

## Review Article



# A Comprehensive and Comparative Review of Global Gastric Cancer Treatment Guidelines

Sang Soo Eom , Wonyoung Choi , Bang Wool Eom , Sin Hye Park ,  
Soo Jin Kim , Young Il Kim, Hong Man Yoon , Jong Yeul Lee , Chan Gyoo Kim ,  
Hark Kyun Kim , Myeong-Cherl Kook , Il Ju Choi , Young-Woo Kim ,  
Young Iee Park, Keun Won Ryu

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Center for Gastric Cancer, National Cancer Center, Goyang, Korea

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### Correspondence to

Keun Won Ryu

Center for Gastric Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea.

Email: docryu@ncc.re.kr

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### ORCID iDs

Sang Soo Eom   
<https://orcid.org/0000-0002-6252-7532>  
Wonyoung Choi   
<https://orcid.org/0000-0002-8292-3903>  
Bang Wool Eom   
<https://orcid.org/0000-0002-0332-2051>  
Sin Hye Park   
<https://orcid.org/0000-0002-5095-203X>  
Soo Jin Kim   
<https://orcid.org/0000-0002-2614-3419>  
Hong Man Yoon   
<https://orcid.org/0000-0002-6218-7080>  
Jong Yeul Lee   
<https://orcid.org/0000-0001-8709-5097>  
Chan Gyoo Kim   
<https://orcid.org/0000-0002-1651-2559>  
Hark Kyun Kim   
<https://orcid.org/0000-0001-9814-1829>

## ABSTRACT

Countries differ in their treatment expertise and research results regarding gastric cancer; hence, treatment guidelines are diverse based on evidence and medical situations. A comprehensive and comparative review of each country's guidelines is imperative to understand the similarities and differences among countries. We reviewed and compared five gastric cancer treatment guidelines in terms of endoscopic, surgical, perioperative, and palliative systemic treatment based on evidence levels and recommendation grades, as well as the postoperative follow-up strategies for each guideline. The Korean, Chinese, and European guidelines provided evidence and grading of the recommendations. The United States guidelines suggested categories for evidence and consensus. The Japanese guidelines suggested evidence and recommendations only for systemic treatment. The Korean and Japanese guidelines described endoscopic treatment, surgery, and lymphadenectomy in detail. The Chinese, United States, and European guidelines more intensively considered perioperative chemotherapy. In particular, the indications for chemotherapy and the regimens recommended by each guideline differed slightly. Considering their medical situations, each guideline had some diversity in terms of adopting evidence, which resulted in heterogeneous recommendations. This review will help medical personnel to comprehensively understand the diversity in gastric cancer treatment guidelines for each country in terms of evidence and recommendations.

**Keywords:** Gastric cancer; Guideline; Review; Treatment

## INTRODUCTION


Gastric cancer is the fifth most common cancer and the third-leading cause of cancer-related deaths worldwide. In 2018, more than one million cases of gastric cancer were diagnosed, with more than 782,000 deaths worldwide [1]. The incidence of gastric cancer is geographically heterogeneous because it is affected by genetic and environmental factors; moreover, mortality differs among countries depending on the presence of a screening program for gastric cancer and a global therapeutic strategy [2,3]. The incidence of gastric cancer is higher in East Asia, particularly Korea and Japan; South and Central America; Eastern Europe compared to Western Europe, Australia, and North America [2,4]. The 5-year survival rate is approximately 20% globally, except for South Korea and Japan, mainly due

Myeong-Cherl Kook 


<https://orcid.org/0000-0002-3435-3301>

Il Ju Choi 

<https://orcid.org/0000-0002-8339-9824>

Young-Woo Kim 

<https://orcid.org/0000-0002-1559-9672>

Keun Won Ryu 

<https://orcid.org/0000-0002-5935-9777>

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No potential conflict of interest relevant to this article was reported.

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to well-organized screening programs that can detect gastric cancer at an early stage [5,6]. The 5-year survival rates are 71.5% in South Korea and 65% in Japan; however, the survival of patients with gastric cancer in Western countries is poor, mainly due to advanced stage at diagnosis [2]. Differences in cancer biology and therapeutic quality have also been attributed to the variations in survival and initial stage at diagnosis [2,7]. Therefore, treatment strategies are also heterogeneous globally based on the differences in incidence, mortality, and medical resources. For these reasons, each country's treatment expertise and research results differ; therefore, gastric cancer treatment guidelines are diverse based on evidence and medical situations.

Several countries have their own consensus or evidence-based guidelines for managing gastric cancer that have been updated for many years. We compared 5 guidelines: the 2018 Korean Practice Guidelines for Gastric Cancer (Korean Gastric Cancer Association; KGCA), the 2018 Japanese Gastric Cancer Treatment Guideline 5th edition (Japanese Gastric Cancer Association; JGCA), the 2021 Chinese guidelines (Chinese Society of Clinical Oncology; CSCO), the 2021 National Comprehensive Cancer Network Guideline for Gastric Cancer version 3 (National Comprehensive Cancer Network; NCCN), and the 2016 European Society for Medical Oncology Guideline for Gastric Cancer (European Society for Medical Oncology; ESMO) [8-12]. We comprehensively reviewed the gastric cancer treatment guidelines of 5 countries in terms of endoscopic, surgical, and perioperative treatment. The first-line, second-line, and subsequent palliative therapies for systemic disease in patients with metastatic disease were reviewed and compared. Finally, the postoperative follow-up surveillance was reviewed and compared for each guideline, as well as the evidence levels and recommendation grades adopted from each guideline.

A comparison of each country's guidelines is helpful not only to medical trainees and clinicians devoted to gastric cancer management but also to patients and their family members and health care authorities for an easy understanding of their similarities and differences.

## LEVELS OF EVIDENCE AND GRADES OF THE RECOMMENDATIONS

Most guidelines suggested levels of evidence and recommendations (**Table 1**). KGCA described recommendations based on the Scottish Intercollegiate Guidelines Network and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology reviews. JGCA classified the "Recommend regimen" and the "Conditionally recommend regimen" only in palliative chemotherapy based on the Medical Information Network Distribution Service (MINDS) clinical guideline manual version 2.0. However, the JGCA did not declare the level of evidence or grades of the recommendation in the other parts. The CSCO suggested its own level of evidence and recommendation grades based on expert consensus. The NCCN suggested categories of evidence, consensus, and preference. The ESMO describes the levels of evidence and grades of recommendation adapted from the Infectious Diseases Society of the America-United States Public Health Service Grading System.

**Table 1.** Levels of evidence and grading for the recommendations included in the review

Levels of evidence and grading
<b>KGCA (2018)</b> Scottish Intercollegiate Guidelines Network Grading of Recommendations, Assessment, Development and Evaluation methodology reviews (GRADE)
<b>JGCA (2018)</b> Medical Information Network Distribution Service (MINDS) clinical guideline manual version 2.0 (Only in palliative chemotherapy regimens)
<b>CSCO (2021)</b> CSCO levels of evidence and consensus CSCO recommendation grades
<b>NCCN (2021)</b> NCCN Categories of Evidence and Consensus NCCN Categories of Preference
<b>ESMO (2016)</b> Infectious Diseases Society of America-United States Public Health Service Grading System

## ENDOSCOPIC TREATMENT

Endoscopic resection (ER) has been used as an alternative to gastrectomy in patients with minimal risk of developing lymph node (LN) metastasis. ER has benefits over surgery in terms of a better quality of life by avoiding gastric resection [13]. Several decades ago, endoscopic mucosal resection (EMR) was used to remove small sized early gastric cancer (EGC). As improvements in endoscopic techniques and instrumental endoscopic submucosal dissection (ESD) have been adopted in patients with EGC, the indication for EMR has widened in patients with minimal risk of LN metastasis [14,15]. Each guideline recommends ER based on histology, tumor size, invasion depth, and ulcer presence (Table 2). The JGCA and CSCO guidelines recommend ER based on absolute, expanded, and relative indications [9,10].

Differentiated-type adenocarcinoma without ulcerative findings, in which the depth of invasion is clinically diagnosed as T1a and the diameter is <2 cm, has a very low risk of LN metastasis [13,16]. Therefore, the KGCA strongly recommends ER in these cases, while the

**Table 2.** Endoscopic resection

Endoscopic resection	KGCA (2018)	JGCA (2018)	CSCO (2021)	NCCN (2021)	ESMO (2016)
<b>ER</b>					
Recommendation	Strong for		Grade I	Category 2A	Grade B
Indication	≤2 cm, T1a, UL (-), Diff	For EMR or ESD ≤2 cm, T1a, UL (-), Diff For ESD 1. >2 cm, T1a, UL (-), Diff or ≤3 cm, T1a, UL (+) 2. ≤2 cm, T1a, UL (-), Undiff	For EMR or ESD ≤2 cm, T1a, UL (-), Diff For ESD 1. >2 cm, T1a, UL (-), Diff or ≤3 cm, T1a, UL (+) 2. ≤2 cm, T1a, UL (-), Undiff	≤2 cm, T1a, Diff, LVI (-), HM (-), VM (-)	≤2 cm, T1a, well diff, UL (-)
<b>ER or surgery</b>					
Recommendation	Weak for				
Indication	1. >2 cm, T1a, UL (-), Diff or ≤3 cm, T1a, UL (+) 2. ≤2 cm, T1a, UL (-), Undiff				
<b>Additional surgery</b>					
Recommendation	Strong for		Grade I	Category 2A	
Indication	Outside ER indication or LVI (+) or VM (+)	eCura C	Outside ER indication	Undiff, LVI (+), T1b, HM (+), VM (+)	Outside ER indication

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; Diff = differentiated; Undiff = undifferentiated; LVI = lymphovascular invasion; UL = ulcerative finding; HM = horizontal margin; VM = vertical margin; ER = endoscopic resection; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; eCura = endoscopic curability.

JGCA and CSCO have classified these criteria as absolute indications for EMR or ESD [8-10]. In cases with well or moderately differentiated tubular or papillary EGC >2 cm, T1a, without ulcerative findings or with ulcerative findings, clinically T1a, and ≤3 cm, the KGCA recommends ER or surgery, while the JGCA and CSCO classified these criteria as absolute indications for ESD [8-10]. The JGCA and CSCO recommended ESD because the LN metastasis or distant metastasis rates after ER are low, ranging between 0% and 0.21% [16-19].

If a tumor is a poorly differentiated tubular or poorly cohesive EGC, ≤2 cm, T1a, and without ulcerative findings, the KGCA recommended ER or surgery as the evidence is insufficient to strongly recommend ER [8]. However, the JGCA and CSCO included these as expanded indication criteria [9,10]. The JGCA guidelines recommend ER instead of surgery in patients with expanded indications [9]. However, it remains unclear whether ESD can be performed in cases with expanded indications. Moreover, these indications can be changed depending on the results of clinical trials, such as the JCOG 1009/1010 study [19]. In addition, the CSCO suggests that it is still being investigated in cases with expanded indications [10].

The NCCN and ESMO guidelines considered ER only in well-differentiated, ≤2 cm, and non-ulcerated lesions, similar to the KGCA. The NCCN and ESMO did not mention ER indications beyond these; they recommended surgery in cases where ER could not be considered [11,12].

After endoscopic treatment, the KGCA recommended additional surgery if the pathologic result of the tumor shows non-curative resection, lymphovascular invasion (LVI), and positive deep or vertical margins because of the risk of LN metastasis [8]. However, the survival benefits of standard surgery after ESD remain controversial. Some studies have shown no significant survival benefit with additional surgery [20-22]. However, most studies have shown significantly improved overall survival (OS) rates in patients who undergo additional curative surgery after ESD [23,24].

The JGCA mentioned endoscopic curability (eCura), which is classified as A, B, C-1, and C-2 [25]. These criteria are classified according to the post-ER results; furthermore, observation, surgery, or repeated ESD is recommended. If the endoscopic resection pathology meets eCura A and B, observation is recommended; however, if it includes eCura C-1, additional ESD, surgery, coagulation, or observation is considered; if it satisfies eCura C-2, additional surgery is recommended [9]. However, patients with a high operative risk can consider ESD rather than surgery, even if the tumors are beyond the expanded indications [9]. Determining which treatment is better for older age, poor general condition, and high-risk operative patients is required.

The NCCN recommended additional surgery for poorly differentiated gastric cancers, LVI, submucosal invasion, or positive lateral or deep margins after ER [11]. Moreover, the ESMO recommended additional surgery in cases with non-ER indications [12].

## SURGICAL TREATMENT

Except for ER, surgery is recommended for resectable gastric cancers. Each guideline recommended perioperative treatment. The standard surgery for gastric cancer consists of gastrectomy with adequate margins, perigastric and extragastric LN dissection (LND), and

consequent gastrointestinal reconstruction [8]. Complete resection without residual disease is the goal of surgical treatment; however, there is controversy regarding the type of gastric resection, extent of LND, and reconstruction [11].

### Principle of surgery

The JGCA recommended a resection margin of at least 2 cm for T1 tumors [9]. JGCA and CSCO recommend obtaining at least a 3 cm proximal margin in T2 or deeper tumors with Borrmann type I and II tumors. Borrmann types III and IV are recommended with a 5 cm proximal margin [9,10]. Surgical methods should be considered to ensure safe resection margins. The KGCA, NCCN, and ESMO recommended distal gastrectomy (DG) for distal gastric cancers if safe margins can be achieved [8,11,12]. The ESMO recommended a proximal margin of 5 cm for stage IB–III gastric cancer and 8 cm for diffuse cancer when performing DG; otherwise, total gastrectomy (TG) was recommended [12].

### Function-preserving surgery

Function-preserving gastrectomy such as proximal gastrectomy (PG) or pylorus-preserving gastrectomy (PPG) was recommended in selected EGC depending on location and TG and DG, especially in the KGCA, JGCA, and CSCO (Table 3) [8-10]. The KGCA recommended both PG and TG for EGC in the upper one-third in terms of survival rate, nutritional status, and quality of life [8]. Several retrospective studies have reported that the survival rates and early postoperative complications of TG and PG do not differ significantly [26-29]. Various reconstructions can be performed after PG, including esophagogastromy, jejunal interposition, and double-tract reconstruction [8]. Although PG with esophagogastromy is simple, it results in a significantly higher frequency of reflux esophagitis and anastomotic stenosis [30-33]. However, can show superior nutritional status, including serum albumin level, body weight maintenance, serum vitamin B12 level, and anemia prevention [31,34]. Both jejunal interposition and double-tract reconstruction after PG showed superior nutritional parameters and anemia compared to TG [28,29,32,35].

The KGCA recommended performing PPG and DG simultaneously in middle-third EGC in terms of survival rate, nutrition, and quality of life for the 2 procedures [8]. Most studies on PPG are retrospective, and long-term survival did not differ significantly from that of DG [36-38]. PPG reduces post-gastric syndromes such as dumping syndrome, bile reflux, and gall stone formation; however, the rate of delayed gastric emptying is reportedly higher than that for DG [8].

**Table 3.** Indications for function-preserving surgery

Operation	KGCA (2018)	JGCA (2018)	CSCO (2021)	NCCN (2021)	ESMO (2016)
<b>PG</b>					
Recommendation	Weak for		Grade II, III		
Indication	Stage Ia Upper third	Stage Ia Remnant distal stomach ≥50%	Stage Ia Proximal side	Proximal side	Not mentioned
Reconstruction	Esophagogastromy Jejunal interposition Double-tract reconstruction	Esophagogastromy Jejunal interposition Double-tract reconstruction	Esophagogastromy (Grade II) Tubular gastroesophageal anastomosis (Grade II) Jejunal interposition (Grade III)		
<b>PPG</b>					
Recommendation	Weak for				
Indication	Stage Ia Middle third	Stage Ia Middle portion	Stage Ia	Not mentioned	Not mentioned

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; PG = proximal gastrectomy; PPG = pylorus-preserving gastrectomy.

**Table 4.** Lymph node dissection

Lymph node dissection	KGCA (2018)	JGCA (2018)	CSCO (2021)	NCCN (2021)	ESMO (2016)
<b>D1</b>					
Recommendation			Grade I	Category 2A	
Indication	Not mentioned	T1aNO T1bNO, Diff, <1.5 cm	T1aNO T1bNO, Diff, <1.5 cm	Localized resectable cancer	Localized resectable cancer
<b>D1+</b>					
Recommendation	Strong for		Grade I		
Indication	T1NO	T1NO	T1NO	Not mentioned	T1 tumors
<b>D2</b>					
Recommendation	Strong for		Grade I	Category 2A	Grade B
Indication	T2-T4, T1N+	T2-T4, T1N+	T2-T4, T1N+	Should be done by experienced surgeon	Only by experienced surgeons
<b>D2+</b>					
Recommendation			Grade II, III		
Indication	Not mentioned	Metastasis to no. 10, 14v, 13, 16 LNs	Metastasis to no. 10, 14v (Grade II), 13 (Grade III) LNs	Not mentioned	Not mentioned
<b>Splenectomy</b>					
Recommendation	Strong against				
Indication	Not recommend	GC, metastasis to No. 4sb LNs, LN metastasis	Not recommend	Not recommend	Not mentioned

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; Diff = differentiated; GC = greater curvature; LN = lymph node.

### LND

In gastric cancer surgery, it is important to perform appropriate LND according to the gastrectomy type and disease extent. The LND range was initially suggested by the JGCA and has recently been classified as D1 +, D1+, and D2 [9]. However, the indications for different LND ranges are heterogeneous, according to each guideline (**Table 4**). Generally, Eastern countries recommend D2 dissection in cases with >T2 lesions or suspected LN metastasis, whereas Western countries recommend D2 dissection by expert surgeons.

Two large-randomized trials in Western countries comparing D1 and D2 dissection failed to demonstrate the survival benefit of D2 [39,40]. However, the 15-year follow-up long-term results were optimistic [41]. Based on these findings, D2 dissection is recommended but not required in Western countries. The NCCN guidelines recommended D1 or D2 LN dissection in localized gastric cancer with the goal of collecting 16 or more LNs. Since there remains controversy regarding D1 and D2 dissection, D2 dissection should only be performed by experienced surgeons at high-volume centers [11]. The ESMO recommended that only experienced surgeons and large centers perform D2 dissection in patients meeting the medical criteria [12].

In Eastern countries, fewer D2 dissection procedures are recommended for EGC. The KGCA recommended D1+ lymphadenectomy in all patients with T1NO gastric cancer who are candidates for surgery because of its relatively comparable oncological safety [8]. However, the JGCA and CSCO recommended D1 LND for T1aNO tumors that are contraindicated for ER, or are of the differentiated type and <1.5 cm in diameter and D1+ LND for T1NO tumors [9,10].

The recommendations concerning splenectomy for splenic hilar LND differ in each guideline. While several randomized trials have compared the survival advantage of splenectomy, no studies have recommended prophylactic splenectomy [42-44]. Therefore, the KGCA did not recommend prophylactic splenectomy for splenic hilar node dissection, during curative resection for advanced gastric cancer (AGC) [8]. The JGCA recommended

splenic hilar LND with or without splenectomy for upper stomach cancer invading the greater curvature or Borrmann type 4 cancer (9). Similarly, the CSCO recommended splenic hilar LND for T3–4 tumors >6 cm in size and located in the upper-middle stomach and greater curvature [10]. The NCCN did not recommend routine splenectomy in cases without splenic invasion or hilar lymphadenopathy [11]. The ESMO guidelines have no specific recommendations for splenectomy [12].

According to the JGCA and CSCO guidelines, as D2+ dissection, No. 14v LND can be performed when infrapyloric LND metastasis is suspected and No. 13 LND in the case of duodenal metastasis [9,10]. The JGCA recommended No. 16 LND for patients undergoing surgery after neoadjuvant chemotherapy [9]. The ESMO and NCCN made no recommendations for D2 LND [11,12].

### **Palliative gastrectomy**

In cases of AGC with distant metastasis, palliative gastrectomy can be performed when surgery is unavoidable and the disease cannot be controlled by noninvasive therapy. However, it remains unclear whether palliative gastrectomy benefits patients in terms of survival. Therefore, the REGATTA trial, a large international phase III study, was conducted to evaluate the benefits of palliative surgery. No significant difference in OS and progression-free survival (PFS) was observed between patients who underwent chemotherapy plus surgery and those who underwent surgery only [45]. None of the guidelines recommended palliative gastrectomy for improved survival in AGC with distant metastasis, except for urgent situations or symptom relief.

### **Minimally invasive surgery**

Minimally invasive surgery guidelines differed slightly depending on the time of publication and the related clinical studies. The EGC, KGCA, CSCO, and NCCN recommended laparoscopic surgery, while the JGCA recommended laparoscopic surgery for distal gastrectomy and relatively recommended it for total gastrectomy [8-11]. The ESMO also recommended this as an option [12]. The randomized phase III KLASS-01 and JCOG0912 trials demonstrated non-inferior survival for laparoscopic gastrectomy compared to open gastrectomy for stage I gastric cancer [46-48]. Several studies, including the KLASS-03, JCOG 1401, and CLASS-02 trials, have proven the safety of laparoscopic total gastrectomy for clinical stage I gastric cancer [49-51]. However, the long-term outcomes have not been confirmed; hence, the efficacy and safety of laparoscopic total gastrectomy remain controversial and research is ongoing.

In AGC, the KGCA recommended open gastrectomy; however, the JGCA is inconclusive [8,9]. The CSCO and NCCN recommend laparoscopic surgery [10,11]. ESMO recommends open gastrectomy in patients with suspected positive nodes [12]. The randomized controlled clinical KLASS-02 trial compared laparoscopic and open distal gastrectomies in patients with gastric cancer in cT2–4a and N0–1. Relapse-free survival (RFS) was comparable between laparoscopic distal gastrectomy with D2 LND and open distal gastrectomy [52]. CLASS-01, a phase III randomized clinical trial conducted on patients with clinical stage T2 to T4a gastric cancer, compared open and laparoscopic gastrectomy. The results showed that laparoscopic distal gastrectomy was non-inferior to open distal gastrectomy in AGC [53]. However, since the other guidelines were published before the results of these studies, they recommended open gastrectomy for AGC; these recommendations will be updated soon.

## PERIOPERATIVE TREATMENT

### Neoadjuvant treatment

Each guideline showed different neoadjuvant chemotherapy recommendations according to the main research. Neoadjuvant treatment is recommended in Western countries but not in Eastern countries. The KGCA was not conclusive; the JGCA conditionally recommended it; and the CSCO, NCCN, and ESMO recommended this treatment [8-12]. The JGCA did not mention any regimens [9]. The CSCO recommended S-1 plus oxaliplatin (SOX); docetaxel plus oxaliplatin plus S-1 (DOS); and fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) as neoadjuvant chemotherapy for locally advanced gastric cancer without distant metastasis (T3/4a, N+) [10]. The NCCN and ESMO recommended the FLOT regimen as neoadjuvant chemotherapy for cT2 or higher and any N gastric cancer patients with good performance status (PS) [11,12]. The results are summarized in **Table 5**.

Several randomized trials have demonstrated the benefits of perioperative chemotherapy. The phase III MAGIC trial showed better PFS and OS for epirubicin, cisplatin, and fluorouracil (ECF) chemotherapy before and after surgery compared to surgery alone [54]. In the FNCLCC/FFCD trial, perioperative chemotherapy with fluorouracil and cisplatin increased the curative resection rate, disease-free survival (DFS), and OS [55]. Although this study was completed early due to low accrual, fluorouracil and cisplatin may also be good options. Furthermore, the randomized controlled phase II/III FLOT-4 trial also reported that FLOT was better than epirubicin, cisplatin, and fluorouracil or capecitabine perioperative chemotherapy regimens [56]. For these reasons, the NCCN recommended FLOT rather than ECF regimens only in patients with a good PS owing to the toxicity of the FLOT regimen [11]. The ESMO recommended a platinum and fluoropyrimidine combination for gastric cancer patients with cT2 or higher, any N [12]. However, at the time that this guideline was

**Table 5.** Perioperative treatments

Perioperative treatment	KGCA (2018)	JGCA (2018)	CSCO (2021)	NCCN (2021)	ESMO (2016)
<b>Neoadjuvant chemotherapy</b>					
Recommendation	Inconclusive	Weakly recommended (Extensive LN metastases)	Grade I (cT3-4aN+M0)	Category 1 (cT2 or higher, any N)	Grade A (cT2 or higher, any N)
Regimen	ECF, FP, FLOT	Not mentioned	SOX	FLOT, Fluoropyrimidine + oxaliplatin	FLOT
<b>Neoadjuvant chemoradiotherapy</b>					
Recommendation	Inconclusive	Not mentioned	Grade I (Gastric cancer invading the EGJ: cT3-4aN+M0)	Category 2B	Not mentioned
<b>Adjuvant chemotherapy</b>					
Recommendation	Strong for (Stage II or III)	Recommended (Stage II or III)	Grade I (Stage II or III)	Category 1 (Primary D2 LND)	Grade A (Primary surgery with ≥Stage IB)
Regimen	S-1, XELOX	S-1, XELOX, S-1 + docetaxel (Stage III)	S-1, XELOX (Stage II) XELOX, SOX (Stage III)	XELOX, 5-FU + oxaliplatin	S-1, XELOX
<b>Adjuvant chemoradiotherapy</b>					
Recommendation	Weak for (<D2 LND and/or R1 resection)	Not mentioned	Grade I (<D2 LND and/or R1 or R2 resection)	Category 2A	Grade B

This table only includes the CSCO “Grade I recommendations,” NCCN “Preferred Regimens.”

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; ECF = epirubicin, cisplatin, and fluorouracil; FP = fluorouracil and cisplatin; FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel; SOX = S-1 and oxaliplatin; DOS = docetaxel, oxaliplatin, and S-1; EGJ = esophagogastric junction; XELOX = capecitabine and oxaliplatin; 5-FU, 5-fluorouracil; LND = lymph node dissection.



published, studies on the regimens mentioned above, such as the FLOT trial, were not yet completed; thus, they should be considered. After the FLOT trial was published, the ESMO guidelines were updated to recommend the FLOT regimen as perioperative chemotherapy for patients with stage IB resectable gastric cancer [57]. After the FLOT trial, the phase III randomized controlled RESOLVE trial showed that perioperative SOX was superior to adjuvant capecitabine plus oxaliplatin (XELOX) in patients with locally advanced cT4a/N + M0 or cT4b/NxM0 [58]. Neoadjuvant DOS and postoperative S-1 monotherapy were superior to postoperative S-1 monotherapy alone in terms of tumor downstaging and 3-year DFS improvement in the PRODIGY study [59]. Therefore, the CSCO recommended SOX, DOS, and FLOT as neoadjuvant chemotherapies [10].

However, the KGCA considered that neoadjuvant chemotherapy was inconclusive if D2 LND was possible and gastric cancer could be potentially resectable because these European studies implemented D2 LND in only 30%–50% of cases, whereas D2 LND was performed in most patients with AGC in Korea [8]. The JGCA conditionally recommended neoadjuvant chemotherapy for patients with extensive LN metastasis [9]. The recently published CSCO guidelines recommended more neoadjuvant regimens than the KGCA or JGCA due to the recent publication of the results of phase III randomized controlled trials conducted in Japan (RESOLVE) and South Korea (PRODIGY). Therefore, other guidelines for neoadjuvant chemotherapy regimens in Eastern countries should be updated soon.

The KGCA, CSCO, and NCCN also mentioned preoperative chemoradiotherapy (CRT). The CSCO recommended neoadjuvant CRT for gastric cancer invading the esophagogastric junction (EGJ) with cT3-4aN+M0 stage III [10]. Although the NCCN recommended several preoperative CRT regimens, the level for these recommendations was low (category 2B) owing to the lack of phase III clinical trials to prove the survival benefit of these regimens for resectable gastric cancer [11]. Moreover, these studies were mostly conducted in Western countries and targeted esophageal and/or EGJ cancers. In Korea, gastric cancer is more common in the antral area; therefore, the KGCA suggested that if D2 LND is performed, the evidence for the efficacy of preoperative CRT is inconclusive [8].

### Adjuvant treatment

Opinions on adjuvant treatment differ between Eastern and Western countries. In Eastern countries, since D2 LND is performed routinely in AGC, adjuvant chemotherapy is recommended thereafter. However, perioperative chemotherapy is preferred in Western countries and CRT or adjuvant chemotherapy is recommended. The KGCA, JGCA, CSCO, and NCCN recommended adjuvant chemotherapy for stage II and III gastric cancer after D2 LND [8-11]. The CSCO guidelines recommended that adjuvant chemotherapy may also be considered in patients with high-risk factors, even for stage I gastric cancer. The risk factors include age <40 years; high or low differentiated histology grade; and nerve bundle, blood, or lymphatic vessel invasion [10]. The ESMO recommended postoperative CRT or adjuvant chemotherapy for patients with stage IB gastric cancer who have not received preoperative chemotherapy (**Table 5**) [12].

The CLASSIC phase III trial demonstrated that XELOX increased OS and DFS after D2 LND in stage II-IIIb gastric cancer [60]. The ACTS-GC trial also demonstrated that S-1 chemotherapy benefitted OS when administered after D2 LND in stage II or III gastric cancer [61]. Therefore, the KGCA and JGCA recommended XELOX or S-1 as adjuvant chemotherapy for patients with stage II or III gastric cancer who have undergone adequate D2 dissection [8,9].

In addition, the CSCO and NCCN recommended the XELOX regimen after D2 dissection for AGC after surgery [10,11]. However, the CSCO recommended S-1 monotherapy only in patients with stage II disease [10] as the ACTS-GC trial subgroup analysis showed that S-1 was not more effective in stage III than in stage II [61]. However, in the CLASSIC trial, XELOX was effective in both stages II and III [60]. The CSCO also recommended SOX for stage II and III gastric cancer with different evidence levels as the RESOLVE trial proved that adjuvant SOX was not inferior to adjuvant XELOX [58]. The JGCA and CSCO recommended the S-1 plus docetaxel regimen for stage III gastric cancer because S-1 plus docetaxel was more beneficial than S-1 monotherapy for RFS in the JACCRO GC-07 trial [62]. The KGCA did not include S-1-based doublet regimens, as these guidelines were published before phase III trials in more advanced-stage (stage III or LN-positive) cancer were reported.

If D0 or D1 LND and/or incomplete resection are performed during gastric cancer surgery, the KGCA recommends considering CRT rather than chemotherapy alone [8]. And CSCO and NCCN recommend CRT [10,11]. In the INT-0116 trial, patients who received radiotherapy after fluorouracil and leucovorin chemotherapy had increased OS compared to patients who underwent surgery alone [63]. However, >50% of patients underwent less than D1 LND. A randomized phase III ARTIST 2 trial showed no survival benefit for postoperative CRT after D2 dissection in node-positive gastric cancer [64]. The ESMO did not recommend postoperative radiotherapy in patients who have received preoperative chemotherapy [12]. In the phase III randomized CRITICS trial, patients who received appropriate preoperative chemotherapy and surgery did not show any survival benefit for additional postoperative radiotherapy [65].

## PALLIATIVE SYSTEMIC TREATMENT

### First-line human epidermal growth factor receptor 2 (HER2)-negative gastric cancer

The ultimate goals of palliative chemotherapy in unresectable or metastatic gastric cancer are symptom relief and prolonged survival. Palliative care has been demonstrated to be superior to best supportive care (BSC) [66,67]. Many studies have proved the efficacy of chemotherapy, and most guidelines recommended regimens with two cytotoxic drug combinations, oral or infusional fluoropyrimidine and platinum, as palliative first-line chemotherapies. The first-line chemotherapy regimens recommended in each guideline differed slightly and were based on fluoropyrimidine and platinum. Several studies have demonstrated that oral fluoropyrimidines are as effective as 5-fluorouracil (5-FU) [68-72]. The effectiveness of cisplatin plus S-1 (SP) or capecitabine (XP) doublet combination regimens was proven based on the results of several phase III studies, including the SPIRITS trial, JCOG 9912 trial, ToGA trial, AVAGAST trial, and JGCA recommendation [71,73-75]. Among platinum agents, cisplatin has been used for the treatment of gastric cancer; however, other platinum agents have also been studied because of their related side effects [8]. The REAL-2 study demonstrated that XELOX was not inferior to 5-FU plus cisplatin (FP), whereas the G-SOX and SOPP studies demonstrated that SOX was as effective as the SP regimen [68,76,77]. SOX and XELOX, which are regimens containing oxaliplatin, have the advantage of not requiring hydration compared to SP and XP, and are recommended as doublet regimens by the JGCA [9]. The SOX-GC phase III trial compared SOX and SP as first-line chemotherapy in cases of diffuse or mixed type gastric cancer, the results of which showed the superiority of SOX over SP in terms of efficacy, survival, and tolerance [78]. Therefore, the CSCO recommended the SOX regimen for non-intestinal gastric cancer [10]. In the GO2 phase III trial, a XELOX

regimen reduced by 60% from the standard dose showed lowered toxicity in elderly and/or frail patients and did not lag PFS [79]. Therefore, low-dose XELOX can be considered for elderly and/or frail patients, according to the NCCN guidelines [11]. Additionally, several studies have demonstrated the efficacy of 5-FU/leovorinate calcium plus oxaliplatin (FOLFOX), which is recommended by the JGCA, NCCN, and ESMO guidelines [80,81]. The JGCA conditionally recommended the S-1 plus docetaxel regimen because the OS was superior to that for S-1 monotherapy for those who cannot use a platinum-containing regimen in the START trial [82]. The combination of irinotecan and fluorouracil (FORFIRI) was also recommended by the NCCN and ESMO guidelines [11,12].

The triplet regimen was controversial: the CSCO, NCCN, and ESMO recommended it; the KGCA conditionally recommended it; and the JGCA did not recommend it [8-12]. The efficacy of the docetaxel, cisplatin, and 5-FU (DCF) combination triplet regimen was demonstrated in a phase III V325 study; however, it was not recommended in the KGCA and JGCA guidelines because of excessive toxicity and was only recommended in select patients [83]. The NCCN and ESMO also mentioned DCF toxicity, which was described in other recommended regimens but not in the preferred regimens [11,12].

In the CheckMate 649 randomized phase III trial, OS and PFS were superior in the group that received nivolumab, an immunoglobulin G4 anti-programmed cell death protein 1 (PD-1) monoclonal antibody, plus chemotherapy compared to chemotherapy alone in patients with programmed cell death-ligand 1 (PD-L1)-combined positive score (CPS)  $\geq 5$  [84]. Therefore, the CSCO recommended the FOLFOX or XELOX plus nivolumab regimen, while the NCCN recommended the fluoropyrimidine and oxaliplatin plus nivolumab regimen for tumors with a PD-L1 CPS  $\geq 5$  [10,11]. The KGCA and JGCA guidelines did not include the FOLFOX or XELOX plus nivolumab regimens because the results of the CheckMate 649 trial were reported after these guidelines were published. Therefore, other guidelines for anti-PD1-based regimens will be updated soon. The palliative systemic treatments recommended by each guideline are summarized in **Table 6**.

### First-line HER2-positive gastric cancer

For HER2-positive gastric cancer, anti-HER2 monoclonal antibody and trastuzumab-based chemotherapy are recommended, with all guidelines recommending a combination of fluoropyrimidine and platinum [8-12]. The ToGA trial demonstrated significantly superior in OS and PFS after the addition of trastuzumab to a cisplatin and fluoropyrimidine (5-FU and capecitabine) regimen for HER2-positive gastric cancer (**Table 6**) [73]. Therefore, trastuzumab has become the standard treatment for HER2-positive gastric cancer, for which all guidelines were in agreement [8-12]. The KGCA recommended XP or FP plus trastuzumab [8]. Recently, because 5-FU is rarely used, the JGCA recommended SP, which proved effective in 2 other phase II trials, in addition to XP, proven in the ToGA trial with trastuzumab [85,86]. Based on the results of phase II studies, the JGCA also conditionally recommended a combination of XELOX, SOX, and trastuzumab for patients who are unsuitable for cisplatin treatment [87,88]. The HERXO trial, a phase II study, also revealed the efficacy of the combination of XELOX and trastuzumab [89]. The CSCO recommended a combination regimen of trastuzumab and XELOX [10]. The NCCN also recommended pembrolizumab with trastuzumab and chemotherapy as “other regimens” based on the results of the KETNOTE-811 trial, which compared pembrolizumab or placebo in combination with trastuzumab to chemotherapy [90]. In this study, the pembrolizumab plus trastuzumab regimen and chemotherapy showed an advantage in objective response rate [91].

**Table 6.** Palliative systemic treatments

Palliative systemic treatment	KGCA (2018)	JGCA (2018)	CSCO (2021)	NCCN (2021)	ESMO (2016)
<b>First-line</b>					
HER2-negative	Platinum + fluoropyrimidine	SP, XP, SOX, XELOX, FOLFOX	Oxaliplatin + fluoropyrimidine Paclitaxel/docetaxel + fluoropyrimidine Cisplatin + fluoropyrimidine FOLFOX/XELOX + nivolumab (PDL1 CPS ≥5)	FOLFOX/XELOX + nivolumab (PD-L1 CPS ≥5) Fluoropyrimidine (5-FU or capecitabine) + oxaliplatin	Platinum + fluoropyrimidine Platinum + fluoropyrimidine + taxanes
HER2-positive	Trastuzumab + XP or FP	Trastuzumab + XP Trastuzumab + SP	Trastuzumab + oxaliplatin/cisplatin + 5-FU/capecitabine	Trastuzumab + XP or FP	Trastuzumab + platinum + fluoropyrimidine
<b>Second-line</b>	Ramucirumab + paclitaxel Taxane Irinotecan Ramucirumab	Ramucirumab + paclitaxel	Paclitaxel Docetaxel Irinotecan	Ramucirumab + paclitaxel Docetaxel Paclitaxel Irinotecan Trastuzumab + deruxtecan for HER2-positive 5-FU + irinotecan	Taxane Irinotecan Ramucirumab Irinotecan + paclitaxel Ramucirumab + paclitaxel
<b>Third-line</b>	Nivolumab Irinotecan Taxane Pembrolizumab	Nivolumab Irinotecan	Apatinib Nivolumab	TAS-102 Pembrolizumab (PDL1 CPS ≥1)	TAS-102

This table only includes JGCA “Recommend regimens,” CSCO “Grade I recommendations,” and NCCN “Preferred Regimens.” KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2, SP = S-1 and cisplatin; XP = capecitabine and cisplatin; SOX = S-1 and oxaliplatin; XELOX = capecitabine and oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; PD-L1 = programmed cell death-ligand 1; CPS = combined positive score; 5-FU = 5-fluorouracil; FP = 5-fluorouracil and cisplatin; TAS-102 = Trifluridine and tipiracil.

### Second-line and subsequent chemotherapy

Several studies have demonstrated that second-line chemotherapy with taxane or irinotecan has a survival advantage over BSC in patients with adequate PS [92-95]. In addition, the efficacy of the anti-vascular endothelial growth factor receptor (VEGFR)-2 monoclonal antibody ramucirumab was proven in the REGARD and RAINBOW randomized phase III trials [96,97]. Therefore, the second-line chemotherapy regimens recommended in all guidelines contain a single agent, taxane, irinotecan, or ramucirumab [8-12]. All guidelines other than the CSCO recommended paclitaxel and ramucirumab combination regimens based on the RAINBOW trial, which showed its superiority over paclitaxel monotherapy [96]. However, while the JGCA recommended a paclitaxel plus ramucirumab combination regimen over taxane, irinotecan, and ramucirumab monotherapy, the CSCO recommended paclitaxel, docetaxel, and irinotecan monotherapy as the first recommendation in second-line chemotherapy [9,10]. The JGCA and CSCO conditionally recommended nab-paclitaxel based on the results of the phase III ABSOLUTE trial, which showed that nab-paclitaxel was not inferior to paclitaxel [98]. The NCCN guidelines recommended FOLFIRI as second-line chemotherapy if it is not used in first-line chemotherapy [11].

If second-line chemotherapy is ineffective, subsequent treatment should be administered; however, evidence regarding the treatment effects is insufficient. Thus, the ESMO guidelines do not mention subsequent treatment; however, the KGCA, JGCA, CSCO, and NCCN guidelines recommend regimens [8-12]. The results of a randomized phase III trial conducted in Korea showed that third-line chemotherapy was more effective than BSC in terms of patient survival [93]. Several studies have shown that regimen containing taxane or irinotecan is effective as a third-line chemotherapy [99-101]. Therefore, the KGCA recommended taxane or irinotecan, while the JGCA recommends irinotecan as third-line

chemotherapy [8,9]. In a randomized phase III TAGS trial, the trifluridine plus tipiracil regimen demonstrated improved OS; therefore, the KGCA and NCCN recommended that it be tried in select patients because of its toxicity [102]. In addition, after this study was published, the ESMO guidelines were updated to recommend the trifluridine plus tipiracil regimen as third-line chemotherapy for PS 0–1 patients [57]. The efficacy of nivolumab was also proven in the phase III ATTRACTION-2 trial; therefore, the KGCA, JGCA, and CSCO recommended nivolumab for subsequent chemotherapy [103]. The KGCA recommended nivolumab regardless of the PD-L1 status in Asian patients [8]. Another PD-L1 antibody, pembrolizumab, was approved by the Food and Drug Administration (FDA) in 2017 based on the results of the KEYNOTE studies and is recommended by the KGCA, CSCO, and NCCN for PD-L1-positive tumors [104,105]. The CSCO recommended apatinib, developed as a selective VEGFR-2 inhibitor, for third-line or later use as monotherapy or combination therapy [10]. However, as ramucirumab is often used as second-line chemotherapy, the KGCA reported that its efficacy remains unclear [8]. The NCCN recommends trastuzumab deruxtecan as a subsequent-line therapy for HER2-positive gastric cancer because it showed improved response and OS compared to standard chemotherapy in a phase II trial [106].

## POSTOPERATIVE FOLLOW-UP SURVEILLANCE

Postoperative follow-up was routinely performed after gastric cancer surgery; however, there is insufficient evidence on the effects of surveillance on improving survival. Therefore, the KGCA and ESMO did not mention a detailed schedule owing to insufficient evidence [8,12]. Other guidelines recommend follow-up surveillance based on retrospective studies and expert consensus. The JGCA, CSCO, and NCCN guidelines recommend 5-year follow-up, with follow-up every 3–6 months and 6–12 months in the early and late postoperative periods, respectively [9–11]. The JGCA and CSCO recommended regular follow-up by esophagogastroduodenoscopy (EGD), computed tomography (CT), and tumor markers (carcinoembryonic antigen [CEA] and cancer antigen [CA] 19-9) to detect recurrence and metachronous cancer [9,10]. However, the NCCN guideline recommended performing CT and EGD only when clinically indicated for both EGC and AGC, and especially mentioned that EGD is not helpful in asymptomatic patients after total gastrectomy [11]. The follow-up surveillance recommended by each guideline differed between EGC and AGC (Tables 7 and 8, respectively). Evidence of postoperative follow-up surveillance for gastric cancer is mandatory for clinical application [107].

## CONCLUSION

The guidelines for each country showed similarities and differences. Each guideline suggested recommendations based on their own medical situation and interpretation of available evidence. In Eastern countries, gastric cancer is often detected at an earlier stage owing to the screening system; therefore, the treatment for EGC is more detailed than that in Western countries. The type of surgery and LND recommended by Eastern and Western countries differed; the degree of LND recommended also differed by each Eastern country. The guidelines in Eastern countries also recommended function-preserving gastrectomy for patients with EGC, whereas the guidelines in Western countries do not suggest this in detail. Moreover, opinions differed regarding recommended chemotherapy and radiotherapy before and after surgery, particularly for neoadjuvant chemotherapy. We comprehensively

**Table 7.** Postoperative follow-up of early gastric cancer

Follow-up	Month	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	56	60
KGCA		Not mentioned due to lack of evidence																				
JGCA	PE, PS, BW	○		○		○		○		○		○		○		○		○		○		○
	Blood test	○		○		○		○		○		○		○		○		○		○		○
	CT			○		○				○				○				○				○
	EGD					○								○								○
CSCO	PE, clinical history, blood test, <i>Helicobacter pylori</i> detection, nutritional status, EGD	3–6 months for 2 years, 6–12 months until 5 years after surgery, annually thereafter																				
	CT	6–12 months for 1 year, annually thereafter																				
NCCN	History, PE	3–6 months for 1–2 years, 6–12 months for 3–5 years, annually thereafter																				
	Blood test	As clinically indicated																				
	CT	As clinically indicated																				
	EGD	As clinically indicated																				
ESMO		Different for each patient																				

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; PE = physical examination; PS = performance status; BW = body weight; CT = computed tomography; EGD, esophagogastroduodenoscopy.

**Table 8.** Postoperative follow-up of advanced gastric cancer

Follow-up	Month	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	56	60
KGCA		Not mentioned due to lack of evidence																				
JGCA	PE, PS, BW	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	Blood test	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
	CT			○		○		○		○		○		○				○				○
	EGD					○								○								○
CSCO	PE, clinical history, Blood test, <i>Helicobacter pylori</i> detection, nutritional status, EGD	3–6 months for 2 years, 6–12 months until 5 years after surgery, annually thereafter																				
	CT	6–12 months for 1 year, annually thereafter																				
NCCN	History, PE	3–6 months for 1–2 years, 6–12 months for 3–5 years, annually thereafter																				
	Blood test	As clinically indicated																				
	CT		○		○		○		○		○		○		○		○		○		○	
	EGD	As clinically indicated																				
ESMO		Different for each patient																				

KGCA = Korean Gastric Cancer Association; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; PE = physical examination; PS = performance status; BW = body weight; CT = computed tomography; EGD, esophagogastroduodenoscopy.

reviewed and integrated these points to allow readers to easily understand the similarities and differences among gastric cancer treatment guidelines. However, since the timing of each guideline differed, the articles also differ because they are evidence-based. This will help medical personnel to understand the guidelines of each country at a glance to precisely compare the global treatment of gastric cancer.

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