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A Comprehensive and Comparative Review of Global Gastric Cancer Treatment Guidelines: 2024 Update

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ABSTRACT

Differences in demographics, medical expertise, and patient healthcare resources across countries have led to significant variations in guidelines. In light of these differences, in this review, we aimed to explore and compare the most recent updates to gastric cancer treatment from five guidelines that are available in English. These English-version guidelines, which have been recently published and updated for journal publication, include those published in South Korea in 2024, Japan in 2021, China in 2023, the United States in 2024, and Europe in 2024. The South Korean and Japanese guidelines provide a higher proportion of content to endoscopic and surgical treatments, reflecting their focus on minimally invasive techniques, function-preserving surgeries, and systemic therapy. The Chinese guidelines provide recommendations addressing not only surgical approaches but also perioperative chemotherapy and palliative systemic therapy. Meanwhile, in the United States and European guidelines, a higher proportion of the content is dedicated to perioperative and palliative systemic therapy, aligning with their approaches to advanced-stage disease management. All guidelines address surgical and systemic chemotherapy treatments; however, the proportion and emphasis of content vary based on the patient distribution and treatment approaches specific to each country. With emerging research findings on gastric cancer treatment worldwide, the national guidelines are being progressively revised and updated. Understanding the commonalities and differences among national guidelines, along with the underlying evidence, can provide valuable insights into the treatment of gastric cancer.

Keywords: Stomach neoplasm; Guideline; Gastrectomy

INTRODUCTION

The incidence and mortality rates of gastric cancer have been gradually decreasing; however, gastric cancer remains the fifth most common malignancy and the fifth leading cause of cancer-related mortality worldwide [1,2]. Although the overall global incidence of gastric cancer has gradually declined in some regions owing to improved healthcare systems and prevention strategies, it remains the leading cause of cancer-related deaths in other areas such as East Asia, Eastern Europe, parts of South-Central Asia, and Latin America [1].

jgc Journal of Gastric Cancer

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Differences in genetic, environmental, and lifestyle factors contribute to regional variations in the prevalence and outcomes of gastric cancer [3,4]. These disparities underscore the necessity for tailored diagnostic and treatment approaches, prompting countries to develop and periodically update their gastric cancer treatment guidelines [5].

Treatment of gastric cancer remains challenging, with active clinical trials conducted on endoscopic resection (ER), surgical treatment, and systemic therapy. Recent studies have focused on establishing indications for ER and investigating stomach-preserving surgical techniques [6]. Additionally, breakthroughs in systemic therapies, including immunotherapy and targeted therapy, have revolutionized the management of advanced gastric cancer (AGC), necessitating frequent updates to treatment guidelines [7].

Adherence to these evidence-based guidelines have improved survival outcomes, emphasizing their critical role in clinical practice [8,9]. However, differences in demographics, medical expertise, and healthcare resources across countries have resulted in significant variations in guideline recommendations [5]. To address these differences, in this study, we aimed to explore and compare recent updates with the English version of the gastric cancer treatment guidelines. The guidelines reviewed in this comparison are as follows.

- The Korean Practice Guideline for Gastric Cancer, scheduled for publication alongside this research in 2024 by the Korean Gastric Cancer Association (KGCA) [10]
- The Japanese Gastric Cancer Treatment Guideline, 6th edition in 2021, published by the Japanese Gastric Cancer Association (JGCA) [11]
- The Chinese Guidelines for Gastric Cancer in 2023, published by the Chinese Society of Clinical Oncology (CSCO) [12]
- The National Comprehensive Cancer Network (NCCN) Guideline for Gastric Cancer in 2024, version 4 [13]
- The European Society for Medical Oncology (ESMO) Guideline for Gastric Cancer in 2022 [14] and its live-updated guideline version 1.4 in September 2024 [15]

Our comparative analysis of the guidelines focused on newly updated endoscopic, surgical, and systemic therapies provided a comprehensive overview of how these updates reflect the evolving landscape of gastric cancer treatment.

LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

Guideline development is evidence-based; however, the methodologies adopted in the guidelines of each country vary accordingly (**Table 1**). The KGCA guidelines redefined the levels of evidence and grading recommendations based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Additionally, all de novo key questions were meta-analyzed, which aided in evaluating the strengths of the recommendations [10]. The JGCA guidelines based its recommendations on the Medical Information Network Distribution Service (MINDS) methodology, which adopts the GRADE methodology, and for certain clinical questions, the recommendation grades were determined through consensus among committee members [11]. The CSCO guidelines developed a unique level of evidence and a recommendation grading system based on expert consensus [12]. The NCCN guidelines assess the level of evidence using the NCCN Categories of Evidence and Consensus and the NCCN Categories of Preference. The NCCN guidelines

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Table 1. Levels of evidence and grading of recommendations

Guidelines	Levels of evidence and grading of recommendations
KGCA (2024)	GRADE methodology reviews; systematic reviews on each key question
JGCA (2021)	MINDS clinical guideline manual which adopts the GRADE methodology
	Strength of recommendation is classified based on systematic review outcomes and consensus
CSCO (2023)	CSCO levels of evidence and consensus
	CSCO recommendation grades
NCCN (2024)	NCCN categories of evidence and consensus
	NCCN categories of preference
ESMO (2024)	Infectious Diseases Society of America-United States Public Health Service Grading System

KGCA = Korean Gastric Cancer Association; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; JGCA = Japanese Gastric Cancer Association; MINDS = Medical Information Network Distribution Service; CSCO = Chinese Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology.

specify evidence categories and preferred regimens but do not include recommendation grades. Preferred regimens were compared in the palliative systemic therapy section, whereas evidence categories were compared in other sections [13]. The ESMO guidelines developed its recommendations based on the Infectious Diseases Society of America-United States Public Health Service Grading System [14,15].

ENDOSCOPIC TREATMENT

The differences in recommendations and indications for ER across the KGCA, JGCA, CSCO, NCCN, and ESMO are detailed in **Table 2**. In the guidelines updated after 2022, compared with the 2018 guidelines, the KGCA elevated the recommendation level for indications of ER or surgery. Furthermore, the JGCA and CSCO expanded the scope of absolute indications of endoscopic submucosal dissection (ESD). Currently, ER, such as endoscopic mucosal resection (EMR) and ESD, is considered the standard treatment for early gastric cancer (EGC) when the risk of lymph node (LN) metastasis is less than 1% [16]. This indication applies to differentiated-type adenocarcinoma confined to the mucosa, with a tumor size of ≤2 cm and no ulceration, commonly referred to as the absolute indication. All 5 guidelines recommend EMR or ESD in cases with absolute indications [10-15]. For tumors >2 cm, confined to the mucosa without ulceration, or tumors ≤3 cm, confined to the mucosa with ulceration, the KGCA recommends either ESD or surgery [10]. Conversely, the JGCA and CSCO classify these as absolute criteria for ESD and advocate ESD as the treatment of choice [11,12]. A notable change in the JGCA guidelines is the reclassification of undifferentiated-type adenocarcinoma, confined to the mucosa, ≤2 cm in size, and without ulceration, from an expanded to an absolute indication [11]. This change was based on the results of the Japan Clinical Oncology Group (JCOG) 1009/1010 trial, a multicenter, single-arm confirmatory study. The trial demonstrated that performing ESD in patients meeting the aforementioned criteria resulted in a 5-year overall survival (OS) rate of 99.3% (95% confidence interval [CI], 97.1–99.8) [17]. The CSCO defines this as an expanded indication and recommends ESD as the treatment of choice [12]. However, the KGCA takes a more cautious stance, recommending ER for undifferentiated-type adenocarcinoma only after thorough discussion and classifying it as a conditional recommendation [10]. The KGCA emphasizes that no randomized controlled trials (RCTs) have compared long-term outcomes between ER and gastrectomy with lymph node dissection (LND) [18]. Although several retrospective studies have shown no significant differences in OS between the two approaches, ER is associated with a higher rate of local recurrence [19,20]. Therefore, the KGCA concluded that defining ER as the standard treatment for this indication is challenging [10]. The ESMO also recommends both ER and gastrectomy with LND for the same indications as outlined by the KGCA [14,15].

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jgc Journal of Gastric Cancer

Table 2. Endoscopic resection

Endoscopic resection	KGCA (2024)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
ER					
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 (–)
ER or surgery					
Recommendation					Grade B
Indication	1. >2 cm, T1a, UL (–), Diff or ≤3 cm, T1a, UL (+) (Strong for) 2. ≤2 cm, T1a, UL (–), Undiff (Conditional for)				1. >2 cm, T1a, UL (–), Diff or ≤3 cm, T1a, UL (+) 2. ≤2 cm, T1a, UL (–), Undiff
Additional ER					
Recommendation	Conditional for				
Indication	Lateral margin positive with curative resection	eCura C-1	eCura C-1		
Additional surgery					
Recommendation	Strong for		Grade I	Category 2A	
Indication	Outside ER indication or LVI (+) or VM (+)	eCura C-2	eCura C-2	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; ER = endoscopic resection; Diff = differentiated; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; UL = ulcerative finding; Undiff = undifferentiated; LVI = lymphovascular invasion; HM = horizontal margin; VM = vertical margin; eCura = endoscopic curability.

Following ER, the JGCA and CSCO use the endoscopic curability (eCura) classification to guide subsequent management, including observation, additional ER, and gastrectomy with LND. The JGCA and CSCO classify cases that meet the indications for ER but have a positive lateral margin as eCura C-1 and recommend additional ER as a treatment option [11,12]. Similarly, the KGCA considers this approach a conditional recommendation based on a meta-analysis of seven retrospective studies that compared the recurrence rates of ER, gastrectomy, and close observation [10]. The JGCA classifies cases of undifferentiated-type adenocarcinoma following ER as eCura A if they meet the criteria of pT1a, no ulceration, tumor size <2 cm, negative margins, and no lymphovascular invasion, recommending observation for these cases [11]. However, the CSCO classifies this indication as eCura B and recommends observation without additional surgery [12]. The NCCN guidelines recommend gastrectomy for all undifferentiated-type adenocarcinoma cases [13]. Differences in ER indications between countries may stem from variations in pathological processing and interpretation. Therefore, rather than assuming uniformity in pathological diagnoses across countries when establishing treatment guidelines, developing these guidelines in collaboration with the Pathology Society of each country may be more appropriate [21].

SURGICAL TREATMENT

Gastrectomy with LND is the treatment of choice for resectable gastric cancers that do not meet the indications for ER. In gastric cancer surgery, determining the extent of resection based on the tumor location, selecting the surgical approach, and deciding the extent of LND are critical. Since the 2020s, revised guidelines have incorporated findings from studies on various types of function-preserving gastrectomy (FPG) for EGC, including distal

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jgc Journal of Gastric Cancer

gastrectomy (DG) and total gastrectomy (TG). Furthermore, research demonstrating the safety and feasibility of laparoscopic and robotic surgeries has contributed to these updates.

FPG

The JGCA and CSCO recommend FPG, such as pylorus-preserving gastrectomy (PPG) and proximal gastrectomy (PG), for clinical T1N0 gastric cancer [11,12]. Additionally, the KGCA has suggested sentinel node navigation surgery (SNNS) as a treatment option for EGC (**Table 3**) [10]. The KGCA conditionally recommends PPG along with standard surgery for EGC if the lesion is located at least 5 cm proximal to the pylorus. This recommendation is based on long-term outcome data from the KLASS-04 prospective RCT and a meta-analysis of retrospective studies comparing laparoscopic PPG with laparoscopic DG [10,22,23]. Similarly, the JGCA and CSCO recommend PPG for cT1N0 tumors when the distal border of the tumor is located at least 4 cm from the pylorus, and the tumor is located in the middle portion of the stomach [11,12]. The KGCA proposed PG with double-tract reconstruction (DTR) as an additional option alongside standard surgery for EGC located in the upper third of the stomach, which cannot preserve the fundus [10]. This recommendation was based on the results of the KLASS-05 prospective RCT and meta-analysis of retrospective studies comparing laparoscopic TG and PG with DTR [24,25]. The JGCA recommends PG for EGC located in the proximal stomach when more than 50% of the distal stomach is preserved [11]. Similarly, the CSCO recommends PG for esophagogastric junction (EGJ) cancers <4 cm in size and without LN metastasis to stations 4d, 5, and 6 in imaging assessments, provided that at least 50% of the distal stomach is retained [12]. The NCCN and ESMO guidelines do not provide detailed recommendations regarding function-preserving surgery [13-15]. Only the KGCA conditionally recommends SNNS as a treatment option for cT1N0 ≤3 cm sized EGC based on the results of SENORITA trial which compared laparoscopic gastrectomy with SNNS and their meta-analysis results in terms of nutritional outcomes, quality of life (QOL) and oncologic outcomes [10,26]. Eastern guidelines, such as those from the KGCA, JGCA, and CSCO, show greater interest and provide more detailed recommendations for FPG for EGC than Western guidelines such as the NCCN and ESMO.

Surgical approach

Minimally invasive surgeries, including laparoscopic and robotic approaches, have garnered increasing interest in gastric cancer surgery, leading to numerous studies of these techniques [27]. The KGCA and CSCO recommend laparoscopic surgery for all cases of EGC and AGC, except for T4b and bulky LN tumors [10,12]. These recommendations are supported by evidence from large-scale prospective RCTs, such as KLASS-01, COACT 0301, and JCOG0912,

Table 3. Function-preserving surgery

Operation	KGCA (2024)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
PG					
Recommendation	Conditional for	Weakly recommend	Grade II, III		Not mentioned
Indication	cT1; Tumor size ≤3 cm; Upper 1/3, not able to preserve fundus	cT1N0; Remnant distal stomach ≥50%	Stage Ia; Proximal side	Proximal side	
PPG					
Recommendation	Conditional for	Weakly recommend	Grade II	Not mentioned	Not mentioned
Indication	cT1; Tumor size ≤3 cm; ≥5 cm from the pylorus	cT1N0; Middle portion; ≥4 cm from the pylorus	Stage Ia		
SNNS					
Recommendation	Conditional for	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Indication	cT1N0; Tumor size ≤3 cm				

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; SNNS = sentinel node navigation surgery.

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jgc Journal of Gastric Cancer

which demonstrated the non-inferiority of laparoscopic distal gastrectomy (LDG) to open distal gastrectomy (ODG) for EGC [28-30]. Furthermore, the prospective RCT KLASS-02 and CLASS-01 comparing LDG and ODG for AGC have validated the efficacy of LDG in terms of both short- and long-term outcomes [31,32]. A meta-analysis conducted by the KGCA also showed that LDG was not inferior to ODG in terms of short- and long-term outcomes for both EGC and AGC [10]. The JGCA recommends laparoscopic surgery for EGC owing to its well-established safety. However, clear recommendations for AGC are not provided because of variations in factors such as estimated blood loss and operating time, as observed in studies such as CLASS-1 (China), KLASS-02 (Korea), and the ongoing JLSSG0901 (Japan) [11,33]. The results of the JLSSG0901 study are now available, and the KGCA incorporated these findings into a meta-analysis to develop recommendations [34]. The JGCA guidelines are also anticipated to be updated based on this evidence.

Robot-assisted gastrectomy (RG) is conditionally recommended by the KGCA and weakly recommended by the JGCA, whereas the CSCO states that further evidence is required to recommend it [10-12]. The KGCA conducted a meta-analysis that included 2 RCTs and several retrospective studies. The analysis demonstrated that, although RG has longer operative times and higher costs than LG, it is not inferior in terms of survival outcomes and postoperative complications [10]. The JGCA formulated recommendations for RG based on the results of its own studies [35,36], whereas the CSCO also developed guidelines based on the outcomes of its respective studies, which demonstrated fewer postoperative complications in RG [37,38].

The NCCN guidelines recommend that laparoscopic and robotic surgeries are recommended for both EGC and AGC when performed by experienced surgeons, as their oncologic outcomes have been demonstrated in both Eastern and Western countries. However, minimally invasive surgery is not recommended for T4b or N2 bulky gastric cancer [13]. Similarly, the ESMO guidelines recommend minimally invasive surgery exclusively for cases managed by experienced surgeons, citing reasons similar to those outlined by the NCCN [14,15].

LND

Japanese guidelines have long provided detailed definitions of the extent of LND, which have been adopted globally. LND is considered a critical component of gastric cancer surgery due to the risk of LN metastasis. Although most countries recommend D1+ dissection for EGC and D2 dissection for AGC, there are minor variations in the specific guidelines among different nations (**Table 4**).

The KGCA recommends D1+ LND for cT1N0 tumors and D2 LND for tumors classified as cT2 or higher [10]. The JGCA and CSCO recommend D1 LND for T1aN0 tumors not meeting ESD indications or T1bN0 tumors that are differentiated type and ≤1.5 cm in size. For all other T1N0 tumors, D1+ LND is recommended, while D2 LND is advised for T2–T4 tumors or T1 tumors with LN metastasis (T1N+) [11,12].

The KGCA conducted a meta-analysis of 3 prospective RCTs regarding prophylactic splenectomy. The analysis revealed that the non-splenectomy group experienced fewer postoperative complications than the splenectomy group; both groups did not significantly differ in survival outcomes [39-41]. An RCT conducted in Japan demonstrated no survival benefits in the splenectomy group [42]. Similarly, an RCT conducted in China indicated that LND at station 10 provided no survival benefit in cases of proximal gastric cancer without

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Table 4. Lymph node dissection

Lymph node dissection	KGCA (2024)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
D1					
Recommendation	Not mentioned		Grade I	Category 2A	
Indication		T1aN0; T1bN0, Diff, <1.5 cm	T1aN0; T1bN0, Diff, <1.5 cm	Localized resectable cancer	Localized resectable cancer
D1+					
Recommendation	Strong for		Grade I	Not mentioned	
Indication	cT1N0	T1N0	T1N0		T1 tumors
D2					
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
D2+					
Recommendation	Not mentioned		Grade II, III	Not mentioned	Not mentioned
Indication		Metastasis to no. 10, 14v, 13, 16 LNs	Metastasis to no. 10, 14v (Grade II), 13 (Grade III) LNs		
Prophylactic splenectomy					
Recommendation	Strong against	Weakly recommend	Not recommend	Not recommend	Not mentioned
Indication	Not recommend	GC invasion			

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; LN = lymph node; GC = greater curvature.

invasion of the greater curvature [43]. To summarize, the updated guidelines from the KGCA, JGCA, and CSCO since 2020, uniformly recommend against prophylactic splenectomy or LND at station 10 for AGC without greater curvature invasion [10-12]. The KGCA states that the meta-analysis included in the 2024 guidelines did not encompass cases with a high likelihood of LN 10 metastasis, such as those involving invasion of the greater curvature or the gastrosplenic ligament [44-46]. Given that splenectomy is associated with increased complications and mortality, the KGCA emphasizes the need for further research to establish treatment criteria for these specific conditions [10]. The JGCA weakly recommends splenectomy or LN 10 dissection on a consensus basis in cases in which the tumor invades the greater curvature [11]. Similarly, the CSCO recommends LN 10 dissection for tumors classified as T3–T4, larger than 6 cm, and located in the middle to upper parts of the stomach along the greater curvature because of the increased likelihood of LN 10 metastasis in such cases [12,42,46,47].

The JGCA recommends No. 14v LND in conjunction with distal stomach tumors with metastasis to No. 6 LN. Additionally, No. 13 LND is recommended for tumors that invade the duodenum [11,48]. The JGCA also recommends No. 16 LND in cases of extensive LN involvement following neoadjuvant chemotherapy (NAC) [11]. The CSCO also recommends No. 14v LND for stage III tumors located in the middle or lower parts of the stomach with metastasis to the No. 6 LN [12]. This recommendation is based on studies demonstrating improved OS in patients with stage III or IV middle and lower gastric cancer who underwent this procedure [49]. In cases where the tumor invades the duodenum, the CSCO recommends NAC followed by D2 LND, with an additional No. 13 LND [12]. This recommendation is based on evidence indicating a 26.7% metastasis rate to No. 13 LN in such cases [50-52].

The NCCN and ESMO guidelines recommend D1 or D1+ LND for localized resectable tumors, with D2 LND advised only for cases managed by experienced surgeons [13-15]. The ESMO, in particular, has established these criteria based on the results of recent studies [53].

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Unresectable/metastatic gastric cancer surgery

Current guidelines do not recommend reductive gastrectomy for unresectable or metastatic gastric cancer. However, all guidelines recommend supportive care interventions or bypass surgery to alleviate symptoms in patients with gastric outlet obstruction (GOO) or bleeding to alleviate symptoms [10-15].

In a meta-analysis of 15 studies, the KGCA compared endoscopic stenting and surgical bypass for GOO. The analysis revealed that both endoscopic stenting and surgical bypass are effective as palliative treatments for GOO, while outlining their respective advantages and disadvantages [10]. The JGCA recommends that surgical intervention is beneficial in terms of QOL in patients with GOO [11].

With the growing interest in the treatment of unresectable or metastatic gastric cancer, updated guidelines have incorporated several surgical treatment recommendations based on recent research findings.

The KGCA conducted a meta-analysis of two retrospective studies addressing the treatment of liver oligometastases in gastric cancer [54,55]. Although many studies have investigated liver metastases in gastric cancer, most were difficult to distinguish from those in conversion surgery, and relatively few studies have focused on the simultaneous resection of liver oligometastases and primary gastric cancer. The analysis demonstrated a survival benefit when gastrectomy and hepatectomy were combined with systemic chemotherapy compared to chemotherapy alone. However, owing to the small sample size and retrospective nature of these studies, the KGCA issued an investigational recommendation for selected patients [10]. The JGCA weakly recommends surgery for patients with liver oligometastasis [11]. The CSCO, citing evidence from systematic reviews, meta-analyses, and surveys (such as those conducted by the European Organisation for Research and Treatment of Cancer and JCOG), issued a Grade II recommendation for systemic chemotherapy combined with resection of both primary and metastatic tumors in cases involving single liver metastasis [56-59]. The ESMO acknowledges that research on surgical treatment for oligometastatic disease remains insufficient and recommends awaiting the results of ongoing RCTs to inform future guidelines [14,15].

Interest in conversion surgery, a surgical treatment option in cases of unresectable or metastatic gastric cancer where the response to systemic chemotherapy is favorable, has increased [60]. The KGCA conducted a meta-analysis of 3 retrospective studies and one prospective study, which demonstrated a benefit in OS with conversion surgery [61,62]. However, owing to inevitable selection bias and advancements in systemic therapies, the KGCA issued an investigational recommendation for this approach [10]. The JGCA, based on consensus, weakly recommends conversion surgery for cases where R0 resection is achievable following chemotherapy [11]. Similarly, the CSCO provides a Grade II recommendation for the same scenario [12]. The KGCA guidelines detailed the consensus rates from an expert consensus meeting on conversion surgery held during the 2024 Korea International Gastric Cancer Week. This meeting marked the first occasion in which conversion therapy for stage IV gastric cancer was discussed, with active debates and voting among experts from various countries, including the United States, Netherlands, China, Japan, Germany, and Poland [10].

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PERIOPERATIVE TREATMENT

NAC

Several guidelines have revised recommendations for NAC. In the KGCA guidelines, updated after 2022, the stance on NAC, which was previously inconclusive in the 2018 guidelines, was upgraded to a conditional recommendation for locally resectable AGC [10]. In contrast, the JGCA downgraded its recommendation from conditional in the fifth edition in 2018 to no clear recommendation in the sixth edition in 2021 [11]. The CSCO upgraded NAC to a Grade I recommendation for stage III gastric cancer [12]. Meanwhile, the NCCN and ESMO maintained their previous positions, recommending NAC for cT2 or higher and any N tumors with Category 1 and Grade A recommendations, respectively [13,14]. The ESMO guidelines further designate NAC as the standard treatment over surgery, followed by adjuvant chemotherapy, particularly in European and Western populations (**Table 5**) [14].

Three prospective RCT on NAC have been conducted in Asia. The PRODIGY trial from Korea demonstrated that NAC using a regimen of docetaxel, oxaliplatin, and S-1 (DOS) showed superior outcomes compared with adjuvant S-1 in terms of complete resection rates and progression-free survival (PFS) [63]. The RESOLVE trial demonstrated the efficacy of S-1 and oxaliplatin (SOX) regimens over adjuvant capecitabine and oxaliplatin (CAPOX) in terms of disease-free survival (DFS) [64]. In recent long-term follow-up analyses, both PRODIGY and RESOLVE trials confirmed that perioperative chemotherapy offers a significant benefit in OS than adjuvant chemotherapy alone [65,66]. The JCOG0501 trial aimed to evaluate the efficacy of NAC combined with S-1 and cisplatin; however, the trial revealed no significant clinical benefit [67]. The KGCA conducted a meta-analysis incorporating 3 RCTs, which revealed that NAC provided a clinical benefit when compared with upfront surgery. The analysis demonstrated an improvement in DFS with a hazard ratio (HR) of 0.81 (95% CI, 0.68–0.97). Based on these findings, the KGCA recommends DOS and SOX regimens for NAC [10]. Additionally, the KGCA states that the fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) regimen, commonly used in Western countries, has not yet been adequately studied in Asian populations and should not be adopted without further evidence [10]. The JGCA

Table 5. Perioperative treatments

Perioperative treatment	KGCA (2024)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
Neoadjuvant chemotherapy					
Recommendation	Conditional for	No clear recommends	Grade I (cStage III)	Category 1 (cT2 or higher, any N)	Grade A (cT2 or higher, any N)
Regimen	DOS, SOX	Not mentioned	SOX	FLOT (fluoropyrimidine + oxaliplatin)	FLOT (Fluoropyrimidine + platinum + docetaxel)
Neoadjuvant chemoradiotherapy					
Recommendation	Investigational	Not mentioned	Grade I (Gastric cancer invading the EGJ: cT3-4aN+M0)	Category 2B	No recommendation
Adjuvant chemotherapy					
Recommendation	Strong for (Stage II or III)	Recommend (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, CAPOX	S-1/S-1 + docetaxel (Stage II/III), CAPOX (Stage II, III)	S-1/CAPOX (Stage II), CAPOX/SOX (Stage III)	CAPOX, FOLFOX	Fluoropyrimidine + oxaliplatin or docetaxel
Adjuvant chemoradiotherapy					
Recommendation	Conditional against (<D2 LND and/or R1 resection)	Not mentioned	Grade I (<D2 LND and/or R1 or R2 resection)	Category 2A (<D2 LND and/or R1 or R2 resection)	Grade D (<D2 LND, R1 resection)

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; DOS = docetaxel, oxaliplatin, and S-1; SOX = S-1 and oxaliplatin; FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel; EGJ = esophagogastric junction; CAPOX = capecitabine and oxaliplatin; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; LND = lymph node dissection.

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jgc Journal of Gastric Cancer

guidelines, referring to the results of the JCOG0501 trial, state that while other countries have demonstrated the efficacy of NAC, Japan is yet to provide clear evidence supporting its use. Consequently, the JGCA issued a consensus-based recommendation without a definitive stance on NAC [11]. Since the 2021 guidelines, the CSCO has placed significant emphasis on NAC and actively included recommendations for its use [68]. The CSCO provides the following recommendations for NAC in non-EGJ gastric cancer: SOX is given a Grade I recommendation, DOS and FLOT are given Grade II recommendations, and CAPOX and 5-fluorouracil (5-FU)/levofolinate calcium plus oxaliplatin (FOLFOX) are given Grade III recommendations [12]. The CSCO, similar to the KGCA, based its recommendations on the SOX regimen in the RESOLVE trial [64]. In addition, the CSCO recommends a DOS regimen for NAC based on the findings of the PRODIGY and 2022 MATCH trials [63,69]. Furthermore, the CSCO recommends the FLOT regimen based on evidence from a large prospective phase III FLOT4 trial [70]. The MAGIC trial first established a perioperative chemotherapy regimen using epirubicin, cisplatin, and fluorouracil (ECF) in Western countries [71]. Subsequently, the FLOT4 trial demonstrated the superiority of FLOT to the ECF regimen. Based on these findings, the FLOT regimen is recommended as the standard NAC treatment regimen in Western countries. The NCCN and ESMO guidelines recommend the FLOT regimen as a NAC option based on the results of the FLOT4 trial [13,14,70]. The NCCN recommends the FOLFOX regimen as an alternative because of the toxicity associated with the FLOT regimen [13]. Furthermore, the ESMO recommends a triplet chemotherapy regimen comprising fluoropyrimidine, platinum, and docetaxel as perioperative treatment [14,15].

Neoadjuvant chemoradiotherapy (NCRT)

In the context of NCRT, guidelines updated since 2020 are consistent with previous recommendations in some regions. The KGCA remained inconclusive in its 2018 guidelines to an investigational recommendation level updated after 2022. The CSCO maintains a Grade I recommendation, and the NCCN continues to issue Category 2B recommendations. As in previous guidelines, the JGCA does not address the topic, whereas the ESMO, which did not mention it in earlier guidelines, now explicitly states no recommendation in the updated version (**Table 5**) [10-15].

The KGCA conducted a meta-analysis of 2 RCT on NCRT [72,73]. Although the analysis demonstrated benefits in terms of complete remission and PFS rates, it did not reveal significant advantages in OS or R0 resection rates [10]. The KGCA notes that most studies on NCRT included cases of EGJ cancers and were predominantly conducted in Western populations. Based on these findings, the KGCA provides investigational recommendations for NCRT [10]. The CSCO also referenced the NEO-AEGIS study, which demonstrated the benefits of NCRT in terms of tumor regression [74]. Considering this, along with the POET study, the CSCO acknowledged the need for further research in the Chinese population but currently provides a Grade I recommendation for NCRT in EGJ cancer treatment [12,73]. The NCCN guidelines, based on the results of studies such as the CROSS, CALGB 9781, and PRODIGE5/ACCORD17 trials, provide Category 2B recommendations for NCRT [13,75-79]. ESMO guidelines state that NCRT remains undefined, emphasizing the need for further clinical trials to establish its role [14,15].

Adjuvant chemotherapy

All 5 guidelines recommended adjuvant chemotherapy following surgery for AGC after D2 LND. However, there are differences in the stages for which adjuvant chemotherapy is advised. The KGCA, JGCA, and CSCO guidelines recommend adjuvant chemotherapy for

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jgc Journal of Gastric Cancer

postoperative stage II and III gastric cancers, whereas the NCCN and ESMO guidelines extend their recommendations to include stage IB cases, such as T2N0 tumors. The recommended adjuvant chemotherapy regimens vary among guidelines depending on the referenced studies (**Table 5**) [10-15].

The CLASSIC trial conducted in South Korea, China, and Taiwan, and the ACTS-GC trial conducted in Japan demonstrated that adjuvant chemotherapy provided a survival benefit compared with observation alone following gastrectomy with D2 LND [80,81]. The CLASSIC trial demonstrated the efficacy of the CAPOX regimen in stage II–IIIB gastric cancer, whereas the ACTS-GC trial established the efficacy of the S-1 regimen in patients with stage II or III gastric cancer [82,83]. A meta-analysis conducted by the KGCA also confirmed that adjuvant chemotherapy provides benefits in terms of OS and DFS (OS: HR, 0.66; 95% CI, 0.56–0.78 and DFS: HR, 0.62; 95% CI, 0.54–0.72; P<0.001). Consequently, the KGCA, JGCA, and CSCO guidelines recommend S-1 and CAPOX as adjuvant chemotherapy regimens [10]. The JACCRO GC-07 trial demonstrated that the S-1 plus docetaxel regimen provided a significant benefit in relapse-free survival (RFS) compared with S-1 monotherapy in stage III gastric cancer [84]. Similarly, the ARTIST2 trial showed that the SOX regimen offers superior DFS compared with S-1 monotherapy [85]. The KGCA conducted a meta-analysis incorporating the results of these two studies, demonstrating that S-1-based doublet regimens provide a significant advantage in DFS compared with S-1 monotherapy (HR, 0.71; 95% CI, 0.59–0.85; P=0.0001). Furthermore, a subgroup analysis of the CLASSIC trial [80] revealed that the efficacy of CAPOX was maintained even at a more advanced stage, which was not observed in the ACTS-GC trial. Based on these results, the KGCA also indicates that for stage II gastric cancer with positive LN or stage III gastric cancer, oral fluoropyrimidine-based doublet regimens may be considered a favorable treatment option compared with S-1 monotherapy [10]. In addition, the JGCA recommends S-1 in pStage II and S-1 plus docetaxel, SOX, and CAPOX regimens as adjuvant chemotherapy options for pStage II and III gastric cancer [11]. Although the CSCO acknowledges that the benefits of adjuvant chemotherapy in stage I patients with high-risk factors have not been conclusively established, adjuvant chemotherapy is recommended as a potential treatment option for this subgroup [12]. The NCCN guidelines recommend the CAPOX regimen as adjuvant chemotherapy based on the CLASSIC trial, with FOLFOX also recommended based on panel consensus [13]. The ESMO guidelines note that most studies on adjuvant chemotherapy have been conducted in Asian populations, which may limit the applicability of these findings to European patients. However, based on a meta-analysis showing that 5-FU-based chemotherapy provides a survival benefit compared to surgery alone, the guidelines recommend fluoropyrimidine plus oxaliplatin or docetaxel regimens as adjuvant chemotherapy options [86]. Additionally, the ESMO guidelines emphasize a stronger preference for NAC over adjuvant chemotherapy [14,15].

Adjuvant chemoradiotherapy

The recommendations for adjuvant chemoradiotherapy have been updated in the guidelines since 2020. Both the KGCA and ESMO downgraded their recommendations, with the KGCA revising its stance from weak for recommendation in the 2018 guidelines to conditional against recommendation in the guidelines updated after 2022. ESMO lowered its recommendation from Grade B in 2016 to Grade D after 2022 [10,14,15]. The JGCA has continued to omit adjuvant chemoradiotherapy [11]. The CSCO and NCCN have maintained their respective positions with Grade I and Category 2A recommendations, respectively (**Table 5**) [12,13].

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jgc Journal of Gastric Cancer

The KGCA conducted a meta-analysis incorporating 6 RCTs and found that adjuvant chemoradiotherapy did not provide a benefit in OS (HR, 1.03; 95% CI, 0.87–1.23; P=0.70) and DFS (HR, 0.91; 95% CI, 0.78–1.07; P=0.24) compared to platinum-based combination chemotherapy [10]. Similarly, the ESMO guidelines cite the results of the CRITICS, ARTIST, and ARTIST 2 trials, which demonstrated that regarding survival benefit, additional adjuvant chemoradiotherapy was not superior to chemotherapy alone in patients who underwent D2 curative resection [85,87-90]. The CSCO provides a Grade I recommendation for adjuvant chemoradiotherapy but specifies that this applies only in cases where adequate D2 LND was not performed or in instances of R1 or R2 resection. In addition, the NCCN guidelines recommend chemoradiotherapy for patients who undergo less than D2 LND. Both the CSCO and NCCN, referencing prospective studies cited in other guidelines, recommend adjuvant chemotherapy instead of chemoradiotherapy in patients who have undergone D2 LND with R0 resection [12].

PALLIATIVE SYSTEMIC TREATMENT

Palliative systemic therapy is the standard treatment for unresectable gastric cancer, and ongoing research focuses on developing novel agents to improve survival outcomes [7]. The results of recent studies on targeted therapy and immunotherapy have been promising, leading to updates in the guidelines based on these findings. Although the regimens recommended by the guidelines are generally similar, the recommendation grades and evidence levels for the same regimens vary. Although many palliative regimens are recommended, this review focuses on comparing the most strongly recommended regimens categorized as “Strong for recommendation” in the KGCA, “Recommended regimen” in the JGCA, “Grade I recommendation” in the CSCO, “Preferred regimen” in the NCCN, and “Grade I recommendation” in the ESMO guidelines (**Table 6**).

Palliative first-line systemic therapy for human epidermal growth factor receptor 2 (HER2)-negative gastric cancer

As more research findings emerge, recently published guidelines have demonstrated increasingly detailed stratifications of the recommended regimens. In palliative first-line systemic therapy, treatment regimens are differentiated based on specific biomarkers such as HER2, programmed cell death-ligand 1 (PD-L1), and claudin 18.2 (CLDN18.2). All guidelines now recommend regimens, including nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody, for HER2-negative tumors as first-line systemic therapy based on the PD-L1 combined positive score (CPS) [10-15]. Additionally, the CSCO has included sintilimab- and tislelizumab-combined regimens as Grade I recommendations, whereas the KGCA, NCCN, and ESMO have added pembrolizumab-combined regimens to their lists of preferred regimens based on recently published research [10,12-15]. In the updated guidelines, the KGCA and ESMO recommend zolbetuximab for patients with CLDN18.2-positive tumors [10,14,15].

The JGCA recommends the S-1 and cisplatin (SP) regimen as standard treatment based on the JCOG 9912 and SPIRITS trials [91,92]. Additionally, the capecitabine and cisplatin (XP) regimen is recommended, as supported by evidence from the ToGA and AVAGAST trials [93,94]. The efficacy of the SOX regimen has also been recognized and supported by the findings of the G-SOX study [95,96]. Furthermore, the FOLFOX regimen is recommended based on recent findings [97]. Consequently, the JGCA endorses fluoropyrimidine- and platinum-based chemotherapy as first-line chemotherapy options except original 5-FU and

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Table 6. Palliative systemic treatments

Palliative systemic treatment	KGCA (2024)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
First-line					
HER2-negative	· FOLFOX/CAPOX + nivolumab (PD-L1 CPS ≥5) · FP/CAPOX + pembrolizumab (PD-L1 CPS ≥1) · FOLFOX/CAPOX + zolbetuximab (CLDN18.2-positive) · Platinum + fluoropyrimidine	· SOX/FOLFOX/CAPOX + nivolumab (PD-L1 CPS ≥5) · SP/XP	· FOLFOX/CAPOX + nivolumab (PD-L1 CPS ≥5) · CAPOX + sintilimab (PD-L1 CPS ≥5) · CAPOX + tislelizumab (PD-L1 CPS ≥5) · Oxaliplatin/cisplatin + fluoropyrimidine · Paclitaxel/docetaxel + fluoropyrimidine	· FOLFOX/CAPOX + nivolumab (PD-L1 CPS ≥5) · FOLFOX/CAPOX + pembrolizumab (PD-L1 CPS ≥1) · FP/XP + pembrolizumab (PD-L1 CPS ≥1) · FOLFOX/CAPOX · FP/XP	· Platinum + fluoropyrimidine · Platinum + fluoropyrimidine + nivolumab (PD-L1 CPS ≥5) · Platinum + fluoropyrimidine + pembrolizumab (PD-L1 CPS ≥1) · Platinum + fluoropyrimidine + zolbetuximab (CLDN18.2-positive) · Platinum + fluoropyrimidine + docetaxel (PD-L1, CLDN18.2-negative)
HER2-positive	· FP/XP + trastuzumab (PD-L1 CPS<1) · FP/CAPOX + trastuzumab + pembrolizumab (PD-L1 CPS ≥1)	· XP/SP/CAPOX/SOX + trastuzumab	· FP/XP/FOLFOX/CAPOX + trastuzumab	· FP/XP/FOLFOX/CAPOX + trastuzumab · FP/XP/FOLFOX/CAPOX + trastuzumab + pembrolizumab (PD-L1 CPS ≥1)	· Platinum + fluoropyrimidine + trastuzumab · Platinum + fluoropyrimidine + trastuzumab + pembrolizumab (PD-L1 CPS ≥1)
Second-line	· Ramucirumab + paclitaxel · Taxane · Irinotecan · Ramucirumab · Pembrolizumab · (MSH-H/dMMR)	· Pembrolizumab +/– · Ramucirumab + weakly paclitaxel	· Ramucirumab + paclitaxel · Paclitaxel · Docetexal · Irinotecan · Envafolimab · Tislelizumab	· Ramucirumab + paclitaxel · T-Dxd for HER2-positive · Docetaxel · Paclitaxel · Irintecan · FOLFIRI	· Ramucirumab + paclitaxel · Ramucirumab · Taxene · Irinotecan
Third-line					
HER2-negative	· Nivolumab · Taxane · Irinotecan · Trifluridine/tipiracil	· Ivolumab · Irinotecan · Trifluridine/tipiracil	· Apatinib · Nivolumab	Trifluridine/tipiracil	· Trifluridine/tipiracil
HER2-positive	· T-Dxd	· T-Dxd	· Disitamab vedotin		· T-Dxd

This table only includes JGCA "Recommend regimens," CSCO "Grade I recommendations," NCCN "Preferred Regimens" and ESMO "Grade I recommendations."
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; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; CAPOX = capecitabine and oxaliplatin; PD-L1 = programmed cell death-ligand 1; CPS = combined positive score; CLDN18.2 = claudin 18.2; SOX = S-1 and oxaliplatin; SP = S-1 and cisplatin; XP = capecitabine and cisplatin; FP = 5-fluorouracil and cisplatin; T-Dxd = trastzumab and deruxtecan; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient; FOLFIRI = 5-FU + irinotecan.

cisplatin (FP). Similarly, the CSCO recommends fluoropyrimidine- and platinum-based dual-drug regimens as first-line chemotherapy, based on the same prospective RCTs and supporting evidence from real-world Chinese data [98,99]. Although a phase III study failed to demonstrate a benefit in OS from adding docetaxel to cisplatin and S-1 regimens in the JCOG1013 trial, the CSCO reported the efficacy and safety of fluorouracil and paclitaxel combination regimens [100,101]. Additionally, the CSCO recommends modified docetaxel plus cisplatin plus 5-FU and paclitaxel plus oxaliplatin plus 5-FU regimens, citing their improved tolerability compared with other 2-drug regimens [102,103]. The KGCA and NCCN also support fluoropyrimidine- and platinum-based dual-drug regimens [10,13]. Additionally, ESMO recommends the addition of docetaxel in select patients [14,15]. However, ESMO guidelines note that S-1 is commonly used in Asian patients, whereas genetic differences affecting drug metabolism in non-Asian populations may necessitate dose adjustments [14,15,92].

All updated guidelines recommend the addition of the PD-1 inhibitor nivolumab to a platinum-fluoropyrimidine regimen as first-line palliative systemic therapy for cases with PD-L1 CPS ≥5 [10-15]. This recommendation was based on the results of the CheckMate-649 and ATTRACTION-4 trials [104,105]. A recently published KEYNOTE-859 trial demonstrated that the addition of pembrolizumab to FP or CAPOX regimens resulted in a survival benefit

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jgc Journal of Gastric Cancer

regardless of the PD-L1 status in the intention-to-treat population [106]. The survival benefit of adding pembrolizumab was more pronounced in patients with PD-L1 CPS ≥1 and CPS ≥10. A meta-analysis by the KGCA revealed that the addition of a PD-1 antibody to chemotherapy resulted in significant benefits in terms of OS, overall response rate (ORR), and disease control rate [10]. Moreover, the results indicated that anti-PD-1 antibody combined with chemotherapy was more effective in the PD-L1-positive group [10]. Based on these studies, the KGCA recommends FP or CAPOX regimens combined with pembrolizumab with a PD-L1 CPS of ≥1 [10]. Also, NCCN and ESMO guidelines recommend a combination regimen of FOLFOX, CAPOX, FP, or XP with pembrolizumab for cases with PD-L1 CPS ≥1 based on KEYNOTE-859 trial [13-15,106]. In the NCCN guidelines, pembrolizumab-based regimens are recommended as Category 2B for the CPS ≥1 population and Category 1 for the CPS ≥10 population, based on the subgroup analysis results from the KEYNOTE-859 trial [13,106].

Subgroup analyses of the CheckMate-649, KEYNOTE-062, and KEYNOTE-859 trials demonstrated significant benefits in patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) gastric cancer [104,106,107]. Based on this evidence, the KGCA, CSCO, NCCN, and ESMO recommend regimens that include anti-PD-1 antibodies, regardless of PD-L1 status, in cases of MSI-H or dMMR [10,12-15].

Additionally, CSCO guideline recommends the combination regimens of sintilimab or tislelizumab with CAPOX for cases with PD-L1 CPS ≥5, based on evidence from the ORIENT-16 and RATIONALE 305 trials [108,109]. The KGCA also noted that tislelizumab, based on the RATIONALE-305 trial, can be recommended as first-line systemic therapy, although it has not yet been approved for use in South Korea [10].

In the most recent guidelines, the KGCA and ESMO provided recommendations for zolbetuximab combined with CAPOX or FOLFOX in HER2-negative and CLDN18.2-positive cases [10,14,15]. CLDN18.2 positivity was defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining by immunohistochemistry (IHC) [110,111]. The KGCA bases its recommendation on the phase III SPOTLIGHT and GLOW trials, while ESMO references GLOW trial, assigning it as a newly emerging “Strong for” recommendation and a “Grade I recommendation,” respectively [110,111]. The phase III SPOTLIGHT trial demonstrated that in patients with HER2-negative and CLDN18.2-positive gastric cancer, the combination of zolbetuximab and FOLFOX6 significantly improved PFS and OS [110]. Similarly, a phase III GLOW trial showed that zolbetuximab combined with the CAPOX regimen provided significant benefits in terms of PFS and OS in the same patient population [111].

Palliative first-line systemic therapy for HER2-positive gastric cancer

All guidelines recommend the addition of trastuzumab, a monoclonal antibody against HER2, to the platinum plus fluoropyrimidine doublet regimen in HER2-positive cases. However, the most strongly recommended regimens differ slightly among guidelines, with the KGCA, NCCN, and ESMO guidelines including recommendations for pembrolizumab-combined regimens.

The ToGA phase III trial demonstrated the efficacy of FP or XP plus trastuzumab for HER2-positive AGC [93]. Based on these findings, the KGCA and ESMO recommend this regimen in HER2 IHC 3+ or IHC 2+ and in situ hybridization-positive tumors. The JGCA, also referencing the ToGA trial, recommends combination therapy with trastuzumab and XP, SP, CAPOX,

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or SOX, based on evidence from several phase II studies [112-117]. This recommendation considers the high toxicity and complex administration of FP-based regimens. The CSCO, citing the EVIDENCE study conducted in a Chinese population, reported that the CAPOX plus trastuzumab regimen demonstrated the most favorable outcomes as the first-line systemic therapy option [118]. The NCCN guidelines also recommend adding trastuzumab to the XP, FP, CAPOX, or FOLFOX regimens as the preferred treatment for HER2-positive gastric cancer, based on the ToGa phase III and the phase II HERXO trials [93,114]. However, XP and FP were classified as Category 1, whereas CAPOX and FOLFOX were classified as Category 2A. Although cisplatin-based regimens have a higher level of evidence, the NCCN guidelines note that oxaliplatin-based regimens are preferred because of their lower toxicity [13].

The KEYNOTE-811 trial demonstrated that adding pembrolizumab to a fluoropyrimidine, platinum, and trastuzumab regimen in patients with HER2-positive gastric cancer provided benefits in terms of PFS and OS [119]. Based on these findings, the CSCO has issued a "Grade III recommendation," while the KGCA, NCCN and ESMO include this regimen as a "Strong for," "Preferred option," and "Grade I recommendation" [10,12-15].

Palliative second-line systemic therapy

All current guidelines strongly recommend the ramucirumab plus paclitaxel regimen as a second-line systemic therapy when cancer progresses after first-line systemic therapy. Additionally, other single-agent regimens, including paclitaxel, taxanes, irinotecan, and pembrolizumab, have been recommended [10-14].

The RAINBOW phase III trial demonstrated that adding weekly paclitaxel to ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2, further improved ORR, OS, and PFS [120]. Based on this evidence, the KGCA strongly recommends the ramucirumab plus paclitaxel regimen as first-line systemic therapy [10]. However, other guidelines strongly recommend this regimen [11-14]. Moreover, the REGARD trial demonstrated that ramucirumab monotherapy improved OS and PFS [121]. Palliative chemotherapy using agents such as irinotecan and taxanes has demonstrated a survival benefit over best supportive care (BSC) [122-125]. A meta-analysis conducted by the KGCA further confirmed that second-line systemic therapy provided a significant OS advantage compared with BSC (HR, 0.69; 95% CI, 0.59–0.82; P<0.001). Therefore, the KGCA recommends irinotecan, docetaxel, paclitaxel, or ramucirumab monotherapy as second-line treatment options [10]. For the same reasons, the JGCA designates the ramucirumab plus paclitaxel regimen as a "recommended regimen" and classifies other monotherapies as "conditionally recommended" regimens [11]. The CSCO, NCCN, and ESMO guidelines recommend doublet and monotherapy options [12-14]. Additionally, the NCCN guidelines recommend fluorouracil plus irinotecan (FOLFIRI) as the preferred treatment option for second-line systemic therapy, based on evidence from several phase II studies demonstrating benefits in ORR and OS [13,126,127].

The KGCA reported that pembrolizumab was effective only in MSI-H or dMMR cases and failed to demonstrate a survival benefit compared to paclitaxel in the overall population of gastric cancer patients who had failed palliative first-line systemic therapy [128-131]. Consequently, the KGCA recommends pembrolizumab as an alternative treatment option for specific cases [10]. The NCCN and ESMO guidelines concur with this recommendation [13,14]. In contrast, the JGCA recommends pembrolizumab monotherapy as a "recommended regimen" based on the results of the KEYNOTE-158 trial and a sub-analysis

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jgc Journal of Gastric Cancer

of the KEYNOTE-061 trial, which included Japanese patients and demonstrated favorable outcomes for MSI-H patients treated with pembrolizumab monotherapy [11,129,131]. A multicenter phase II clinical study in China demonstrated that envafolimab-treated patients showed significant benefits in terms of ORR, disease control rate, duration of response, PFS, and OS [132]. Similarly, the RATIONALE-209 study reported that the tislelizumab-treated group showed improvement in partial response and ORR [133]. Consequently, CSCO recommends envafolimab and tislelizumab more strongly than pembrolizumab for patients with MSI-H or dMMR [12].

The KGCA noted that the efficacy of the HER2-directed antibody-drug conjugate trastuzumab deruxtecan (T-Dxd) has only been demonstrated in Western populations [134]. This emphasizes the need for further research in Eastern populations. Similarly, the JGCA acknowledges that T-Dxd has demonstrated efficacy in third-line or later treatments but emphasizes the need for further research to establish its role as a second-line treatment [11]. However, the NCCN and ESMO guidelines recommend T-Dxd for second-line or later treatment in patients who previously received trastuzumab-based therapy [13-15]. This recommendation is based on the DESTINY-Gastric 02 phase II trial, which provided clinical evidence for second-line treatment in Western populations only [135]. However, the DESTINY-Gastric01 trial specifically targeted patients who had already received 2 or more lines of chemotherapy, including trastuzumab-based regimens. Based on this evidence, the KGCA and JGCA recommend T-Dxd as third-line or later treatment [10,11]. The CSCO notes that although the DESTINY-Gastric02 study demonstrated the efficacy of T-Dxd as second-line treatment in cases where first-line trastuzumab-containing regimens failed, it did not include Asian populations [12,136]. The KGCA also highlighted the upcoming results of the DESTINY-Gastric04 trial, which compared the survival outcomes between T-Dxd and ramucirumab plus paclitaxel in an Asian population and could potentially influence future guideline recommendations.

Palliative third line and subsequent systemic therapy

A phase III RCT demonstrated that docetaxel and irinotecan provided benefits as third-line therapies compared with BSC [122]. The phase III TAGS trial demonstrated that trifluridine/tipiracil significantly improves OS [137]. Additionally, the phase III ATTRACTION-2 trial reported that nivolumab provided a survival benefit as a third-line systemic therapy [138]. Recent updates further indicated that this survival benefit was observed regardless of the PD-L1 expression status [139]. For these reasons, the KGCA recommends nivolumab, taxane, irinotecan monotherapy, and trifluridine/tipiracil as third-line or subsequent systemic therapies. Similarly, the JGCA, based on the previous studies, also recommends irinotecan, nivolumab, and trifluridine/tipiracil as third-line "recommended regimen." Specifically, irinotecan is preferred over taxanes in this setting, as the ramucirumab plus paclitaxel regimen is frequently used as second-line systemic therapy. The CSCO recommends apatinib as a third-line systemic therapy option based on evidence from a phase III study showing benefits in median PFS and disease control rates [140]. The NCCN, based on the TAGS trial, recommends the trifluridine/tipiracil regimen as a "preferred regimen" for third-line systemic therapy [13]. ESMO includes this as a "Grade I recommendation" [14].

The KGCA, JGCA, and ESMO recommend T-Dxd for patients with HER2-positive gastric cancer as a third-line or subsequent treatment, based on the findings of the DESTINY-Gastric01 trial [10,11,14,15,141]. Additionally, a phase II C008 multicenter study demonstrated that in HER2-positive patients who received 2 or more lines of chemotherapy, treatment with

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jgc Journal of Gastric Cancer

disitamab vedotin resulted in improved ORR and median OS [142]. Based on these findings, the CSCO recommends disitamab vedotin as the third-line systemic therapy regimen [12].

CONCLUSION

With emerging research findings on gastric cancer treatments worldwide, the national guidelines are being progressively revised and updated. However, in addition to research findings, evidence for decision frameworks that consider clinical guidelines, insurance coverage, and healthcare policies vary across countries, leading to differences in guideline recommendations. Understanding the commonalities and differences among national guidelines, along with the underlying evidence, can provide valuable insights into the treatment of gastric cancer.

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