-month OS of 74.5% [203]. Among the 3 gastric cancer patients who had received second-line treatment, with a median follow-up time of 7.16 months, 1 achieved PR and had an ORR of 33.3%. Due to the limited sample size, more clinical data accumulation is needed for MSI-H gastric cancer patients who have failed standard treatment and are treated with serplulimab.

[o]Based on the ATTRACTION-2 study [204], nivolumab monotherapy was approved for third-line treatment of advanced gastric cancer. However, with the publication of first-line studies like CheckMate 649, which have reshaped the landscape of first-line immunotherapy for gastric cancer, there are few applicable scenarios in clinical practice for third-line treatment. It should only be considered cautiously in patients who have not received PD-1/PD-L1 monoclonal antibody therapy in the first and second lines after evaluating the patient's physical condition, potential risk of hyperprogression, and adverse reactions. Merck announced the voluntary withdrawal of an accelerated approval indication for Keytruda in the United States for the treatment of PD-L1-positive locally advanced or metastatic gastric and EGJ adenocarcinoma that has progressed after second-line or later-line therapy. Therefore, it is removed from the recommendations for third-line treatment of gastric cancer.

[p]A phase II clinical study from South Korea comprising patients with treatment-resistant gastric/EGJ adenocarcinoma reported that among the 61 patients, 6 were positive for EBV infection and had an ORR of 100%, suggesting that EBV infection might be a potential biomarker for predicting potential PD-1 monoclonal antibody therapy response. However, two observational studies in the Chinese population showed that the efficacy of ICIs in EBV-positive gastric cancer patients who have failed first-line treatment is 33.3% [205, 206]. Therefore, whether EBV infection is an accurate key biomarker requires further validation in prospective studies.

[q]Claudin18.2 is moderately to highly expressed in approximately 40% of gastric cancer patients. In the phase III randomized SPOTLIGHT study [207], the patients with advanced gastric/esophagogastric junction cancer who were claudin18.2-positive and HER2-negative received zolbetuximab, a Claudin18.2 monoclonal antibody, combined with mFOLFOX6 as a first-line treatment compared to modified FOLFOX6 chemotherapy alone. The median PFS (10.61 months vs. 8.67 months, HR: 0.751, $P = 0.0066$) and OS (18.23 months vs. 15.54 months, HR: 0.750, $P = 0.0053$) improved. In a phase I study initiated by researchers, 28 Claudin18.2-positive gastric cancer patients who had failed standard treatment received Chimeric antigen receptor (CAR)-T cell therapy and achieved an ORR of 57.1%. Among 18 patients who had previously failed second-line treatment, the ORR was as high as 61.1%, with median PFS and OS of 5.4 months and 9.5 months, respectively [208]. In another phase Ib study involving 14 Claudin18.2-positive gastric cancer patients who had failed second-line treatment, an ORR of 57.1% with median PFS and OS of 5.6 months and 10.8 months were observed [209]. These results showed significant improvements compared to existing third-line treatments. Confirmatory studies are currently being conducted for validation.

### 2.2.2 | Comprehensive treatment of gastric cancer with peritoneal metastasis[a]

| Site | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Patients with only positive peritoneal cytology (cy1P0) | Systemic chemotherapy ± molecular targeted therapy ± intraperitoneal chemotherapy or encourage participation in clinical trials (Evidence 2A) | Radical surgery if conversion to cy0 after conversion therapy[b] (Evidence 2B) | Standard D2 surgery followed by adjuvant chemotherapy[c] (Evidence 2B) |
| Patients with only gross peritoneal metastasis (P1) | Refer to late-stage gastric cancer treatment or recommend participation in clinical trials | Systemic chemotherapy ± molecular targeted therapy ± intraperitoneal chemotherapy or encourage participation in clinical trials[f] (Evidence 2A) | For potentially resectable tumors who turned CR/PR and CY(-) after conversion therapy, palliative surgery can be considered[d] (Evidence 2B) |
| Patients with gross peritoneal and other organ metastasis[e] | Refer to late-stage gastric cancer treatment or recommend participation in clinical trials | | |

Abbreviations: cy, cytologic results of peritoneal lavage.

**Notes**

[a]Gastric cancer with peritoneal metastasis can be divided into two types: Type 1, only positive peritoneal cytology for cancer cells in the abdominal cavity, without gross metastasis, and these can be further classified as the presence of cancer in the cytologic results of peritoneal lavage (CY1) absence of local peritoneal metastatic nodules (P0); Type 2, visible gross peritoneal metastases in the abdominal cavity, which can be recorded as P1 [210].

[b]Compared with CY0P0, CY1P0 gastric cancer is a stage IV gastric cancer that is technically considered operable but biologically considered unresectable with poorer overall prognosis [211]. At present, the initial treatment for patients with CY1P0 tumors is systemic chemotherapy unless they are symptomatic and require surgery.

A systematic review including 21 studies, which comprised 6499 patients, was conducted to evaluate the role of peritoneal cytology as a predictor of staging and survival of gastric cancer and whether positive cytology can improve the prognosis through neoadjuvant therapy [212]. The results showed that negative cytology after neoadjuvant therapy was associated with significant improvement in OS (HR: 0.64, 95% CI: 0.56-0.73, $P < 0.0001$). Intraoperative peritoneal chemotherapy (IPC) and extensive intraoperative peritoneal lavage (EIPL) have also been shown as effective treatments. Results of a meta-analysis showed that, compared

with surgery alone, surgery combined with IPC could improve the 5-year survival rate (risk ratio [RR] = 3.10) and reduce the risk of recurrence (odds ratio [OR] = 0.45), while IPC combined with EIPL could further increase the above benefits (corresponding RR = 6.19, OR = 0.13) [213]. For CY1P0 patients, multidisciplinary comprehensive treatment using hyperthermic intraperitoneal perfusion chemotherapy (HIPEC)/peritoneal lavage combined with surgery and systemic chemotherapy has been explored in many centers. In Japan, these patients are more likely to receive preoperative IPC combined with radical D2 gastrectomy [214]. However, due to inconsistencies in patient selection, treatment types (palliative or radical), surgical techniques, usage of intraperitoneal chemotherapy, as well as systemic chemotherapy drug selection, the results of such treatments remain inconsistent. Overall, for CY+P0 patients, preliminary results of the exploratory study suggest that systemic chemotherapy has the possibility of converting the positive cytology of CY1P0 to negative and can improve the outcome. However, the significance and indications of gastrectomy for patients whose cytology turned from positive to negative are still inconclusive. For such cases, chemotherapy should be prioritized before surgery, and after repeated confirmation of CY0P0 diagnosis by laparoscopic exploration, resection of the primary lesion can be considered.

[c]There are few randomized controlled studies focused on gastric cancer with positive exfoliative cytology. The CCOG0301 study [215] suggests radical gastrectomy followed by adjuvant S-1 chemotherapy for CY1P0 patients. According to the result of a report [216], radical surgery combined with S-1 monotherapy in solitary CY1P0 patients can increase their mOS to 22.3 months.

[d]For patients with only gross peritoneal metastasis, chemotherapy has been associated with shrinking or reducing the number of peritoneal metastases, but it is difficult to eliminate all micrometastases with chemotherapy, even if the initial response is satisfactory [217, 218]. When peritoneal metastases have responded well to chemotherapy, the primary tumor and/or metastases can be considered for resection. Since most of these cases recur in the abdominal cavity after surgery, it is defined as cytoreductive surgery or tumor reduction surgery.

[e]For gastric cancer patients with gross peritoneal and other organ metastasis, palliative chemotherapy remains the first choice. Conversion therapy can only be considered in a small number of patients, and the possibility of R0 resection depends mainly on the response to first-line chemotherapy. For those with gastrointestinal bleeding and/or obstruction, palliative surgery such as primary tumor resection and/or bypass surgery can be considered [219].

[f]The palliative treatment recommendations for patients with peritoneal metastasis can be referred from the late-stage treatment of gastric cancer or consider participation in clinical trials. Drainage of ascites and intraperitoneal perfusion chemotherapy can be considered for patients with symptomatic abdominal pain. The PHOENIX-GC study compared intraperitoneal and intravenous paclitaxel plus S-1 versus cisplatin plus S-1 in gastric cancer patients with peritoneal metastasis and showed that although no significant improvement in OS in the overall population was observed, patients with moderate to severe ascites had some survival benefits [220].

### 2.2.3 | Comprehensive treatment of recurrent or solitary distant metastatic gastric cancer[a]

a) A solitary distant metastatic lesion is defined as one that has the possibility of being locally treated, regardless of the primary gastric lesion and regional lymph nodes [221–223]. Presently, there are no large-scale prospective randomized controlled clinical study data to provide scientific-based evidence for the treatment of gastric cancer with recurrence or solitary distant metastasis. Most of the evidences are from retrospective or small-scale studies. For patients with non-radically resectable primary tumors or PS ≥ 2, the basic treatment strategy is to treat recurrent and metastatic gastric cancer or the best supportive treatment. For the patients with radically resectable primary lesions and regional lymph nodes and PS 0-1, the basic treatment strategy is based on the treatment of recurrent and metastatic gastric cancer, and the optional strategy includes systemic therapy (chemotherapy, targeted therapy, immunotherapy) combined with potentially curative surgery. The optimal therapeutic option for such patients should be discussed through an MDT.

*Treatment of locally recurrent gastric cancer after operation*

| Site | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Local recurrence | To treat as recurrent/metastatic gastric cancer or encourage participation in clinical trials | • Surgery combined with drug therapya (Evidence 2B)<br>• Radiotherapy combined with drug therapyb (Evidence 2A) | |
| Recurrence at the remnant stomach or anastomotic region[c] | • ESD<br>• Total remnant gastrectomy + lymph node dissection ± combined organ resection | Palliative surgery | • Endoscopic stent placement<br>• Bypass surgery<br>• Jejunal nutrition tube placement |

Abbreviations: ESD, endoscopic submucosal dissection.

**Notes**

[a]Local recurrence is defined as the re-occurrence of tumor at the resection site after radical gastrectomy and regional lymph node metastasis. Most studies regarding local recurrence of gastric cancer are retrospective and single-institution studies, and there is a lack of large-scale prospective studies. Findings from one study suggested that surgery may be an important prognostic factor for survival as the mOS of patients who underwent surgery was significantly better than unresectable patients (25.8 vs. 6.0 months) [224]. Although some local recurrent diseases can be surgically treated, the indications for surgical intervention must be strictly followed.

[b]For patients with local recurrence who did not receive any previous radiotherapy, concurrent chemoradiotherapy has been associated with survival benefits. A retrospective study showed that concurrent chemoradiotherapy in gastric cancer patients with local recurrence at the anastomic site or regional lymph nodes was associated with an ORR of 61.9% and mOS of 35 months [225]. Compared with chemotherapy alone, concurrent chemoradiotherapy resulted in a higher ORR

(87.8% vs. 63.0%, $P = 0.01$), longer mOS (13.4 vs. 5.4 months, $P = 0.06$), and better control of symptoms such as pain, bleeding, and obstruction (85.0% vs. 55.9%, $P = 0.06$) [226, 227].

[c]Recurrence in the remnant stomach after radical gastrectomy usually occurs within 10 years after surgery [228], and the possibility of resection is high. ESD can be performed for early gastric remnant recurrence without lymph node metastasis. The en bloc resection rate and complete resection rate were reported to be 91%-100% and 74%-94% [229]. The resection of advanced-stage recurrent remnant gastric cancer should include total gastrectomy, lymph node dissection, and combined resection of invaded organs. The regional lymph nodes that were not resected at initial surgery should be resected. Of note, the metastasis rate of the jejunal mesentery and root lymph nodes near the anastomotic stoma of Billroth II anastomosis is high and should be included in the field for lymph node dissection [230]. For patients with unresectable tumors who are symptomatic, palliative resection, bypass surgery, stent implantation, or jejunal nutrition tube implantation can be considered.

### *Treatment of gastric cancer with non-peritoneal single distant metastasis*

| Site | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Para-aortic lymph node (no.16a2/b1) metastasis | Refer to the treatment of recurrent and metastatic gastric cancer or encourage participation in clinical trials | Neoadjuvant chemotherapy combined with radical gastrectomy[a] (Evidence 2B) | Radical surgery combined with chemoradiotherapy (Evidence 3) |
| Single liver metastasis[b,c,e] | | Sequential systemic chemotherapy and surgery for the primary and metastatic tumors[b] (Evidence 2A) | Systemic chemotherapy combined with local treatment[c] (Evidence 2B) |
| Ovarian metastasis | | Surgery for the primary and metastatic tumor combined with systemic chemotherapy[d,f] (Evidence 2B) | |

**Notes**

[a]Prophylactic dissection of the para-aortic lymph nodes in gastric cancer was not found to be beneficial in the JCOG9501 study [231]. In the REGATTA study [232], subgroup analysis of the para-aortic lymph node (no. 16a2/b1) metastasis showed that surgery combined with chemotherapy was associated with a good curative effect. At present, the main mode of treating para-aortic lymph node metastasis is neoadjuvant chemotherapy followed by sequential surgery. In the JCOG0001 study [233], it was reported that 2-3 cycles of sequential chemotherapy with irinotecan and cisplatin before surgery were associated with a clinical effective rate of 56%, R0 resection rate of 65%, and 3-year survival rate of 27%. However, because of the high death rate in the study, it was terminated early. The JCOG0405 study [234] reported that 2 cycles of neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis was associated with a curative rate of 64.7%, R0 resection rate of 82%, and 3-year OS of 58.8%. In the JCOG1002 study [235], docetaxel was added to the S-1 combined with the cisplatin regimen of the JCOG0405 study (DCS regimen) and the observed clinical remission rate was found to be 57.7%, R0 resection rate 84.6%, and pathological remission rate was 50.0%, suggesting that the addition of docetaxel did not increase treatment efficacy. S-1 combined with cisplatin is still considered the first choice for these patients [236]. A prospective study from the Zhongshan Hospital Affiliated to Fudan University showed that the overall PFS of gastric cancer patients with isolated para-aortic lymph node metastasis after neoadjuvant chemotherapy combined with radical surgery was 18.1 months [237].

[b]Synchronous liver metastasis of gastric cancer refers to the liver metastasis occurring 6 months before, during or 6 months after surgery [238]. Single liver distant metastasis refers to single hepatic metastasis of diameter ≤5 cm, and the metastasis is limited to one lobe without involvement of blood vessels and bile ducts. Currently, there is a lack of prospective randomized controlled clinical study data for the treatment of such patients. Results from the REGATTA study showed that palliative surgery only for primary lesion was not associated with survival benefit [232]. A retrospective study showed that selective gastric cancer patients with liver metastasis, i.e., including those aged <65 years old, with normal carcinoembryonic antigen (CEA) and cancer antigen 199 (CA199) levels at the time of diagnosis and non-EGJ cancer, could obtain survival benefits through sequential chemotherapy and surgery [239]. Findings from a meta-analysis showed that the prognosis of patients whose liver metastasis was resected was significantly better than non-resected ones (mOS, 23.7 vs. 7.6 months) [240]. A systematic review showed that the 1-, 2-, 3-, and 5-year OS rates of patients who underwent gastrectomy plus hepatectomy were significantly higher than those with gastrectomy alone [241]. A systematic review of 39 retrospective studies found that resection of liver metastases could significantly improve prognosis (HR: 0.50; $P < 0.001$), especially in Far Eastern compared with Western studies, and patients with solitary liver metastasis [242]. A meta-analysis found that relatively early T and N stage, no vascular invasion, maximum diameter of liver metastases <5 cm, negative margin, normal preoperative CEA and CA199 levels were important factors for better prognosis in gastric cancer patients with liver metastases who underwent systemic chemotherapy followed by surgery [243]. Findings from an EORTC and JCOG questionnaire survey [244], conducted in 2017 in 17 European countries and 55 research centers in Japan on gastric cancer patients with liver metastases whose primary and metastatic foci could be resected found that most centers recommend preoperative chemotherapy followed by resection of the primary and metastatic foci.

[c]For patients with solitary liver distant metastasis not suitable for surgery, systematic chemotherapy combined with other local treatments, including radiofrequency ablation (RFA) [245], microwave ablation (MWA) [246], hepatic artery infusion chemotherapy (HAIC) [247, 248], transarterial chemoembolization (TACE) [249] and stereotactic body radiotherapy (SBRT) [250], can be considered. A retrospective multicenter study from Japan found no significant difference in the survival between patients who underwent surgical resection and those who underwent local treatment but also observed that patients staged as N0/N1 after the resection of their single metastatic and primary lesion had significantly better benefit from surgery or local treatment [251]. The results of a meta-analysis showed that compared with systemic chemotherapy, systemic chemotherapy combined with RFA in patients with liver metastasis (diameter <3 cm) could significantly prolong the survival time of these patients, with an mOS of 22.93 months [252].

[d]Krukenberg tumors are metastatic lesions of gastric cancer that have metastasized to the ovary. Systematic chemotherapy is still the main treatment for these patients. However, some retrospective studies have shown that systematic chemotherapy combined with surgical resection of the primary tumor and/or ovarian

metastasis could provide some survival benefits to these patients by increasing their median survival from 6-9 months to 19-23.7 months [253]. The most determining prognostic factors of these patients were an ECOG PS of 0-1, R0 resection (radical resection of the primary lesion and the ovarian metastatic lesion), and postoperative systemic chemotherapy [254], while signet ring cell pathology and peritoneal metastasis were the poor prognostic factors [255]. For patients with single distant ovarian metastasis, only some highly selected patients were found to benefit from surgery combined with systemic chemotherapy. However, there is no definite consensus regarding the selection of patients, timing of treatments, and methods for such operations.

For e and f, please view the notes below.

*Treatment of metachronous single distant metastasis gastric cancer without peritoneal metastasis*

For gastric cancer patients with metachronous single distant metastasis without peritoneal metastasis, resection of the primary tumor and treatment principles can be followed using recommendations of section "2.2.3 Comprehensive treatment of recurrent or solitary metastatic gastric cancer".

**Notes**

e) The term "metachronous liver metastasis" is used to define liver metastasis that occurs more than 6 months after gastric cancer curative surgery. Studies have shown that there is no significant difference in survival between patients with metachronous liver metastasis and those with synchronous liver metastasis [256]. Some research even suggests that patients with metachronous liver metastasis may have a better prognosis than those with synchronous liver metastasis [257]. Patients who undergo liver surgery tend to have better survival outcomes compared to those who do not receive surgery [256]. When liver metastases are localized (H1 and H2), and the metastatic lesions are smaller than 5cm, surgery has been shown to improve survival rates compared to chemotherapy alone [258]. Retrospective studies have demonstrated that radiofrequency ablation (RFA), when compared to systemic chemotherapy, can significantly prolong the median survival of patients with metachronous liver metastasis (25 months vs. 12 months, $P = 0.015$) [259]. Additionally, there have been reports of RFA combined with systemic chemotherapy resulting in a median PFS of 9.8 months and a mOS of 20.9 months for the treatment of liver metastatic lesions [260].
f) Ovarian resection combined with drug therapy is an important treatment for patients with metachronous ovarian metastasis after gastric cancer surgery. Compared with chemotherapy alone, ovarian resection combined with chemotherapy can increase the mOS [261]. Compared to synchronous ovarian metastasis, surgical resection of metachronous ovarian metastasis was associated with superior survival benefit; mOS was 36 months and 17 months, respectively [262].

## 2.3 | Supportive care of gastric cancer

Gastric cancer patients, especially end-stage patients, often suffer from bleeding, obstruction, pains, malnutrition, fatigue, anorexia, cachexia, etc. The goal of supportive care is to prevent and manage cancer-related symptoms and treatment-related adverse effects and alleviate cancer- or treatment-related sufferings (physical, social and psychological) so as to improve the quality of life of the patients, families, and caregivers. Supportive care is relevant throughout the entire cancer journey, from diagnosis through treatment to post-treatment care. It needs interdisciplinary multimodal management, with the medical oncologist as a primary prover, but also includes other specialists in gastroenterology, geriatrics, palliative care, pain, nutrition, oncology psychology, social work, physiotherapy and nurses, and specialists in other fields [263]. Early interdisciplinary supportive care would not only improve the nutritional and psychological status of patients with advanced gastric cancer but could also significantly prolong their survival [264].

### 2.3.1 | Nutritional therapy

| Nutritional therapy category[a] | Recommendations |
|---|---|
| Nutritional risk screening and malnutrition assessment[b] | • Nutritional risk screening and malnutrition assessment should be completed within 24 and 48 hours after admission, respectively;<br>• NRS guide: NRS-2002;<br>• Malnutrition assessment guide: PG-SGA; |
| Early perioperative patients[c] | • Patients with severe or moderate malnutrition should be given nutritional therapy for 7-14 days before surgery;<br>• The route for nutrition can be ONS or EN. When EN cannot provide sufficient energy and protein or is not feasible, the PN route can be considered;<br>• Nutrition intake should be reverted to oral, ONS, or EN route soon after surgery (within 24-48 hours), and for suitable patients, ERAS treatment can be implemented;<br>• Consider referring to the "CSCO guidelines for nutritional therapy of patients with malignant tumors" and "Chinese expert consensus on perioperative nutritional therapy of gastric cancer (2019 Edition)" for further details; |
| Late-stage patients[d,e] | • Nutritional risk screening and malnutrition assessment for non-end-stage patients should be regularly performed, and nutritional treatment plans should be formulated. Nutrition treatment should follow the five-step principle;<br>• For end-stage patients, the main goal of nutritional therapy is to reduce symptoms and maintain body weight, and individualized nutrition plans should be formulated for them.<br>• For additional details, refer to the "CSCO guidelines for nutritional therapy for patients with malignant tumor"; |
| Patients at home[f] | To provide nutritional and family rehabilitation guidance. Regular outpatient nutrition consultation at least once every 3 months is recommended. |

Abbreviations: NRS, nutrition risk screening; PG-SGA, patient-generated subjective global assessment; ONS, oral nutritional supplements; EN, enteral; PN, parenteral; ERAS, enhanced recovery after surgery; CSCO, Chinese Society of Clinical Oncology.

**Notes**:

[a]Malnutrition is common in patients with gastric cancer. Studies have shown that the rate of moderate to severe malnutrition in hospitalized patients with gastric cancer in China was 80.4%, seriously affecting the quality of life of the patients [265]. Recently, a phase III clinical study in China showed that for patients with metastatic gastric cancer, the combination of early nutritional therapy and physiotherapy on the basis of standard chemotherapy could significantly prolong survival [264]. Therefore, nutritional therapy should be an important part of anti-tumor therapy for gastric cancer. Every gastric cancer patient should undergo timely and accurate nutritional risk screening, early nutritional guidance, and MDT consultation on the whole process of disease management.

[b]Nutritional Risk Screening 2002 (NRS-2002) is recommended for nutritional risk screening. Those with NRS-2002 score ≥3 are at risk for malnutrition and need further assessment [266–268]. Patient-generated subjective global assessment (PG-SGA) is recommended for nutritional assessment. The PG-SGA is a specific nutritional assessment tool for quick identification of cancer patients with malnutrition [266, 269]. According to the score, patients are divided into no malnutrition (score, 0-1), suspected malnutrition (score, 2-3), moderate malnutrition (score, 4-8), and severe malnutrition (score, ≥9).

[c]Perioperative nutritional therapy is an important aspect of enhanced recovery after surgery (ERAS). For eligible gastric cancer patients, nutritional therapy is recommended according to the ERAS principles and procedures [267, 270]. Some studies suggested that the immune-enhanced enteral preparation could be beneficial to maintain lean body weight, reduce postoperative complications and infections and shorten the length of hospital stay, but more clinical evidence is still needed prior to clinical recommendation [267].

[d]Nutritional intervention follows a five-tier principle. Initially, nutritional education is chosen, followed by progressing upward to select oral nutritional supplements (ONS), total enteral nutrition (TEN), partial enteral nutrition combined with partial parenteral nutrition (PEN+PPN), and total parenteral nutrition (TPN), if the next tier cannot meet 60% of the target energy requirements for 3-5 days, the previous tier should be selected [271].

[e]Nutritional problems in late-stage gastric cancer patients may include digestive tract obstruction, hemorrhage, gastroparesis, and more. Enteral nutrition is often not enough, and parenteral nutrition should be provided as per the patient's needs. Nutritional routes, such as nasogastric tube, nasointestinal tube and percutaneous gastrostomy, should be available to support the patient's nutritional requirements. If the symptoms of obstruction and bleeding can be improved with appropriate treatment, it is advisable to cautiously attempt to transition to EN under the premise of safety, and then to conduct comprehensive treatment in MDT discussion. In the whole process of gastric cancer management, attention should be paid to actively prevent and treat cachexia. Active prevention, accurate evaluation, early diagnosis and timely treatment should be offered because once the patient enters the cachexia stage, it is difficult to reverse.

[f]For patients with gastric cancer at home, it is suggested that proper nutritional and rehabilitation guidance should be offered to the caregiver. Regular nutrition consultation at least once every 3 months is recommended. ONS should be encouraged, and body weight assessment should be performed every 2 weeks [271].

## 2.3.2 | Management of complications

| Bleeding[a] | Obstruction[b] | Pain[c] |
|---|---|---|
| Endoscopic treatment:<br>• Metallic hemostatic clips<br>• Injection therapy: e.g., ethanol, adrenaline<br>• Ablation therapy: laser photocoagulation, argon plasma coagulation<br>Medical treatments:<br>• Proton pump inhibitors<br>• Somatostatin analogs<br>Transcatheter arterial embolization<br>Palliative gastrectomy | Gastrointestinal decompression<br>Endoscopic treatments<br>• Stent placement<br>• Gastrostomy/jejunostomy<br>• Gastrojejunostomy<br>• Internal/external radiation therapy<br>Surgical treatments<br>• Gastrojejunostomy<br>• Gastrostomy/jejunostomy<br>• Gastrectomy<br>Chemotherapy[d]<br>Medical treatments<br>• Pain management<br>• Antiemetics<br>• Antisecretory<br>• Antispasmodic | Analgesic: non-opioid analgesics (acetaminophen or NSAIDs) or opioid analgesics<br>Chemotherapy[d]<br>External radiotherapy |

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

**Notes**:

[a]Hemorrhage is a common symptom of gastric cancer and can be caused by the tumor itself or as a side effect of cancer treatment. Acute and severe hemorrhage can be life-threatening and require immediate endoscopic examination. However, the effectiveness of endoscopic treatment in hemorrhagic gastric cancer is still not well-established, and limited data suggest that its initial success rate is high, but the rate of recurrent bleeding is also significant [272]. If endoscopic treatment fails, other options can be considered to control bleeding. Transcatheter arterial embolization (TAE), in which the main blood vessels supplying the stomach are blocked to reduce bleeding, may be an option [273]. Alternatively, palliative gastroctomy can be performed to control bleeding. External radiation therapy can also be effective in managing both acute and chronic hemorrhage but may take time to fully take effect and is more suitable for chronic hemorrhage. Although proton pump inhibitors (PPIs) are commonly believed to be beneficial for chronic bleeding, a randomized study from Korea showed that PPIs did not significantly reduce the occurrence of tumor bleeding [272].

[b]The aim of treating gastrointestinal obstruction is to reduce symptoms such as nausea and vomiting and restore intestinal nutrition absorption. The most common causes of obstruction in stomach cancer include pyloric obstruction due to gastric antral cancer, cardia obstruction due to esophagogastric junction cancer, and small bowel obstruction caused by peritoneal metastases. For resectable gastric cancer, if symptoms of obstruction occur, it is recommended to remove the primary tumor to control and improve symptoms. In cases of advanced or non-operable gastric cancer with pyloric or cardia obstruction, as the effectiveness of medical oncology improves, patients in good nutritional condition can undergo chemotherapy-based treatment to address the obstruction. For patients with poor nutritional status or those for whom treatment is ineffective, endoscopy can be performed to assess the extent of narrowing and determine if endoscopic interventions are possible, such as stent placement, percutaneous endoscopic gastrostomy/jejunostomy, or ultrasound-guided gastrojejunostomy [272]. Single-dose brachytherapy may have superior long-term efficacy and lesser complication rates compared to metal stent placement. External beam radiation therapy can achieve symptom relief in 75% to 83% of obstruction cases, but it may initially worsen symptoms. Multimodal interventions such as stenting, surgery, endoscopic or internal/external radiation therapy and medical oncology treatment may yield better results. If endoscopic access is challenging, surgical interventions like laparoscopic gastrojejunostomy, gastrostomy/jejunostomy, or palliative gastrectomy should be considered [274, 275]. For small bowel obstruction caused by peritoneal metastases, which is often associated with a "frozen pelvis" presentation and represents a terminal stage of the disease, surgical interventions may be challenging and should generally be avoided. Instead, supportive measures such as nutritional support, spasm relief, antisecretory, antiemetics, and pain management should be employed. Benign strictures of the esophagus and cardia can be treated with esophageal dilation procedures.

[c]Patients with gastric cancer often have pain. Cancer pain can be caused by tumor invasion and metastasis, organ involvement, treatment-related pain such as stent placement, etc. It is important to differentiate surgical emergencies such as perforation or obstruction. Anti-tumor therapy, such as chemotherapy and radiotherapy, can shrink the tumor and reduce the pain caused by the compression on the nerves or other organs. Cancer pain can be evaluated and managed based on the WHO three-step analgesic ladder [276]. The common analgesics are opioids, paracetamol, and nonsteroidal anti-inflammatory drugs. The most common route of administration is oral, and other routes (i.e., intravenous, subcutaneous, rectal, transdermal, and transmucosal) can be considered in patients with gastrointestinal obstruction.

[d]Gastric cancer patients are prone to treatment-related myelosuppression. The related treatments include chemotherapy, targeted therapy, radiotherapy, immunotherapy, and so on. The Common Terminology Criteria for Adverse Events (CTCAE) are commonly used for grading and managing adverse events. For treatment-related anemia, iron, vitamin B12, and folic acid should be supplemented, especially in patients after gastrectomy, after hemorrhagic or nutritional anemia was ruled out. For treatment-related anemia, recombinant erythropoietin (EPO) can be given. A red cell suspension can be given if necessary. For treatment-related granulocytopenia, recombinant human granulocyte colony-stimulating factor (rhG-CSF) or long-acting rhG-CSF (polyglycosylated rhG-CSF) can be considered for prophylactic or therapeutic use accordingly. For treatment -related thrombocytopenia, the bleeding degree or risk should be first assessed. Based on the assessment and patient's conditions, measures such as giving thrombopoietin (TPO), interleukin (IL)-11, and platelet infusion can be implemented.

## 3 | FOLLOW-UP VISITS

| Settings[a] | Grade I recommendations | Grade II recommendations |
|---|---|---|
| Early-stage gastric cancer[b] | Once every 3-6 months in the first 2 years, followed by once every 6-12 months until 5 years after surgery | Annually thereafter |
| | Follow-up contents*:<br>1. Clinical history;<br>2. Physical examination;<br>3. Blood chemistry (whole blood count, liver-renal function test, tumor markers, etc)[d];<br>4. *Helicobacter pylori* detection;<br>5. Chest/abdominal/pelvic CT with IV contract as clinically indicated (once every 6-12 months for the 1st year and annually thereafter)[e];<br>6. Gastroscopy[f]; | FGD-PET/CT as clinically indicated[h] |
| Advanced or non-resectable gastric cancer[c] | Once every 3-6 months in the first 2 years, followed by once every 6-12 months until 5 years after surgery | Annually thereafter |
| | Follow-up contents*:<br>1. Clinical history;<br>2. Physical examination;<br>3. Blood chemistry (whole blood count, liver-renal function test, tumor markers, etc.)[d];<br>4. *Helicobacter pylori* detection;<br>5. Chest/abdominal/pelvic CT with IV contract as clinically indicated (once every 6-12 months for the 1st year, and annually thereafter) [e];<br>6. Gastroscopy[f];<br>7. Nutritional status monitoring (vitamin B12, iron, etc.)[g]; | FDG-PET/CT as clinically indicated[h] |
| New symptoms or symptom deterioration | Follow-up visit at any time | |

Abbreviations: FDG, 2-[(18)F]fluoro-2-deoxy-D-glucose; PET, positron emission tomography; CT, computed tomography.

*Can be performed at each visit unless specified otherwise based on the patient's condition.

**Notes**:

[a]The main objective of follow-up/monitoring is to assess the possibility of radical treatment for recurrence or metastatic lesion or timely identification and intervention of tumor recurrence or second primary gastric cancer, with the aim to improve OS and quality of life [277]. Currently, there is no high-level evidence to support which follow-up/monitoring strategy is optimal. The follow-up strategy should be personalized based on the patient's condition and tumor stage [278]. If the patient's physical condition does not allow him to receive anti-cancer treatment once his/her tumor relapses, routine tumor follow-up/monitoring should not be forced. *Helicobacter pylori* infection has been found to have a direct implication on the prognosis of gastric cancer patients and should be recommended as a routine follow-up examination [278].

[b]The follow-up of patients with early gastric cancer includes patients with carcinoma in situ and those who underwent abdominal or endoscopic resection. For early gastric cancer patients treated with endoscopic resection, gastroscopy is recommended once every six months of the first year of treatment, then once a year until 5-year post-treatment. For early gastric cancer patients who underwent radical resection, gastroscopy is recommended as a routine postoperative follow-up [278].

[c]The follow-up for advanced gastric cancer patients, irrespective of whether they have had neoadjuvant or adjuvant therapy, are the same [278].

[d]Detection of tumor markers (e.g., CEA and CA19-9) can effectively identify tumor recurrence as they may be increased 2-3 months prior to evidence of tumor recurrence/metastasis detected by imaging examination [279].

[e]For early gastric cancer with clinical cancer-related anomalies, enhanced CT of the chest, abdomen and pelvis is recommended to identify possible recurrent or new lesions and to assess any risk of metastasis to other regions [279–282].

[f]Gastroscopic follow-up strategy [279–281]: gastroscopy is recommended as a routine follow-up method for gastric cancer patients who underwent surgical resection. During follow-up of patients with early or advanced gastric cancer, if clinical or imaging abnormalities are observed, gastroscopy is recommended. The aim is to assess the anastomotic region, to timely identify new or recurrent lesions, and to biopsy any suspected cancerous lesion.

[g]Nutritional status assessment is recommended in the follow-up of gastric cancer patients who underwent surgical resection. Those who had total gastrectomy should also be assessed for vitamin B12 and iron levels [278].

[h]FDG-PET/CT is currently not recommended as a routine follow-up/monitoring imaging modality. It is only recommended for suspected recurrence when there is no clear evidence from conventional imaging examinations (CT or ultrasound) despite continuous elevation of blood tumor markers (e.g., CEA and CA19-9).

# 4 | SCREENING AND DIAGNOSIS OF HEREDITARY GASTRIC CANCER

## 4.1 | Types and definitions of hereditary gastric cancer

Most gastric cancer cases are sporadic. About 5%-10% of gastric cancer is considered familial aggregated gastric cancer, and 1%-3% have a genetic predisposition [283].

There are three types of hereditary gastric cancer, namely, hereditary diffuse gastric cancer (HDGC), family internal gastric cancer (FIGC), gastric adenocarcinoma and gastric proximal polyposis of the stomach (GAPPS). In addition to the three types mentioned above, Lynch's syndrome, Lie Flemeini's syndrome, familial adenomatous dysplasia (FAP), polytype-associated polyposis, Boyz Jeg's syndrome, juvenile polyposis syndrome, and serrated polyposis syndrome are the most common juvenile polyposis and hereditary breast-ovarian cancer syndrome and other genetic diseases can also be combined with gastric cancer [284, 285]. Detailed descriptions of the three types of hereditary gastric cancer are provided below:

1. HDGC: This is an autosomal dominant genetic disease that is mainly caused by the inactivation of CDH1 germline mutation. It has also been reported that alpha-E-catenin 1 (*CTNNA1*) pathogenic mutation is associated with HDGC.
2. FIGC: The diagnosis of FIGC mainly depends on clinical diagnosis and can be considered in individuals with:
   - ≥2 first- or second-degree relatives diagnosed as FIGC, and at least one of them was diagnosed before 50 years old;
   - ≥3 first- or second-degree relatives diagnosed as FIGC, regardless of age;
3. GAPPS: The diagnosis of GAPPS also mainly depends on clinical diagnosis and can be considered in individuals with [286, 287]:
   - polyps confined to the fundus and body of the stomach and without evidence of colorectal or duodenal polyposis;
   - >100 polyps in the proximal part of the stomach or a history of FAP with proximal gastric polyps >30;
   - most of the polyps are located in the gastric fundus, of which some are identified as atypical dysplasia on histopathology (or family members with a history of atypical dysplasia or gastric adenocarcinoma);
   - has autosomal dominant inheritance pattern;
   - exclusion of other conditions such as hereditary gastric polyposis syndrome and current use of proton pump inhibitors;

## 4.2 | Types and definitions of hereditary gastric cancer

It is recommended to screen for gastric cancer in individuals with the following characteristics or family history of gastric cancer:

- onset of gastric cancer before the age of 40.
- onset of gastric cancer before the age of 50 with at least one first- or second-degree relative affected by gastric cancer.
- regardless of age at onset, having two or more first- or second-degree relatives affected by gastric cancer.
- concurrent diagnosis of both gastric and breast cancer, with one of the diseases occurring before the age of 50.
- regardless of age at onset, having a first- or second-degree relative affected by breast cancer before the age of 50.
- regardless of age at onset, having a family history of JP syndrome, gastrointestinal polyps, or Lynch syndrome.
- relatives with known genetic mutations associated with gastric cancer susceptibility.
- having a first- or second-degree relative diagnosed with gastric cancer before the age of 40.
- having two first- or second-degree relatives diagnosed with gastric cancer before the age of 50.
- having three or more first- or second-degree relatives affected by gastric cancer, regardless of age at onset.
- having relatives with concurrent diagnoses of gastric cancer and breast cancer, with one of the diseases occurring before the age of 50, and a family history of Juvenile polyposis (JP) syndrome or gastrointestinal polyp syndrome.

HDGC is an autosomal dominant genetic disorder, accounting for less than 3% of all gastric cancer cases worldwide [288]. Susceptibility genes identified include the *CDH1* gene encoding E-cadherin [289–291] and the *CTNNA1* gene encoding α-E-catenin [292, 293]. Literature reports suggest that 30% to 50% of HDGC patients have truncating mutations in *CDH1* [294]. Exome and targeted sequencing results from 284 clinical HDGC patients' leukocyte samples and paired 186 tumor samples in China showed that the germline mutation rate of *CDH1* was only 2.8% [295], indicating that the genetic susceptibility to HDGC in China may differ from Western countries. Carriers of *CDH1* gene mutations have a cumulative risk of developing gastric cancer by the age of 80, estimated at approximately 67% for males and 83% for females. Additionally, female carriers also have a 60% risk of developing lobular breast cancer [296].

Based on the 2020 International Gastric Cancer Linkage Consortium (IGCLC) screening guidelines [291], it is recommended to perform CDH1 gene mutation testing in individuals who meet the following criteria:

- families with ≥2 cases of gastric cancer, with at least 1 case of diffuse gastric cancer (DGC) present;
- families with ≥1 case of DGC and ≥1 case of invasive lobular breast cancer occurring before the age of 70;
- families with ≥2 cases of invasive lobular breast cancer occurring before the age of 50;
- diagnosis of DGC before the age of 50, regardless of family history;
- any age group of Maori individuals with DGC;
- individuals or families with a history of cleft lip or palate in DGC patients;
- individuals with a history of both DGC and invasive lobular breast cancer, with both occurring before the age of 70;
- patients with bilateral invasive lobular breast cancer diagnosed before the age of 70;
- patients with gastric in situ or pagetoid spread of signet-ring cell carcinoma diagnosed before the age of 50;

*CTNNA1* encodes the α-catenin protein, which is related to cell adhesion. The detection rate of *CTNNA1* in HDGC is ~1%. For *CDH1* and *CTNNA1* non-carriers having a family history of breast cancer or colon cancer, *breast cancer susceptibility gene 1 (BRCA1)*, *BRCA2*, or Lynch syndrome-related genes such as *Epithelial Cell Adhesion Molecule* (*EPCAM)*, *MLH1*, *MSH2*, *MSH6, PMS2*, should be assessed.

The susceptibility genes of FIGC are not clear. The screening of GAPPS is mainly via endoscopy accompanied by gross detection of >100 polyps, mostly <10 mm in diameter, with some being >20 mm, mostly located in the gastric fundus and body, while some seen spreading to the lesser curvature and have the risk of becoming cancerous based on endoscopic findings such as carpet-like densely distributed polyps, along with multiple fusion polyps displaying a mound-like distribution. Unlike Peutz-Jeghers syndrome, GAPPS polyps do not usually involve the esophagus, antrum, pylorus and duodenum.

## 4.3 | Risk control of gastric cancer-associated genetic syndrome

| Hereditary syndrome | Gene | Genetic pattern | Risk management suggestions |
|---|---|---|---|
| Hereditary diffuse gastric cancer | *CDH1* | Autosomal dominance | • Prophylactic gastrectomy is recommended for *CDH1* mutation carriers age 8-40-years old;<br>• For *CHD1* carriers who do not undergo gastrectomy, endoscopy is recommended every 6-12 months with random multi-point biopsy;<br>• The risk of breast cancer in female *CDH1* mutation carrier is high and regular breast imaging examination is advised |
| Lynch syndrome | *EPCAM, MLH1, MSH2, MSH6, PMS2* | Autosomal dominance | Upper gastrointestinal endoscopy with careful assessment of the duodenum can be considered for some patients or offspring of Asian family origin |
| Juvenile polyposis syndrome | *SMAD4, BMPR1A* | Autosomal dominance | Upper gastrointestinal endoscopy screening is advised after the age of 15.<br>• If polyps are found, they should be reexamined every year;<br>• If no polyps are found, reexamination every 2-3 years is advised |
| Boytz Jegher syndrome | *STK11* | Autosomal dominance | Upper gastrointestinal endoscopy screening is advised from late adolescence and reexamination every 2-3 years |
| FAP/AFAP | *APC* | Autosomal dominance | • Currently, not enough evidence to suggest screening for gastric cancer in FAP/AFAP persons.<br>• FAP is more prone to duodenal cancer and while screening for it, the stomach can also be examined.<br>• Currently, upper gastrointestinal endoscopy is suggested for those aged ≥25-30 years old, and the frequency of reexamination should be determined based on characteristics of duodenal polyps |

Abbreviations: FAP, familial adenomatous dysplasia; AFAP, attenuated FAP; *EPCAM, Epithelial Cell Adhesion Molecule; H1*, MutL Homolog 1; *PMS2*, Postmeiotic Segregation Increased Homolog 2; *SMAD4, SMAD family member 4; BMPR1A*, Bone Morphogenetic Protein Receptor Type 1A; *STK11*, Serine/Threonine Kinase 11; *APC*, Adenomatous Polyposis Coli.

*CDH1* germline gene mutation detection is recommended for families meeting the clinical diagnostic criteria of hereditary diffuse gastric cancer (recommended grade: III; Evidence 2B)

## 4.4 | Principles of treatment for carriers of CDH1 pathogenic germline gene mutation [283, 289]

1. Prophylactic total gastrectomy could be advised for *CDH1* pathogenic germline gene mutation carriers age 18-40 years old (recommendation grade: III; Evidence: 2B);
2. Gastroscopy every 6-12 months, including random biopsies at multiple sites (recommendation grade: III; Evidence: 2B);
3. Annual breast MRI for women from the age of 30 (recommendation grade: III; Evidence: 2B).

# 5 | APPENDIX

## 5.1 | Classification of esophageal and gastric cancer

The clinical, pathological, and post-neoadjuvant staging of esophageal and gastric cancer mentioned in this guideline is based on the 8th edition of the AJCC/UICC TNM staging system.

## 5.2 | Reference for CT staging signs of gastric cancer and report contents

| cT classification | Pathological definition | Conventional reference signs[a] | Auxiliary reference signs[b] |
|---|---|---|---|
| cT1 | Invasion of the mucosa or submucosa | Continuous and complete low-enhanced bands between the highly enhanced inner layer of the cancer and the slightly high-enhanced outer stomach muscle | The high-enhanced of the cancer does not exceed 50% of the total thickness of the gastric wall |
| cT2 | Invasion of the muscularis propria | Interruption or absence of the low enhancement band in the middle layer of the stomach and the slightly high enhanced muscle layer partially remains | The high-enhanced of the cancer exceeding 50% of the total thickness of the gastric wall |
| cT3 | Invasion of the subserosal connective tissue without invading the visceral peritoneum | High enhancement cancer invades the whole layer of the gastric wall, and the outer surface of the serosa is smooth or with tiny spiculation | Tiny spiculation or blurring of the serosal layer comprising <1/3 of the total lesion area |
| cT4a | Invasion of the serosa (visceral peritoneum) but not adjacent structures/organs | Irregular or nodular appearance of the outer surface of serosal, intensive spiculation or strand-like infiltration of the surrounding fat space | A hyperattenuating serosa sign [286], cross-sectional location [287], extension from the outer gastric wall reaching beyond the perigastric vascular plane |
| cT4b | Invasion of adjacent structures/organs | Disappearance of the fat space between cancer and adjacent organs, with definite signs of finger press-like interface or direct infiltration | |
| cN | Classified as N0-N3 based on the number of metastatic lymph nodes | Short diameter of round-like enlarged lymph node >6-8mm | High or heterogenous enhancement, CT attenuation, short-to-long axis ratios >0.7, clustered small lymph nodes |
| Imaging report contents | 1. Involved area: ☐ Lower thoracic esophagus ☐ Abdominal esophagus ☐ Esophagogastric junction ☐ Gastric fundus ☐ Gastric body ☐ Gastric angle ☐ Gastric antrum ☐ Pylorus ☐ Duodenum ☐ Greater curvature ☐ Lesser curvature ☐ Anterior wall ☐ Posterior wall<br>2. Central location: ☐ Esophagogastric junction (Siewert type: ☐ Type I ☐ Type II ☐ Type III) ☐ Upper stomach ☐ Middle stomach ☐ Lower stomach ☐ Pylorus<br>3. Borrmann classification: ☐ Type I ☐ Type II ☐ Type III ☐ Type IV ☐ Type V < Mixed type ><br>4. cT stage: ☐ cT0 stage ☐ cT1 stage ☐ cT2 stage ☐ cT3 stage ☐ cT4a stage ☐ cT4b stage<br>5. Organ involvement: ☐ None ☐ Liver ☐ Colon ☐ Pancreas ☐ Spleen ☐ Diaphragm ☐ Other____<br>6. cN stage: ☐ cN0 stage ☐ cN1 stage ☐ cN2 stage ☐ cN3a stage ☐ cN3b stage<br>7. Lymph node metastasis stations:<br>8. cM stage: ☐ cM0 stage ☐ cM1 stage (Metastasis to organ(s):____)<br>9. Peritoneal metastasis risk (☐ Low ☐ High)<br>10. Measurement values (Primary lesion____, Length of esophageal involvement____, Metastatic lymph nodes____, Organ metastasis____, Other____)<br>11. Other information (Image quality, report quality, diagnostic confidence score, etc.) | | |

Notes

[a]Reference for clinical T staging. The accuracy of T staging is 70%-90%, and N staging is 60%-70%. For CT staging of EGJ cancer, it is necessary to combine axial, coronal, or curved reconstructed images to measure the distance from the center of the tumor to the EGJ line to determine whether staging should be done according to gastric cancer or esophageal cancer standards. In cases where the lesion borders are not clearly defined on CT, X-ray barium double-contrast imaging (dynamic images taken from three angles: anteroposterior, left anterior oblique, and right anterior oblique) can be used to assess upper margin involvement of the esophagus.

[b]Atypical, uncommon signs or signs that have not been validated through multicenter large-sample clinical studies can be used as references for staging in cases with atypical signs.

[c]It is recommended to use a structured reporting approach. The report content should contain important clinical treatment-related information, including but not limited to tumor location, classification, staging, lymph node grouping, risk assessment for peritoneal metastasis, precise lesion measurements, and other relevant findings. Additionally, it should provide details about image quality, report quality and diagnostic confidence to enhance the clarity and utility of the reference report for comprehensive clinical evaluation.

## 5.3 | Template of pathological report

| | | | | |
|---|---|---|---|---|
| **Pathology report no.:** | | | **Previous pathology report no:** | |
| Name: | Gender: | Age: | Occupation: | Phone no.: |
| Ward: | Bed no.: | Medical record no.: | | ID no.: |
| Name of institution sending specimen: | | | Sending doctor: | Sending date: |

Specimen type: Proximal/Distal/Total Stomach/Unspecified
Tumor margin from: Lesser curvature: cm; Greater curvature: cm; Thickness: cm;
Tumor location: Cardia/Body/Fundus/Pylorus
Tumor distance from upper margin: cm
Tumor distance from lower margin: cm
Macroscopic characteristics: Ulcerative/Infiltrative/Fungating/Elevated Tumor size: cm × cm × cm
Color: Grey-red/Grey-yellow/Grey-white/Grey-brown Texture: Soft/Medium/Hard/Bleeding/Necrosis
Depth of Invasion: Gross infiltration depth

Histological type: (e.g., tubular adenocarcinoma)

| | |
|---|---|
| Histological grade (e.g., moderately differentiated) | Lauren classification: Diffuse/Intestinal/Mixed |
| Depth of infiltration | Involvement of adjacent organs |
| Vascular invasion | Perineural invasion |
| Upper resection margin status: | Lower resection margin status: |

Lymph node involvement: Number of metastatic/Total lymph nodes ( / )
Lesser curvature: ( / ); Left gastric artery: ( / ); Right gastric artery: ( / ); Upper pyloric: ( / );
Lower pyloric: ( / ); Cardiac: ( / ); Greater curvature: ( / ); Hepatic artery: ( / ).

Associated lesions:

Other specimens:

Immunohistochemistry: MLH1 ( ), PMS2 ( ), MSH2 ( ), MSH6 ( ), HER-2 (), EBERs ( ),
Others:

Pathological staging: pT N M

Primary physician: Audit physician:
Signature: Signature: Date of report:

Note:
1. If the clinical physician has any doubts about the pathological diagnosis, please contact the pathologist as soon as possible.
2. Pathological diagnosis of small or fragmented tissue samples may not represent the full extent and nature of the lesion. Please be aware of this as a clinical physician.
3. This report is effective after the physician's signature.

Address: Postal code: Phone: Page:

## 5.4 | Categories of Evidence of the 2021 CSCO Clinical Practice Guidelines for Common Malignant Tumors

| **Level of evidence** | | | |
|---|---|---|---|
| **Category** | **Quality of level** | **Source** | **CSCO expert consensus** |
| 1A | High | Based on data from well-structured and rigorously controlled meta-analyses and/or large-scale randomized controlled clinical trials | Uniform consensus (support level: ≥80%) |
| 1B | High | Based on data from well-structured and rigorously controlled meta-analyses and/or large-scale randomized controlled clinical trials | Consensus with minimum disagreement (support level: 60%-80%) |
| 2A | Relatively low | Based on data from meta-analysis, small-scale randomized controlled trials, well-designed large-scale retrospective studies, and/or case-control studies | Uniform consensus (support level: ≥80%) |

Continued.

| Level of evidence | | | |
|---|---|---|---|
| Category | Quality of level | Source | CSCO expert consensus |
| 2B | Relatively low | Based on data from meta-analysis, small-scale, randomized controlled trials, well-designed large-scale retrospective studies, and/or case-control studies | Consensus with minimum disagreement (support level: 60%-80%) |
| 3 | Low | Based on data from single-arm clinical studies, case reports, and/or expert opinions | No consensus was reached, and had major disagreement (support level: <60%) |

Abbreviation: CSCO, Chinese Society of Clinical Oncology.

## 5.5 | Criteria for the recommendation grades of CSCO Clinical Practice Guidelines

| Recommendation grade | Criteria |
|---|---|
| Grade I | Evidence level 1A and some Evidence level 2A:<br>The CSCO guidelines designate Grade I recommendations by considering 1A evidence and certain 2A evidence that has reached a strong consensus in China. These recommendations are applicable in situations where the indications are well-defined, the treatment is easily accessible, and their value in cancer therapy is established. These recommendations are part of the "National Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance Drug Catalog", making them essential for diagnosis and treatment procedures. |
| Grade II | Evidence level 1B and some Evidence level 2A:<br>The CSCO guidelines designate Grade II recommendations based on 1B evidence and some 2A evidence that, while showing a high level of expert consensus, may not be based on research in China. Specifically, these recommendations rely on both Chinese and international randomized controlled studies that provide substantial evidence but may have limited accessibility or cost-effectiveness. If a clinical trial demonstrates clear patient benefits despite being relatively expensive, it can also be considered as a Grade II recommendation. |
| Grade III | Evidence level 2B and 3:<br>The CSCO guidelines designate Grade III recommendations for certain clinical interventions that are commonly used in clinical practice or have exploratory value. Even if the evidence from evidence-based medicine is relatively limited, they can still be considered Grade III recommendations if the expert panel believes they are acceptable. |

Abbreviation: CSCO, Chinese Society of Clinical Oncology.

## AUTHOR CONTRIBUTIONS

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