Received: 5 June 2021 | Revised: 21 June 2021 | Accepted: 23 June 2021

DOI: 10.1002/cac2.12193

CANCER COMMUNICATIONS Open Access

GUIDELINES AND CONSENSUS

# The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021

**Feng-Hua Wang[1,#] | Xiao-Tian Zhang[2,#] | Yuan-Fang Li[3] | Lei Tang[4] | Xiu-Juan Qu[5] | Jie-Er Ying[6] | Jun Zhang[7] | Ling-Yu Sun[8] | Rong-Bo Lin[9] | Hong Qiu[10] | Chang Wang[11] | Miao-Zhen Qiu[1] | Mu-Yan Cai[12] | Qi Wu[13] | Hao Liu[14] | Wen-Long Guan[1] | Ai-Ping Zhou[15] | Yu-Jing Zhang[16] | Tian-Shu Liu[17] | Feng Bi[18] | Xiang-Lin Yuan[10] | Sheng-Xiang Rao[19] | Yan Xin[20] | Wei-Qi Sheng[21] | Hui-Mian Xu[22] | Guo-Xin Li[14] | Jia-Fu Ji[23] | Zhi-Wei Zhou[3] | Han Liang[24] | Yan-Qiao Zhang[25] | Jing Jin[26] | Lin Shen[2,##] | Jin Li[27,##] | Rui-Hua Xu[1]**

**Abbreviations:** 3D-CRT, three-dimensional conformal radiotherapy; 5-FU, 5-fluorouracil; ADC, apparent diffusion coefficient; AJCC/UICC, American Joint Cancer Committee/Union Internationale Contre le Cancer; CPS, combined positive score; CSCO, Chinese Society of Clinical Oncology; CT, computed tomography; CTCAE, common terminology criteria for adverse events; cTNM, clinical tumor-node-metastasis; cTNM, clinical tumor-node-metastasis classification; CY, cytologic results of peritoneal lavage; D, type of lymphadenectomy; DCFdocetaxel plus cisplatin plus 5-FU DOS, docetaxel plus cisplatin plus 5-FU DOSdocetaxel plus oxaliplatin plus S1; DFS, disease-free survival; DGC, diffuse gastric cancer; dMMR, deficient DNA mismatch repair; DoR, duration of response; DPD, dihydropyrimidine dehydrogenase deficiency; DS, docetaxel plus S-1; DW-MRI, diffusion-weighted- MRI; EBV, Epstein-Barr Virus; ECC, epirubicin plus cisplatin plus capecitabine; ECF, epirubicin plus cisplatin plus 5-FU; ECX, epirubicin plus cisplatin plus capecitabine; EGJ, esophagogastric junction; EIPL, extensive intraoperative peritoneal lavage; EMR, endoscopic mucosal resection; EN, enteral; EOC, epirubicin plus oxaliplatin plus capecitabine; EPO, erythropoietin; ERAS, enhanced recovery after surgery; ESD, endoscopic sub-mucosal dissection; EUS, endoscopic ultrasound; FAP, familial adenomatous dysplasia; FIGC, family internal gastric cancer; FLOT, 5-FU plus leucovorin plus oxaliplatin plus docetaxel; FOLFOX, leucovorin calcium plus 5-FU plus oxaliplatin; F-OX, fluoropyrimidine plus oxaliplatin; GAPPS, gastric proximal polyposis of the stomach; HAIC, hepatic artery infusion chemotherapy; HDGC, hereditary diffuse gastric cancer; HER2, human epidermal growth factor receptor 2; HIPEC, hyperthermic intraperitoneal perfusion chemotherapy; IHC, immunohistochemistry; IL, interleukin; IMRT, intensity-modulated radiotherapy; IPC, intraperitoneal chemotherapy; ISH, *in situ* hybridization; LADG, laparoscopic-assisted distal gastrectomy; LAPG, laparoscopic-assisted proximal gastrectomy; LATG, laparoscopic-assisted total gastrectomy; LTG, laparoscopic total gastrectomy; mAb, monoclonal antibody; mDCF, modified DCF; MDT, multidisciplinary team; mECF, modified ECF; mECF, modified ECF; mOS, median OS; mPFS, median progression-free survival; MRI, magnetic resonance imaging; MSI, microsatellite instability; MWA, microwave ablation; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NMPA, National Medical Products Administration; NR, not reached; NRS, nutrition risk screening; NTRK, neurotrophic tyrosine receptor kinase; ODG, open distal gastrectomy; ONS, oral nutritional supplements; OR, odds ratio; ORR, overall response rate; P, presence of local peritoneal metastatic nodules; PACX, paclitaxel plus capecitabine; pCR, pathological complete response; PD-L1 CPS, programmed death ligand-1 combined positive score; PD-L1, programmed death ligand 1; PET, positron emission tomography; PF, cisplatin plus 5-FU; PG-SGA, patient generated subjective global assessment; pM, pathological distant metastasis classification; PN, parenteral; pN, pathological nodal classification; POF, paclitaxel plus FOLFOX; pT, pathological tumor depth invasion classification; pTNM, pathological tumor-node-metastasis classification; R, radicality criteria of surgery; RDG, robotic distal gastrectomy; RFA, radiofrequency ablation; rhG CSF, recombinant human granulocyte colony-stimulating factor; RR, risk ratio; SBRT, stereotactic body radiotherapy; SOX, S-1 plus oxaliplatin; SP, cisplatin plus S-1 TE, docetaxel plus oxaliplatin; TACE, transarterial chemoembolization; TEF, docetaxel plus oxaliplatin plus 5-FU; TEX, docetaxel plus oxaliplatin plus capecitabine; TMB, tumor mutational burden; TPO, thrombopoietin; TRG, tumor regression grade; WHO, World Health Organization; XELOX, capecitabine plus oxaliplatin; XP, capecitabine plus cisplatin; ypTNM, post neoadjuvant pathological tumor-node-metastasis classification

[1] Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

[2] Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing 100142, P. R. China

[3] Department of Gastric Surgery, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

[4] Department of Radiology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing 100142, P. R. China

[5] Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, Liaoning 110001, P. R. China

[6] Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang 310006, P. R. China

[7] Department of Medical Oncology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, P. R. China

[8] Department of Surgical Oncology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, P. R. China

[9] Department of Medical Oncology, Fujian Cancer Hospital, Fuzhou, Fujian 350000, P. R. China

[10] Department of Medical Oncology, Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei 430030, P. R. China

[11] Cancer Center of The First Hospital of Jilin University, Changchun, Jilin 130021, P. R. China

[12] Department of Pathology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

[13] Department of Endoscopy Center, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing 100142, P. R. China

[14] Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, P. R. China

[15] Department of Oncology, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, P. R. China

[16] Department of Radiotherapy, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

[17] Department of Medical Oncology, Zhongshan Hospital Affiliated to Fudan University, Shanghai 200032, P. R. China

[18] Department of Abdominal Oncology, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, P. R. China

[19] Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai 200032, P. R. China

[20] Pathology Laboratory of Gastrointestinal Tumor, The First Hospital of China Medical University, Shenyang, Liaoning 110001, P. R. China

[21] Department of Pathology, Zhongshan Hospital Affiliated to Shanghai Fudan University, Shanghai 200032, P. R. China

[22] Department of Gastrointestinal Oncology Surgery, The First Hospital of China Medical University, Shenyang, Liaoning 110001, P. R. China

[23] Department of Gastrointestinal Surgery, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing 100142, P. R. China

[24] Department of Gastric Surgery, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300060, P. R. China

[25] Department of Gastrointestinal Medical Oncology, Cancer Hospital of Harbin Medical University, Harbin, Heilongjiang 150081, P. R. China

[26] Department of Radiation Oncology, Shenzhen Center, Cancer Hospital of Chinese Academy of Medical Sciences, Shenzhen 518000, P. R. China

[27] Department of Oncology, East Hospital Affiliated to Shanghai Tongji University, Shanghai 200120, P. R. China

**Correspondence**
Rui-Hua Xu, Department of Medical Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, Guangdong, P. R. China.
Email: xurh@sysucc.org.cn

[#]Fenghua Wang and Xiaotian Zhang are the first co-authors.
[##]Jin Li and Lin Shen are the co-corresponding authors.

**Abstract**

There exist differences in the epidemiological characteristics, clinicopathological features, tumor biological characteristics, treatment patterns, and drug selections between gastric cancer patients from the 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. Taking into account regional differences, giving full consideration to the accessibility of diagnosis and treatment resources, these experts have conducted expert consensus judgment on relevant evidence and made various grades of recommendations for the clinical diagnosis and treatment of gastric cancer to reflect the value of cancer treatment and meeting health economic indexes in China. The 2021 CSCO Clinical Practice Guidelines for Gastric Cancer covers the diagnosis, treatment, follow-up, and screening of gastric cancer. Based on the 2020 version of the CSCO Chinese Gastric Cancer guidelines, this updated guideline integrates the results of major clinical studies from China and overseas for the past year, focused on the inclusion of research data from the Chinese population for more personalized and clinically relevant recommendations. For the comprehensive treatment of non-metastatic gastric cancer, attentions were paid to neoadjuvant treatment. The value of perioperative chemotherapy is gradually becoming clearer and its recommendation level has been updated. For the comprehensive treatment of metastatic gastric cancer, recommendations for immunotherapy were included, and immune checkpoint inhibitors from third-line to the first-line of treatment for different patient groups with detailed notes are provided.

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

## 1 | BACKGROUND

Gastric cancer is the fifth commonest cancer and the fourth leading cause of cancer mortality worldwide. It has the highest incidence and mortality rates in Eastern and Western Asia, Latin America, and some Eastern European countries [1]. The disease burden of gastric cancer in China is high. According to the Global Burden of Disease Study 2019, the disability-adjusted life-years (DALYs) in China accounted for 44.21% of the total number of gastric cancer worldwide [2]. Gastric cancer is the second most frequently diagnosed cancer and the second leading cause of cancer-related deaths in China. China has a higher mortality/incidence ratio (0.845) and 5-year prevalence (27.6/100,000) than most developed countries and highlights a worrisome feature of a consistent increase in the incidence of early-onset gastric cancer (EOGC) among the young population [3].

The common risk factors of gastric cancer include Helicobacter pylori infection, smoking, high salty diets, susceptibility to hereditary gastric cancer syndrome. During the last decade, the incidence of gastric cancer has decreased steadily owing to the reduction in gastric cancer-related risk factors in China and other countries. However, since gastric cancer has a complex microenvironment and is a heterogeneous disease, there exist differences between the Western and Eastern gastric cancer populations as to the etiology, epidemiological characteristics, primary tumor site, histopathology, treatment strategies, prognoses, molecular biological characteristics, and immunological characteristics. As such, the purpose of this guideline is to standardize the treatment

for different stages of gastric cancer in the Chinese population.

## 2 | DIAGNOSIS

### 2.1 | Basic principles

The tumor-node-metastasis (TNM) staging system from 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 intra-peritoneal 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 report should clearly describe observations to support the clinical stage evaluation and classification (cTNM) 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 prognosticate and plan personalized treatment strategies. Currently, the molecular classification of gastric cancer is based on the human epidermal growth factor receptor 2 (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 microsatellite instability [MSI]) by polymerase chain reaction (PCR) or deficient DNA mismatch repair (dMMR) status by immunohistochemistry (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 are still in an investigational phase.

## 2.2 | Imaging and endoscopy

| Purpose (diagnosis/evaluation) | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Definitive diagnosis | Gastroscopy + biopsy (Evidence 1A) | Cytological examination (Evidence 2A)[a] | |
| 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: EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed 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 and expanded by drinking enough liquid, water preferably, before the examination [4, 5]. A multiphase and multi-planar enhanced contrast scan is recommended for diagnosis [6]. Plain abdominal CT scans are not recommended. If patients have contraindications to the contrast agent used for enhanced CT scan, MRI or EUS is recommended [4, 5]. CT imaging texture analysis can be used for assisting physicians' evaluation and could potentially increase staging accuracy [7].

[c]Chest CT can detect lung metastasis more effectively than X-ray examination [6]. For EGJ carcinoma, enhanced CT scan of the chest is recommended to assess the metastatic status and range of mediastinal lymph nodes.

[d]EUS should be carried out in qualified centers. In the 8th edition of the AJCC/UICC staging system for gastric cancer, esophageal cancer, and EGJ cancer, EUS is recommended as the preferred modality for the clinical evaluation of tumor depth invasion (cT) [5]. 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 which could suggest the destruction of corresponding layers of the gastric wall. Simultaneously, EUS can detect enlarged perigastric lymph nodes and metastatic lesions in the gastric-neighboring parts of the liver and peritoneal cavity. Thus, EUS is helpful for the diagnosis and clinical staging of gastric cancer, and assessment of response to neoadjuvant therapy. A systematic meta-analysis of 50 studies ($n = 4397$) 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 [8]. Further, the diagnostic capacity 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 [8].

[e]When liver metastasis is suspected on a CT scan, abdominal contrast MRI is recommended for further confirmation. If the patients' conditions permit, a liver-specific contrast agent can be used to increase the diagnostic sensitivity [9].

[f]Diagnostic laparoscopic exploration and examination of intraperitoneal washings are recommended for detecting occult metastasis and when peritoneal metastasis is suspected [5]. 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 (RECIST) 1.1 criteria [10], nodules of the liver, lung, or peritoneal metastasis with a long-axis diameter ≥1 cm or lymph nodes with a short-axis diameter ≥1.5 cm should be used as target lesions for treatment evaluation. The thickness of primary lesions can be used as a reference for therapeutic assessment but should not be considered as a target lesion. In regard to immunotherapy, treatment efficacy can be evaluated using the iRECIST criteria [11].

[h]Small sample-sized studies have shown that volume measurement on imaging examinations [12] and functional imaging parameters such as the apparent diffusion coefficient value of diffusion-weighted MRI (DW-MRI) [13] and iodine concentration of spectral CT examinations [14] 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, CT deep learning technology has also shown potential in assisting the evaluation of gastric cancer chemotherapy efficacy [15].

## 2.3 | Pathological diagnosis

### 2.3.1 | Histopathological diagnosis

| Sample type | Grade I recommendations | | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|
| | Gross examination | Light microscopic examination | | |
| Biopsy specimen[a] | Evaluation of the size and number of fragments | Confirm the histopathology of the lesion:<br>• Cancerous/non-cancerous<br>• Benign/malignant<br>• Histological subtype<br>• Depth of invasion (if possible) | Immunohistochemical assessment 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 (high grade)<br>Invasive carcinoma:<br>• Histological subtype[d]/Lauren classification[e]<br>• Histological grade<br>• The depth of penetration into wall<br>• The proximal/distal margin and the deep margin<br>• Vascular and lymphatic invasion | • Immunohistochemical assessment for diagnosis if needed[j]<br>• Gastric cancer with the early stage[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 from tumor<br>• The stations and number and of lymph nodes retrieved<br>(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)[f]<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 assessment for diagnosis if needed[j]<br>• Gastric cancer with the advanced stage[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 from tumor<br>• The stations and number and of lymph nodes retrieved<br>(at least 16 lymph nodes and/or preferentially >30 lymph nodes to be retrieved)[c]<br>(If lesion is not evident, careful examination and multipoint sampling should be made to avoid misdiagnosis or down staging) | • Histological subtype/Lauren classification/Histological grade (G1, G2, G3)<br>• The depth of penetration into the gastric wall (pT classification)[f]<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] | • Immunohistochemical assessment for diagnosis if needed[j]<br>• 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 | Light microscopic examination | | |
| | | • Distant metastasis (pM stage)[h]<br>• pTNM stage (8th AJCC/UICC edition)<br>• TRG[i]<br>• ypTNM stage (8th AJCC/UICC edition) | | |

*When diagnosis cannot be made via biopsy, cytological brushings or lavage fluid can be used to confirm the presence of tumor. For unresectable advanced gastric cancer, exfoliative cytological examination of their peritoneal ascites or pleural effusion and biopsy of distant metastases can be used for pathological diagnosis.

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;

**Notes**:

[a]Endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) has become the new alternative treatment for early-stage gastric cancer [16, 17]. EMR/ESD specimens should be meticulously resected, collected, and prepared, based on standard protocols, by the endoscopists or surgeons. All samples are recommended to be sectioned at intervals of 2-3 mm and perpendicular to the mucosal surface [18–20].

[b]According to the 8th edition of the AJCC/UICC staging system for gastric cancer, esophageal cancer, and EGJ carcinoma [5], the staging criteria for EGJ carcinoma or gastric-cardia carcinoma are defined as follows: 1) if the tumor has invaded the gastroesophageal boundary and the tumor's epicenter is <2 cm proximal from the EGJ (Siewert I and II), staging criteria for esophageal cancer should be used; 2) if the tumor has invaded the gastroesophageal boundary but its epicenter is located ≥2 cm distal from the EGJ (Siewert III), the staging criteria for gastric cancer should be used. Therefore, it is very important to accurately determine the location of the gastroesophageal boundary and assess whether it has been invaded by the tumor.

[c]For patients who underwent radical gastrectomy without neoadjuvant therapy, ≥16 lymph nodes should be pathologically evaluated for proper tumor staging. For a more accurate staging evaluation, the preferred number of lymph nodes should be >30. For clinicians to accurately determine the range of lymph node metastasis, it is recommended that surgeons and pathologists collect and group the peri-gastric lymph nodes according to their respective stations, which should be accordingly mentioned in the postoperative pathological report in addition to providing the total number of metastatic lymph nodes and total number of lymph nodes examined.

[d]The histopathological classification of gastric cancer is referred from the "WHO classification of tumours of the digestive system (2010 edition)" [18]. For hospital with adequate amenities, the "2019 WHO classification of tumours of the digestive system" [19] can be used for the histopathological classification of gastric cancer. If pathological diagnosis is difficult at lower-tier hospitals, it is recommended to send the specimen samples to a specialized center/hospital for further evaluation.

[e]From the Lauren classification [21], gastric adenocarcinoma is classified as intestinal type, diffuse type, and mixed type based on its histological growth patterns. Intestinal type often manifests as intestinal metaplasia, is mainly composed of highly to moderately differentiated atypical glands, and may sometimes be poorly differentiated at the proximal location of tumor invasion. Diffuse type is composed of poorly adherent cells which can extensively infiltrate the gastric walls with little or no glandular formation. The cells are usually small, round, scattered, or clustered, with obvious interstitial fiber proliferation. The mixed type is composed of approximately the same number of intestinal type and diffuse type.

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

[g]The detection of carcinomatous nodules in sub-serous adipose tissues adjacent to the primary tumor site is to be considered as regional lymph node metastasis even if there is no evidence of residual lymph node tissues [5]. It is recommended to separately record regional metastatic lymph nodes and carcinomatous nodules.

[h]If tissues obtained from non-neighboring regions of the stomach are pathologically confirmed as metastatic, these are to be regarded as distant metastasis (pM1). These include metastatic tissues from distant lymph node stations and cancerous cells detected in other organs (including intraperitoneal washings or peritoneal seedings) [5].

[i]Pathological evaluation of the tumor regression grade (TRG) (refer to section 5.3 for detailed scoring criteria) is based on residual tumor cells and the degree of fibrosis after anti-cancer treatment, proposed by the 8th AJCC TNM classification [5] or the National Comprehensive Cancer Network (NCCN) guidelines [22]. The 8th edition of the AJCC staging system proposed the post-neoadjuvant pathological tumor-node-metastasis classification (ypTNM) system to represent the postoperative pathological staging after neoadjuvant therapy.

[j]When a pathological diagnosis is difficult to determine, gastric cancer-related markers can be used for differential diagnosis, prognostic evaluation, and follow-up/treatment needs [23].

[k]Early-stage gastric cancer is defined as gastric cancer confined to the mucosa and submucosa, regardless of evidence of regional lymph node metastasis.

[l]Advanced gastric cancer is defined as a tumor that has invaded the muscularis propria or deeper layer of the gastric wall. The Borrmann classification includes four subtypes: Type I: nodular polypoid tumor; Type II: local central, bowl-shaped ulcer with easily identified elevated margins; Type III: infiltrating ulcerative tumor with poorly defined margins; and Type IV: poorly demarcated, infiltrative, and diffuse tumor (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 requires the recording of the Helicobacter pylori infection status [5].

## 2.3.2 | Molecular diagnosis

| Molecular classification | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| After a pathological diagnosis of gastric cancer, molecular profiling[a] should be conducted and treatment should be guided according to the molecular classification. | • All cases of gastric adenocarcinoma should undergo HER2 assessment[b-d] (Evidence 1A);<br>• Evaluation of MSI/dMMR status in gastric cancer tissues is also recommended[e-g] (Evidence 1B) | Evaluation of PD-L1 expression status for patients intended to be treated with PD-1/PD-L1 inhibitors is recommended[h] (Evidence 2A) | Detection of *NTRK* fusion gene[i] (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]For patients with advanced gastric cancer who experienced treatment failure after standard treatment, NGS can be used to identify potential therapeutic targets. It is emphasized that certified platforms and products abiding by strict quality control and standardized operation process are recommended to ensure the reliability of obtained results.

[b]HER2 status has been associated with response and survival prediction of patients with advanced gastric cancer to trastuzumab treatment. Therefore, HER2 status testing is recommended for all gastric cancer [24–27].

[c]According to some reports [28, 29], high-throughput sequencing-based serial circulating tumor DNA (ctDNA) genotyping was found to be an efficient approach to monitor resistance to trastuzumab based on differences in HER2 copy numbers in HER2 positive gastric cancer. If tissue biopsy cannot be obtained, assessment of *HER2* amplification via liquid biopsy could be an effective alternative. *HER2* amplification from ctDNA can also be used to monitor gastric cancer patients' response to trastuzumab.

[d]IHC and *in situ* hybridization (ISH) techniques for HER2 assessment should be strictly performed according to the "Guidelines for HER2 detection in gastric cancer (2016)" [30]. These and related tests (IHC, FISH/double signal *in situ* hybridization [DSISH]) should be performed using the China Food and Drug Administration (CFDA) approved kits.

[e]Immune checkpoint inhibitors targeting programmed death protein-1 (PD-1) and its ligand-1 (PD-L1) have become a research hotspot in tumor immunotherapy in recent years. For patients who are to undergo immunotherapy, evaluation of MSI/MMR status and the association of PD-L1 expression to tumor mutational burden (TMB) is recommended. The association of Epstein-Barr virus (EBV) status with immunotherapy is still to be fully elucidated.

[f]MMR protein detection: immunohistochemistry detection of MLH1, PMS2, MSH2, MSH6 proteins in the nucleus of the tumor should be performed. If absence of any one of these four proteins is observed, the patient can be classified as dMMR, and if all four are present, the patient can be classified as proficient MMR (pMMR).

[g]MSI detection: it is recommended to use the 5 microsatellite loci (BAT25, BAT26, D5S346, D2S123, D17S250) proposed by the US National Cancer Institute (NCI). The grading criteria are as follows: MSS, if all the 5 loci are found as stable; MSI-L, if 1 locus is found unstable; high MSI status (MSI-H) if ≥2 loci are unstable. MSI is mostly caused by MMR gene mutation and functional defect, and its status can be reflected based on MMR protein analysis. Thus, dMMR can be considered equivalent to MSI-H, and pMMR to low MSI status (MSI-L) or microsatellite stability (MSS).

[h]For a sample to be deemed suitable for PD-L1 assessment, there should be at least 100 tumor cells present in the sample. PD-L1 combined positive score (CPS) = total number of PD-L1-stained cells (including tumor cells, macrophages, and lymphocytes) / total number of tumor cells under microscope (× 100) [31].

[i]The U.S.FDA has authorized the use of TRK inhibitors (i.e., larotrectinib or entrectinib) in patients with neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion-positive solid tumors. For gastric cancer patients who have failed with standard treatment, *NTRK* gene fusion can be detected via multiple methods. Immunohistochemistry is a fast and convenient preliminary screening method, but it still needs to be verified by FISH or NGS.

## 3 | COMPREHENSIVE TREATMENT OF GASTRIC CANCER

### 3.1 | Treatment of non-metastatic gastric cancer

#### 3.1.1 | Treatment of resectable gastric cancer

The treatment of resectable gastric cancer is based on the evaluated clinical stage. The primary choice of treatment for early-stage gastric cancer is endoscopic treatment which includes EMR or 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 chemoradiation therapy 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, but a best supportive treatment plan can be formulated 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 therapy 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;

**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 [32]. 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) [33], the 5th edition of the Japanese Gastric Cancer Guidelines [34] 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. 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 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 [33, 35, 36].

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.

## *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[d] | D1 gastrectomy (Evidence 1A) | Laparoscopic D1 gastrectomy (distal or total)[b] (Evidence 1B) | |
| | cT1bN0M0 | Patients suitable for surgery[d] | D1 gastrectomy (differentiated type, <1.5 cm) or D1+ gastrectomy (other indications) (Evidence 1A) | Laparoscopic D1/D1+ gastrectomy (distal or total)[b] (Evidence 1B) | |
| | cT2N0M0 | Patients suitable for surgery[d] | D2 gastrectomy (Evidence 1A) | Laparoscopic D2 gastrectomy (distal)[b] (Evidence 1A) | |
| II | • cT1-2N1-3M0<br>• cT3-4N0M0 | Non-EGJ cancer and patients suitable for surgery[d] | D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy (Evidence 1A) | Laparoscopic D2 gastrectomy (distal)[b] (Evidence 1A) + adjuvant chemotherapy[e] (Evidence 1A) | |
| | | EGJ cancer and patients suitable for surgery[d] | • Neoadjuvant chemotherapy + D2 gastrectomy + adjuvant chemotherapy[d] (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[e] | • D2 gastrectomy (Evidence 1A) + adjuvant chemotherapy (Evidence 1A)<br>• Laparoscopic exploration[e] (Evidence 1B) + Neoadjuvant chemotherapy + D2 gastrectomy + adjuvant chemotherapy[e] (Evidence 1B) | Laparoscopic D2 gastrectomy (distal) (Evidence 1A) + adjuvant chemotherapy[e] (Evidence 1A) | |
| | | EGJ cancer and patients suitable for surgery[e] | Laparoscopic exploration[e] (Evidence 1B) + Neoadjuvant chemotherapy/ chemoradiotherapy + D2 gastrectomy + adjuvant chemotherapy[e] (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[e] (Evidence 1B) + neoadjuvant chemoradiotherapy + gastrectomy (combined resection of invading organs) + adjuvant chemoradiotherapy (Evidence 2B) | Encourage participation in clinical trials |
| Stage I-IVA | | Patients unsuitable for surgery | Refer to section "2.1.2 Comprehensive Treatment for Unresectable Gastric Cancer" | | |

*The 8th edition of the AJCC/UICC clinical staging system (cTNM).

**Unresectable factors are 1) tumors with involvement of the mesenteric root or para-aortic lymph nodes (highly suspected on imaging or confirmed by biopsy), 2) tumors have invaded or encapsulated important blood vessels (excluding the splenic artery), and 3) distant metastasis or peritoneal seeding (including positive cytological examination of intraperitoneal washings).

Abbreviations: EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; D, type of lymphadenectomy; EGJ, esophagogastric junction;

*Principles of surgery.*

| Technical requirement | Type of gastrectomy | Type of lymphadenectomy | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|---|
| Lymphadenectomy recommendations[a] | Distal gastrectomy | D1 | Stations: 1, 3, 4sb, 4d, 5, 6, 7 (Evidence 1A) | | |
| | | D1+ | Stations: D1 and 8a, 9 (Evidence 1A) | | |
| | | D2 | Stations: D1 and 8a, 9, 11p, 12a (Evidence 1A) | D2 stations and station 14v[*] (Evidence 2A) | Resection of duodenal invaded part + D2 stations + station 13 (Evidence 2B) |
| | Pylorus preserving partial gastrectomy | D1 | Stations: 1, 3, 4sb, 4d, 6, 7 (Evidence 1A) | | |
| | | D1+ | Stations: D1 and 8a, 9 (Evidence 1A) | | |
| | Proximal gastrectomy | D1 | Stations: 1, 2, 3, 4sa, 4sb, 7 (Evidence 1A) | | |
| | | D1+ | Stations: D1 and 8a, 9, 11p (Evidence 1A) | | |
| | | D2 | Stations: D1 and 8a, 9, 10, 11 (Evidence 1B) | Stations D2 and station 10[**] (Evidence 2A) | |
| | Total gastrectomy | D1 | Stations: 1-7 | | |
| | | D1+ | Stations: D1 and 8a, 9, 11p | | |
| | | D2 | Stations: 1-7, 8a, 9, 10, 11, 12a (If tumor invaded the esophagus, include stations 19, 20, 110, and 111) (Evidence 1A) | Stations D2 + station 10 (Evidence 2A) | |
| Digestive tract reconstruction[c] | Distal gastrectomy | | • Billroth I (Evidence 1A)<br>• Billroth II (Evidence 1A) | | Roux-en-Y anastomosis (Evidence 2B) |
| | Proximal gastrectomy | | | • Esophagogastrostomy (Evidence 1A)<br>• Tubular gastroesophageal anastomosis (Evidence 2A) | Jejunal interposition for gastric replacement (Evidence 2B) |

| Technical requirement | Type of gastrectomy | Type of lymphadenectomy | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|---|---|
| | Total gastrectomy | | Roux-en-Y anastomosis (Evidence 1A) | | • Roux-en-Y anastomoses with jejunal pouch reconstruction (Evidence 2B)<br>• Jejunal interposition for gastric replacement (Evidence 2B) |

*For stage cIII patients with metastatic lymph nodes at the middle and lower portions of the stomach and lower part of the pylorus;

**For patients preoperatively staged as cT3 or cT4, primary tumor >6 cm, and located at the upper or middle portions of the stomach near the greater curvature;

Abbreviations: D, type of lymphadenectomy;

**Notes**

[a]**Principles of surgery**

The scope of gastrectomy is based on the location of the tumor, with the aim to ensure adequate surgical resection margin. Based on data from recent studies [37, 38], 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 [39], 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.

The resection of perigastric lymph nodes and those alongside accompanying vessels of the abdominal cavity should be performed according to the type of gastrectomy [37, 38]. 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, celiac artery, splenic hilum, and splenic artery. 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 [40].

Currently, there is still controversy regarding the necessity for splenic hilar lymph node dissection. The rate of splenic hilar lymph node metastasis varies greatly in different reports but the risk of splenic hilar lymph node metastasis has been found to be higher for tumors located at the upper part of the stomach than the lower part [41]. At present, it is recommended that splenic hilar lymph node dissection should not be performed in stage cT1-2 gastric cancer patients as the risk of lymph node metastasis is low [42]. 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 [42]. 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 near the greater curvature, and preoperatively staged as cT3-4 [43, 44]. Splenectomy for the purpose of 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 scope of D2 lymphadenectomy in the 3rd edition of the Japanese Gastric Cancer Treatment Guidelines [45], it has been observed that D2 with station 14v lymph node dissection may improve overall survival (OS) in clinically staged III/IV patients with 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% [46, 47]. D2 lymphadenectomy with resection of station 14v lymph nodes can improve the OS of stage cIII/IV middle and lower gastric cancer patients [48]. The Expert Committee recommends these 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 scope of D2 dissection, studies have found that for advanced lower gastric cancer, the metastasis rate to station 13 was 2.53%-9%, and if the tumor has invaded the duodenum, the metastasis rate is even higher, at 26.7% [49–51]. 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. However, the rate of postoperative complications of station 13 dissection is about 15.18%. 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 and station 13 dissection can be considered for such patients.

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 [52], and the value of therapeutic para-aortic lymph node dissection is still controversial. Suitable patients should be encouraged to participate in clinical trials.

[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 [53] and KLASS-01 [54], 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 total and proximal laparoscopy-assisted gastrectomy (LTG and LAPG) of early gastric cancer. The KLASS-03 study was a single-arm prospective multicenter clinical study, from South Korea, to explore the clinical value of LTG in stage I gastric cancer ($N = 160$) [55]. The results showed that the rates of postoperative complications and deaths were 20.6% and 0.6%, suggesting that LTG performed by experienced surgeons was clinically effective in stage cI patients. In the JCOG1401 study [56], a phase II clinical study from Japan exploring the value of LATG ($n = 195$)/LAPG ($n = 49$) in stage cI gastric cancer ($N = 244$), the rate of conversion surgery was 1.7%, the overall rate of grade 3/4 complications was 29%, and no surgery-related death was observed,

confirming the safety of LATG/LAPG in stage cI patients. The CLASS-02 study [57] was a randomized controlled study ($N = 214$) carried out in China to explore the safety of LTG ($n = 105$) in the treatment of stage cI gastric cancer compared to open total gastrectomy (OTG; $n = 109$). The postoperative complications of the two groups were 19.1% and 20.2% respectively, and the death rate was 1.0%, demonstrating comparable safety of LTG to that of OTG, with lymphadenectomy performed by experienced surgeons for stage cI gastric cancer. These three studies preliminarily confirmed the safety of LTG and LATG/LAPG. However, the long-term benefit of LTG and LAPG for early gastric cancer has not yet been confirmed. Therefore, the Expert Committee recommends further investigations of such cases in experienced medical centers.

For advanced gastric cancer, the CLASS-01 [58] and KLASS-02 [59] 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 had 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 research evidence. The recent results of a Chinese randomized controlled study, comparing the safety and recovery indices 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 [60].

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. LTG 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 LTG 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.

A recent randomized controlled study from China which investigated the safety and efficacy of indocyanine green tracer-guided lymph node dissection during laparoscopic radical gastrectomy in patients with potentially resectable gastric adenocarcinoma (cT1-cT4a, N0/+, M0) showed that indocyanine green fluorescence imaging could be used for routine lymphatic mapping during laparoscopic gastrectomy and could also noticeably increase the number of lymph node dissections and reduce lymph node noncompliance without increased complications in patients undergoing D2 lymphadenectomy [61].

Further, robotic gastric cancer surgery has attracted much attention in recent years. Although there is no large sample prospective study to confirm its efficacy in the treatment of gastric cancer, a retrospective study from Korea which compared robotic gastric cancer surgery ($n = 421$) with open/laparoscopic surgery ($n = 1663$) [62] 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 randomized controlled clinical study from China compared robotic distal gastrectomy (RDG) against LADG in 283 patients with cT1-4aN0/+M0 disease, and the short-term efficacy results showed that the postoperative complications of RDG were lower, and more peri-gastric lymph nodes could be removed [63]. Currently, the Expert Committee believes 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 surgeries are mostly adopted for distal gastrectomy. The postoperative complication rates for both surgeries 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 surgery is recommended because these patients can have a second chance for surgery in case of tumor recurrence [64]. 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 [65].

Gastroesophageal anastomosis is frequently used for proximal gastrectomy as the anastomosis is relatively easy to perform, has shorter operative time, lesser number of anastomosis, and often accompanied with lower risk of postoperative complications, but the risk of esophageal reflux is common and serious [66]. The modified tubular gastroesophageal anastomosis can significantly reduce the risk of severe esophageal reflux [67]. Compared with gastroesophageal anastomosis, the Jejunal interposition method 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 [68]. 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.

Roux-en-Y is the preferred reconstruction method for total gastrectomy [38]. 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 [69]. 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.

For d and e, please view the notes below.

*Perioperative treatment of resectable gastric cancer.*

Postoperative 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 | Postoperative adjuvant chemotherapy:<br>• XELOX (Evidence 1A)<br>• S-1 alone (Evidence 1A) | Postoperative adjuvant chemotherapy:<br>• XP (Evidence 1B)<br>• SOX (Evidence 1B) | Postoperative adjuvant chemotherapy: FOLFOX (Evidence 2A) |
| Stage III:<br>• pT1N3bM0<br>• pT2N3M0<br>• pT3N2-3M0<br>• pT4aN1-3M0<br>• pT4bN0-3M0<br>with R0 resection and D2 dissection | Postoperative adjuvant chemotherapy:<br>• XELOX (Evidence 1A)<br>• SOX (Evidence 1A) | Postoperative adjuvant chemotherapy: DS sequential S-1 (Evidence 1B) | • Postoperative adjuvant chemotherapy: FOLFOX (Evidence 2A)<br>• Postoperative adjuvant chemoradiotherapy: DT 45-50.4 Gy (concurrent fluorouracil) (Evidence 3) |
| • pT2-4NanyM0 with R0 resection but less than D2 dissection | Postoperative chemoradiotherapy: DT 45-50.4 Gy (concurrent fluoropyrimidine) (Evidence 1A) | MDT discussion for optimal treatment regimen | |
| pT2-4NanyM0 and R1/R2 resection | Postoperative chemoradiotherapy[**]: DT 45 to 50.4 Gy (concurrent fluoropyrimidine) (Evidence 2A) | MDT discussion for optimal treatment regimen | |

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

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

Abbreviations: XELOX, oxaliplatin + capecitabine; FOLFOX, leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; SOX, S-1 + oxaliplatin; XP, capecitabine + cisplatin; SOX, S-1 + oxaliplatin; DS, docetaxel plus S-1; MDT, multidisciplinary team; D, type of lymphadenectomy;

Neoadjuvant therapy[e]

| Stratification* | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Non-EGJ gastric cancer: cT3-4aN+M0, stage cIII | Neoadjuvant chemotherapy: SOX regimen (Evidence 1) | • DOS (Evidence 1B)<br>• FLOT4 (Evidence 1B) | • XELOX (Evidence 2A)<br>• FOLFOX (Evidence 2A) |
| Gastric cancer invading the EGJ[e,f]: cT3-4aN+M0, stage cIII | Neoadjuvant chemoradiotherapy: DT 45-50.4gy (concurrent fluorouracil, platinum or taxanes) (Evidence 1B) | • 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) |
| cT4bNanyM0, stage cIVA (without non-resectable factors) | MDT discussion for optimal personalized treatment | • Neoadjuvant chemoradiotherapy + gastrectomy (with adjacent organ resection) + adjuvant chemoradiotherapy (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 | |

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

Abbreviations: EGJ, esophagogastric junction; MSI-H, high microsatellite instability status; cTNM, clinical tumor-node-metastasis classification; SOX, S-1 + oxaliplatin; DOS, docetaxel + oxaliplatin + S-1; 5-FU, 5-fluorouracil; FLOT, 5-FU+ leucovorin + oxaliplatin + docetaxel; XELOX, capecitabine + oxaliplatin; MDT, multidisciplinary team;

**Notes**

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

There are several large phase III clinical trials supporting the use of postoperative adjuvant chemotherapy for patients who had undergone D2 radical gastrectomy [70–73]. The indications of postoperative adjuvant chemotherapy for resectable gastric cancer are D2 radical gastrectomy and no prior neoadjuvant therapy for stage pII and pIII patients. For stage II patients, the recommended regimen is S-1 (oral; till 1 year after operation) or capecitabine combined with oxaliplatin or cisplatin [70, 71]. In the JACCRO GC-07 study [72, 74], 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 advanced gastric cancer compared to S-1 monotherapy (3-year recurrence-free survival [RFS] rate, S-1/docetaxel arm, 65.9%, vs S-1 arm, 49.6%; $P = 0.0007$) and suppressed all types of recurrences, including hematogenous, lymphatic, and peritoneal recurrences. The RESOLVE trial [75] 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 [76] 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 months of SOX versus SOX 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. [77] reviewed the data of 1464 pT3-4 or N+ gastric cancer patients who received adjuvant fluoropyrimidine plus oxaliplatin (F-OX) after D2 gastrectomy from 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 or low histological grade 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 [78], from the U.S, confirmed that concurrent radiotherapy and 5-fluorouracil (5-FU) chemotherapy after surgery improved OS compared to surgery alone, but the surgery performed were mainly D0/D1 gastrectomy, whilst in countries like China, Korea, and Japan, mostly

D2 gastrectomy are performed. The ARTIST study from South Korea [71], 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. They 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%; $P = 0.0365$). Subsequently, the ARTIST-II study [76] was performed to compare the efficacy of different chemotherapy regimens and chemoradiotherapy (adjuvant S-1 monotherapy versus SOX versus SOXRT) in patients with D2-resected, stage II/III, node-positive gastric cancer. The results were published by the American Society of Clinical Oncology (ASCO) in 2019 and no difference in DFS between SOX and SOXRT ($P = 0.667$) were observed but both adjuvant SOX and SOXRT were effective in prolonging DFS when compared to S-1 monotherapy; thereby demonstrating that the addition of radiotherapy could not provide addition survival benefits [76]. 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), postoperative chemoradiotherapy [79] 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 [72, 74], 4.8% in the ARTIST study [71], 2.3% in the CLASSIC study [70], and 1.4% in the ACTS-GC study [80]. 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/radiotherapy) for gastric cancer has been proven to be superior to surgery alone in Western countries as they could downstage the tumor, increase the rate of radical resection, and improve survival whilst not increasing the risks of postoperative complications and deaths [81, 82]. Also, neoadjuvant chemotherapy prior to radical gastrectomy in Asian studies has also been associated with significantly improved tumor remission rates, R0 resection rates, and treatment safety [83, 84]. 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 [75], 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) against perioperative SOX (neoadjuvant SOX followed 5 cycles of adjuvant SOX; arm C) in locally advanced gastric cancer patients after D2 radical gastrectomy. They found that perioperative SOX was superior to adjuvant XELOX (3-year DFS rate: 62.0% vs. 54.8%; $P = 0.045$) 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 with 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 [85] 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. Thus, the DOS regimen can also be recommended as neoadjuvant chemotherapy for locally advanced gastric cancer patients.

Currently, the recommended neoadjuvant chemotherapy regimens for gastric cancer include XELOX [86], FOLFOX [87], cisplatin combined with S-1 (SP) [88], and SOX [89]. Results of the large prospective phase III FLOT4-AIO study [90] 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 regard to HER2-positive gastric cancer, there have been several investigations on the perioperative treatment of anti-HER2 drugs, including double- or triple-drug chemotherapy, combination with a monoclonal antibody (mAb) or double anti-HER2 treatment. However, as the final results of these trials are to be published, currently no standard treatment strategy has been proposed.

Results of the international multicenter CRITICS study [91] showed that 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) and same chemotherapy regimen as adjuvant treatment administrated alone or in combination with adjuvant radiotherapy. The investigators found no improvement in survival in those who underwent adjuvant chemoradiotherapy compared to patients with resectable gastric cancer treated with neoadjuvant chemotherapy, adequate surgery, and adjuvant chemotherapy. 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 [92–94], 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 [95] which explored the associations of MSI status with postoperative prognosis and perioperative chemotherapy efficacy in patients with resectable gastric cancer enrolled in the CLASSIC [70], ARTIST [71], MAGIC [81], and ITACA-S trials [96] 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-sized 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. Overall, considering the low number of corresponding patients in these studies, conflicting evidence in current literature, adverse reactions related to chemotherapy and patients' financial implications, 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, post-operative observation or chemotherapy can be considered.

For EGJ adenocarcinoma, clinical studies [97, 98] have shown that neoadjuvant chemoradiotherapy plus surgery plus adjuvant chemotherapy was effective in tumor downstaging, could increase R0 resection rate and improve survival, and was not associated with increased risk of complications or postoperative deaths. The long-term follow-up results of the POET study [97], which investigated the addition of radiotherapy to preoperative chemotherapy in lower esophageal and gastric cardia adenocarcinoma, demonstrated that, although the trial was terminated early as it did not meet its accrual goals and could not provide statistical significance, preoperative chemoradiotherapy appeared to reduce the risk of local recurrence and tended to prolong survival, compared to preoperative chemotherapy, without an increase in adverse events and surgery-related complications in patients with localized EGJ adenocarcinoma. Also, the RTOG-9904 multicenter

phase II clinical trial [98] demonstrated satisfactory results for locally advanced gastric cancer patients undergoing preoperative chemoradiotherapy. Therefore, the current recommendation for stage III EGJ adenocarcinoma is neoadjuvant chemoradiotherapy followed by radical D2 gastrectomy. For locally advanced gastric cancer, encouragement of patient participation in clinical trials for preoperative chemoradiotherapy is recommended for confirmation evidence. Recommended regimens for concurrent chemotherapy include paclitaxel combined with 5-FU, paclitaxel combined with platinum, or 5-FU combined with platinum. At present, the TOPGEAR (NCT01924819) [99], CRITICS-II (NCT02931890) [100] and the phase III prospective Neo-CRAG clinical trial (NCT01815853) [101] launched by the Sun Yat-sen University Cancer Center are actively investigating the effects of preoperative chemoradiotherapy in this category of patients.

Studies investigating neoadjuvant chemotherapy and perioperative chemotherapy in patients with EGJ cancer are gradually increasing, including studies from Asia such as the RESOLVE [75], PRODIGY [85], and RESONANCE studies [102]. In the PRODIGY study [85], EGJ cancer accounted for 5.6% of the study population, and the results showed that neoadjuvant chemotherapy with DOS regimen could achieve tumor downstaging, improve R0 resection rate, and prolong PFS. In the RESOLVE study [75], EGJ cancer accounted for 36.5% of the study population, and the results showed that compared with the adjuvant XELOX chemotherapy, perioperative SOX chemotherapy was associated with improved R0 resection rate and prolonged DFS. A propensity score-matching study from Zhongshan Hospital of Fudan University [103], comprising of 32% of patients with EGJ cancer, showed that neoadjuvant DOS regimen was more effective than neoadjuvant XELOX regimen in improving both PFS and OS, without any added adverse effects. According to these findings, the DOS and SOX regimens can be considered for neoadjuvant chemotherapy of EGJ cancer patients.

The efficacy of neoadjuvant therapy should be timely evaluated 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 [104]. 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 pathological complete response (pCR) after neoadjuvant therapy, it is recommended that the same neoadjuvant regimen to 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 to 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 postoperative 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]Perioperative treatment for EGJ cancer**

The choice of perioperative treatment for EGJ cancer has some particularity because of the differences in clinical research design and results between Eastern and Western countries. The proportion of patients with EGJ cancer was very low in a number of clinical trials which had positive results for postoperative adjuvant chemotherapy after D2 gastrectomy in Asian countries. Although the overall population can benefit from postoperative adjuvant chemotherapy, it is uncertain whether patients with EGJ cancer in Asian countries would benefit from such treatment. Comparatively, in European clinical trials which investigated perioperative treatment for gastric cancer, the proportion of patients with EGJ cancer was higher, i.e., in the FFCD ($n = 60\%$) [105] and FLOT4-AIO study ($n = 56\%$) [90], suggesting that perioperative chemotherapy was indeed an effective treatment for patients with EGJ cancer in Western countries. In the RESOLVE study [75], EGJ cancer patients comprised of 36.5% of the study population, suggesting that perioperative chemotherapy could also be an effective treatment in the Asian population.

In addition, due to inconsistent findings on neoadjuvant therapy studies, it is difficult to identify the optimal neoadjuvant therapy (neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy) for EGJ cancer. The POET study [97] only demonstrated potential advantages of preoperative chemoradiotherapy for EGJ cancer. However, a meta-analysis by Petrelli et al. [106] showed that neoadjuvant chemoradiotherapy, compared with neoadjuvant chemotherapy, was associated with increased pCR rate and reduced local recurrence in EGJ adenocarcinoma, but did not prolong OS, which was different from the conclusion of the POET study. As such, based on the current research evidence, for EGJ cancer, perioperative chemoradiotherapy could be more suitable than adjuvant chemotherapy.

### 3.1.2 | 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-e,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-e,②] (Evidence 2B)<br>• Radiotherapy[b-d, f, g ,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 + radiotherapy[b-g] or concurrent chemoradiotherapy[a-e ,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-g] (Evidence 2A)<br>• After nutritional support, if the patient's 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;

[①]Concurrent chemoradiotherapy regimen:

– Carboplatin + paclitaxel (Evidence 1A) [107]
– Cisplatin + 5-FU or capecitabine or tegafur (Evidence 1A) [108]
– Oxaliplatin + 5-FU or capecitabine or tegafur (Evidence 2B) [109]
– Paclitaxel + 5-FU or capecitabine or tegafur (Evidence 2B) [98, 110]
– Capecitabine (Evidence 2B) [71, 111]
– Tegafur (Evidence 2B) [112–114]
– 5-FU (Evidence 1a) [115]

[②]Chemotherapy regimen: refer to section Chemotherapy regimen for late-stage 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 has 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 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 [116, 117]. If the tumor responds well after treatment, the possibility of radical resection should be evaluated. Some studies have shown that if a patient is fit for surgery, radical or palliative resection could both provide survival benefits [116, 117]. Retrospective studies have shown that for unresectable patients, chemoradiotherapy was associated with superior survival benefits than chemotherapy alone [118, 119].

[b]For patients with extensive tumor invasion or lymph node metastasis, wide irradiation fields could lead to intolerance to concurrent chemoradiotherapy, and for such cases, chemotherapy alone or radiotherapy alone could be considered as an alternative. For patients with favorable responses after treatment, referral to an MDT is recommended to judge the potential for surgical resection. If the tumor is still found unresectable, chemotherapy with sequential or concurrent radiotherapy may be considered, and tumor resectability should be re-evaluated after the treatment.

[c]Radiologists should perform a comprehensive evaluation based on the patients' physical condition and the scope of the irradiation field before performing sequential or concurrent chemoradiotherapy. In general, concurrent chemoradiotherapy is superior to radiotherapy alone [120]. For concurrent chemoradiotherapy, the choice of chemotherapy regimen should be based on the tumor location (i.e., the EGJ or stomach), and radiotherapy alone can be considered if the patient cannot tolerate concurrent chemoradiotherapy. However, patients who had prior chemotherapy may have poor tolerance to radiotherapy, and a double-drug regimen with concurrent chemoradiotherapy may reduce the completion rate of radiotherapy. For such cases, single-drug chemotherapy using 5-FU with concurrent chemoradiotherapy can be considered [71, 111-114].

[d]Consideration for radiotherapy. 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

radiotherapy 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, 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, avoid inclusion of the regional lymph nodes. The recommended dose for palliative radiotherapy is DT 30-40 Gy (10-20 cycles). The dosage and scope of irradiation should be based on the patient's general condition, the size of the irradiation field, expected lifespan, and possible irradiation damage to surrounding normal tissues and organs.

[e]Compared to best supportive care, chemotherapy can prolong the survival of metastatic or late-stage gastric cancer patients [121]. 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 can then be considered. If not, best supportive care can be continued. The main chemotherapy drug regimens could be 5-FU-based, platinum-based, taxanes-based, and irinotecan regimen. 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 [122]. For those who cannot tolerate combined chemotherapy, single-drug chemotherapy such as 5-FU alone can be considered.

[f]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 [123–125]. Palliative radiotherapy may be considered for patients of old age, with advanced disease, decreased cardiopulmonary functions, multiple underlying diseases, and difficulty sustaining surgical intervention.

[g]Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) are recommended as related studies have demonstrated that, compared with conventional two-dimensional radiotherapy, 3D-CRT or IMRT was superior in targeting the dose distribution area and protecting normal organ tissue, especially in the gastrointestinal tract, liver, and kidneys, against adverse events from irradiation [126, 127].

### 3.2 | Treatment of late-stage metastatic gastric cancer

For the patients who cannot undergo radical resection or with metastatic disease, comprehensive treatment based on systemic antitumor therapy such as palliative surgery, radiotherapy, radiofrequency ablation (RFA), intraperitoneal perfusion, and arterial embolization is recommended as these may help to prolong survival and improve the quality of life. Such cases should be discussed via an MDT for optimal personalized treatment strategy.

Currently, the main drugs for gastric cancer treatment in China comprised of chemotherapy, targeted therapy, and immune checkpoint inhibitors. For chemotherapy, there are sufficient scientific-based evidence and experiences in clinical practice to support their use. In regard to targeted therapy, although there have been extensive studies on its use in gastric cancer, only few targeted drugs have obtained approval for clinical practice, i.e., anti-HER2 drugs such as trastuzumab and anti-angiogenic pathway drugs such as apatinib. In regard to immunotherapy, despite breakthroughs in research concerning PD-1 antibodies have been achieved, single-drug immunotherapy has not been satisfactorily effective. Due to the heterogeneity of gastric cancer, complicated tumor microenvironment, non-consistent epidemiologic characteristics of gastric cancer patients in the East and West, differences in clinicopathological characteristics, and wide drug selection, suitable patients should be encouraged to participate in corresponding clinical trials.

The stomach is an important digestive organ where the primary lesion may directly affect the nutritional status, leading to complications such as bleeding, digestive tract obstruction, and/or perforation. Therefore, maintenance of nutritional status, as well as active prevention and timely treatment of complications should be given special attention during the entire antitumor treatment process to improve the patient's quality of life.

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

**First-line treatment**

| HER2 status | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Positive[i] | Trastuzumab combined with oxaliplatin/cisplatin + 5-FU/capecitabine (Evidence 1A) | Trastuzumab combined with oxaliplatin/cisplatin + tegafur (Evidence 2B) | Trastuzumab combined with other first-line chemotherapy regimens, excluding anthracyclines (Evidence 3) |
| Negative[b-f] | Oxaliplatin + fluorouracil (5-FU/capecitabine/tegafur) (Evidence 1A) | Three-drug combination regimens, i.e. DCF and mDCF (Evidence 1B) for patients in good physical conditions and with large tumor burden | |
| | Paclitaxel/docetaxel + fluorouracil (5-FU/capecitabine/tegafur) (Evidence 2A) | | |
| | Cisplatin + fluorouracil (5-FU/capecitabine/tegafur) (Evidence 1A) | | |
| | For PD-L1 CPS≥5 patients, Chemotherapy (FOLFOX/XELOX) combined with nivolumab (Evidence 1a)[m,n]. | | For PD-L1 CPS≥1 patients, pembrolizumab monotherapy can be recommended[n] |

Abbreviations: HER2, human epidermal growth factor receptor 2; 5-FU, 5-fluorouracil; ECF, Epirubicin + Cisplatin + 5-FU; DCF, Docetaxel + Cisplatin + 5-FU; mDCF, modified DCF; FOLFOX, leucovorin calcium + 5-FU + oxaliplatin; XELOX, capecitabine + oxaliplatin; PD-L1 CPS, programmed death ligand-1 combined positive score;

**Second-line treatment (irrespective of HER2 status)**[f,h,l]

| HER2 status | Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|---|
| Positive | Monotherapy (paclitaxel/docetaxel/irinotecan) (Evidence 1a) | For those who failed with platinum therapy and did not receive trastuzumab, trastuzumab in combination with paclitaxel is recommended (Evidence 2a) | If there is no previous use of trastuzumab, trastuzumab plus anthracycline plus other line chemotherapy can be considered (Evidence 3)<br>Refer to the chemotherapy drug selection of HER2 negative gastric cancer or encourage participation in clinical trial |
| Negative | Monotherapy (paclitaxel/docetaxel/irinotecan) (Evidence 1a) | • Two drug chemotherapy, according to the previous regimens: irinotecan + 5-FU, paclitaxel/docetaxel + fluorouracil (5-FU/capecitabine/tegafur) (Evidence 2b)<br>• Paclitaxel monotherapy (Evidence 1b)<br>• Pembrolizumab in MSI-H patients (Evidence 2a)[o] | Cisplatin or oxaliplatin-based chemotherapy if previous failure without platinum therapy (Evidence 3) |

Abbreviations: HER2, human epidermal growth factor receptor 2; 5-FU, 5-fluorouracil;

**Third and above lines of treatment (irrespective of HER2 status)**[g,j,k]

| Grade I recommendations | Grade II recommendations | Grade III recommendations |
|---|---|---|
| Apatinib[j] (Evidence 1A) | Pembrolizumab monotherapy for PD-L1 CPS ≥ 1 patients[k] (Evidence 1B) | According to the previous drug use, refer to the second-line recommendations for selection of single drug chemotherapy[g] (Evidence 3) |
| Nivolumab monotherapy[k] (Evidence 1A) | | |

Abbreviations: PD-L1 CPS, programmed death ligand-1 combined positive score;

**Notes**

[a]The overall prognosis of advanced gastric cancer is poor. Traditional chemotherapy drugs remain among the last evidence-based treatments available as the choice of targeted drugs remains limited and the efficacy of immunotherapy alone has not been satisfactory. Thus, considering the heterogeneity of gastric cancer, these patients are encouraged to participate in clinical trials for the advancement of precision medicine.

[b]Fluoropyrimidine, platinum, and taxanes are the main therapeutic drugs for late-stage gastric cancer. Usually, first-line regimens are based on fluoropyrimidine combined with platinum and/or taxanes to constitute a two- or three-drug regimen [122, 128-136]. In China, the two-drug therapy consisting of fluoropyrimidine and platinum is recommended, and oxaliplatin is preferred over platinum-based on Chinese real-world data and better-observed tolerability [130, 134]. In the phase III SOX-GC clinical trial [134], 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 a certain extent of improved efficacy, survival, and tolerance. Further, the rates of grade ≥3 adverse events, such as neutropenia, anemia, nausea, vomiting, nausea, vomiting, anorexia (except neurosensory toxicity), were significantly lower in the SOX group than in the SP group. Therefore, the SOX regimen is 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 [131]. Although the three-drug DCF regimen has attained its endpoint in phase III clinical trials, its high toxicity limits its clinical application [132]. The modified docetaxel plus cisplatin plus 5-FU (mDCF) [133] and paclitaxel plus FOLFOX (POF) regimens [137] 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 [138]. A phase II study showed that the efficacy and survival rate of docetaxel plus oxaliplatin plus 5-FU (TEF) was superior to docetaxel plus oxaliplatin (TE) or docetaxel plus oxaliplatin plus capecitabine (TEX) regimens [139]. 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 [140], and those suspected of irinotecan-associated metabolic disorders can undergo the *UGT1A1* gene polymorphism testing [141].

[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 study showed that first-line chemotherapy with paclitaxel plus capecitabine therapy followed by capecitabine for maintenance (PACX) was not associated with improved median progression-free survival (mPFS) and mOS, compared to the XP regimen, but significantly improved quality of life and decreased treatment-related adverse events [131].

[e]Studies have shown that two-drug regimens were better than single-drug regimens for elderly or frail patients [142, 143]. In the GO2 study [136], 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 dose, patients with Level C dose 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 results of studies for second-line chemotherapy comparing the efficacy of single-drug treatment showed that for patients with Eastern Cooperative Oncology Group performance score (ECOG PS) 0-1, two-drug chemotherapy was safe and was associated with better tumor control, although the investigated cohort size was relatively small [144, 145]. 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 [146]. 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 late-stage gastric cancer, although comprised of a limited number of patients, and did not find significant benefit from chemotherapy in this group of patients. 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]The ToGA trial [26] showed that, compared with chemotherapy alone, trastuzumab combined with first-line chemotherapy was associated with improved efficacy and survival in HER2-overexpressed, treatment-naïve, late-stage gastric cancer patients. A number of phase II clinical studies have evaluated the combination of trastuzumab and other chemotherapy regimens, showing good efficacy and safety [147, 148]. The EVIDENCE study [149] was designed to evaluate the efficacy, safety, treatment mode, and clinical outcomes of trastuzumab in Chinese HER2-positive, metastatic gastric cancer patients. Its findings showed that, compared to chemotherapy alone, trastuzumab was associated with improved OS and PFS in Chinese HER2+ metastatic gastric cancer patients, was well tolerated and effective when combined with a range of other therapies in a real-world setting. In the case of combined chemotherapy using the XELOX regimen, the best efficacy of trastuzumab demonstrated an OS of 34.6 months [150]. For HER2-positive late-stage gastric cancer patients with no prior use of trastuzumab, paclitaxel combined with trastuzumab was found to be effective and safe in a Chinese phase II clinical study [147]. However, after failure with trastuzumab, recent evidence from phase II clinical trials and retrospective analyses suggested different significance for trastuzumab cross-line application, and more evidence is required [147]. 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 that the indications of trastuzumab analogue HLX02 for HER2-positive breast cancer and the combination of capecitabine/5-FU and cisplatin for newly diagnosed, metastatic, HER2-positive gastric cancer.

[i]No positive response from other HER2-targeted drugs, including pertuzumab (anti-HER2 mAb, JACOB study) [151], lapatinib (small molecule tyrosine kinase inhibitor; LOGIC and TyTAN study) [152, 153], and antibody-drug conjugate (ADC) TDM-1 (drug coupled anti-HER2 mAb) [154], as second-line treatment of metastatic gastric cancer in phase II clinical study was observed. The use of ADCs targeting HER2 remains promising.

[j]Ramucirumab (anti-VEGFR2 mAb) and apatinib mesylate (VEGFR2 small-molecule tyrosine kinase inhibitor) are the common anti-angiogenic drugs for late-stage gastric cancer patients. For metastatic gastric/EGJ adenocarcinoma that progressed after first-line platinum- and/or fluorouracil-based chemotherapy, the

REGARD study [155] showed that ramucirumab monotherapy, compared with placebo, as second-line treatment could prolong the mOS (5.2 vs. 3.8 months, $P = 0.047$). The RAINBOW study [156] showed that compared with paclitaxel alone, second-line ramucirumab combined with paclitaxel could prolong mOS (9.63 vs. 7.36 months, $P = 0.0169$) and had tolerable adverse reactions, which led to the approval of ramucirumab alone or in combination with paclitaxel by the U.S FDA as a second-line treatment for late-stage gastric cancer. A phase III clinical study [157] which enrolled 273 patients who had treatment failure after using second-line/subsequent-lines chemotherapeutic regimens showed that apatinib, compared with the placebo, 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 mesylate is approved for third- or higher lines of treatment in patients with advanced gastric or EGJ adenocarcinoma. The CSCO Anti-tumor Drug Safety management Expert Committee suggests the use of the "Expert Consensus on Clinical Application of Apatinib Mesylate" guidelines to assist clinicians regarding the application and safety of apatinib [158].

[k]Based on the results of prospective clinical studies, immune checkpoint inhibitors have been approved for the third-line treatment of gastric cancer worldwide. In regard to the treatment of Asian populations, results of the ATTRACTION-2 study [159] showed that the risk of death in patients with recurrent or metastatic gastric or EGJ adenocarcinoma when treated with nivolumab as the third-line treatment was significantly lower than that of placebo. The 1-year OS rates of the two groups were 26.2% and 10.9%, respectively. In 2020, the updated 3-year follow-up data in ASCO-GI showed continued survival benefits for patients treated in the nivolumab group [160]. In March 2020, the NMPA of China approved the use of nivolumab for patients with advanced or recurrent gastric/EGJ adenocarcinoma who had received two or more systemic treatment regimens. The results of the KEYNOTE-059 study [161] showed that pembrolizumab as a third-line treatment for recurrent or metastatic adenocarcinoma of gastric/EGJ cancer with PD-L1 CPS $\geq 1$ had an OS of 6 months and overall response rate (ORR) of 12%. At present, the use of PD-1 antibodies in Chinese clinical research of advanced gastric cancer who failed with standard chemotherapy have demonstrated an ORR of 10%-20% and controllable safety.

[l]For second-line treatment using immunotherapy in gastric cancer, a clinical trial that enrolled 11 types of dMMR/MSI-H malignant tumors including gastric cancer that failed conventional treatment showed that treatment with pembrolizumab could be beneficial and was associated with an ORR of 53% and CR of 21% [162]. Results of the KEYNOTE-061 study [31] showed that compared with paclitaxel, the second-line treatment with pembrolizumab did not significantly prolong the OS of patients with PD-L1 CPS $\geq 1$, although follow-up analysis showed that the TMB and PD-L1 CPS scores were related to pembrolizumab benefit, but pembrolizumab had a better safety profile than paclitaxel. The status of immunosuppressive agents in the treatment of late-stage gastric cancer has not been confirmed, and it is not recommended to use immunosuppressive agents alone or as combination in routine practice. Patients are encouraged to participate in relevant clinical studies.

[m]Immunotherapy strategy for gastric cancer includes PD-1 mAb or combination with chemotherapy. For combination therapy, there are three phase III randomized controlled trials that compared PD-1 mAb combined with chemotherapy or chemotherapy alone. Results of the KEYNOTE-062 phase III clinical study [163] showed that for patients with PD-L1 CPS $\geq 1$, pembrolizumab combined with chemotherapy (capecitabine or 5-FU + cisplatin) was not associated with significant OS improvements compared to chemotherapy alone. The CheckMate-649 study [164] showed that for patients with PD-L1 CPS $\geq 5$, the mOS of nivolumab combined chemotherapy (FOLFOX or XELOX) was longer than that of chemotherapy alone (mOS: 14.4 vs. 11.1 months, hazard ratio (HR) = 0.71, $P < 0.0001$); significant survival benefit was also observed in the secondary endpoint group which consisted of OS in all randomized patients and those with a PD-L1 CPS of 1 or greater. Further, combination therapy demonstrated PFS benefit in patients with CPS $\geq 1$ and in all randomized patients, and statistical significance in patients with CPS $\geq 5$ (mPFS = 7.7 vs. 6.0 months, HR = 0.68, $P < 0.0001$). Thus, nivolumab combined with FOLFOX/XELOX is recommended for late-stage gastric cancer with PD-L1 CPS $\geq 5$. The ATTRACTION-4 clinical trial [165], a phase II/III multicenter randomized clinical trial, evaluated the efficacy and safety of nivolumab plus chemotherapy (SOX/XELOX) versus chemotherapy as first-line treatment in patients with HER2-negative, advanced or recurrent gastric/EGJ cancer. The study findings showed that mPFS of the nivolumab plus chemotherapy group was significantly superior to chemotherapy alone (10.5 vs. 8.3 months, HR = 0.68, $P = 0.0007$). Further, the ORR and duration of response (DoR) of the nivolumab plus chemotherapy group was significantly higher than that of the chemotherapy group (ORR, 57.5% vs. 47.8%, $P = 0.0088$). However, it should be noted that the mOS of the two groups was similar (17.45 vs. 17.15 months, HR = 0.90), and in regard to ethnicity, only ~5% of the participants were from Taiwan, China. For patients with unknown PD-L1 status, conventional therapy combined with PD-1 mAb is not recommended.

[n]For first-line use of single-drug immunotherapy in gastric cancer, the KEYNOTE-059 study showed that for patients with PD-L1 CPS $\geq 1$, pembrolizumab was associated with an ORR of 26%, DCR of 36%, mPFS of 3.3 months, and mOS of 20.7 months [161]. The phase III KEYNOTE-062 study showed that for patients with PD-L1 CPS $\geq 1$, the OS of pembrolizumab was not inferior to chemotherapy (10.6 vs. 11.1 months), but crossing of their survival curves was observed, and the risk of progression should be considered [163]. It was suggested that pembrolizumab should be considered only in patients with chemotherapy contraindications or who refused chemotherapy, and careful monitoring of their performance status and nutritional function should be implemented. In MSI-H subgroup, the ORR of the pembrolizumab group was 57.1% (versus chemotherapy, 36.8%) and the mOS was not reached (NR) in both pembrolizumab arms; for comparison, pembrolizumab versus chemotherapy, mOS was NR (95% CI, 10.7 months-NR) versus 8.5 months (95% CI, 5.3-20.8 months), respectively, and mOS was NR (95% CI, 3.6 months-NR) with pembrolizumab plus chemotherapy compared to 8.5 months (95% CI, 5.3-20.8 months) with chemotherapy. In addition, Asian subgroup analysis showed that pembrolizumab monotherapy was associated with superior survival advantages than chemotherapy, with an OS of 22.7 vs. 13.8 for patients with CPS $\geq 1$ and 28.5 vs. 14.8 for patients with CPS <1. Due to the lack of sufficient data on the risk of over-progression with pembrolizumab monotherapy, first-line use of single-drug immunotherapy is not recommended for patients with PD-L1 CPS $\geq 1$ but can be considered if chemotherapy contraindications exist. For MSI-H patients, pembrolizumab monotherapy has shown obvious survival benefit compared with chemotherapy alone, and thus, chemotherapy alone is not recommended in this group of patients.

[o]At present, dMMR/MSI-H is recognized as a predictor for the efficacy of immunotherapy in gastric cancer [162]. The U.S FDA has approved pembrolizumab and nivolumab as second- or third-line treatment for all patients with solid tumors with MSI-H or dMMR. Apart from the above clinical studies in which PD-L1 CPS score was used as a screening criterion, results from the KEYNOTE-061 study [31] showed that for patients with PD-L1 CPS $\geq 1$, 5, and 10, compared with paclitaxel alone, pembrolizumab was associated with an extended OS of 0.8, 1.9, and 2.4 months, respectively, showing an association between PD-L1 CPS score and treatment response, which was also confirmed in the CheckMate649 study [164]. The KEYNOTE-061 study [31] also showed that in patients with high TMB, pembrolizumab was associated with superior ORR, PFS, and OS than paclitaxel. In a Chinese phase II study using toripalimab for the treatment of refractory gastric cancer, the ORR (33.3% vs. 7.1%, $P = 0.017$) and OS (14.6 vs. 4.0 months, $P = 0.038$) of patients with high TMB ($\geq$ 12 muts/Mb) were also found to be significantly better than those of patients with low TMB (<12 muts/Mb) [166].

[p]In a prospective phase II clinical trial from Korea [167] which enrolled 61 metastatic gastric cancer patients treated with pembrolizumab as salvage treatment, in patients with MSI-H or EBV-positive tumors, dramatic responses to pembrolizumab were observed (ORR 85.7% in MSI-H metastatic gastric cancer and ORR 100% in EBV-positive metastatic gastric cancer). Thus, EBV positivity in gastric cancer could be associated with positive response to PD-1 antibody therapy. However,

two observational studies in the Chinese population showed that the effective rate of EBV-positive gastric cancer patients receiving immunosuppressive agents was 33.3% [168, 169]. Therefore, whether EBV infection could be used as a key marker for immunotherapy still needs to be confirmed in prospective studies.

[q]Several phase II studies have shown that combined therapy using anti-HER2 drugs combined with PD-1 antibody or antiangiogenic inhibitor combined with PD-1 antibody could be a potential treatment strategy in HER2-positive gastric cancer patients; i.e., pembrolizumab plus trastuzumab in combination with XELOX for first-line treatment of late-stage gastric cancer (NCT0365326, CTR20182551) [170], and camrelizumab combined with XELOX followed by camrelizumab and apatinib as first-line therapy for advanced or metastatic gastric or gastroesophageal junction cancer [171]. Such regimens are still currently being investigated in stage III clinical trials (NCT03813784, CTR20200660) and are not recommended for routine clinical practice.

### 3.2.2 | 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 postoperative 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 (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 | 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 [45].

[b]Compared with CY0P0, CY1P0 gastric cancer is a stage IV gastric cancer that is technically considered operable but biologically considered unresectable and has a poorer overall prognosis [172]. At present, the initial treatment for patients with CY1P0 tumors is systemic chemotherapy, unless they are symptomatic and require surgery.

A systematic review of 21 studies which comprised of 6499 patients was conducted to evaluate the value of peritoneal cytology as a predictor of staging and survival of gastric cancer and whether positive cytology can improve the prognosis through neoadjuvant therapy [173]. 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 intraperitoneal chemotherapy (IPC) and extensive intraoperative peritoneal lavage (EIPL) have also been shown as effective treatments. 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) [174]. 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 [175]. However, due to inconsistencies in patient selection, treatment purpose (palliative or radical), surgical techniques, use of intraperitoneal chemotherapy, and 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 positive cytology of CY1P0 to negative and can improve their survival. 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 on gastric cancer with positive exfoliative cytology. The CCOG0301 study [176] suggests radical gastrectomy followed by adjuvant S-1 chemotherapy for CY1P0 patients. According to a report [177], 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 metastasis, but it is difficult to eliminate all micrometastases with chemotherapy even if the initial response is satisfactory [178, 179]. 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-line of treatment. 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 cases with gastrointestinal bleeding and/or obstruction, palliative surgery such as primary tumor resection and/or bypass surgery can be considered [180].

[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 trial. Abdominal drainage 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 [181].

### 3.2.3 | Comprehensive treatment of recurrent or solitary distant metastatic gastric cancer[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 [182–184].

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 tumor or PS $\geq$ 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 lesion 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 is individualized decision-making. 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 therapy[a] (Evidence 2B)<br>• Radiotherapy combined with drug therapy[b] (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 studies, single institution and there is a lack of large-scale prospective study. 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) [185]. 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 [186]. 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%, $P = 0.06$) [187].

[c]Recurrence in the remnant stomach after radical gastrectomy usually occurs within 10 years after surgery [188], 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% [189]. 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 [190]. For patients with unresectable tumors and 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 [191]. In the REGATTA study [192], 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 [193], it was reported that 2-3 cycles of sequential chemotherapy with irinotecan and cisplatin before surgery was associated with a clinical effective rate of 56%, R0 resection rate of 65%, and 3-year survival rate of 27%. However, because of high death rate in this study, it was terminated early. The JCOG0405 study [194] 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 [195], docetaxel was added to the S-1 combined with 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 as the first choice for these patients [196]. 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 [197].

[b]Synchronous liver metastasis of gastric cancer refers to the liver metastasis occurring 6 months before, during, or 6 months after surgery [198]. 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 [192]. 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 [199]. 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) [200]. 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 [201]. 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 [202]. 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 CA19-9 levels were important factors for better prognosis in gastric cancer patients with liver metastases who underwent systemic chemotherapy followed by surgery [203]. Findings from an EORTC and JCOG questionnaire survey [204], 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 RFA [205], microwave ablation (MWA) [206], hepatic artery infusion chemotherapy (HAIC) [207], transarterial chemoembolization (TACE) [208] and stereotactic body radiotherapy (SBRT) [209], 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 [210]. 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 [211].

[d]Krukenberg tumors are the metastatic lesion of gastric cancer that have been 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 [212]. 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 [213], while signet ring cell pathology and peritoneal metastasis were the poor prognostic factors [214]. 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.

*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]Liver metastasis discovered more than 6 months after radical gastrectomy is defined as metachronous liver metastasis. Findings from a retrospective study and meta-analysis have shown that patients who underwent hepatectomy for their metachronous lesion had better survival than non-resected tumors, with mOS of 22-26 months versus 3-7 months ($P < 0.001$) [202, 215]. Further, for similar treatment, no difference in survival was found between patients with synchronous and metachronous liver metastases. It was also reported that the prognosis of patients with metachronous liver metastasis was better than those with synchronous liver metastasis [216]. A retrospective study showed that percutaneous RFA for metachronous liver metastases of gastric cancer was limited to patients with a single, unilobar metastasis without extrahepatic metastatic lesions, but combination with systemic chemotherapy was beneficial for the prolongation of OS [217].

[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 [218]. 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 [219].

## 3.3 | Supportive care of gastric cancer

Gastric cancer patients, especially end-stage patients, often suffer from bleeding, obstruction-related pains, malnutrition, fatigue, anorexia, cachexia, etc. The overall goal of supportive care is to prevent, reduce, and relieve gastric cancer-related symptoms, adverse effects and sufferings (physical, social, and psychological), so as to improve the quality of life of the patients, families, and caregivers. Supportive care englobes the entire course of cancer treatment, from diagnosis till the end of life of the patient. It requires interdisciplinary and multimodal treatment, with the oncologist being the main medical personnel but also includes other specialists in the field of gastroenterology, geriatrics, palliative care, pain, nutrition and oncology psychology, physiotherapy, nursing, and other relevant medical personnel. Early multidisciplinary supportive care would not only improve the nutritional and psychological status of patients with advanced gastric cancer but could also significantly prolong their survival time.

### 3.3.1 | Nutritional therapy

| Nutritional therapy category[a] | Recommendations |
|---|---|
| Nutritional risk screening and malnutrition assessment[b] | • Nutritional screening and malnutrition risk 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 food and protein requirement, 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 screening and malnutrition risk 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>• Individualized nutrition plans should be formulated for end-stage patients for reducing symptoms and maintaining body weight<br>• For additional details, refer to the "CSCO guideline of nutritional therapy for patients with malignant tumor"; |
| Patients unable to leave their home[f] | To provide nutritional and rehabilitation guidance. Regular 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 [220]. 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 [221]. 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 [222–224]. 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 [222, 225]. 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 [223, 226]. 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 [223].

[d]The 5-step principle for nutritional treatment starts from diet sensitization, oral nutrition supplement, enteral nutrition, enteral to parenteral nutrition, and finally to parenteral nutrition [227].

[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 gastric tube, intestinal tube, and stoma, should be actively available to support the patient's nutritional requirements. If the symptoms of obstruction and bleeding can be improved with appropriate treatment, transition to higher order physiological eating routes should be carefully assessed via MDT discussion. In the whole process of gastric cancer management, 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 to normal.

[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. Oral nutritional supplements (ONS) should be encouraged and body weight assessment should be performed every 2 weeks [228].

### 3.3.2 | Management of complications

| Bleeding | Obstruction | Pain |
|---|---|---|
| • Endoscopic treatment<br>• Medical therapy<br>• Proton pump inhibitors; Somatostatin;<br>• Transcatheter arterial embolization (TAE);<br>• Palliative gastrectomy | • Intestinal decompression;<br>• Endoscopic treatment;<br>• Gastrojejunostomy;<br>• Gastric/jejunal stoma;<br>• Chemotherapy;<br>• Medical treatment such as analgesia, antiemetic, proton pump inhibition, anticonvulsants; | • Drug therapy: non-opioid analgesics (acetaminophen or NSAID) or opioid analgesics;<br>• Chemotherapy;<br>• External radiation therapy/chemoradiotherapy; |

Hemorrhage is a common symptom of gastric cancer. Acute and severe hemorrhage can be fatal and timely endoscopic assessment and treatment should be performed. The success rate of hemostasis via endoscopy is high (31%-100%), but the hemorrhage recurrence rate is also high (41%-80%) [229]. In case of hemostasis failure with endoscopy, transarterial embolization of the main blood vessels supplying the stomach or palliative gastrectomy can be considered [230]. Radiotherapy can also effectively control hemorrhage, but it takes time to take effect. Proton pump inhibitors are known to be effective but a randomized study from South Korea showed that proton pump inhibitors did not significantly reduce the rate of cancer-related hemorrhage [229].

The aim of relieving digestive tract obstruction is to reduce vomiting and restore enteral nutrition. The most common obstruction of gastric cancer is pyloric obstruction caused by antral carcinoma, cardiac obstruction caused by EGJ carcinoma, and small bowel paralytic obstruction caused by peritoneal metastasis. For resectable gastric cancer, if the above symptoms appear, it is recommended to resect the primary lesion to control and improve the symptoms. For late-stage gastric cancer or patients unsuitable for surgery, gastrointestinal decompression can be performed first, followed by gastroscopy to evaluate the degree of obstruction, so as to determine whether stenting, endoscopic gastrojejunostomy, or ultrasonic gastroscopy-guided gastrojejunostomy can be performed [229]. If it is difficult to pass the gastroscope, surgical intervention such as laparoscopic gastrojejunostomy, gastrojejunostomy, or palliative gastrectomy could be considered [231, 232]. For intestinal paralytic obstruction caused by peritoneal metastasis, it is often accompanied by "frozen basin" and other manifestations, which associates with end-stage disease. If alleviating symptoms by surgery and nutritional therapy is not effective, antispasmodic treatment, inhibition of gastric acid secretion, antiemesis, and analgesia can be offered depending on the patient's condition and requirement.

Patients with gastric cancer often have pain, including cancer pain caused by tumor invasion and metastasis, pain caused by organ involvement, pain-related with treatments such as stent placement, etc. After excluding surgical emergencies such as perforation or obstruction, it is important to determine whether it is cancer pain. 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 World Health Organization (WHO) 3-step pain principle. The main analgesic drugs are opioids, paracetamol, and steroidal anti-inflammatory drugs. The route of administration is usually based on oral administration. In patients with gastrointestinal obstruction, intravenous, subarachnoid, and transvaginal routes can also be considered.

Gastric cancer patients are prone to treatment-related myelosuppression. The related treatments include chemotherapy, targeted therapy, radiotherapy, and immunotherapy. The Common Terminology Criteria for Adverse Events (CTCAE) are commonly used for grading and managing adverse events. For treatment-related myelosuppression, chemotherapy-related anemia should be first excluded, then iron, vitamin B12, and folic acid should be supplemented, especially in patients after gastrectomy. For chemotherapy-related anemia, recombinant erythropoietin (EPO) can be given. EPO suspension can also be given if necessary. For chemotherapy-associated granulocytopenia, recombinant human granulocyte colony-stimulating factor (rhG-CSF) or long-acting rhG-CSF (polyglycosylated rhG-CSF) can be prescribed based on the actual situation, i.e., preventive or therapeutic use. For chemotherapy-related thrombocytopenia, the degree and potential associated risk of the patient's bleeding should be first assessed. Based on the assessment and patient's conditions, measures such as giving thrombopoietin (TPO), interleukin (IL)-11, platelet infusion can be implemented.

## 4 | 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<br>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, and pelvic CT (once every 6-12 months for the 1st year, then once every year)[e];<br>6. Gastroscopy[f];<br>7. Nutritional status monitoring (vitamin B12, iron, etc)[g]; | Once every year for more than 5 years after surgery<br>PET/CT[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<br>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, and pelvic CT (once every 6-12 months for the 1st year, then once every year)[e];<br>6. Gastroscopy[f];<br>7. Nutritional status monitoring (vitamin B12, iron, etc)[g]; | Once every year for more than 5 years after treatment<br>PET/CT[h] |
| New symptoms or symptom deterioration | Follow-up visit at any time | |

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

Abbreviations: PET, positron emission tomography; CT, computed tomography;

**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 [233]. 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 [22]. 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 [22].

[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 [22].

[c]The follow-up for advanced gastric cancer patients irrespective of whether they have had neoadjuvant or adjuvant therapy are the same [22].

[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 [34].

[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 [22, 34, 234, 235].

[f]Gastroscopic follow-up strategy [22, 34, 234]: 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 [22].

[h]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).

# 5 | SCREENING AND DIAGNOSIS OF HEREDITARY GASTRIC CANCER

## 5.1 | Types and definitions of hereditary gastric cancer

The vast majority of gastric cancer are sporadic. About 5%-10% of gastric cancer is considered as familial aggregated gastric cancer, and 1%-3% have a genetic predisposition.

There are three types of hereditary gastric cancer, namely, hereditary diffuse gastric cancer (HDGC), family internal gastric cancer (FIGC), and gastric adenocarcinoma and gastric proximal polyposis of the stomach (GAPPS).

HDGC is an autosomal dominant genetic disease which 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. The detection criteria for HDGC are as follows [236]:

1. HDGC
   a. Criteria for family history:
      - ≥2 cases of gastric cancer in the family regardless of age, with at least one case of diffuse gastric cancer (DGC);
      - ≥1 case of DGC, regardless of age, and ≥1 case of lobular breast cancer at age <70 years in different family members;
      - ≥2 cases of lobular breast cancer in family members <50 years of age.
   b. Criteria for individual case:
      - DGC diagnosis at age <50 years;
      - DGC diagnosis, regardless of age, in individuals of Māori ethnicity;
      - DGC diagnosis, regardless of age, in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate;
      - History of DGC and lobular breast cancer, both diagnosed at an age <70 years old;
      - Bilateral lobular breast cancer, diagnosed at age <70 years old;
      - Gastric *in situ* signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age.
2. FIGC
   The diagnosis of familial intestinal-type gastric cancer 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:
   - 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 familial adenomatous dysplasia (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;

In addition to the three types mentioned above, Lynch's syndrome, Lie Flemeini's syndrome, 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.

## 5.2 | Risk assessment and screening of hereditary gastric cancer

HDGC is an autosomal dominant disease that accounts for <3% of all gastric cancers worldwide. It is mainly caused by germline alterations in *CDH1* (E-cadherin) and *CTNNA1* genes. It has been reported that 30%-50% of HDGC patients have *CDH1* truncated mutation. The cumulative risk of *CDH1* gene mutation carriers, up to 80 years old, having gastric cancer is about 67% in males and 83% in females. Further, female carriers may also have a 60% risk of breast lobular cancer [237].

*CTNNA1* encodes the $\alpha$-catenin protein which is related to cell adhesion. The detection rate of *CTNNA1* in HDGC is ~1% [238]. For *CDH1* and *CTNNA1* non-carriers having a family history of breast cancer or colon cancer, *BRCA1*, *BRCA2*, or Lynch syndrome-related genes such as *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, whilst 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.

### 5.3 | 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 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 |
| Familial adenomatous polyposis/light phenotype FAP (AFAP) | *APC* | Autosomal dominance | • Currently, not enough evidence to suggest screening of 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 |

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

Abbreviations: FAP, familial adenomatous dysplasia;

### 5.4 | Principles of treatment for carriers of CDH1 pathogenic germline gene mutation

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) [236, 238-245].

## 6 | APPENDIX

### 6.1 | 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 8$^{th}$ edition of the AJCC/UICC TNM classification.

## 6.2 | Reference for CT imaging classification of gastric cancer

| cT classification | Pathological definition | Conventional reference signs[a] | Auxiliary reference signs[b] |
|---|---|---|---|
| cT1 | Invasion of the mucosa or submucosa | Continuous and complete low enhancement bands between the high enhancement of the inner part of the tumor and the slightly high enhancement of the outer stomach muscle | The high-enhancement of the cancer does not exceed 50% of the total thickness of the gastric wall [246] |
| cT2 | Invasion of the muscularis propria | Interruption or absence of the low enhancement band in the middle layer of the stomach | The high-enhancement of the cancer exceeding 50% of the total thickness of the gastric wall [246] |
| cT3 | Invasion of the subserosal connective tissue without invading the visceral peritoneum | High enhancement of the tumor showing invasion of the whole layer of the gastric wall | Short thin tubular appearance or blurring of the serosal layer comprising of <1/3 of the total lesion area [247, 248] |
| cT4a | Invasion of the serosa (visceral peritoneum) but not adjacent structures/organs | Irregular or nodular appearance of the serosal surface and densely burred or banded infiltration of the surrounding fat space | A hyperattenuating serosa sign [249], serosal exposure grading [250], extension from the outer gastric wall reaching beyond the perigastric vascular plane [251] |
| cT4b | Invasion of adjacent structures/organs | Finger-like or direct infiltration showing signs of invasion of the fat space with adjacent organs | |
| cN | Classified as N0-N3 based on the number of metastatic lymph nodes | Short diameter of circular enlarged lymph node >1 cm [5] | High or uneven enhancement, CT attenuation, short-to-long axis ratios, nodal clusterations [252, 253] |

Abbreviations: c, clinical; T, tumor classification; N, nodal classification; CT, computed tomography; CT report description should contain the following descriptions[c]:

1. Primary lesion observations:
   (i) Location (EGJ, fundus, body, antrum, pyloric canal, greater curvature, lesser curvature, anterior wall, posterior wall);
   (ii) Distal and proximal boundary (Siewert classification should be reported for carcinoma of EGJ);
   (iii) Morphology (mass, localized ulcer, infiltrative ulcer, diffuse thickening), thickness, enhancement features, depth of invasion, mucosal and serosal surface;
   (iv) Relationship with adjacent organs.
2. Lymph node observations:
   (i) Number of lymph nodes with clear signs of metastasis (or the number range of N staging);
   (ii) Length and diameter of the largest lymph nodes;
   (iii) Shape, boundary, and enhancement of the lymph nodes.
3. Metastasis status:
   (i) Location, distribution, shape, size, density, and enhancement characteristics of the metastasis;
   (ii) Peritoneal morphology;
   (iii) Presence of ascites.

**Notes**

[a]Referential use for clinical T staging. The accuracy of T staging is 70%-90% [4, 246, 254], and N staging is 60%-70% [4, 248].

[b]Atypical, uncommon signs or signs without large sample and multicenter clinical validation. Can be used as a reference for staging atypical cases.

[c]Mainly involved in the Borrmann classification and cTNM staging, and applied according to tumor location and progression.

## 6.3 | Assessment of treatment response. The tumor regression grade criteria

| Tumor regression grade | Description |
|---|---|
| 0 (complete response) | Absence of viable cancer cells, including lymph nodes |
| 1 (near-complete response) | Presence of single cells or few small groups of cancer cells |
| 2 (partial response) | Presence of residual cancer cells with evident tumor regression but a larger number of single cells or groups of cancer cells |
| 3 (poor or no response) | Presence of extensive residual cancer without evident tumor regression |

**Note**:

1. The tumor regression score mainly applies to primary tumor lesion.
2. Cancer cells refer to live cancer cells excluding regressions and necrotic cells.
3. Large acellular mucus-like appearances could be observed after radiotherapy/chemotherapy and should not be confused with residual tumor.

## 6.4 | 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-analysis, and/or large-scale, randomized controlled clinical trials | Uniform consensus achieved (support level: ≥80%) |
| 1B | High | Based on data from well-structured and rigorously controlled meta-analysis, and/or large-scale, randomized controlled clinical trials | Consensus achieved 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 achieved (support level: ≥80%) |
| 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 achieved 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 reached and had major disagreement (support level: <60%) |

**Criteria for the Recommendation grades of CSCO Clinical Practice Guidelines**

| Recommendation grade | Criteria |
|---|---|
| Grade I | Evidence level 1A and some Evidence level 2A:<br>Grade I recommendations include Evidence level 1A and some Evidence level 2A which obtained high consensus from the expert panel and has suitable applicability for Chinese gastric cancer patients.<br>Specifically, in the CSCO Guidelines, Grade I recommendations include the following: universally accepted measures with clear indications for diagnosis and treatment, has adequate applicability for Chinese gastric cancer patients, and is included in the National Reimbursement Drug List (NRDL). The priority for allocating Grade I recommendations is solely for the benefits of the patients and is independent of changes regarding commercial medical insurance. |
| Grade II | Evidence level 1B and some Evidence level 2A:<br>Grade II recommendations include Evidence level 1B and some Evidence level 2A which obtained satisfactory consensus with minimum disagreements from the expert panel and has limited applicability for Chinese gastric cancer patients.<br>Specifically, Grade II recommendations include the following: high-level evidence provided by multi-center studies that have been randomly controlled internationally or domestically (in China), but may have limited applicability for Chinese patients or low potency ratio, in addition to drugs or treatments that may exceed the purchasing power of the general public of gastric cancer patients; treatments that are expensive but may have substantial benefits for the patients are also regarded as Grade II recommendations. |
| Grade III | Evidence level 2B and 3:<br>Despite the lack of strong evidence-based data, however, these are recommendations that have obtained satisfactory consensus with minimum disagreements from the expert panel and are provided as a reference for medical personnel usage. |
| Not recommended/objection | Recommendations for which the expert panel has uniform consensus that adequate evidence to prove that the drugs or medical technologies do not have sufficient benefits or may even cause harm to Chinese patients. These are labeled as "experts do not recommend" or, when applicable as "experts' disapproval". It can be allocated to any grade recommendations. |

## AUTHOR CONTRIBUTIONS

Conception and design of the guidelines: Xu RH; Shen Lin; Li Jin; Zhou ZW; Liang Han; Ji JF; Li GX; Xu HM.

Manuscript writing: Wang FH; Zhang XT; Tang Lei; Xin Yan; Jin Jing; Zhang YJ; Yuan XL; Liu TS; Wu Qi; Li YF; Wang X; Yu S; Li Hao

Assembly of data: Guan WL

Final approval of manuscript: All authors

## CONSENT FOR PUBLICATION

This paper was first published in Chinese by the Beijing: People's Medical Publishing House, entitled the "Guideline of Chinese Society of Clinical Oncology (CSCO): Gastric Cancer. 2021" from the Committee on Guidelines of Chinese Society of Clinical Oncology. With appropriate permission, this English version is published in *Cancer Communications*.

## ACKNOWLEDGMENTS

We also thank Dr. Sharvesh Raj Seeruttun for his contribution to translating and revising this guideline.

## FUNDING

None to be declared.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## DATA AVAILABILITY STATEMENT

Not applicable.

## REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F.Global Cancer Statistics 2020.GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. He Y, Wang Y, Luan F, Yu Z, Feng H, Chen B, Chen W. Chinese and global burdens of gastric cancer from 1990 to 2019. Cancer Med 2021;10(10):3461–73.
3. Cao W, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J. 2021;134(7):783–91.
4. Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer. 2012;15(1):S3–18.

5. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. AJCC Cancer Staging Manual, 8th ed. Springer, New York 2017.
6. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Association of Upper Gastrointestinal Surgeons of Great B, Ireland tBSoG, the British Association of Surgical O: Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449–72.
7. Dong L, Neuzil J. Targeting mitochondria as an anticancer strategy. Cancer Commun. 2019;39(1):63.
8. Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer. Cochrane Database Syst Rev. 2015;(2):CD009944.
9. Kim YK, Lee MW, Lee WJ, Kim SH, Rhim H, Lim JH et al. Diagnostic accuracy and sensitivity of diffusion-weighted and of gadoxetic acid-enhanced 3-T MR imaging alone or in combination in the detection of small liver metastasis (</= 1.5 cm in diameter). Invest Radiol. 2012;47(3):159–66.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.
11. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e152.
12. Wang ZC, Wang C, Ding Y, Ji Y, Zeng MS, Rao SX.CT volumetry can potentially predict the local stage for gastric cancer after chemotherapy. Diagn Interv Radiol. 2017;23(4):257–62.
13. Giganti F, De Cobelli F, Canevari C, Orsenigo E, Gallivanone F, Esposito A, et al. Response to chemotherapy in gastric adenocarcinoma with diffusion-weighted MRI and (18) F-FDG-PET/CT: correlation of apparent diffusion coefficient and partial volume corrected standardized uptake value with histological tumor regression grade. J Magn Reson Imaging. 2014;40(5):1147–57.
14. Tang L, Li ZY, Li ZW, Zhang XP, Li YL, Li XT, et al. Evaluating the response of gastric carcinomas to neoadjuvant chemotherapy using iodine concentration on spectral CT: a comparison with pathological regression. Clin Radiol. 2015;70(11):1198–1204.
15. Jiang Y, Jin C, Yu H, Wu J, Chen C, Yuan Q, et al. Development and Validation of a Deep Learning CT Signature to Predict Survival and Chemotherapy Benefit in Gastric Cancer: A Multicenter, Retrospective Study. Ann Surg. 2020.
16. Xu G, Zhang W, Lv Y, Zhang B, Sun Q, Ling T, et al. Risk factors for under-diagnosis of gastric intraepithelial neoplasia and early gastric carcinoma in endoscopic forceps biopsy in comparison with endoscopic submucosal dissection in Chinese patients. Surg Endosc. 2016;30(7):2716–22.
17. Zhou PH, Schumacher B, Yao LQ, Xu MD, Nordmann T, Cai MY, et al. Conventional vs. waterjet-assisted endoscopic submucosal dissection in early gastric cancer: a randomized controlled trial. Endoscopy. 2014;46(10):836–43.
18. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. In: 4th edn. France: IARC Press, 2010.
19. Nagtegaal I, Odze R, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2019;76.
20. Sun Q, Fan XS, Huang Q. Suggestions on the pathological standardization of endoscopic mucosal dissection specimens for early proximal gastric cancer and precancerous lesions (Chinese). Zhonghua Xiaohua Neijing Zazhi 2016;33(9):585–88.
21. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. Acta Pathol Microbiol Scand 1965;64:31-49.
22. Ajani J, D'Amico T, Baggstrom M, Bentrem D, Chao J, Das P, et al. Gastric Cancer (Version 1, 2020). NCCN Clinical Practice Guidelines in Oncology. In; 2020.
23. Xue WC, Fan XS, Meng G. Expert Committee Consensus. Selection of immunohistochemical markers for gastric cancer (2014) (Chinese). Linchuang yu Shiyan Binglixue Zazhi. 2014;000(009):951–3.
24. Expert Committee on Safety Management of Anti-neoplastic Drugs of Chinese Society of Clinical Oncology, Society of Gastric Cancer of Chinese Anti-Cancer Association, Society of Pathology of Chinese Anti-Cancer Association. Consensus of Chinese experts on molecular targeted therapy for HER2 positive advanced gastric cancer (2016) (Chinese). Linchuang Zhongliuxue Zazhi. 2016;21(9):831–9.
25. Sheng WQ, Huang D, Ying JM, Lu N, Wu HM, Liu YH, et al. Du X: HER2 status in gastric cancers: a retrospective analysis from four Chinese representative clinical centers and assessment of its prognostic significance. Ann Oncol. 2013;24(9):2360–4.
26. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376(9742):687–97.
27. Qiu MZ, Li Q, Wang ZQ, Liu TS, Liu Q, Wei XL, et al. HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: a prospective cohort observation. Int J Cancer. 2014;134(10):2468–77.
28. Wang DS, Liu ZX, Lu YX, Bao H, Wu X, Zeng ZL, et al. Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer. Gut. 2019;68(7):1152–61.
29. Wang H, Li B, Liu Z, Gong J, Shao L, Ren J, et al. HER2 copy number of circulating tumour DNA functions as a biomarker to predict and monitor trastuzumab efficacy in advanced gastric cancer. Eur J Cancer. 2018;88:92–100.
30. Expert Committe Consensus. Guidelines for HER2 detection in gastric cancer (2016) (Chinese). Zhonghua Binglixue Zazhi. 2016;45 (8):528–32.
31. Shitara K, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392(10142):123–33.
32. Gotoda T. Endoscopic resection of early gastric cancer. Gastric Cancer. 2007;10(1):1–11.
33. Hasuike N, Ono H, Boku N, Mizusawa J, Takizawa K, Fukuda H, et al. A non-randomized confirmatory trial of an expanded

indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): the Japan Clinical Oncology Group study (JCOG0607). Gastric Cancer. 2018;21(1):114–23.
34. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2021;24(1):1–21.
35. Abdelfatah MM, Barakat M, Lee H, Kim JJ, Uedo N, Grimm I, Othman MO. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. Gastrointest Endosc. 2018, 87(2):338–47.
36. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, et al. A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: "eCura system". Am J Gastroenterol. 2017;112(6):874–81.
37. National Health and Family Planning Commission of the People's Republic of China. Guidelines for standardized diagnosis and treatment of gastric cancer (trial implementation) (Chinese). Manxingbingxue Zazhi. 2013(10):47–51.
38. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20(1):1–19.
39. Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, et al. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. Lancet Oncol. 2006;7(8):644–51.
40. Biondi A, D'Ugo D, Cananzi FC, Papa V, Borasi A, Sicoli F, et al. Does a minimum number of 16 retrieved nodes affect survival in curatively resected gastric cancer?. Eur J Surg Oncol. 2015;41(6):779–86.
41. Zhang CH, Wu AW, Li ZY, Zhang LH, Bu ZD, Wu XJ, et al. Analysis of splenic hilar lymph node metastasis in advanced gastric cancer and dissection techniques (Chinese). Zhonghua Wei Chang Wai Ke Za Zhi. 2011;14(8):589–92.
42. Sasada S, Ninomiya M, Nishizaki M, Harano M, Ojima Y, Matsukawa H, et al. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. Anticancer Res. 2009, 29(8):3347–51.
43. Aoyagi K, Kouhuji K, Miyagi M, Imaizumi T, Kizaki J, Shirouzu K.: Prognosis of metastatic splenic hilum lymph node in patients with gastric cancer after total gastrectomy and splenectomy. World J Hepatol. 2010;2(2):81–6.
44. Sano T, Sasako M, Mizusawa J, Yamamoto S, Katai H, Yoshikawa T, et al. Randomized Controlled Trial to Evaluate Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma. Ann Surg. 2017;265(2):277–83.
45. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14(2):101–12.
46. Jiao X, Liang H, Deng J, Wang L, Liu H, Liang Y. Analysis of risk factors for station 14v lymph node metastasis in advanced gastric cancer (Chinese). Zhonghua Xiaohua Waike Zazhi. 2014;13(1):30–3.
47. Liang YX, Liang H, Ding XW, Wang XN, Wu LL, Liu HG, et al. Significance of station 14v lymph node dissection for patients with advanced gastric cancer undergoing D2 lymphadenectomy (Chinese). Zhonghua Wei Chang Wai Ke Za Zhi. 2013;16(7):632–6.
48. Eom BW, Joo J, Kim YW, Reim D, Park JY, Yoon HM, et al. Improved survival after adding dissection of the superior mesenteric vein lymph node (14v) to standard D2 gastrectomy for advanced distal gastric cancer. Surgery 2014;155(3):408–16.
49. Shen DF, Chen DW, Quan ZW, Dong P, Wang XF, Xu HZ, et al. Dissection of No. 13 lymph node in radical gastrectomy for gastric carcinoma. World J Gastroenterol. 2008;14(6):936–8.
50. Eom BW, Joo J, Kim YW, Park B, Park JY, Yoon HM, et al. Is there any role of additional retropancreatic lymph node dissection on D2 gastrectomy for advanced gastric cancer? Ann Surg Oncol. 2013;20(8):2669–75.
51. Eto K, Hiki N, Kumagai K, Shoji Y, Tsuda Y, Kano Y, et al. Prophylactic effect of neoadjuvant chemotherapy in gastric cancer patients with postoperative complications. Gastric Cancer. 2018;21(4):703–9.
52. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359(5):453–62.
53. Katai H, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. Lancet Gastroenterol Hepatol. 2020;5(2):142–51.
54. Kim HH, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. JAMA Oncol. 2019;5(4):506–13.
55. Hyung WJ, Yang HK, Han SU, Lee YJ, Park JM, Kim JJ, et al. A feasibility study of laparoscopic total gastrectomy for clinical stage I gastric cancer: a prospective multi-center phase II clinical trial, KLASS 03. Gastric Cancer. 2019;22(1):214–22.
56. Katai H, Mizusawa J, Katayama H, Kunisaki C, Sakuramoto S, Inaki N, et al. Single-arm confirmatory trial of laparoscopy-assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG1401. Gastric Cancer. 2019;22(5):999–1008.
57. Liu F, Huang C, Xu Z, Su X, Zhao G, Ye J, et al. Morbidity and Mortality of Laparoscopic vs Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASS02 Multicenter Randomized Clinical Trial. JAMA Oncol. 2020;6(10):1590–7.
58. Yu J, Huang C, Sun Y, Su X, Cao H, Hu J, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. JAMA. 2019;321(20):1983–92.
59. Hyung WJ, Yang HK, Park YK, Lee HJ, An JY, Kim W, et al. Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial. J Clin Oncol. 2020;38(28):3304–13.
60. Li Z, Shan F, Ying X, Zhang Y, E J-E, Wang Y, et al. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. JAMA Surg. 2019;154(12):1093–1101.
61. Chen QY, Xie JW, Zhong Q, Wang JB, Lin JX, Lu J, et al. Safety and Efficacy of Indocyanine Green Tracer-Guided Lymph Node Dissection During Laparoscopic Radical Gastrectomy in

Patients With Gastric Cancer: A Randomized Clinical Trial. JAMA Surg. 2020;155(4):300–11.
62. Shin HJ, Son SY, Wang B, Roh CK, Hur H, Han SU.: Long-term Comparison of Robotic and Laparoscopic Gastrectomy for Gastric Cancer: A Propensity Score-weighted Analysis of 2084 Consecutive Patients. Ann Surg. 2020.
63. Lu J, Zheng CH, Xu BB, Xie JW, Wang JB, Lin JX, et al. Assessment of Robotic Versus Laparoscopic Distal Gastrectomy for Gastric Cancer: A Randomized Controlled Trial. Ann Surg. 2021;273(5):858–67.
64. Kang KC, Cho GS, Han SU, Kim W, Kim HH, Kim MC, et al. Comparison of Billroth I and Billroth II reconstructions after laparoscopy-assisted distal gastrectomy: a retrospective analysis of large-scale multicenter results from Korea. Surg Endosc. 2011;25(6):1953–61.
65. Shiraishi N, Hirose R, Morimoto A, Kawano K, Adachi Y, Kitano S. Gastric tube reconstruction prevented esophageal reflux after proximal gastrectomy. Gastric Cancer. 1998;1(1):78–9.
66. Kim HH, Han SU, Kim MC, Hyung WJ, Kim W, Lee HJ, et al. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. J Clin Oncol. 2014;32(7):627–33.
67. Nunobe S, Okaro A, Sasako M, Saka M, Fukagawa T, Katai H, et al. Billroth 1 versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years. Int J Clin Oncol. 2007;12(6):433–9.
68. Liang H. Visual Lectures on Operation For Gastric Cancer (Chinese), May 1, 2013 edn: Tianjin Science and Technology Translation Publishing Co., Ltd; 2013.
69. Fein M, Fuchs KH, Thalheimer A, Freys SM, Heimbucher J, Thiede A. Long-term benefits of Roux-en-Y pouch reconstruction after total gastrectomy: a randomized trial. Ann Surg. 2008;247(5):759–65.
70. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315–21.
71. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30(3):268–73.
72. Yoshida K, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, et al. Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07, a Randomized Controlled Trial. J Clin Oncol. 2019;37(15):1296–1304.
73. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29(33):4387–93.
74. Kodera Y, Yoshida K, Kochi M, Ichikawa W, Kakeji Y, Sano T, et al. A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected stage III gastric cancer (JACCRO GC-07 trial). J Clin Oncol. 2018;36(15):4007.
75. Ji J, Shen L, Li Z, Zhang X, Liang H, Xue Y, et al. Perioperative Chemotherapy of Oxaliplatin Combined with S-1 (SOX) versus Postoperative Chemotherapy of SOX or Oxaliplatin with Capecitabine (XELOX) in Locally Advanced Gastric Adenocarcinoma with D2 Gastrectomy: a Randomized Phase III Trial (RESOLVE Trial). Ann Oncol. 2019;30(5):v851–v934. 101093/annonc/mdz394 2019.
76. Park SH, Zang DY, Han B, Ji JH, Kim TG, Oh SY, et al. ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC). J Clin Oncol. 2019;37(15):4001.
77. Wang ZX, Li GX, Zhou ZW, Huang ZP, Wang F, Xu RH. Validation of a nomogram for selecting patients for chemotherapy after D2 gastrectomy for cancer. Br J Surg. 2017;104(9):1226–34.
78. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725–30.
79. Stiekema J, Trip AK, Jansen EP, Boot H, Cats A, Ponz OB, et al. The prognostic significance of an R1 resection in gastric cancer patients treated with adjuvant chemoradiotherapy. Ann Surg Oncol. 2014;21(4):1107–14.
80. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine. N Engl J Med. 2007;357(18):1810–20.
81. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
82. D'Ugo D, Rausei S, Biondi A, Persiani R. Preoperative treatment and surgery in gastric cancer: friends or foes? Lancet Oncol. 2009;10(2):191–5.
83. Kim YW, Kim MJ, Ryu KW, Lim HS, Lee JH, Kong SY, et al. A phase II study of perioperative S-1 combined with weekly docetaxel in patients with locally advanced gastric carcinoma: clinical outcomes and clinicopathological and pharmacogenetic predictors for survival. Gastric Cancer. 2016;19(2):586–96.
84. Wang X, Zhao L, Liu H, Zhong D, Liu W, Shan G, et al. A phase II study of a modified FOLFOX6 regimen as neoadjuvant chemotherapy for locally advanced gastric cancer. Br J Cancer. 2016;114(12):1326–33.
85. Kang YK, Yook JH, Park YK, Kim YW, Kim J, Ryu MH, et al. LBA41 - Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY). Ann Oncol. 2019;30:v876–v877.
86. Sumpter K, Harper-Wynne C, Cunningham D, Rao S, Tebbutt N, Norman AR, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer. 2005;92(11):1976–83.
87. Li ZY, Koh CE, Bu ZD, Wu AW, Zhang LH, Wu XJ, et al. Neoadjuvant chemotherapy with FOLFOX: improved outcomes in Chinese patients with locally advanced gastric cancer. J Surg Oncol. 2012;105(8):793–9.

88. Kochi M, Fujii M, Kanamori N, Mihara Y, Funada T, Tamegai H, et al. Phase II Study of Neoadjuvant Chemotherapy With S-1 and CDDP in Patients With Lymph Node Metastatic Stage II or III Gastric Cancer. Am J Clin Oncol. 2017;40(1):17–21.
89. Li T, Chen L. Efficacy and safety of SOX regimen as neoadjuvant chemotherapy for advanced gastric cancer (Chinese). Zhonghua Wei Chang Wai Ke Za Zhi. 2011;14(2):104–6.
90. Al-Batran S-E, Homann N, Schmalenberg H, Kopp H-G, Haag GM, Luley KB, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. J Clin Oncol. 2017;35(15):4004.
91. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, Meershoek-Klein Kranenbarg E, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):616–28.
92. Mita K, Ito H, Katsube T, Tsuboi A, Yamazaki N, Asakawa H, et al. Prognostic Factors Affecting Survival After Multivisceral Resection in Patients with Clinical T4b Gastric Cancer. J Gastrointest Surg. 2017;21(12):1993–9.
93. Roberts P, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. Systematic review of pancreaticoduodenectomy for locally advanced gastric cancer. Gastric Cancer. 2012;15(1):S108–115.
94. Xiao L, Li M, Xu F, Ye H, Wu W, Long S, et al. Extended multiorgan resection for cT4 gastric carcinoma: A retrospective analysis. Pak J Med Sci. 2013;29(2):581–5.
95. Pietrantonio F, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, et al. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer. J Clin Oncol. 2019;37(35):3392–3400.
96. Bajetta E, Floriani I, Di Bartolomeo M, Labianca R, Falcone A, Di Costanzo F, et al. Randomized trial on adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus 5-fluorouracil and folinic acid for radically resected gastric cancer. Ann Oncol. 2014;25(7):1373–8.
97. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851–6.
98. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol. 2006;24(24):3953–8.
99. Leong T, Smithers BM, Michael M, Gebski V, Boussioutas A, Miller D, et al. TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). BMC Cancer. 2015;15:532.
100. Slagter AE, Jansen EPM, van Laarhoven HWM, van Sandick JW, van Grieken NCT, Sikorska K, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. BMC Cancer. 2018;18(1):877.
101. Neoadjuvant Chemoradiotherapy vs. Chemotherapy With Radical Gastrectomy and Adjuvant Chemotherapy for Advanced Gastric Cancer (Neo-CRAG) (ClinicalTrials.gov Identifier: NCT01815853). https://www.clinicaltrials.gov/ct2/show/NCT01815853. In.
102. Li T, Chen L.: Randomized, multicenter, controlled evaluation of S-1 and oxaliplatin (SOX regimen) as neoadjuvant chemotherapy for advanced gastric cancer patients (RESONANCE trial). J Clin Oncol. 2014;32(3):90.
103. Wang Y, Cheng X, Cui YH, Hou J, Ji Y, Sun YH, et al. Efficacy after preoperative capecitabine and oxaliplatin (XELOX) versus docetaxel, oxaliplatin and S1 (DOS) in patients with locally advanced gastric adenocarcinoma: a propensity score matching analysis. BMC Cancer. 2018;18(1):702.
104. Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. Am J Surg. 2006;191(1):134–38.
105. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715–21.
106. Petrelli F, Ghidini M, Barni S, Sgroi G, Passalacqua R, Tomasello G.Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Gastric Cancer. 2019;22(2):245.
107. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
108. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086–92.
109. Khushalani NI, Leichman CG, Proulx G, Nava H, Bodnar L, Klippenstein D, et al. Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. J Clin Oncol. 2002;20(12):2844–50.
110. Ajani JA, Mansfield PF, Crane CH, Wu TT, Lunagomez S, Lynch PM, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol. 2005;23(6):1237–44.
111. Hu JB, Sun XN, Gu BX, Wang Q, Hu WX. Effect of intensity modulated radiotherapy combined with s-1-based chemotherapy in locally advanced gastric cancer patients. Oncol Res Treat. 2014;37(1-2):11–6.
112. Inoue T, Yachida S, Usuki H, Kimura T, Hagiike M, Okano K, et al. Pilot feasibility study of neoadjuvant chemoradiotherapy with S-1 in patients with locally advanced gastric cancer featuring adjacent tissue invasion or JGCA bulky N2 lymph node metastases. Ann Surg Oncol. 2012;19(9):2937–45.

113. Wang X, Zhao DB, Jin J, Chi Y, Yang L, Tang Y, et al. A Randomized Phase II Trial of Neoadjuvant Chemotherapy Compared With Chemoradiation Therapy in Locally Advanced Gastroesophageal and Gastric Adenocarcinoma: Preliminary Results. Int J Radiat Oncol Biol Phys. 2016;96(2):S32.
114. Wang X, Zhao DB, Yang L, Chi Y, Tang Y, Li N, et al. S-1 chemotherapy and intensity-modulated radiotherapy after D1/D2 lymph node dissection in patients with node-positive gastric cancer: a phase I/II study. Br J Cancer. 2018;118(3):338–43.
115. Ajani JA, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol. 2004;22(14):2774–80.
116. A comparison of combination chemotherapy and combined modality therapy for locally advanced gastric carcinoma. Gastrointestinal Tumor Study Group. Cancer. 1982;49(9):1771–7.
117. Gunderson LL, Hoskins RB, Cohen AC, Kaufman S, Wood WC, Carey RW. Combined modality treatment of gastric cancer. Int J Radiat Oncol Biol Phys. 1983;9(7):965–75.
118. Li R, Hou WH, Chao J, Woo Y, Glaser S, Amini A, et al. Chemoradiation Improves Survival Compared With Chemotherapy Alone in Unresected Nonmetastatic Gastric Cancer. J Natl Compr Canc Netw 2018;16(8):950–58.
119. Mizrak Kaya D, Nogueras-Gonzáles GM, Harada K, Amlashi FG, Thomas I, Rogers JE, et al. Potentially curable gastric adenocarcinoma treated without surgery. Eur J Cancer. 2018;98:23–9.
120. Moertel CG, Childs DS, Jr., Reitemeier RJ, Colby MY, Jr., Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet. 1969;2(7626):865–7.
121. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24(18):2903–9.
122. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26(9):1435–42.
123. Hiramoto S, Kikuchi A, Tetsuso H, Yoshioka A, Kohigashi Y, Maeda I. Efficacy of palliative radiotherapy and chemoradiotherapy for unresectable gastric cancer demonstrating bleeding and obstruction. Int J Clin Oncol. 2018;23(6):1090–4.
124. Coia LR, Paul AR, Engstrom PF. Combined radiation and chemotherapy as primary management of adenocarcinoma of the esophagus and gastroesophageal junction. Cancer. 1988;61(4):643–9.
125. Kim MM, Rana V, Janjan NA, Das P, Phan AT, Delclos ME, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol. 2008;47(3):421–7.
126. Minn AY, Hsu A, La T, Kunz P, Fisher GA, Ford JM, et al. Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. Cancer. 2010;116(16):3943–52.
127. Wang X, Li G, Zhang Y, Bai S, Xu F, Wei Y, Gong Y. Single-arc volumetric-modulated arc therapy (sVMAT) as adjuvant treatment for gastric cancer: dosimetric comparisons with three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). Med Dosim. 2013;38(4):395–400.
128. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20(4):666–73.
129. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215–21.
130. Luo HY, Xu RH, Wang F, Qiu MZ, Li YH, Li FH, et al. Phase II trial of XELOX as first-line treatment for patients with advanced gastric cancer. Chemotherapy. 2010;56(2):94–100.
131. Lu Z, Zhang X, Liu W, Liu T, Hu B, Li W, et al. A multicenter, randomized trial comparing efficacy and safety of paclitaxel/capecitabine and cisplatin/capecitabine in advanced gastric cancer. Gastric Cancer. 2018;21(5):782–91.
132. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24(31):4991–7.
133. Wang J, Xu R, Li J, Bai Y, Liu T, Jiao S, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. Gastric Cancer. 2016;19(1):234–44.
134. Xu RH, Wang ZQ, Shen L, Wang W, Lu JW, Dai GH, et al. S-1 plus oxaliplatin versus S-1 plus cisplatin as first-line treatment for advanced diffuse-type or mixed-type gastric/gastroesophageal junction adenocarcinoma: A randomized, phase 3 trial. J Clin Oncol. 2019;37(15):4017.
135. Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol. 2015;26(1):141–8.
136. Hall PS, Swinson D, Waters JS, Wadsley J, Falk S, Roy R, et al. Optimizing chemotherapy for frail and elderly patients (pts) with advanced gastroesophageal cancer (aGOAC): The GO2 phase III trial. J Clin Oncol. 2019;37(15):4006.
137. Lin R, Chen Y, Zhu J, Lin P, Chen W, Fang W, et al. POF (paclitaxel plus FOLFOX) versus IP PAC (intraperitoneal paclitaxel plus FOLFOX) versus FOLFOX as a first-line treatment in advanced gastric cancer (AGC): Update from a multicenter, randomized phase II trial, FNF-004 trial. J Clin Oncol. 2019;37(15):4035.
138. Yamada Y, Boku N, Mizusawa J, Iwasa S, Kadowaki S, Nakayama N, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4(7):501–10.
139. Van Cutsem E, Boni C, Tabernero J, Massuti B, Middleton G, Dane F, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol. 2015;26(1):149–56.

140. He MM, Zhang DS, Wang F, Wang ZX, Yuan SQ, Wang ZQ, et al. Phase II trial of S-1 plus leucovorin in patients with advanced gastric cancer and clinical prediction by S-1 pharmacogenetic pathway. Cancer Chemother Pharmacol. 2017;79(1):69–79.
141. Zhou CF, Ma T, Su Y, Ye ZB, Ji J, Yu YY, et al. UGT1A1 gene polymorphisms and the toxicities of FOLFIRI in Chinese Han patients with gastrointestinal cancer. Anticancer Agents Med Chem. 2013;13(2):235–41.
142. Hwang IG, Ji JH, Kang JH, Lee HR, Lee HY, Chi KC, et al. A multi-center, open-label, randomized phase III trial of first-line chemotherapy with capecitabine monotherapy versus capecitabine plus oxaliplatin in elderly patients with advanced gastric cancer. J Geriatr Oncol. 2017;8(3):170–5.
143. Hall PS, Lord SR, Collinson M, Marshall H, Jones M, Lowe C, et al.: A randomised phase II trial and feasibility study of palliative chemotherapy in frail or elderly patients with advanced gastroesophageal cancer (321GO). Br J Cancer. 2017;116(4):472.
144. Hawkes E, Okines AF, Papamichael D, Rao S, Ashley S, Charalambous H, et al. Docetaxel and irinotecan as second-line therapy for advanced oesophagogastric cancer. Eur J Cancer. 2011;47(8):1146–51.
145. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013;31(35):4438–44.
146. Shitara K, Takashima A, Fujitani K, Koeda K, Hara H, Nakayama N, et al. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2017;2(4):277–87.
147. Li Q, Jiang H, Li H, Xu R, Shen L, Yu Y, et al. Efficacy of trastuzumab beyond progression in HER2 positive advanced gastric cancer: a multicenter prospective observational cohort study. Oncotarget. 2016;7(31):50656–65.
148. Nishikawa K, Takahashi T, Takaishi H, Miki A, Noshiro H, Yoshikawa T, et al. Phase II study of the effectiveness and safety of trastuzumab and paclitaxel for taxane- and trastuzumab-naive patients with HER2-positive, previously treated, advanced, or recurrent gastric cancer (JFMC45-1102). Int J Cancer. 2017;140(1):188–96.
149. Qin S, Ji J, Xu R-h, Wang W, Tang Y, Bi F, et al. Treatment patterns and outcomes in Chinese gastric cancer by HER2 status: A non-interventional registry study (EVIDENCE). J Clin Oncol. 2019;37(15):4025.
150. Qin S, Ji J, Xu RH, Wang W, Tang Y, Bi F, et al. Treatment patterns and outcomes in Chinese gastric cancer patients by HER2 status: a non-interventional registry study (EVIDENCE). Oncologist. 2021.
151. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–1384.
152. Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC–A Randomized Phase III Trial. J Clin Oncol. 2016;34(5):443–51.
153. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN–a randomized, phase III study. J Clin Oncol. 2014;32(19):2039–49.
154. Kang Y-K, Shah MA, Ohtsu A, Cutsem EV, Ajani JA, Horst Tvd, et al. Thuss-Patience PC: A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC). J Clin Oncol. 2016;34(4):5.
155. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
156. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.
157. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J Clin Oncol. 2016;34(13):1448–54.
158. Qin SK, Li J. Expert Committe Consensus. Clinical application of apatinib in the treatment of gastric cancer (Chinese). Linchuang Zhongliuxue Zazhi. 2015;000(009):841–7.
159. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461–71.
160. Boku N, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, et al. Nivolumab in previously treated advanced gastric cancer (ATTRACTION-2): 3-year update and outcome of treatment beyond progression with nivolumab. Gastric Cancer. 2021.
161. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018;4(5):e180013.
162. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–13.
163. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The

KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020;6(10):1571–80.
164. Moehler M, Shitara K, Garrido M, Salman P, Shen L, Wyrwicz L, et al. LBA6_PR - Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. Ann Oncol. 2020;31(4):S1142-S1215. https://doi.org/10.1016/annonc/annonc325
165. Boku N, Ryu MH, Oh DY, Oh SC, Chung HC, Lee KW, et al. LBA7_PR Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. Ann Oncol. 2020;31:S1192.
166. Wang F, Wei XL, Wang FH, Xu N, Shen L, Dai GH, et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. Ann Oncol. 2019;30(9):1479–86.
167. Kim ST, Cristescu R. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med. 2018;24(9):1449–58.
168. Qiu MZ, He CY, Yang DJ, Zhou DL, Zhao BW, Wang XJ, et al. Observational cohort study of clinical outcome in Epstein-Barr virus associated gastric cancer patients. Ther Adv Med Oncol. 2020;12:1758835920937434.
169. Xie T, Liu Y, Zhang Z, Zhang X, Gong J, Qi C, et al. Positive Status of Epstein-Barr Virus as a Biomarker for Gastric Cancer Immunotherapy: A Prospective Observational Study. J Immunother. 2020;43(4):139–44.
170. Janjigian YY, Maron SB, Chatila WK, Millang B, Chavan SS, Alterman C, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2020;21(6):821–31.
171. Shen L, Peng Z, Zhang YQ, et al. Camrelizumab combined with capecitabine and oxaliplatin followed by camrelizumab and apatinib as first-line therapy for advanced or metastatic gastric or gastroesophageal junction cancer: updated results from a multicenter, open label phase II trial [abstract no. 4031]. J Clin Oncol. 2019;37(15).
172. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer. 2012;15(1):S27–37.
173. Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. Gastric Cancer. 2018;21(1):10–18.
174. Coccolini F, Catena F, Glehen O, Yonemura Y, Sugarbaker PH, Piso P, et al. Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis. Eur J Surg Oncol. 2016;42(9):1261–67.
175. Lopez-Basave HN, Quiroz-Sandoval OA, Padilla-Rosciano AE, Leon-Takahashi AM, Miranda-Devora G, Arrollo-Monroy A. Role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Cir Cir. 2018;86(3):277–84.
176. Kodera Y, Ito S, Mochizuki Y, Ohashi N, Tanaka C, Kobayashi D, et al. Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study. Gastric Cancer. 2012;15(3):335–37.
177. Kano K, Aoyama T, Maezawa Y, Nakajima T, Ikeda K, Yamada T, et al. The survival and prognosticators of peritoneal cytology-positive gastric cancer patients who received upfront gastrectomy and subsequent S-1 chemotherapy. Int J Clin Oncol. 2017;22(5):887–96.
178. Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol. 2014;40(1):12–26.
179. Yamaguchi H, Kitayama J, Ishigami H, Emoto S, Yamashita H, Watanabe T. A phase 2 trial of intravenous and intraperitoneal paclitaxel combined with S-1 for treatment of gastric cancer with macroscopic peritoneal metastasis. Cancer. 2013;119(18):3354–8.
180. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer. 2016;19(2):329–38.
181. Ishigami H, Fujiwara Y, Fukushima R, Nashimoto A, Yabusaki H, Imano M, et al. Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial. J Clin Oncol. 2018;36(19):1922–9.
182. Niibe Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol. 2010;40(2):107–111.
183. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys. 2012;83(3):878–86.
184. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.
185. Badgwell B, Cormier JN, Xing Y, Yao J, Bose D, Krishnan S, et al. Attempted salvage resection for recurrent gastric or gastroesophageal cancer. Ann Surg Oncol. 2009;16(1):42–50.
186. Ishido K, Higuchi K, Tanabe S, Azuma M, Sasaki T, Katada C, et al. Chemoradiotherapy for patients with recurrent lymph-node metastasis or local recurrence of gastric cancer after curative gastrectomy. Jpn J Radiol. 2016;34(1):35–42.
187. Xu C, Xie J, Liang N, Wang J, Qiao L, Luo H, et al. Concurrent involved-field radiotherapy and XELOX in gastric cancer patients with postoperative oligometastatic recurrence. Journal of Cancer Research and Therapeutics. 2014;10(8):267–71.
188. Maruyama K, Kaminishi M, Hayashi K, Isobe Y, Honda I, Katai H, et al. Japanese Gastric Cancer Association Registration Committee. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer. 2006;9(2):51–66.
189. Ohira M, Toyokawa T, Sakurai K, Kubo N, Tanaka H, Muguruma K, et al. Current status in remnant gastric cancer after distal gastrectomy. World J Gastroenterol. 2016;22(8):2424–33.
190. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma (Japanese), 13 edn: JinYuan; 1999.

191. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy–Japan Clinical Oncology Group study 9501. J Clin Oncol. 2004;22(14):2767–73.
192. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309–18.
193. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg. 2009;96(9):1015–22.
194. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Stomach Cancer Study Group of the Japan Clinical Oncology G: 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. Br J Surg. 2014;101(6):653–60.
195. Ito S, Sano T, Mizusawa J, Takahari D, Katayama H, Katai H, et al. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. Gastric Cancer. 2017;20(2):322–31.
196. Katayama H, Tsuburaya A, Mizusawa J, Nakamura K, Katai H, Imamura H, et al. An integrated analysis of two phase II trials (JCOG0001 and JCOG0405) of preoperative chemotherapy followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis. Gastric Cancer. 2019;22(6):1301–7.
197. Wang Y, Yu YY, Li W, Feng Y, Hou J, Ji Y, et al. A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. Cancer Chemother Pharmacol. 2014;73(6):1155–61.
198. Thelen A, Jonas S, Benckert C, Lopez-Hanninen E, Neumann U, Rudolph B, et al. Liver resection for metastatic gastric cancer. Eur J Surg Oncol. 2008;34(12):1328–34.
199. Li W, Jiang H, Yu Y, Wang Y, Wang Z, Cui Y, et al. Outcomes of gastrectomy following upfront chemotherapy in advanced gastric cancer patients with a single noncurable factor: a cohort study. Cancer Manag Res. 2019;11:2007–13.
200. Liao YY, Peng NF, Long D, Yu PC, Zhang S, Zhong JH, Li LQ. Hepatectomy for liver metastases from gastric cancer: a systematic review. BMC Surg. 2017;17(1):14.
201. Gavriilidis P, Roberts KJ, de'Angelis N, Sutcliffe RP. Gastrectomy Alone or in Combination With Hepatic Resection in the Management of Liver Metastases From Gastric Cancer: A Systematic Review Using an Updated and Cumulative Meta-Analysis. J Clin Med Res. 2019;11(8):600–8.
202. Markar SR, Mikhail S, Malietzis G, Athanasiou T, Mariette C, Sasako M, Hanna GB. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. Ann Surg. 2016;263(6):1092–1101.
203. Montagnani F, Crivelli F, Aprile G, Vivaldi C, Pecora I, De Vivo R, et al. Long-term survival after liver metastasectomy in gastric cancer: Systematic review and meta-analysis of prognostic factors. Cancer Treat Rev. 2018;69:11–20.
204. Kataoka K, Kinoshita T, Moehler M, Mauer M, Shitara K, Wagner AD, et al. Current management of liver metastases from gastric cancer: what is common practice? New challenge of EORTC and JCOG. Gastric Cancer. 2017;20(5):904–12.
205. Guner A, Son T, Cho I, Kwon IG, An JY, Kim HI, Cheong JH, Noh SH, Hyung WJ: Liver-directed treatments for liver metastasis from gastric adenocarcinoma: comparison between liver resection and radiofrequency ablation. Gastric Cancer. 2016;19(3):951–60.
206. Zhou F, Yu XL, Liang P, Cheng Z, Han ZY, Yu J, et al. Microwave ablation is effective against liver metastases from gastric adenocarcinoma. Int J Hyperthermia. 2017;33(7):830–5.
207. Fukami Y, Kaneoka Y, Maeda A, Takayama Y, Takahashi T, Uji M, Kumada T. Adjuvant hepatic artery infusion chemotherapy after hemihepatectomy for gastric cancer liver metastases. Int J Surg. 2017;46:79–84.
208. Liu SF, Lu CR, Cheng HD, Xi HQ, Cui JX, Li JY, et al. Comparison of Therapeutic Efficacy between Gastrectomy with Transarterial Chemoembolization Plus Systemic Chemotherapy and Systemic Chemotherapy Alone in Gastric Cancer with Synchronous Liver Metastasis. Chin Med J. 2015;128(16):2194–2201.
209. Goodman KA, Wiegner EA, Maturen KE, Zhang Z, Mo Q, Yang G, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys. 2010;78(2):486–93.
210. Oki E, Tokunaga S, Emi Y, Kusumoto T, Yamamoto M, Fukuzawa K, et al. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). Gastric Cancer. 2016;19(3):968–76.
211. Tang K, Liu Y, Dong L, Zhang B, Wang L, Chen J, et al. Influence of thermal ablation of hepatic metastases from gastric adenocarcinoma on long-term survival: Systematic review and pooled analysis. Medicine (Baltimore). 2018;97(49):e13525.
212. Brieau B, Auzolle C, Pozet A, Tougeron D, Bouche O, Soibinet P, et al. Efficacy of modern chemotherapy and prognostic factors in patients with ovarian metastases from gastric cancer: A retrospective AGEO multicentre study. Dig Liver Dis. 2016;48(4):441–45.
213. Cho JH, Lim JY, Choi AR, Choi SM, Kim JW, Choi SH, Cho JY. Comparison of Surgery Plus Chemotherapy and Palliative Chemotherapy Alone for Advanced Gastric Cancer with Krukenberg Tumor. Cancer Res Treat. 2015;47(4):697–705.
214. Yan D, Du Y, Dai G, Huang L, Xu Q, Yu P. Management Of Synchronous Krukenberg Tumors From Gastric Cancer: a Single-center Experience. J Cancer. 2018;9(22):4197–4203.
215. Shinohara T, Maeda Y, Hamada T, Futakawa N. Survival benefit of surgical treatment for liver metastases from gastric cancer. J Gastrointest Surg. 2015;19(6):1043–51.
216. Cui JK, Liu M, Shang XK. Hepatectomy for Liver Metastasis of Gastric Cancer: A Meta-Analysis. Surg Innov. 2019;26(6):692–7.
217. Hwang JE, Kim SH, Jin J, Hong JY, Kim MJ, Jung SH, et al. Combination of percutaneous radiofrequency ablation and systemic chemotherapy are effective treatment modalities for metachronous liver metastases from gastric cancer. Clin Exp Metastasis. 2014;31(1):25–32.

218. Aurello P, Berardi G, Antolino L, Antonelli G, Rampini A, Moschetta G, Ramacciato G. Is a Surgical Approach Justified in Metachronous Krukenberg Tumor from Gastric Cancer? A Systematic Review. Oncol Res Treat. 2018;41(10):644–9.
219. Rosa F, Marrelli D, Morgagni P, Cipollari C, Vittimberga G, Framarini M, et al. Krukenberg Tumors of Gastric Origin: The Rationale of Surgical Resection and Perioperative Treatments in a Multicenter Western Experience. World J Surg. 2016;40(4):921–28.
220. Guo ZQ, Yu JM, Li W, Fu ZM, Lin Y, Shi YY, et al. Survey and analysis of the nutritional status in hospitalized patients with malignant gastric tumors and its influence on the quality of life. Support Care Cancer. 2020;28(1):373–80.
221. Lu Z, Fang Y, Liu C, Zhang X, Xin X, He Y, et al. Early Interdisciplinary Supportive Care in Patients With Previously Untreated Metastatic Esophagogastric Cancer: A Phase III Randomized Controlled Trial. J Clin Oncol. 2021;39(7):748–56.
222. Guidelines Committee of the Chinese Society of Clinical Oncology. Chinese Society of Clinical Oncology (CSCO) guidelines for nutritional therapy in patients with malignant tumor. Beijing: People's Medical Publishing House, 2019.
223. Gastric Cancer Committee of the China Anti-Cancer Association Committee and the Gastrointestinal Surgery Committee of the Chinese Society of Surgery. Chinese Expert Consensus on the perioperative nutritional therapy for gastric cancer (2019 Edition). Zhongguo Shiyong Waike Zazhi. 2020;40(2): 145–51.
224. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;2(3):321–36.
225. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr. 2002;56(8):779–85.
226. Mortensen K, Nilsson M, Slim K, Schäfer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Br J Surg. 2014;101(10):1209–29.
227. Shi H, Xu H, Li S, Cao W, Li W, Ba Y, et al. The 5-step principle for the treatment of malnutrition. Zhongliu Daixie yu Yingyang Dianzi Zazhi. 2015;000(001):29–33.
228. Shi HP, Li SY, Wang KH, Wu XT, Li Y, Zhao QC, et al. Guidelines for nutritional therapy in patients with gastric cancer (Chinese). Zhongliu Daixie yu Yingyang Dianzi Zazhi. 2015; (02):488–91.
229. Kim YI, Choi IJ.Endoscopic management of tumor bleeding from inoperable gastric cancer. Clin Endosc. 2015;48(2):121–27.
230. Chen Y, Yang Y, Xu WJ, Xin YJ, Wang YN, Zhou X, Li X. Clinical application of interventional embolization in tumor-associated hemorrhage. Ann Transl Med. 2020;8(6):394.
231. Bian SB, Shen WS, Xi HQ, Wei B, Chen L: Palliative Therapy for Gastric Outlet Obstruction Caused by Unresectable Gastric Cancer: A Meta-analysis Comparison of Gastrojejunostomy with Endoscopic Stenting. Chin Med J. 2016;129(9):1113–21.
232. Liu H, Xu Q, Ma FH, Marshal M, Li Y, Li WK, Tian YT. Clinical results of total laparoscopic partial gastrectomy for gastric cancer with pyloric obstruction. Zhonghua Zhongliu Zazhi. 2020;42(06):445–48.
233. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, Committee EG. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(5):v38–v49.
234. Association Japanese Gastric Cancer. Japanese Classifcation of Gastric Carcinoma (Japanese). 15th ed. Tokyo: Kanehara Shuppan; 2017.
235. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20(1):1-19.
236. Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8):e386-e397.
237. Pharoah PD, Guilford P, Caldas C. International Gastric Cancer Linkage C: Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121(6):1348–53.
238. Majewski IJ, Kluijt I, Cats A, Scerri TS, de Jong D, Kluin RJ, et al. An alpha-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer. J Pathol. 2013;229(4):621–29.
239. Kluijt I, Sijmons RH, Hoogerbrugge N, Plukker JT, de Jong D, van Krieken JH, et al. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer. 2012;11(3):363–9.
240. van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. 2015;52(6):361–74.
241. de Boer WB, Ee H, Kumarasinghe MP. Neoplastic Lesions of Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS) Are Gastric Phenotype. Am J Surg Pathol. 2018;42(1):1–8.
242. Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. Gut. 2012;61(5):774–79.
243. Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. JAMA Oncol. 2015;1(1):23–32.
244. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW.American College of G: ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 263.
245. Capelle LG, Van Grieken NC, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology. 2010;138(2):487–92.
246. Kim JW, Shin SS, Heo SH, Choi YD, Lim HS, Park YK, et al. Diagnostic performance of 64-section CT using CT gastrography in preoperative T staging of gastric cancer according to 7th edition of AJCC cancer staging manual. Eur Radiol. 2012;22(3):654–62.
247. Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, et al. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. Radiology. 2004;230(2):465–71.
248. Hasegawa S, Yoshikawa T, Shirai J, Fujikawa H, Cho H, Doiuchi T, et al. A prospective validation study to diagnose

serosal invasion and nodal metastases of gastric cancer by multidetector-row CT. Ann Surg Oncol. 2013;20(6):2016–22.
249. Kim TU, Kim S, Lee JW, Lee NK, Jeon TY, Park DY. MDCT features in the differentiation of T4a gastric cancer from less-advanced gastric cancer: significance of the hyperattenuating serosa sign. Br J Radiol. 2013;86(1029):20130290.
250. Lee SL, Ku YM, Jeon HM, Lee HH. Impact of the Cross-Sectional Location of Multidetector Computed Tomography Scans on Prediction of Serosal Exposure in Patients with Advanced Gastric Cancer. Ann Surg Oncol. 2017;24(4):1003–9.
251. You MW, Park S, Kang HJ, Lee DH, Radiologic serosal invasion sign as a new criterion of T4a gastric cancer on computed tomography: diagnostic performance and prognostic significance in patients with advanced gastric cancer. Abdom Radiol (NY). 2020;45(10):2950–9.
252. Fukuya T, Honda H, Hayashi T, Kaneko K, Tateshi Y, Ro T, et al. Lymph-node metastases: efficacy for detection with helical CT in patients with gastric cancer. Radiology. 1995;197(3):705–11.
253. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer. 2009;12(1):6–22.
254. Kumano S, Murakami T, Kim T, Hori M, Iannaccone R, Nakata S, et al. T staging of gastric cancer: role of multi-detector row CT. Radiology. 2005;237(3):961–6.

**How to cite this article:** Wang F-H, Zhang X-T, Li Y-F, Tang L, Qu X-J, Ying J-E, et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. Cancer Commun. 2021;**41:**747–795. https://doi.org/10.1002/cac2.12193