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Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach

Guideline Committee of the Korean Gastric Cancer Association (KGCA),
Development Working Group & Review Panel

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Conflict of Interest

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INTRODUCTION

Background

Gastric cancer is the most common cancer and the fourth most common cause of cancer death in South Korea [1]. Despite the large number of gastric cancer patients newly diagnosed and treated annually in South Korea, there has been no appropriate practice guideline for domestic medical situations. Although Korean guidelines for gastric cancer were published through interdisciplinary collaborations in 2004 and 2014 [2,3], they were not widely used in South Korea. Therefore, we have produced the present clinical practice guideline to create guidelines that can provide the standard of gastric cancer treatment in accordance with the medical reality in South Korea.

Scope

The present clinical practice guideline is intended for physicians to treat patients with gastric cancer. This guideline is specific and comprehensive for gastric cancer treatment and pathological evaluations; however, it does not address issues related to prevention, screening, diagnosis, and postoperative follow-up. It is based on domestic and overseas evidence and has been developed to be applied to Korean gastric cancer patients under the current medical situation and to ensure their widespread adoption in clinical practice.

This guideline is intended to help medical staffs and educate training physicians at secondary and tertiary care medical institutions, including endoscopists, surgeons, medical oncologists, radiology oncologists, and pathologists. Additionally, the guideline was designed to allow patients and populations to receive optimum care by providing adequate medical information. Furthermore, it is intended for widespread adoption to increase the standard of gastric cancer treatment, thereby contributing to improving patient quality of life as well as national health care.

Chronology

The present guideline was initiated by the Korean Gastric Cancer Association (KGCA) based on the consensus for national need with the associated academic societies. This guideline was prepared in an integrated and comprehensive manner through an interdisciplinary approach that included the KGCA, the Korean Society of Medical Oncology (KSMO), the Korean Society of Gastroenterology (KSG), the Korean Society for Radiation Oncology (KOSRO), and the Korean Society of Pathologists (KSP), along with the participation of experts in the methodology of guideline development (National Evidence-based Healthcare

Collaborating Agency). To complete this guideline, the Guideline Committee of the KGCA established the Development Working Group and Review Panel for Korean Practice Guidelines for Gastric Cancer 2018. The members were nominated by each participant association and society. This guideline will be revised every 3 to 5 years when there is solid evidence that can affect the outcomes of patients with gastric cancer.

Method

We systematically searched published literature using databases including MEDLINE, EMBASE, and the Cochrane Library through January 2018. Manual searches were also performed to complement the results. The selection of relevant studies was performed by panels composed of pairs of clinical experts. The selection and exclusion criteria were predefined and tailored to key questions. The articles were screened by title and abstract and full texts were then retrieved for selection. In each step, 2 panels were independently selected and reached agreements.

We critically appraised the quality of the selected studies using risk-of-bias tools. We used Cochrane Risk of Bias (ROB) for randomized controlled trials (RCTs), ROB for Nonrandomized Studies for non-RCTs, Quality Assessment of Diagnostic Accuracy Studies-2 for diagnostic studies, and A Measurement Tool to Assess Systematic Reviews for systematic reviews/meta-analysis [4-7]. The panels independently assessed and reached a consensus. Disagreements were resolved by discussion and the opinion of a third member. We extracted data using a predefined format and synthesized these data qualitatively. Evidence tables were summarized according to key questions.

The levels of evidence and grading of the recommendations were modified based on the Scottish Intercollegiate Guidelines Network and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology reviews [8,9].

The evidence was classified into 4 levels. The main factors were study design and quality (Table 1). Additionally, we considered outcome consistency. The grading of the recommendations was performed according to a modified GRADE methodology into 5 levels including strong for, weak for, weak against, strong against, and inconclusive (Table 2). The

Table 1. Levels of evidence

Class	Explanation
High	At least 1 RCT or SR/meta-analysis with no concern regarding study quality
Moderate	At least 1 RCT or SR/meta-analysis with minor concern regarding study quality or at least 1 cohort/case-control/diagnostic test design study with no concern regarding study quality
Low	At least 1 cohort/case-control/diagnostic test study with minor concern regarding study quality or at least 1 single arm before-after study, cross-sectional study with no concern regarding study quality
Very low	At least 1 cohort/case-control/diagnostic test design study with serious concern regarding study quality or at least 1 single arm before-after study, cross-sectional study with minor/severe concern regarding study quality

Table 2. Grading of recommendations

Grade classification	Explanation
Strong for	The benefit of the intervention is greater than the harm, with high or moderate levels of evidence. The intervention can be strongly recommended in most clinical practice.
Weak for	The benefit and harm of the intervention may vary depending on the clinical situation or patient/social value. The intervention is recommended conditionally according to the clinical situation.
Weak against	The benefit and harm of the intervention may vary depending on the clinical situation or patient/social values. The intervention may not be recommended in clinical practice.
Strong against	The harm of the intervention is greater than the benefit, with high or moderate levels of evidence. The intervention should not be recommended in clinical practice.
Inconclusive	It is not possible to determine the recommendation direction owing to a lack of evidence or a discrepancy in results. Thus, further evidence is needed.

recommendation factors considered evidence level, clinical applicability, and benefit and harm. The Development Working Group simultaneously reviewed the draft and discussed for consensus.

Review and approval process

The Review Panel examined the final version of the draft by careful expert review. Revisions were made reflecting the Review Panel's opinions. The guideline was then approved by the KSMO, the KSP, the KSG, the KOSRO, and the KGCA at a Korean Gastric Cancer Guideline Presentation Symposium held on 30th November 2018.

OVERALL TREATMENT ALGORITHM

All statements in this guideline are summarized in **Table 3**. The tumor description was confined to adenocarcinoma and the tumor status (TNM and stage) was based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control 8th edition [10].

Table 3. Summary of statements

No.	Recommendations	Level of evidence	Grade of recommendation
Statement 1	Endoscopic resection is recommended for well or moderately differentiated tubular or papillary early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor.	Moderate	Strong for
Statement 2	Endoscopic resection could be performed for well or moderately differentiated tubular early gastric cancer or papillary early gastric cancers with the following endoscopic findings: endoscopically estimated tumor size >2 cm, endoscopically mucosal cancer, and no ulcer in the tumor or endoscopically estimated tumor size ≤3 cm, endoscopically mucosal cancer, and ulcer in the tumor.	Moderate	Weak for
Statement 3	Endoscopic resection could be considered for poorly differentiated tubular or poorly cohesive (including signet-ring cell) early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor.	Low	Weak for
Statement 4	After endoscopic resection, additional curative surgery is recommended if the pathologic result is beyond the criteria of the curative endoscopic resection or if lymphovascular or vertical margin invasion is present.	Moderate	Strong for
Statement 5	Proximal as well as total gastrectomy could be performed for early gastric cancer in terms of survival rate, nutrition, and quality of life. Esophagogastrostomy after proximal gastrectomy can result in more anastomosis-related complications including stenosis and reflux; caution is needed in the selection of reconstruction method.	Moderate	Weak for
Statement 6	PPG could be performed for early gastric cancer as well as DG in terms of survival rate, nutrition, and quality of life.	Moderate	Weak for
Statement 7	Gastroduodenostomy and gastrojejunostomy (Roux-en-Y and loop) are recommended after DG in middle and lower gastric cancers. There are no differences in terms of survival, function, and nutrition between the different types of reconstruction.	High	Strong for
Statement 8	D1+ is recommended during the surgery for early gastric cancer (cT1N0) patients in terms of survival.	Low	Strong for
Statement 9	Prophylactic splenectomy for splenic hilar LND is not recommended during curative resection for advanced gastric cancer in the proximal third stomach.	High	Strong against
Statement 10	Lower mediastinal LND could be performed to improve oncologic outcome without increasing postoperative complications for adenocarcinoma of the EGJ.	Low	Weak for
Statement 11	Laparoscopic surgery is recommended in early gastric cancer for postoperative recovery, complications, quality of life, and long-term survival.	High	Strong for
Statement 12	Laparoscopic gastrectomy could be performed for advanced gastric cancer in terms of short-term surgical outcomes and long-term prognosis.	Moderate	Weak for
Statement 13	Adjuvant chemotherapy (S-1 or capecitabine plus oxaliplatin) is recommended in patients with pathological stage II or III gastric cancer after curative surgery with D2 LND.	High	Strong for
Statement 14	Adjuvant chemoradiation could be added in gastric cancer patients after curative resection with D2 lymphadenectomy to reduce recurrence and improve survival.	High	Weak for

(continued to the next page)

Table 3. (Continued) Summary of statements

No.	Recommendations	Level of evidence	Grade of recommendation
Statement 15	Neoadjuvant chemotherapy for potentially resectable gastric cancer is not conclusive if D2 LND is considered.	High	Inconclusive
Statement 16	The evidence for the effectiveness of neoadjuvant chemoradiation in locally advanced gastric cancer is not conclusive if D2 LND is considered.	High	Inconclusive
Statement 17	Palliative gastrectomy is not recommended for metastatic gastric cancer except for palliation of symptoms.	High	Strong against
Statement 18-1	Palliative first-line combination platinum/fluoropyrimidine is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved.	High	Strong for
Statement 18-2	Palliative trastuzumab combined with capecitabine or fluorouracil plus cisplatin is recommended in patients with HER2 IHC 3+ or IHC 2+ and ISH-positive advanced gastric cancer.	High	Strong for
Statement 19	Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved. Ramucirumab plus paclitaxel is preferably recommended and monotherapy with irinotecan, docetaxel, paclitaxel, or ramucirumab could also be considered.	High	Strong for
Statement 20	Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved.	High	Strong for
Statement 21	Palliative RT could be offered to alleviate symptoms and/or improve survival in recurrent or metastatic gastric cancer.	Moderate	Weak for
Statement 22	Peritoneal washing cytology is recommended for staging. Advanced gastric cancer patients with positive cancer cells in the peritoneal washing cytology are associated with frequent cancer recurrence and a poor prognosis.	Moderate	Strong for

PPG = preserving gastrectomy; DG = distal gastrectomy; LND = lymph node dissection; EGJ = esophagogastric junction; IHC = immunohistochemistry; ISH = in situ hybridization; RT = radiotherapy.

Gastric adenocarcinoma was divided into localized (non-metastatic [M0]) and metastatic-1 (M1) disease according to the status of distant metastasis (**Fig. 1**).

In cases of M0 gastric cancer, clinical (c) T- and N-stages can be determined based on preoperative esophagogastroduodenoscopy or endoscopic ultrasound examination findings and computed tomography. Endoscopic resection can be indicated for selected cT1aNO gastric cancer with minimal risk of lymph node (LN) metastasis (statements 1–3). The necessity of additional curative gastrectomy after endoscopic treatment is determined based on the pathologic review of the endoscopic resection specimen (statement 4).

Surgical resection is recommended if the tumor is outside of endoscopic resection indications in cT1a and \geq cT1b or cN+. The extent of gastrectomy (statements 5 and 6) and lymphadenectomy (statements 8, 9, and 10), reconstruction methods (statement 7), and approach methods (statements 11 and 12) should be considered when deciding surgical procedures.

Adjuvant chemotherapy is recommended in patients with pathological stage II or III gastric cancer after curative R0 resection with D2 LN dissection (LND) (statement 13). Adjuvant chemoradiation can be considered in patients with incomplete resection, including R1 resection and/or less than D2 LND, and after curative R0 resection with D2 LND, especially with LN metastasis (statement 14). When the result of primary gastrectomy is R1 resection, 3 treatment options can be considered, according to the location of microscopic residual tumor: re-resection, adjuvant chemoradiotherapy, or palliative therapy, depending on the clinical situation.

Although neoadjuvant chemo (radio) therapy has high levels of evidence, we did not reach a conclusion on whether to recommend it in Asian populations because the backgrounds of almost all clinical trials on preoperative therapy were not consistent with Asian situations (statements 15 and 16).

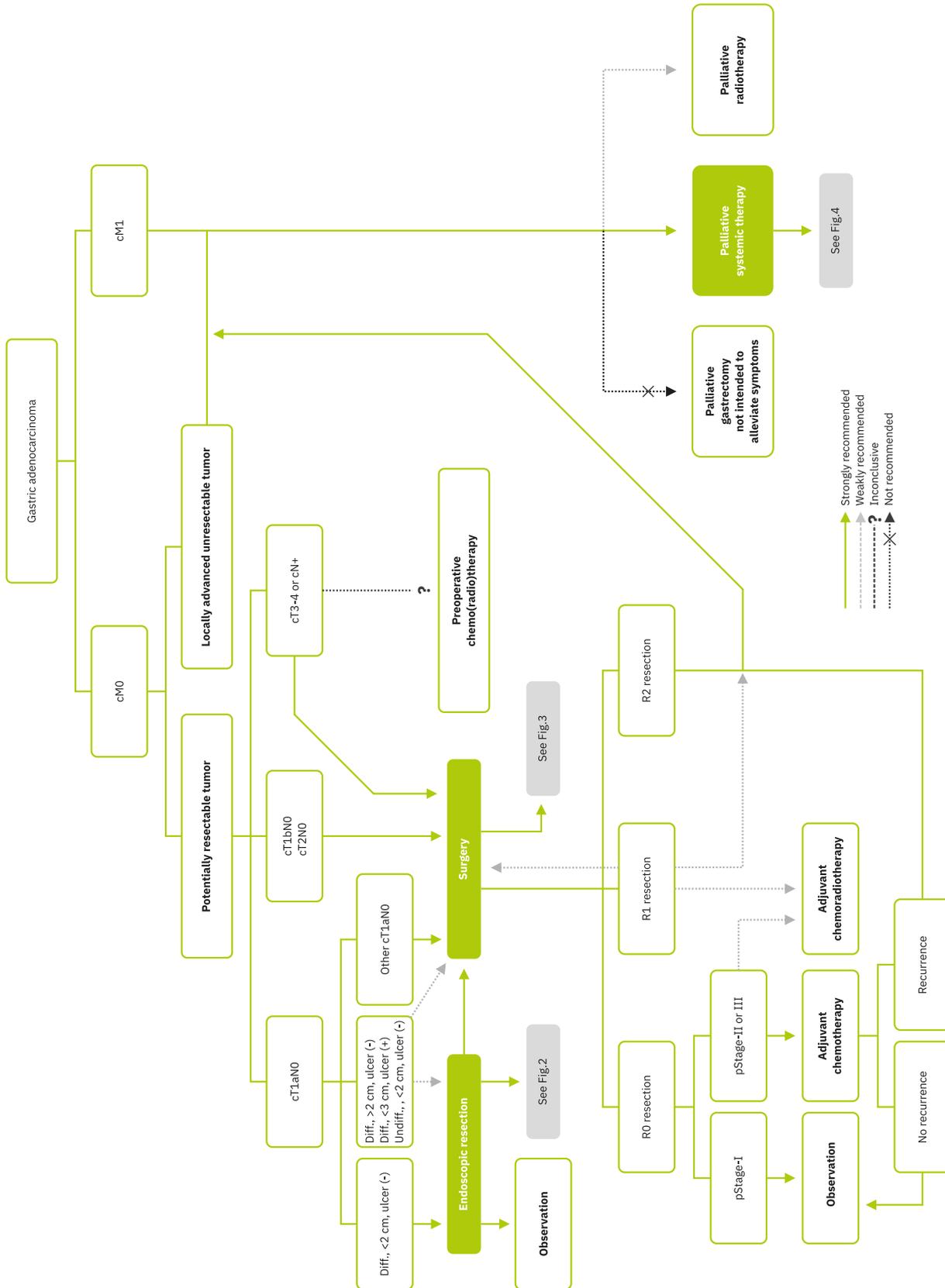


Fig. 1. Overall treatment algorithm. Diff. = differentiated; Undiff. = undifferentiated.

Palliative systemic therapy is the primary treatment to be considered in patients with locally advanced unresectable or those after non-curative resection or metastatic disease (M1) (statements 18–20). Palliative radiotherapy (RT) can be considered for the alleviation of tumor-related symptoms or to improve survival (statement 21); however, palliative gastrectomy not intended to alleviate tumor-related symptoms or complications (i.e., obstruction, bleeding, perforation, etc.) is not recommended for the purpose of improving overall survival (OS) (statement 17).

ENDOSCOPIC RESECTION

Statement 1. Endoscopic resection is recommended for well or moderately differentiated tubular or papillary early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size ≤ 2 cm, endoscopically mucosal cancer, and no ulcer in the tumor (evidence: moderate, recommendation: strong for).

Endoscopic submucosal dissection (ESD) has been used as a minimally invasive treatment modality for early gastric cancer since the early 2000s in Korea [11,12]. A total of 7,734 early gastric cancer patients underwent ESD in 2014 [12]. Many studies have indicated that ESD should be considered as the first-line treatment modality for the early gastric cancer with well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma with tumor size ≤ 2 cm, confined to the mucosal layer, and without ulcer in the tumor as these findings definitely indicated that the lesions had a very low-risk of LN metastasis [13,14] and ESD allows high rates of en bloc curative resection with low adverse event rates [11,14–18] (**Fig. 2**).

The 5-year OS rates of patients meeting this definite indication for ESD did not differ significantly from those of patients who received endoscopic resection (93.6%–96.4%) and surgery (94.2%–97.2%) in large retrospective cohort studies in Korea [16–18]. The 10-year OS rates were comparable between endoscopic resection (81.9%) and surgery (84.9%) ($P=0.14$) [17].

However, the 5-year cumulative metachronous recurrence rates were significantly higher after endoscopic resection (5.8%–10.9%) than those after surgery (0.9%–1.1%) [16–18]. Therefore, close surveillance should be performed after ESD to detect early-stage metachronous gastric cancer that can be treated with endoscopic resection. Nevertheless, endoscopic treatment for early gastric cancer can provide a better quality of life, though stomach preservation might provoke worries of metachronous cancer recurrence [19]. Moreover, ESD had lower treatment-related complication rates [17,18], shorter hospital stay, and lower costs than those of surgery [16].

In the aspect of patient preference, ESD can provide better health-related quality of life for early gastric cancer patients, especially in terms of physical function, eating limits, dyslexia, diarrhea, and body image [20].

Statement 2. Endoscopic resection could be performed for well or moderately differentiated tubular early gastric cancer or papillary early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size > 2 cm, endoscopically mucosal cancer, and no ulcer in the tumor or endoscopically estimated tumor size ≤ 3 cm, endoscopically mucosal cancer, and ulcer in the tumor (evidence: moderate, recommendation: weak for).

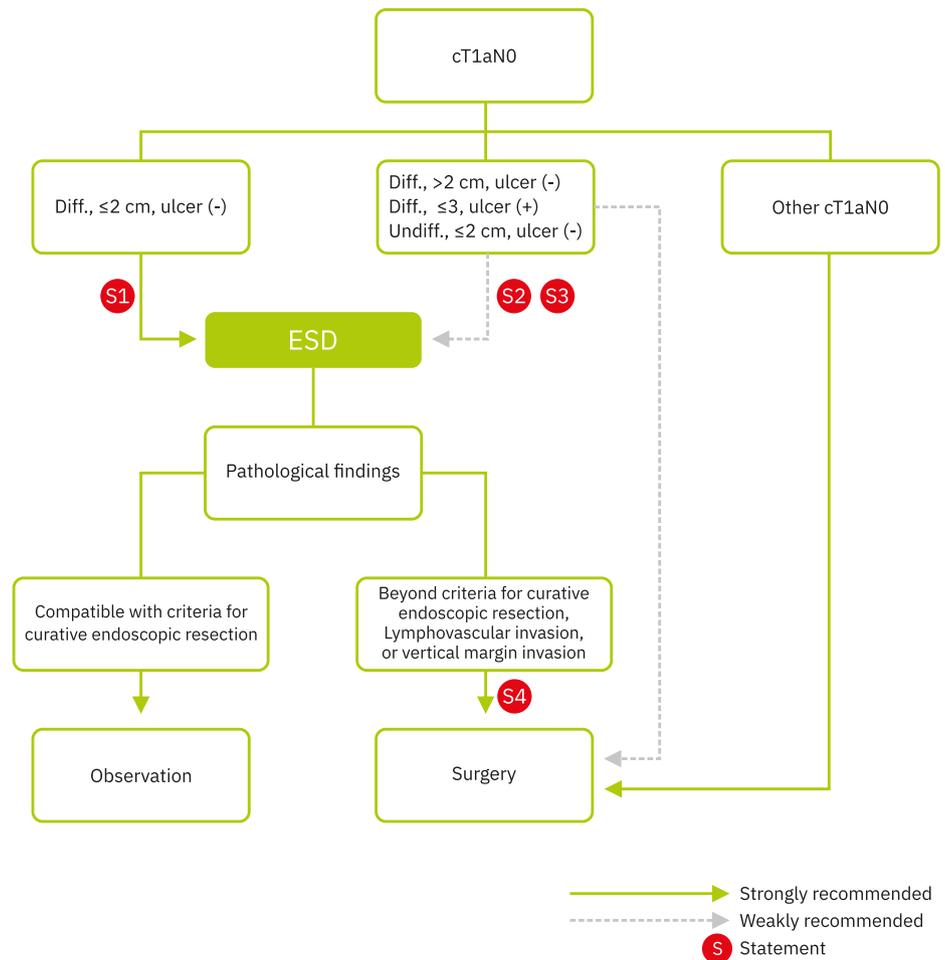


Fig. 2. Treatment algorithm for endoscopic resection.
 Diff. = differentiated; Undiff. = undifferentiated; ESD = endoscopic submucosal dissection.

Endoscopic resection for early gastric cancer is limited in that LND cannot be performed during the procedure. Therefore, to achieve curative resection and comparable survival to that of surgery with endoscopic resection, early gastric cancers with very low-risk of LN metastasis should be carefully selected. The clinically acceptable rate of LN metastasis might be determined in the context of perioperative mortality associated with radical gastrectomy (0.1%–0.3% in a high-volume center in Korea and Japan) [21-23]. In addition, it is required that en bloc resection is technically feasible with endoscopic resection to avoid the possibility of remnant tumor or local recurrence after the procedure. When the following criteria 1 or 2 were met, the extragastric recurrence (LN or distant metastasis) rate after endoscopic resection was between 0 and 0.21%, which is comparable to that of perioperative mortality associated with radical gastrectomy [24-27].

Although standard gastrectomy with LND is recommended when submucosal invasion of the tumor (T1b) is suspected in preoperative evaluation, the extragastric recurrence rate after ESD ranged from 0.9% to 1.5% in large retrospective cohort studies when the pathologic specimen of ESD fulfilled criteria 3 [24-26]. Because the diagnosis of minute submucosal invasion ($\leq 500 \mu\text{m}$) of the tumor before ESD is very difficult, criteria 3 applies to post-ESD pathologic specimens.

When criteria 1, 2, or 3 were met, the OS was comparable between patients undergoing endoscopic resection and those treated with radical surgery [18,28-38].

Criteria 1, 2, and 3: well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma, en bloc resection, negative lateral resection margins, negative vertical resection margin, no lymphovascular invasion (LVI), and 1) tumor size >2 cm, mucosal cancer, no ulcer in the tumor, or 2) tumor size ≤3 cm, mucosal cancer, ulcer in the tumor, or 3) tumor size ≤3 cm, submucosal invasion depth ≤500 μm from the muscularis mucosa layer.

Because many the factors of these criteria can be confirmed after ESD (i.e., en bloc resection, resection margin, LVI, and minute submucosal invasion), ESD can be considered if the early gastric cancer meets the following endoscopic findings: 1) Well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma on forceps biopsy specimen, endoscopically estimated tumor size >2 cm, endoscopically mucosal cancer, and no ulcer in the tumor, or 2) Well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma on forceps biopsy specimen, endoscopically estimated tumor size ≤3 cm, endoscopically mucosal cancer, and ulcer in tumor (**Fig. 2**).

Until now, the standard treatment for these criteria has been gastrectomy with LND. Although a number of retrospective cohort studies support these criteria, no prospective trial has compared the outcomes of endoscopic resection with those of standard operation based on these criteria. A significant portion of these criteria estimated by pre-ESD workup is confirmed to be out of criteria by the pathologic examination of ESD specimens [39-43]. Thus, standard operation (gastrectomy with LND) may also be considered for cases meeting these criteria.

Statement 3. Endoscopic resection could be considered for poorly differentiated tubular or poorly cohesive (including signet-ring cell) early gastric cancers meeting the following endoscopic findings: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor (evidence: low, recommendation: weak for).

Poorly-differentiated tubular and poorly cohesive (including signet-ring cell) early gastric cancers are associated with a higher risk of LN metastasis than those of well and moderately differentiated tubular early gastric cancer. Thus, endoscopic resection can be considered very cautiously within strict criteria. When the following criteria were fulfilled, a few retrospective cohort studies reported extragastric recurrence after endoscopic resection [24,26,44-49] and a comparable OS between patients undergoing endoscopic resection and those treated with radical gastrectomy [18,29,35,36,49].

Poorly differentiated tubular adenocarcinoma or poorly cohesive carcinoma (including signet-ring cell carcinoma), en bloc resection, negative lateral resection margins, negative vertical resection margin, no LVI, and tumor size ≤ 2 cm, mucosal cancer, and no ulcer in the tumor.

Because many factors of these criteria can be confirmed after ESD (i.e., en bloc resection, resection margin, and LVI), ESD can be considered for poorly-differentiated tubular and poorly cohesive (including signet-ring cell) early gastric cancers meeting the following endoscopic findings (**Fig. 2**).

Poorly differentiated tubular adenocarcinoma or poorly cohesive carcinoma (including signet-ring cell carcinoma) on forceps biopsy specimen, endoscopically estimated tumor size ≤ 2 cm, endoscopically mucosal cancer, and no ulcer in the tumor.

Until now, the standard treatment for these criteria has been gastrectomy with LND. A few retrospective cohort studies support these criteria for ESD and the results of prospective trials are lacking (level of evidence is low, and the level of recommendation is weak). A significant portion of these criteria estimated by pre-ESD workup is confirmed to be out of criteria by the pathologic examination of ESD specimens [39-43]. Thus, standard operation (gastrectomy with LND) can also be considered for cases meeting these criteria.

Statement 4. After endoscopic resection, additional curative surgery is recommended if the pathologic result is beyond the criteria of the curative endoscopic resection or if lymphovascular or vertical margin invasion is present (evidence: moderate, recommendation: strong for).

Early gastric cancer patients who received endoscopic resection could be considered as being beyond the criteria of endoscopic resection by pathologic specimen evaluation. Resected tumor characteristics beyond the following criteria are also considered for non-curative resection: 1) Differentiated (well or moderately differentiated tubular or papillary) intramucosal cancer measuring > 2 cm in the long diameter without ulcer (active or scar), 2) differentiated mucosal cancer measuring < 3 cm with ulcer (active or scar), 3) undifferentiated (poorly differentiated tubular or poorly cohesive) mucosal cancer measuring < 2 cm without ulcer (active or scar), and 4) differentiated mucosal cancer measuring < 3 cm with subtle submucosal invasion (< 500 μm). LVI and positive vertical margin, which are confirmed after endoscopic resection, are also important reasons for the recommendation of rescue surgery (**Fig. 2**).

Many studies have investigated the long-term outcomes with or without additional surgery in patients who did not meet the curative criteria for endoscopic resection in early gastric cancer [39-42,50-57]. All studies were retrospective cohort designs and only 2 used propensity score matching analysis, which is used to minimize potential selection bias and mimic randomization in observational studies [39,50]. Although several small studies showed no difference in OS between rescue surgery and follow-up [51-53], most studies, including the 2 studies that used propensity score matching, showed a significant survival benefit (OS or disease-specific survival [DSS]) for additional curative surgery compared to that for follow-up [39-42,50,54-57]. Patients with LVI or deep vertical margins showed a particularly evident survival benefit for additional curative surgery [40,54,55,57].

The Japanese multicenter retrospective cohort study that used propensity score matching analysis reported 5-year DSS rates after ESD of 99.0% in the additional curative surgery group and 96.8% in the no additional curative surgery group ($P=0.013$). The 5-year OS rates were 91.0% and 75.5%, respectively ($P<0.001$) [50]. In the Korean single-center retrospective cohort study using propensity score matching analysis, the 5-year overall mortality in no additional curative surgery group (26.0%; 95% confidence interval [CI], 13.5%–49.9%) was higher than that of the matched initial standard surgery patients (14.5%; 95% CI, 6.3%–33.6%; $P=0.04$). The overall mortality did not differ significantly between the initial ESD with additional curative surgery group and the corresponding initial standard surgery group [39]. Thus, additional curative surgery is strongly recommended in patients undergoing non-curative endoscopic resection (exceeding the criteria of endoscopic resection) for early gastric cancer.

The survival benefit of additional curative surgery in older patients (>75 years) is controversial. Two studies showed a significant survival benefit but another study showed no difference in long-term outcomes [42,54,56]. Selection bias is inevitable in retrospective cohort designs. For example, all studies showed a younger age in the additional curative surgery group compared to that in the follow-up group, although the age difference disappeared after propensity score matching in 2 studies. Patients undergoing noncurative resection without additional curative surgery also tended to have a higher incidence of comorbidity [41,42]. Although 2 of 12 studies used propensity score matching analysis, selection and measurement biases are still possible. Additional curative surgery may be not feasible in some patients because of very old age, poorly-controlled underlying diseases, or poor general condition. In these patients, follow-up observation could be a feasible option after they are provided an explanation of the risk of recurrence.

SURGICAL THERAPY

Standard surgery is recommended in cases of cT1a, which are outside of the indication for endoscopic resection, and \geq cT1b or cN+ and M0 gastric cancer (**Fig. 3A**).

Standard surgery is defined as total or subtotal gastrectomy with D2 LND. Subtotal gastrectomy in distal gastric cancer has been recognized as a standard surgery based on the results of 2 RCTs in which the subtotal gastrectomy group showed similar long-term oncologic results and lower morbidity and mortality rates compared to those in the total gastrectomy group [58-60]. Although the standard extent of LND has been debated for decades among Eastern and Western countries, there has been an international trend to accept D2 LND as a standard surgery [2,61-63], which was supported by results of prospective trials and meta-analyses [64-66]. The extent of LND in each gastrectomy was defined according to Japanese guidelines [63].

Palliative systemic therapy is the primary treatment in cases of locally advanced unresectable or cM1 gastric cancer (**Fig. 1**). However, conversion surgery could be considered if R0 resection is possible after palliative systemic therapy, which is currently under investigation. Surgery with curative intent could also be considered in cases of locally advanced unresectable or cM1 gastric cancer not detected in preoperative evaluation but incidentally identified during surgery and if R0 resection is possible, which should be investigated in future studies. Intraperitoneal chemotherapy with or without hyperthermia could be applied to patients with peritoneal metastasis in a clinical trial setting; however, this requires additional evidence.

Gastric resection and reconstruction

Statement 5. Both proximal and total gastrectomy could be performed for early gastric cancer in terms of survival rate, nutrition, and quality of life. Esophagogastrostomy after proximal gastrectomy can result in more anastomosis-related complications including stenosis and reflux, and caution is needed in the selection of reconstruction method (evidence: moderate, recommendation: weak for).

A prospective randomized controlled study comparing proximal and total gastrectomy with sufficient numbers of cases and power to evaluate the survival rate as the primary endpoint has not been conducted. However, several retrospective studies reported non-inferior long-

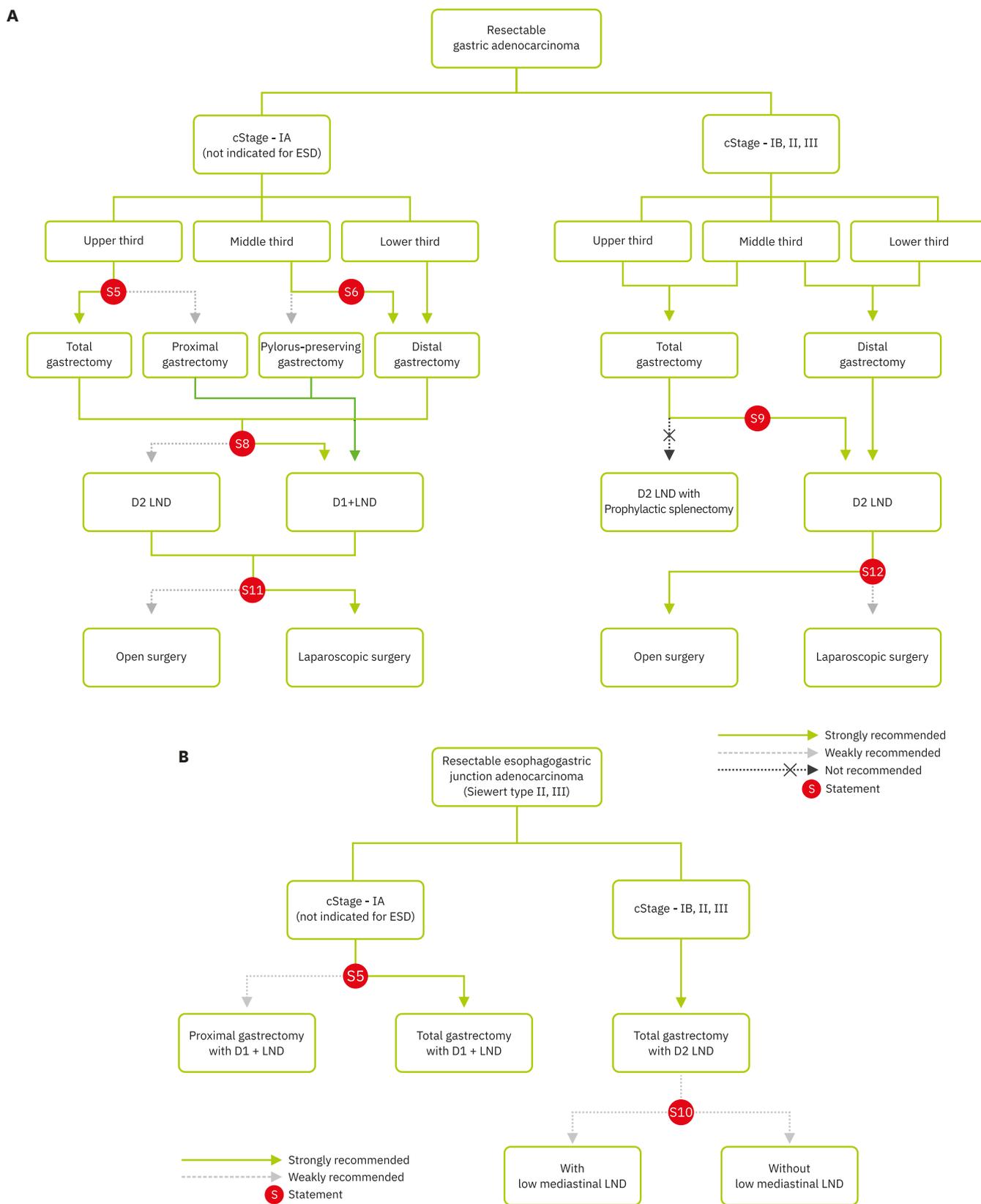


Fig. 3. (A) Treatment algorithm for resectable gastric adenocarcinoma. (B) Treatment algorithm for resectable esophagogastric junction adenocarcinoma. ESD = endoscopic submucosal dissection; LND = lymph node dissection.

term survival rates after proximal gastrectomy as compared to that of total gastrectomy [67-74]. In addition, the incidences of early postoperative complications after proximal gastrectomy were similar to those after total gastrectomy in most studies [68,70,71,73,75-77]; however, they have also been reported to be more [72] and less [69] frequent.

Although various reconstructions after proximal gastrectomy have been tried in order to reduce short- or long-term complications, they remain controversial. Esophagogastrectomy after proximal gastrectomy is the simplest procedure but resulted in significantly more frequent reflux esophagitis (16.2%–42.0% vs. 0.5%–3.7%) and symptoms of reflux [67,69,72,74,76,77], as well as stenosis at the anastomosis site (3.1%–38.2% vs. 0%–8.1%) [67,69,71,72,74,76,77]. An et al. [69] and Ahn et al. [70] concluded that proximal gastrectomy with esophagogastrectomy is an inferior surgical method to total gastrectomy due to the significantly higher incidence of anastomosis-related and/or postoperative complications and no nutritional benefit. However, other studies have reported that proximal gastrectomy with esophagogastrectomy can be still beneficial compared to total gastrectomy in terms of serum albumin level [71,72,77], maintenance of body weight [74,76-78], prevention of anemia [72,74,77], and serum vitamin B12 level [72].

Jejunal interposition could be another option after proximal gastrectomy. Anastomosis with jejunal interposition has been shown to be beneficial in the context of nutritional parameters and anemia [71,74-76]. Postgastrectomy syndrome including dumping syndrome occurred less frequently in patients who underwent proximal gastrectomy with jejunal interposition compared to that in patients who underwent total gastrectomy [75,76]. A study including 115 cases that received esophagogastrectomy and 78 that received jejunal interposition also reported less frequent diarrhea and dumping syndrome for proximal gastrectomy (2.0 vs. 2.3 points on a 7-point scale) [78].

Recently, double-tract reconstruction after proximal gastrectomy has been proposed as an option that did not increase the incidence of complications or reflux and showed superiority to total gastrectomy in terms of body weight, anemia, and serum vitamin B12 level [73]. A multicenter prospective randomized clinical trial was launched in 2016 in Korea based on this result (NCT02892643).

The incidence of metachronous cancer in the remnant stomach after proximal gastrectomy was 33.1% (6/192) and 6.2% (4/65) in reports by Huh et al. [72] and Ohashi et al., [76] respectively.

In conclusion, proximal gastrectomy is a surgical option with possible benefits in aspects of shorter operative time, less blood loss, better maintenance of postoperative nutrition, lower incidence of anemia, better maintenance of vitamin B12 level, and lower incidence of post-gastrectomy syndrome (**Fig. 3A**). However, proximal gastrectomy requires caution in the choice of reconstruction technique because of the significantly increased incidence of anastomosis-related complications and reflux to the esophagus after esophagogastrectomy.

Statement 6. Pylorus-preserving and distal gastrectomy (DG) could be performed for early gastric cancer in terms of survival rate, nutrition, and quality of life (evidence: moderate, recommendation: weak for).

Conventional DG and pylorus-preserving gastrectomy (PPG) can be performed for middle-third early gastric cancer. PPG preserves the pre-pyloric antrum and the pylorus to

prevent the rapid transit of food into the duodenum and reflux of the duodenal contents. Consequently, the postoperative incidence of dumping syndrome and reflux gastritis is decreased, and a nutritional benefit is expected.

Most of the literature on PPG is retrospective studies. All studies that assessed the long-term survival concluded that there was no difference in long-term survival between conventional DG and PPG (5-year survival rates: 95% for PPG vs. 87% for DG, $P=0.087$ [79]; 3-year survival rates: 98.2% for PPG vs. 98.8% for DG, $P=0.702$ [80]; odds ratio [OR] of PPG, 0.83, 95% CI, 0.10–6.66, $P=0.86$ [81]; hazard ratio [HR] for recurrence in PPG, 0.393, 95% CI, 0.116–1.331, $P=0.12$ [82]). In addition, except for 1 report from Japan [79], most of the reports concluded that there was no difference in the incidence of postoperative complications [80,81]. As expected, after PPG, patients showed a significantly low incidence of postoperative dumping syndrome and reflux (reflux: 4% for PPG vs. 40% for DG; reflux gastritis: 8% for PPG vs. 68% for DG [83]; dumping syndrome: OR, 0.02, 95% CI, 0.10–0.41, $P<0.001$; bile reflux: OR, 0.16, 95% CI, 0.06–0.45, $P<0.01$; remnant gastritis: OR, 0.2, 95% CI, 0.08–0.50, $P<0.001$; reflux esophagitis: OR, 0.78, 95% CI, 0.43–1.40, $P=0.41$ [81]). Some studies reported significantly reduced development of gallstones after PPG [80,81]. However, significantly more patients complained of delayed gastric emptying after PPG (symptoms of delayed gastric emptying at 1 postoperative year: 15.8% for PPG vs. 0% for DG; 7.8% for PPG vs. 1.7% for DG [80]; and OR for delayed gastric emptying, 2.12, 95% CI, 1.43–3.15, $P<0.001$ [81]).

PPG for middle-third early gastric cancer can be performed with relatively similar incidences of surgical complications and long-term survival (**Fig. 3A**). Although it is evident that PPG significantly reduces the incidence of post-gastrectomy syndromes such as dumping syndrome, reflux and gallstone formation, postoperative delayed gastric emptying is not uncommon. Thus, we are awaiting the results of a large-scale, prospective randomized trial. Therefore, PPG can be performed at the surgeon's discretion with caution regarding postoperative delayed emptying.

Statement 7. Gastroduodenostomy and gastrojejunostomy (Roux-en-Y and loop) are recommended after DG in middle and lower gastric cancer. There are no differences in terms of survival, function, and nutrition between the different types of reconstruction (evidence: high, recommendation: strong for).

A variety of reconstructions after subtotal gastrectomy have been proposed, including Billroth I, Billroth II, and Roux-en-Y; however, there is still no consensus regarding a standard reconstruction method. Complications after subtotal gastrectomy, such as reflux gastritis and esophagitis, dumping syndrome, and delayed gastric emptying, could depend on the reconstruction method [84]. A recent meta-analysis of the types of reconstruction method and endoscopic findings showed no difference in the incidence of dumping syndrome. Roux-en-Y reconstruction is superior to Billroth I and Billroth II reconstruction in terms of preventing bile reflux (OR, 0.095; 95% CI, 0.010–0.63 and OR, 0.064; 95% CI, 0.0037–0.84, respectively) and remnant gastritis (OR, 0.33; 95% CI, 0.16–0.58 and OR, 0.40; 95% CI, 0.17–0.92, respectively). Meanwhile, Roux-en-Y gastric anastomosis resulted in more frequent delayed gastric emptying than did Billroth I (OR, 3.4; 95% CI, 1.1–13) [85]. However, there was no difference in patient quality of life according to the type of reconstruction ($P=0.290$ – 0.994) [86]. In addition, there were no differences in nutritional aspects among those methods [86,87]. Although no prospective study has assessed the incidence of remnant gastric cancer according to the anastomotic method, a nationwide survey in Japan reported no difference in terms of remnant gastric cancer [88].

In conclusion, there are no significant differences in the functional, nutritional, and long-term prognosis of each reconstruction method.

Lymphadenectomy

Statement 8. D1+ is recommended during surgery for early gastric cancer (cT1N0) patients in terms of survival (evidence: low, recommendation: strong for).

In gastric cancer surgery, adequate resection of regional LNs is essential along with resection of the primary lesion. It is recommended to perform modified D2, D1, or D1+ if early gastric cancer is not clinically suspected to have LN metastasis. Standard D2 is recommended for early gastric cancer with suspected LN metastasis. However, no prospective clinical trials have compared the survival of patients after modified D2 or standard D2.

The results of a retrospective study published in Italy indicated that LN metastasis was a poor prognostic factor for early gastric cancer patients, suggesting that standard D2 should be performed even for early gastric cancer [89]. Other Italian researchers have reported 10-year survival rates of 95% and 87.5% after standard D2 and D1, respectively, in early gastric cancer patients. There were no statistically significant differences in 10-year survival between groups ($P=0.80$) [90]. In a report from Japan, the 5- and 10-year survival rates were 97% and 91% in patients after standard D2 and 98% and 91% after modified D2 (D1+). There were no cases with metastasis to second-tier LNs in patients with cT1N0 or cT1N1 disease [91].

In conclusion, D1+ is recommended for the treatment of T1N0 gastric cancer patients, with relatively comparable oncological safety (**Fig. 3A**).

Statement 9. Prophylactic splenectomy for splenic hilar LND is not recommended during curative resection for advanced gastric cancer in the proximal-third stomach (evidence: high, recommendation: strong against).

The standard surgical procedure for proximal-third gastric carcinoma is total gastrectomy with proper lymphadenectomy. Therapeutic splenectomy is necessary if the tumor directly invades the spleen or if LN metastasis around the splenic hilum is suspected. However, there is debate regarding whether the spleen should be preserved or resected during total gastrectomy in patients diagnosed with proximal-third gastric cancer without a definite indication for splenectomy.

Three prospective randomized clinical trials have evaluated the survival advantage of prophylactic splenectomy in proximal-third gastric carcinoma [92-94]. However, no studies recommend prophylactic splenectomy to dissect macroscopically-negative LNs around the splenic hilum for proximal-third gastric cancer. The only study in Korean patients showed a slightly better 5-year OS in the splenectomy group but the difference was not statistically significant ($P=0.50$) [93]. A recent large-scale study showed that postoperative complications were more common for splenectomy than for spleen preservation (30.3% and 16.7%, $P<0.010$), without a survival advantage [94]. However, prophylactic splenectomy for patients with Borrmann type IV or tumors located in the greater curvature remains inconclusive because they were not included in the enrollment criteria of the largest randomized controlled clinical trial [94].

A systemic review of splenectomy for proximal-third gastric cancer concluded that spleen-preserving total gastrectomy decreased postoperative complications without negatively affecting the OS [95]. In addition, a meta-analysis indicated that splenectomy did not show a beneficial effect on survival rate compared to splenic preservation [96].

Therefore, prophylactic splenectomy for LND is not recommended in the curative resection for proximal-third gastric cancer without macroscopically LN metastasis near the spleen or direct invasion of the spleen or distal pancreas (**Fig. 3A**). This statement addresses the need for prophylactic splenectomy and does not address the need for prophylactic LN #10 dissection, which should be investigated in the future and is not conclusive in the present guideline.

Statement 10. Lower mediastinal LND could be performed to improve oncologic outcome without increasing postoperative complications for adenocarcinoma of the esophagogastric junction (EGJ) (evidence: low, recommendation: weak for).

Dissection of the lower mediastinal LN as a part of the treatment for Siewert type II or III EGJ adenocarcinoma is controversial. High level of evidence is lacking regarding the necessity for lower mediastinal LND. Although LN metastasis in the lower mediastinal LNs is frequently found in Siewert type II or III EGJ cancer, it usually indicates a poor prognosis. In a retrospective analysis conducted in Korea, the 5-year disease-free survival (DFS) rates were 62.6% and 82.5% for Siewert type II and III cancers, respectively [97]. In this study, when these cancers were early gastric cancer, survival was good and comparable (93.2% vs. 96.7% vs. 98.7% for Siewert type II, III, and upper-third gastric cancer, $P=0.158$); however, for advanced cancer, the survival was worse in Siewert type II than that in Siewert type III cancer (47.9% vs. 75.4% vs. 71.8% in Siewert type II, III, and upper-third gastric cancer, $P<0.001$).

Most randomized clinical trials on this issue have compared the surgical outcomes of transabdominal and transthoracic approaches [98-101]. However, no study has demonstrated a survival benefit of transthoracic approaches by thorough dissection of the lower mediastinal LNs and negative surgical margins over transabdominal approaches for Siewert type II and III EGJ cancer. In a Japanese phase III randomized clinical trial comparing outcomes between the left thoracoabdominal and transhiatal approaches for EGJ cancer, the 5-year OS were 37.9% and 52.3%, respectively. The HR of death for the left thoracoabdominal approach compared to the transhiatal approach was 1.36 (0.89–2.08, $P=0.92$).

A cohort study was also performed in the UK of Siewert type I and II EGJ cancer with data from 2 institutions [102]. In this study, the in-hospital mortality rates were 1.1% and 3.2% ($P=0.110$) and there were no differences in OS (HR, 1.07; 95% CI, 0.84–1.36) or time to tumor recurrence (HR, 0.99; 95% CI, 0.76–1.29) between the transhiatal and transthoracic approaches. A meta-analysis reported the transthoracic approach to be associated with higher incidences of systemic complications such as respiratory and cardiovascular problems, longer hospital stay, and early postoperative mortality compared to those in the transabdominal approach [103]. Survival did not differ between the 2 approaches.

Based on the results from these studies, lower mediastinal LND for EGJ adenocarcinoma, especially by means of transthoracic approaches, to obtain more LNs and a negative surgical margin may not be recommended (**Fig. 3B**).

Surgical approach

Statement 11. Laparoscopic surgery is recommended in early gastric cancer for improved postoperative recovery, complications, quality of life, and long-term survival (evidence: high, recommendation: strong for).

Laparoscopic gastrectomy is currently widely performed in the treatment of early gastric cancer. Since the first clinical trial was reported in the early 2000s [104], studies comparing laparoscopic and open surgery for early gastric cancer have proven the oncologic safety and excellence of laparoscopic gastrectomy [23,105-111].

The 5-year survival rates of laparoscopic gastrectomy did not significantly differ from those of open gastrectomy for early gastric cancer in a Korean single-center RCT with a large number of enrolled patients (DFS, 98.8% vs. 97.6%; $P=0.514$ and OS, 97.6% vs. 96.3%; $P=0.721$) [107]. In addition, the complication rate was significantly lower for laparoscopic than that for open gastrectomy (23.2% vs. 41.5%; $P=0.012$). A multicenter RCT conducted in Korea (KLASS-01) recently demonstrated better short-term outcomes of laparoscopic gastrectomy than those of open gastrectomy. In this study, the overall complication rate was significantly lower for laparoscopic than for open gastrectomy (13.0% vs. 19.9%, $P=0.001$) and the mortality rates did not differ between the 2 groups (0.6% vs. 0.3%, $P=0.687$) [23].

Therefore, laparoscopic surgery comprised of gastrectomy and adequate LND demonstrated a more beneficial effect for patients with early gastric cancer in terms of all oncologic aspects compared to those for open surgery. In early gastric cancer, laparoscopic surgery should be the first option for treatment (**Fig. 3A**).

Statement 12. Laparoscopic gastrectomy could be performed for advanced gastric cancer in terms of short-term surgical outcomes and long-term prognosis (evidence level: moderate, recommendation: weak for).

Most previous studies suggesting the feasibility of laparoscopic gastrectomy for locally advanced gastric cancer were small retrospective studies. Meta-analyses of those retrospective studies have demonstrated that laparoscopic gastrectomy required longer operating times but led to less operative blood loss, faster postoperative bowel recovery, and reduced hospital stay compared to those for open surgery [112-118]. The postoperative morbidity and mortality rates of laparoscopic gastrectomy were also lower or similar compared to those for open surgery. As for the quality of LND, most studies have reported that the number of harvested LNs during laparoscopic surgery does not differ significantly from that of open surgery. Furthermore, the long-term outcomes including OS and DFS were comparable between laparoscopic and open surgery.

Despite reports from a number of retrospective studies, the long-term outcomes of laparoscopic gastrectomy for advanced gastric cancer have rarely been investigated in prospective studies. Park et al. [119] performed a randomized phase II trial comparing non-compliance of D2 LND, short-term surgical outcomes, and 3-year DFS between laparoscopy-assisted DG (LADG) and open DG (ODG) for cT2-4/cN0-2 gastric cancer. In their study, there were no significant differences between groups in postoperative morbidity (17% in

LADG vs. 18.8% in ODG, $P=0.749$) and hospital stay (9.8 days in LADG vs. 9.1 days in ODG, $P=0.495$). The non-compliance rates of D2 LND, defined as the proportion of patients with more than 1 empty LN station, were also similar between the 2 groups (47.0% in LADG vs. 43.2% in ODG, $P=0.648$). There was no significant difference in 3-year DFS between the 2 groups (80.1% in LADG vs. 81.9% in ODG, $P=0.648$). In addition, other small RCTs from Western countries have also reported that laparoscopic gastrectomy showed no significant differences in disease recurrence and OS of advanced gastric cancer compared to open surgery [120,121]. However, these studies are limited by their small sample sizes and inappropriate study designs; the final results of ongoing large multicenter randomized trials are awaited to determine the long-term outcomes of laparoscopic gastrectomy for locally advanced gastric cancer [122,123].

The short-term outcomes of laparoscopic gastrectomy with D2 LND for locally advanced gastric cancer have relatively been well demonstrated in clinical trials. Interim analysis of a large multicenter RCT in China (CLASS-01) reported no significant difference in postoperative complications between LADG and ODG (15.2% in LADG vs. 12.9% in ODG, $P=0.285$) [123]. In their study, patients with LADG also showed better postoperative recovery, such as faster bowel recovery and reduced hospital stay, than those with ODG (10.8 days in LADG vs. 11.3 days in ODG, $P<0.001$). Another small RCT reported similar numbers of harvested LNs and postoperative morbidity between open and laparoscopic gastrectomy with D2 LND [124]. More recently, a Japanese multicenter randomized trial (JLSSG 0901) reported interim results on the short-term outcomes of laparoscopic gastrectomy with D2 LND [125]. In their study, the incidence of anastomosis leakage or pancreatic fistula was 4.7%, which was within their expected target range and the study is ongoing.

In conclusion, with advances in laparoscopic surgery, short-term surgical outcomes and technical adequacy of laparoscopic gastrectomy with D2 LND have been well demonstrated both in retrospective studies and large RCTs. However, the long-term outcomes of laparoscopic gastrectomy for locally advanced gastric cancer require further investigation in large multicenter RCTs (**Fig. 3A**).

Robot gastrectomy

The current robotic surgical systems provide advantages such as 3-dimensional views, wristed instruments with 7 degrees of freedom, and tremor filtration, which enable surgeons to perform more accurate and thorough operations compared to that for conventional laparoscopic surgery [97,126-128]. Although it remains unclear whether the benefits of robotic gastrectomy outweigh the cost, the use of robotic gastrectomy has expanded gradually since the first clinical application of robotic surgery for the treatment of gastric cancer [97,129]. Robotic gastrectomy has shown several clinical benefits, including reduced blood loss and a possibly larger number of retrieved LN than those for conventional laparoscopic gastrectomy [126,130-132]. However, these advantages did not seem to significantly improve the short-term outcomes of patients [97,126,129]. These negative results were also demonstrated in a prospective multicenter study in Korea, although it was a non-randomized trial comparing the relatively early experience of robotic gastrectomy to well-established laparoscopic surgery [129]. The long-term oncologic outcomes of robotic gastrectomy reported by a few retrospective analyses are similar to those for laparoscopic surgery, but evidence is still lacking [126,130,131]. Overall, robotic gastrectomy seems to be feasible, safe, and easy to learn, but its advantages over laparoscopic gastrectomy are not obvious from the patient's standpoint.

ADJUVANT THERAPY

Statement 13. Adjuvant chemotherapy (S-1 or capecitabine plus oxaliplatin) is recommended in patients with pathological stage II or III gastric cancer after curative surgery with D2 LND (evidence: high, recommendation: strong for).

Surgical resection with D2 LND is the standard of care in gastric cancer. However, high rates of locoregional and distant recurrences have been reported in these cases, for which the prognosis is usually very poor [133].

European phase III studies demonstrated that perioperative chemotherapy including adjuvant chemotherapy was superior to surgery alone for patients with resectable gastroesophageal cancer [134,135]. As only 30%–50% of these European cases involved D2 LND, perioperative chemotherapy was not accepted as a treatment for such cases in East Asia.

Recently, 2 large randomized phase III trials conducted in Asian patients showed a significant survival benefit for adjuvant chemotherapy over observation after curative surgery with D2 LND in patients with resectable gastric cancer [136,137]. In the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) in Japan, 1,059 patients with stage II (excluding T1) or III gastric cancer (by Japanese classification, 2nd English edition [138]) following D2 gastrectomy received observation or S-1 for 1 year after surgery [136]. The rates of relapse-free survival at 3 years were 72.2% in the S-1 group and 59.6% in the surgery-only group (HR, 0.62; 95% CI, 0.50–0.77; $P < 0.001$) and the 3-year OS rates were 80.1% and 70.1%, respectively (HR, 0.68; 95% CI, 0.52–0.87; $P = 0.003$). In the capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) conducted in South Korea, China, and Taiwan, 1,035 patients with stage II–IIIB gastric cancer (by AJCC 6th edition [139]) following D2 gastrectomy received either observation or capecitabine and oxaliplatin for 6 months [137]. The 3-year DFS rates were 74% in the chemotherapy and surgery group and 59% in the surgery-only group (HR, 0.56; 95% CI, 0.44–0.72; $P < 0.001$). The 5-year follow-up data in these 2 studies confirmed these findings [140,141].

Based on the results of these studies, both chemotherapy regimens (S-1 or capecitabine plus oxaliplatin) are currently accepted as standard treatment in pathological stage II or III gastric cancer after D2 gastrectomy in East Asia (**Fig. 1**).

Statement 14. Adjuvant chemoradiation could be added for gastric cancer patients after curative resection with D2 lymphadenectomy to reduce recurrence and improve survival (evidence: high, recommendation: weak for).

High rates of loco-regional recurrence (LRR) have been reported in gastric cancer even after complete resection, especially in locally advanced stages of gastric cancer [142]. There have been attempts to minimize recurrences and improve outcomes through adjuvant RT, usually combined with chemotherapy, and several prospective or retrospective studies have shown promising outcomes of improved survival by reducing LRR [143–145]. In this context, a randomized phase III trial comparing surgery followed by adjuvant chemoradiation therapy (CRT) versus surgery alone in stage IB through IV (M0) gastric cancer (by AJCC 6th edition [139]) was performed (South Western Oncology Group-Directed Intergroup Study 0116 [INT-

0116)) [146,147]. There was a clear advantage when adding adjuvant CRT, with a significant prolongation of survival as well as reduction of recurrences. Despite the positive outcomes of the INT-0116 study, however, several limitations were revealed. First, D2 lymphadenectomy, highly recommended as a standard surgical procedure in locally advanced gastric cancer, was performed in only 10% of the enrolled patients [65]. Second, this study was mainly conducted in gastric cancer patients from a Western population with different characteristics from those of Asian populations including Korean [148]. Because of these limitations, the necessity of adjuvant RT in completely resected stomach cancer remains controversial. Meanwhile, a retrospective pooled analysis of Dutch Gastric Cancer Group Trial reported that adjuvant CRT improved survival as well as local control in the D1 but not D2 resected subgroup [149].

However, adjuvant chemotherapy without RT showed a survival benefit over surgery alone in following randomized phase III trials and has become a standard of care [136,137,140,141]. Thus, the role of RT in addition to chemotherapy has been further questioned. Several RCTs have compared adjuvant CRT versus chemotherapy alone in gastric cancer after complete resection with D2 lymphadenectomy [150-154]. Among them, one trial performed by a single Korean institution (Lee et al., [153] Adjuvant Chemoradiation Therapy in Stomach Cancer [ARTIST] trial) completed the preplanned patient accrual but 3 other trials (2 Korean and 1 Greek trial) failed to complete the planned registration and were terminated prematurely [150-152]. There was no mention of the planned number of patients or completion of registration in the 1 remaining multicenter Chinese trial [154].

A meta-analysis of the aforementioned trials found that adjuvant CRT can improve not only LRR-free survival (LRRFS) but also DFS compared to chemotherapy alone [155-160]. However, improved OS in adjuvant CRT was not demonstrated. Furthermore, the ARTIST trial failed to confirm the superiority of adjuvant CRT over chemotherapy alone in terms of DFS as well as OS for all patients even after long-term follow-up, although it showed a significant benefit in LRRFS [153,161,162]. The beneficial effect of DFS on adjuvant CRT was limited to patients with nodal involvement. This trial is considered to be the most reliable study in terms of adjuvant RT in gastric cancer for Korean patients because it is a well-designed prospective study that was conducted and completed in Korea.

Based on the results of these studies, adjuvant CRT can be considered in gastric cancer patients with incomplete resection and/or less than D2 lymphadenectomy (**Fig. 1**). Adjuvant CRT could also be considered in patients with gastric cancer after complete resection with D2 lymphadenectomy, especially for those with LN metastasis.

NEOADJUVANT THERAPY

Statement 15. Neoadjuvant chemotherapy for potentially resectable gastric cancer is not conclusive if D2 LND is considered (evidence: high, recommendation: inconclusive).

European phase III studies demonstrated that perioperative chemotherapy including neoadjuvant chemotherapy was superior to surgery alone in potentially resectable gastric cancer. The outcomes of patients treated with surgery alone were compared to those of patients treated with perioperative epirubicin, cisplatin, and infusional 5-fluorouracil (5-FU)

in the MAGIC trial or with perioperative cisplatin and infusional 5-FU in the FNCLCC/FFCD trial [135,163]. In these studies, perioperative chemotherapy significantly prolonged both OS and progression-free survival (PFS) or DFS. The FLOT-4 study showed that a perioperative regimen comprising 5-FU, leucovorin, oxaliplatin, and docetaxel was superior to perioperative epirubicin, cisplatin, and 5-FU or capecitabine [134]. However, as D2 LND was performed in only 30%–50% of patients in these European studies, these perioperative chemotherapeutic regimens might not be applicable to patients in Korea, where D2 LND is the standard of care. Recently, the Japanese phase III JCOG 0501 study compared 2 cycles of neoadjuvant S-1 plus cisplatin followed by D2 surgery and adjuvant S-1 to D2 surgery followed by adjuvant S-1 in far-advanced localized gastric cancer. This trial observed no statistically significant difference in OS and PFS between the 2 arms [164].

Therefore, neoadjuvant chemotherapy for potentially resectable gastric cancer is not conclusive at present in Korea except in clinical trials (**Fig. 1**).

Statement 16. The evidence for the effectiveness of neoadjuvant chemoradiation in locally advanced gastric cancer is not conclusive if D2 LND is considered (evidence: high, recommendation: inconclusive).

Neoadjuvant CRT is mainly studied for cancer of the esophagus, EGJ, and/or gastric cardia, where obtaining a complete R0 resection is challenging and thus, there is a higher probability of locoregional relapse. Two RCTs have been conducted and 1 trial is ongoing to compare the outcomes of neoadjuvant CRT versus neoadjuvant chemotherapy alone in resectable cancer of the EGJ or stomach [165-168].

The PreOperative therapy in Esophagogastric adenocarcinoma Trial (POET) showed a higher probability of pathologic complete response (15.6% vs. 2.0%) and pathologic N0 (64.4% vs. 37.7%) after neoadjuvant CRT compared to those for neoadjuvant chemotherapy alone [168]. Additionally, improved OS was also noticed after neoadjuvant CRT (47.4% vs. 27.7% at 3 years), although the difference failed to reach statistical significance ($P=0.07$). The improved OS remained in long-term analysis (39.5% vs. 24.4% at 5 years, $P=0.06$) with a significant benefit of LRRFS ($P=0.01$; HR, 0.37) [167]. Similar benefits of neoadjuvant CRT were also reported in another RCT from Sweden and Norway [165]. Neoadjuvant CRT showed higher probabilities of complete pathologic response (28% vs. 9%, $P=0.002$), pathologic N0 (62% vs. 35%, $P=0.001$), and R0 resection rate (87% vs. 74%, $P=0.04$) in this study. The Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma (TOPGEAR) also demonstrated that neoadjuvant CRT can be safely delivered to the majority (85%) of patients without a significant increase in treatment-related toxicities or surgical morbidity [166]. Those findings have been confirmed in several meta-analyses of randomized trials [159,169-171].

Despite their promising outcomes, the aforementioned studies were performed mainly in patients with esophageal and/or EGJ cancer. EGJ cancer is common in Western countries [148] and most studies evaluating the efficacy of neoadjuvant CRT for gastric cancer (mainly EGJ cancer) were also performed in Western populations. Thus, it might be inappropriate to simply apply these results to Asian populations, especially to Koreans, where gastric cancer occurs mainly in the antral area [148] (**Fig. 1**). To evaluate the effect of neoadjuvant CRT in gastric cancer, further prospective studies targeting Asian populations with non-junction cancer are mandatory.

PALLIATIVE THERAPY

The prognosis for locally advanced unresectable or metastatic gastric cancers is dismal, and these patients have a median OS of 6–13 months. The goals of therapy for these patients are to palliate disease-related symptoms and to prolong survival. Such palliative systemic therapy also provides a greater quality of life than best supportive care. Thus, systemic therapy is the primary treatment to be considered in patients with locally advanced unresectable (unresectable T4b or extensive nodal disease) or metastatic disease or those after non-curative resection. Palliative systemic therapy for advanced gastric cancer should be determined based on patient performance status, medical comorbidities, and organ function. Furthermore, systemic therapy regimens can be individualized for each patient, with the regimen determined by the clinician according to various patient or gastric cancer-related conditions and participation in clinical trials can be actively considered. A recent study conducted in Germany reported that patients' preferences impacted the specific responses, including low toxicity of chemotherapy, self-care ability, and additional survival benefits [172]. Therefore, patient preferences should also be considered in making decisions regarding palliative therapy

Surgery

Statement 17. Palliative gastrectomy is not recommended for metastatic gastric cancer except for palliation of symptoms (evidence level: high, recommendation: strong against).

Palliative surgery is usually indicated for metastatic gastric cancer for the control of urgent symptoms such as obstruction, bleeding, or perforation. However, the effect of palliative gastrectomy on the survival of patients with metastatic gastric carcinoma has long been debated. Several retrospective studies have reported inconsistent results depending on patient population and analytic methods. Some studies have reported significantly improved patient survival for gastrectomy plus chemotherapy compared to chemotherapy alone in carefully selected patients [173-179]. Some reports have suggested that patients with hepatic metastasis might benefit from gastrectomy plus partial hepatectomy when no other distant metastasis existed [180-183]. In contrast, other studies have reported that gastrectomy neither prolonged patient survival nor improved the quality of life in patients with metastatic gastric carcinoma [184-191]. Meanwhile, a meta-analysis of 14 retrospective studies showed that gastrectomy followed by chemotherapy could significantly improve patient survival (median survival, 14.96 vs. 7.07 months; HR, 0.56; 95% CI, 0.39–0.80), compared to that for chemotherapy alone [192]. Another meta-analysis of 19 non-randomized studies reported that gastrectomy could improve patient survival (1-year survival: OR, 2.6; 95% CI, 1.7–4.3; $P < 0.001$) in metastatic gastric carcinoma [193]. However, these studies are mostly biased by patient selection, in which surgery was usually indicated for patients with relatively better performance status and less advanced disease.

To investigate the survival benefit of gastrectomy for metastatic gastric carcinoma, a large international phase III trial was performed in Korea, Japan, and Singapore (REGATTA trial) [194]. In this trial, 175 advanced gastric cancers with a single non-curable factor (liver, peritoneum, or distant nodal metastasis) were randomly assigned to receive gastrectomy plus chemotherapy or chemotherapy alone. The results of an interim analysis revealed that gastrectomy prior to chemotherapy had no effect on OS (HR, 1.08; 95% CI, 0.74–1.58;

P=0.66) or PFS (HR, 1.01; 95% CI, 0.74–1.37; P=0.96). Based on these findings, this trial was interrupted in 2013, concluding that gastrectomy did not show any survival benefit compared to that for chemotherapy alone in advanced gastric carcinoma with a single non-curable factor.

In conclusion, although some retrospective studies have reported a possible survival benefit of palliative gastrectomy for metastatic gastric carcinoma, a well-designed multi-institutional randomized trial proved that gastrectomy does not improve patient survival in metastatic gastric carcinoma. Therefore, gastrectomy should only be performed with a palliative intent to relieve patient symptoms (**Fig. 1**).

First-line systemic therapy

Statement 18-1. Palliative first-line platinum/fluoropyrimidine combination is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (evidence: high, recommendation: strong for).

The effective cytotoxic agents for advanced gastric cancer include infusional 5-FU, oral fluoropyrimidines, platinum agents, taxanes, irinotecan, and anthracyclines. Randomized studies have evaluated various 5-FU-based regimens for the treatment of locally advanced unresectable or metastatic gastric cancer [195-197]. In a meta-analysis, significant OS benefits were shown for chemotherapy versus best supportive care, with increased survival of approximately 6 months. In addition, combination chemotherapy showed a statistically significant survival benefit over single-agent chemotherapy, with a difference in weighted mean average survival of approximately 1 month [198] (**Fig. 4**).

Although infusional 5-FU is one of the most commonly used cytotoxic agents for advanced gastric cancer, continuous intravenous infusions can prolong hospital stays and result in thrombosis and infection. Randomized phase III studies have demonstrated that the oral fluoropyrimidines capecitabine [199-201] and S-1 [202,203] are as effective as infusional 5-FU. Therefore, oral fluoropyrimidines (capecitabine or S-1) are safe and convenient alternatives to 5-FU for combinations with platinum compounds in patients with advanced gastric cancer. For many years, cisplatin was the leading compound used for the treatment of patients with advanced gastric cancer. To avoid some of the associated side effects such as nausea, vomiting, nephrotoxicity, and ototoxicity, other platinum compounds were investigated. The results of the REAL-2 study suggested that pooled oxaliplatin-based regimens are not inferior to pooled cisplatin-based regimens in terms of OS [199]. A randomized trial in Germany showed that oxaliplatin had better efficacy than that of cisplatin in older adult patients and a more favorable overall toxicity profile [204]. The G-SOX study in Japan and the SOPP study in Korea showed that S-1 plus oxaliplatin is as effective as S-1 plus cisplatin for the treatment of advanced gastric cancer, with a favorable safety profile [205,206]. Therefore, oxaliplatin is at least as effective as cisplatin for prolonging survival and is generally better tolerated.

Regarding combination therapies, it remains unclear if there is a benefit from combining 3 rather than 2 cytotoxic agents. The phase III V325 study showed an increased overall response rate, PFS, and OS for docetaxel, cisplatin, 5-FU (DCF) compared to those of cisplatin/5-FU [207]. However, the implementation of DCF is difficult in clinical practice

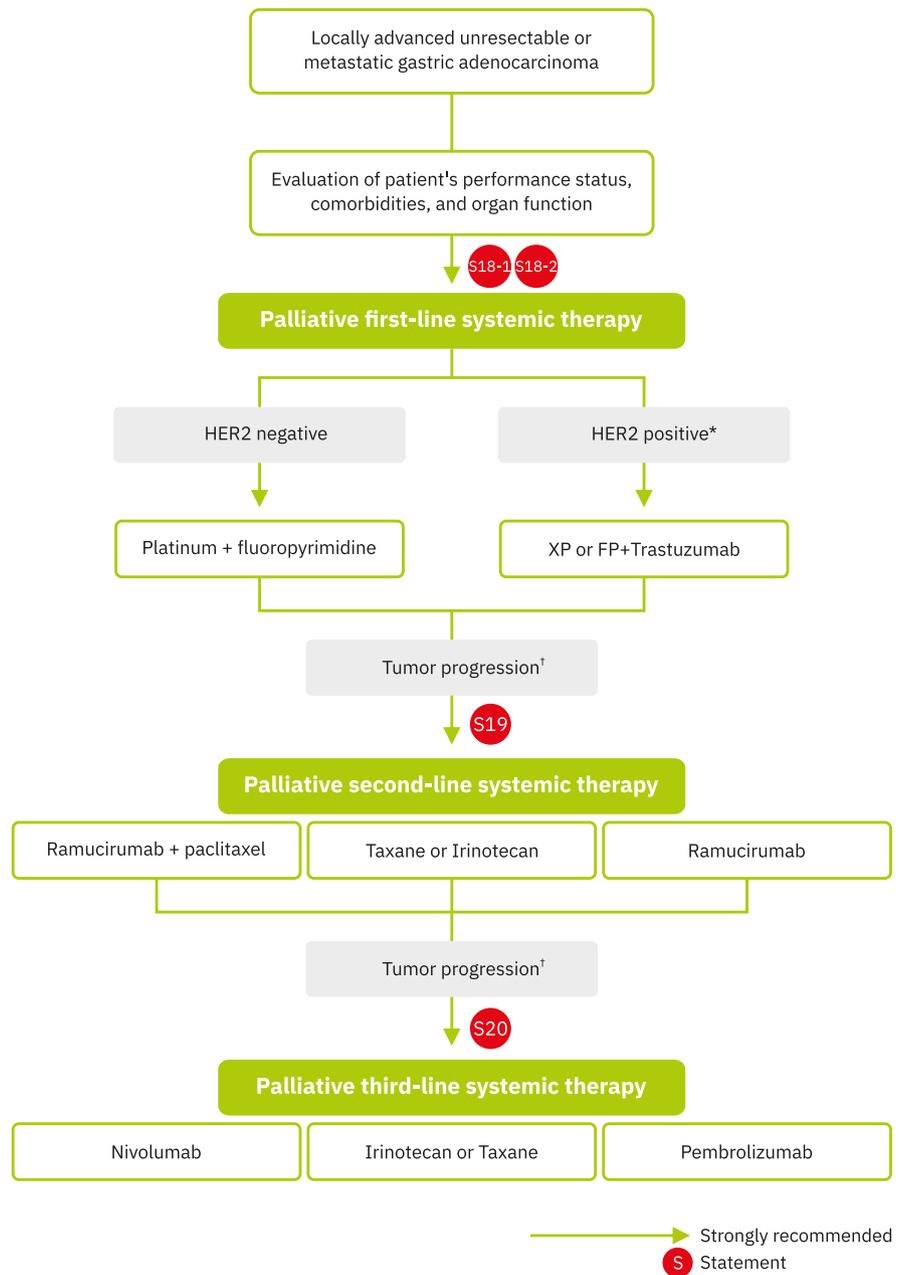


Fig. 4. Treatment algorithm for palliative systemic therapy.

HER2 = human epidermal growth factor receptor 2; XP = capecitabine and cisplatin; FP = fluorouracil and cisplatin; IHC = immunohistochemistry.

*HER2 IHC 3+ or IHC 2+ and in situ hybridization-positive; †Evaluation of patient performance status, comorbidities, and organ function.

because the DCF regimen showed only a modest OS benefit (9.2 [DCF] vs. 8.6 months [CF]) but caused markedly increased hematological and gastrointestinal toxicity in this highly selected study population, with a median age of 55 years. In various clinical trials, modifications of this DCF regimen have demonstrated efficacy with improved safety profiles in patients with advanced gastric cancer. Therefore, selected patients can benefit from docetaxel-containing triplet combinations but increased side effects should be considered (high, weak for).

Statement 18-2. Palliative trastuzumab combined with capecitabine or fluorouracil plus cisplatin is recommended in patients with human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 3+ or IHC 2+ and in situ hybridization (ISH)-positive advanced gastric cancer (evidence: high, recommendation: strong for).

Trastuzumab is a humanized anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody and the first successful biologic agent, with documented clinical activity as a first-line treatment in advanced gastric cancer (**Fig. 4**). The Trastuzumab for Gastric Cancer (ToGA) trial demonstrated clinically and statistically significant improvements in OS with the addition of trastuzumab to a cisplatin/fluoropyrimidine doublet (13.8 vs. 11.1 months; HR, 0.74; 95% CI, 0.60–0.91; $P < 0.01$) [208]. A post hoc subgroup analysis revealed that the addition of trastuzumab to chemotherapy substantially improved the OS of patients whose tumors were IHC 3+ or IHC 2+ and ISH-positive (16.0 vs. 11.8 months; HR, 0.65; 95% CI, 0.51–0.83). Therefore, a trastuzumab-containing regimen is recommended in patients with HER2-positive gastric cancer and a combination of trastuzumab, cisplatin, and either capecitabine or infusional 5-FU is recommended in clinical practice based on the results of this trial.

Various agents targeting epidermal growth factor receptor, hepatocyte growth factor receptor, and vascular endothelial growth factor receptor (VEGFR) have been evaluated as first-line treatments for advanced gastric cancer; however, except for trastuzumab, none of these agents demonstrated a significant OS benefit in global phase III trials.

Second-line systemic therapy

Statement 19. Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved. Ramucirumab plus paclitaxel is preferably recommended and monotherapy with irinotecan, docetaxel, paclitaxel, or ramucirumab could also be considered (evidence: high, recommendation, strong for).

Randomized trials and a meta-analysis have demonstrated the survival benefit of second-line palliative chemotherapy (with irinotecan or taxanes) compared to best supportive care alone for patients with locally advanced unresectable or metastatic gastric cancer (HR, 0.64; 95% CI, 0.52–0.79; $P < 0.001$) [209–212] (**Fig. 4**). Weekly paclitaxel resulted in a similar OS to that achieved with irinotecan in phase III trials [213,214]. In addition, ramucirumab, a monoclonal antibody targeting VEGFR-2, was shown to significantly improve survival in 2 phase III double-blind placebo-controlled trials. In the REGARD trial, patients receiving ramucirumab had improvements in both OS and PFS compared to those in patients receiving placebo [215]. Similarly, in the RAINBOW trial, the addition of ramucirumab to weekly paclitaxel significantly prolonged the median OS (9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.678–0.962; $P = 0.017$) compared to that for paclitaxel plus placebo [216].

Based on the available data, ramucirumab in combination with paclitaxel is recommended as the most preferred second-line treatment. Irinotecan, docetaxel, paclitaxel, or ramucirumab as single agents can also be considered as a second-line option if not previously administered in the first-line treatment.

Pembrolizumab, an anti-programmed cell death 1 (PD-1) antibody, was recently approved by the Food and Drug Administration (FDA) for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (MMR) solid tumors that have progressed after initial treatments, thus representing a second-line or later option for such gastric cancer cases [217].

Third-line systemic therapy

Statement 20. Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (evidence: high, recommendation: strong for).

Despite the lack of clear evidence for third-line cytotoxic chemotherapy, data from several phase II and retrospective studies indicate a 15%–20% response rate with third-line taxane- or irinotecan-based chemotherapy [218–220] (**Fig. 4**). In a randomized phase III trial in Korea, second- or third-line salvage chemotherapy significantly prolonged patient survival compared to that for best supportive care [210]. Therefore, palliative third-line chemotherapy with cytotoxic agents (e.g., irinotecan, paclitaxel, or docetaxel) not used in second-line therapy can be recommended (moderate, strong for). Recently, a phase III study of patients with metastatic gastric cancer refractory to standard therapies showed a benefit in terms of OS with TAS-102 (trifluridine/tipiracil) compared to that for best supportive care [221]. TAS-102 can be considered if it is approved for use in gastric cancer (high, weak for).

In a randomized phase III trial, apatinib mesylate, a small-molecule inhibitor of VEGFR-2, significantly prolonged the survival of patients who experienced disease progression after 2 or more lines of systemic therapy [222]. However, with an increasing number of patients receiving ramucirumab in the second-line setting, the efficacy of apatinib mesylate in overcoming resistance to ramucirumab is unclear. Moreover, the only results with apatinib mesylate have been reported among Chinese patients; therefore, additional studies are needed to confirm these results (high, weak for).

Recently, immune checkpoint inhibitors have been shown to enhance antitumor T-cell activity via inhibition of the PD-1 receptor. Nivolumab is a humanized IgG4 anti-PD-1 monoclonal antibody. ATTRACTION-2 (ONO-4538-12), the first phase III trial of third-line or later nivolumab versus placebo, showed the efficacy and safety of nivolumab in heavily pretreated patients with advanced gastric cancer (median OS, 5.26 vs. 4.14 months; HR, 0.63; 95% CI, 0.51–0.78; $P < 0.001$) [223]. Another such antibody, pembrolizumab, also showed promising activity and manageable safety in advanced gastric cancer patients who had received at least 2 lines of treatment in a phase Ib trial (KEYNOTE-012) (8) as well as a phase II trial (KEYNOTE-059; cohort 1), in which the overall response rates trended higher in PD-L1-positive versus PD-L1-negative tumors [224,225]. Nivolumab improves OS as third-line treatment irrespective of PD-L1 status in Asian patients with gastric cancer and is registered in Korea, Japan, and Taiwan (high, strong for). Pembrolizumab shows significant efficacy as a third-line treatment, especially in PD-L1-positive patients in whom its use is approved by the US FDA (moderate, weak for).

Radiotherapy (RT)

Statement 21. Palliative RT could be offered to alleviate symptoms and/or improve survival in recurrent or metastatic gastric cancer (evidence: moderate, recommendation: weak for).

Systemic chemotherapy is the mainstay treatment for the management of recurrent or metastatic gastric cancer, even for isolated LRR [50]. However, the addition of local modalities including RT may add a benefit over chemotherapy alone in certain situations [226-231].

Unfortunately, no prospective randomized phase III trial has evaluated the efficacy of adding RT in recurrent or metastatic gastric cancer. However, successful symptom alleviation has been reported with the addition of RT in symptomatic advanced gastric cancer [228-230] and prolongation of survival is suggested according to the results of several prospective and retrospective reports [226-228,231]. Tey et al. [230] reported improvement of symptoms such as tumor bleeding (83/103, 80.6%), obstruction (9/17, 52.9%), and pain (5/11, 45.5%) after RT, with an acceptable rate (2.6%) of grade 3 gastrointestinal toxicities [230]. Sun et al. [228] reported that clinical symptoms were relieved after RT in 19 of 21 patients (90.5%) with recurrent gastric cancer with abdominal LN metastasis. Hingorani et al. [227] reported the outcomes of a retrospective study comparing chemotherapy followed by RT to primary tumor and chemotherapy alone in metastatic EGI cancer patients with responding or stable disease after 3 months of chemotherapy. Both OS and time to local progression were significantly improved in irradiated patients, at 23.3 vs. 14.0 months ($P < 0.001$) and 17.3 vs. 8.3 months ($P = 0.006$), respectively.

Despite a lack of evidence from randomized phase III trials on the efficacy of RT in recurrent or metastatic stomach cancer, RT could be used for palliation of symptoms in localized primary and/or metastatic disease and could possibly improve survival by maximizing local control in patients with responding or stable disease after chemotherapy (**Fig. 1**). The efficacy and necessity of RT in recurrent or metastatic stomach cancer should be evaluated in larger studies.

PATHOLOGY

This guideline only describes in detail several pathological topics important to gastric cancer treatment. For topics not described here, please refer to the existing guidelines [2,232].

Histologic classification

World Health Organization (WHO) classification is used for the pathologic classification of gastric carcinoma [233]. Lauren classification is added in resected specimens, including ESD specimens [234].

WHO classifications

1) Papillary adenocarcinoma

Although the diagnostic criteria for papillary carcinoma are not clearly defined in the 2010 WHO Blue Book, many publications define papillary carcinoma as more than 50% of the tumor present in the papillary [235]. Papillary adenocarcinoma is graded as well, moderately, or poorly differentiated [233]. Most papillary adenocarcinomas are well-differentiated.

However, the prognosis is poor if the nuclear atypia is severe [236]. Therefore, such cases should be classified as poorly differentiated.

2) Tubular adenocarcinoma

Tubular adenocarcinoma, the most common histologic type of gastric carcinoma, is graded as well, moderately, or poorly differentiated. Well-differentiated tubular adenocarcinoma is composed of well-formed tubular structures. Poorly differentiated adenocarcinoma shows irregular glands with indistinct lumens. Moderately differentiated adenocarcinomas are intermediate between well- and poorly differentiated [233].

3) Mucinous adenocarcinoma

This variant of adenocarcinoma is defined by the presence of >50% of tumor lesions with an extracellular mucin pool regardless of the tumor cell type, signet ring cell or not [233].

4) Poorly cohesive carcinoma

This tumor is composed of poorly cohesive neoplastic cells that are isolated or form small aggregates [233]. This type includes signet ring cell carcinoma and other cellular variants composed of poorly cohesive neoplastic cells [233]. However, signet ring cell carcinoma is usually diagnosed separately if the signet ring cell component exceeds 50% rather than diagnosed as poorly cohesive carcinoma.

5) Mixed carcinoma

This type of carcinoma has a discrete mixture of both glandular (tubular or papillary) and signet ring/poorly cohesive components [233]. The latter component is associated with a poor prognosis [233].

Addendum: In Japan, gastric carcinomas are commonly divided into 2 major categories, differentiated and undifferentiated types, especially with respect to the indications for endoscopic resection [237,238]. Although the WHO classifications do not completely match to this classification, the differentiated type generally includes well and moderately differentiated tubular adenocarcinomas and papillary adenocarcinoma, while the undifferentiated type includes poorly differentiated tubular adenocarcinoma and poorly cohesive carcinoma. Mucinous adenocarcinoma is classified as differentiated (with tubules) or undifferentiated (with signet ring cells) according to the type of tumor cell and is sometimes also categorized as undifferentiated type.

Lauren classifications

The Lauren classification divides tumors into intestinal, diffuse, and mixed types [234]. Intestinal carcinomas form glands with various degrees of differentiation and are almost invariably associated with intestinal metaplasia and variable degrees of atrophic gastritis. Diffuse carcinoma consists of poorly cohesive cells with little or no gland formation. Tumors containing approximately equal quantities of intestinal and diffuse components are termed “mixed.”

Pathologic diagnosis of mixed histology

In early gastric cancer, the histologic type and grade of the biopsy tissue are important for determining the treatment modality. Tumor heterogeneity and inter- and intra-observer discrepancies may lead to differences in histological types before and after ESD [239-241]. Submucosal and even intramucosal cancer with heterogeneity have recently been reported to have a higher incidence of LN metastasis than that of homogeneously differentiated types

of tumor [242,243]. Thus, there is a view that the minor component of undifferentiated histology should be reported in cases of biopsy and ESD specimens. However, this requires more discussion and consensus of clinical and pathologic departments.

Biomarkers

HER2

IHC tests should first be performed for evaluation of HER2 status. IHC results are scored as 0, 1+, 2+, or 3+ (Table 4). IHC 3+ is considered positive for HER2 overexpression, while IHC 0-1+ is considered negative. IHC 2+ is regarded as an equivocal finding and should be followed by ISH tests. The area with the strongest IHC intensity should be selected and stained for HER2 and chromosome enumeration probe (CEP) 17. The criteria for HER2 amplification is a HER2:CEP17 ratio of ≥ 2 . If CEP17 polysomy is present and the ratio is < 2 , an average HER2 signal of > 6 is interpreted as a positive finding. IHC 3+ or IHC 2+ and ISH-positivity are considered HER2-positive [244,245]. HER2-positivity is an indication for anti-HER2 targeted therapy in the palliative setting [208].

Microsatellite instability (MSI)

MSI is assessed by polymerase chain reaction (PCR)-based tests, which can be replaced by IHC tests for the 4 MMR proteins (MMR deficient [dMMR]) [246,247]. Instability is examined by PCR of a representative panel of microsatellites. The grade of the instability is determined by the numbers of unstable microsatellites: MSI-H, MSI-low (MSI-L), or microsatellite stable (MSS) [248,249]. MSI-H is considered MSI-positive. In the IHC method, the IHC staining is done for the 4 MMR proteins: MLH1, MSH2, PMS2, and MSH6. When the expression of any one of the MMR proteins is lost, the case is considered to be dMMR. MSI positivity is the criteria for MSI-subtype gastric cancer. MSI-positive gastric cancer is classified as a separate subtype in the molecular classifications of gastric cancer and shows elevated mutation rates and distinctive patterns of methylation [250,251]. This subtype has unique clinical characteristics, including distal location, high frequency of intestinal-type histology, lower stage, and good prognosis [252]. In the palliative setting, MSI positivity is an indication for immune checkpoint inhibitor therapy (pembrolizumab) [253].

Epstein-Barr virus (EBV)

The presence of the EBV genome can be examined by several methods. The most widely used method for tissue sections, performed in almost all hospitals, is ISH to EBV-encoded RNA (EBER) [254]. When signals in the tumor cell nuclei are observed, the case is considered to be EBV-positive gastric cancer. EBV positivity is the criteria for EBV-positive gastric cancer. EBV-positive gastric cancer is classified as a separate subtype in the molecular classification of gastric cancer and shows hypermethylation different from that of the MSI subtype [250]. This subtype is distinct in its proximal location, relation to poorly differentiated histology, lower stage, and good prognosis [255,256].

Table 4. Interpretation of IHC findings [244,245]

HER2 status	Intensity	IHC staining
Negative	0	Reactivity in $< 10\%$ * of tumor cells
Negative	1+	Faint membranous [†] reactivity in $\geq 10\%$ of tumor cells; reactive only in part of their membrane
Equivocal	2+	Weak to moderate complete or basolateral membranous reactivity in $\geq 10\%$ of tumor cells
Positive	3+	Strong complete or basolateral membranous reactivity in $\geq 10\%$ of tumor cells

IHC = immunohistochemistry; HER2 = human epidermal growth factor receptor 2.

*For biopsy samples, measure scores when stained tumor cell clusters (≥ 5 cells) are present, irrespective of the percentage of tumor cells; [†]Only membranous staining should be considered true reactivity.

PD-L1

Several systems can be used for the interpretation of IHC staining of PD-L1. The combined positive score (CPS) [224] is the number of PD-L1-stained viable tumor cells, lymphocytes, and macrophages divided by the number of viable tumor cells, multiplied by 100.

Lymphocytes or macrophages are scorable when they are contiguous: intercalated within a confluent area of neoplastic cells or a part of a confluent area adjacent to neoplastic cells (within a 20× field) [257]. The tumor proportion score (TPS) is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity [258]. The criteria for PD-L1 positivity differs depending on the therapeutic agent. For pembrolizumab, PD-L1 positivity is defined as CPS ≥ 1 . In a clinical trial that enrolled 259 patients, the objective response rates were 15.5% and 6.4% in patients with CPS ≥ 1 and < 1 , respectively [225]. For nivolumab, the cut-off for PD-L1 expression has not been established. In a clinical trial, an exploratory subgroup analysis was performed with a TPS of $> 1\%$ vs. $\leq 1\%$ but the median survival increased regardless of PD-L1 level [223].

Peritoneal washing cytology

Statement 22. Peritoneal washing cytology is recommended for staging. Advanced gastric cancer patients with positive cancer cells in the peritoneal washing cytology are associated with frequent cancer recurrence and poor prognosis (evidence: moderate, recommendation: strong for).

The association between peritoneal washing cytology results and prognosis in patients with advanced gastric cancer has been reported in prospective [259,260] and retrospective [261-264] studies but not in any randomized case-control studies. The exact prognostication of advanced gastric cancer patients with positive peritoneal washing cytology result is difficult due to variability in enrolled patients, peritoneal washing methods, and treatment of cancer patients in these studies. Recent systemic reviews and meta-analyses have shown that peritoneal washing cytology is useful for determining the prognosis of advanced gastric cancer patients [265-268].

Although some studies have reported that peritoneal washing cytology results are not related to prognosis, most studies and meta-analyses have observed a high recurrence rate and short survival time in advanced gastric cancer patients with positive washing cytology. In 2 meta-analyses, the HRs for survival among cytology-positive patients were 3.27 (95% CI, 2.82–3.78) [267] and 3.46 (95% CI, 2.77–4.31) [265], respectively, which was significantly higher than those for cytology-negative patients. The HR of cancer recurrence (4.15; 95% CI, 3.10–5.57) was also higher in cytology-positive patients [267].

The positivity rate of peritoneal washing cytology varies from 7% to 58% [259-261,263-265,267]; this range may be due to differences in the study populations, including early gastric cancer patients. The diverse pathologic criteria of positive cancer cells could also contribute to the wide range of positivity. Although most of the studies did not address the pathologic criteria for 'positive' cancer cells in peritoneal washing cytology, there is a need for further studies to establish these pathologic criteria for the clinical application of peritoneal washing cytology in advanced gastric cancer patients.

In conclusion, peritoneal washing cytology is recommended for accurate staging and prognosis for advanced gastric cancer even though there remain several controversies.

MULTIDISCIPLINARY TEAM (MDT) APPROACH

The effectiveness of MDTs in cancer treatment has been controversial because there was no strong evidence and MDT also requires significant time and resources [269,270]. However, MDT has been important for the treatment of cancer because treatment methods are diverse, complex, and specialized. The advantages of MDT include correct diagnosis, changing to a better treatment plan, and survival benefit. For these reasons, health services in several countries have produced guidelines citing MDTs as the preferred system for cancer treatment [271].

Several studies have shown the advantages of MDT in gastrointestinal malignancy. After MDT meetings, changes in diagnosis occurred in 18.4%–26.9% of evaluated patients [272,273], and the treatment plan was changed in 23.0%–76.8% of cancer patients [273–275]. Furthermore, the National Comprehensive Cancer Network guideline emphasizes the recommendation for MDT and the European Society for Medical Oncology and European Cancer Organization guidelines indicate that MDT before determining cancer treatment is mandatory [61,62,276].

The many types of MDT include conferences the without patient present, face-to-face with the patient, and telemedicine. There is no strong evidence regarding which type is better, although Kunkler et al. [277] reported no difference between telemedicine and face-to-face medicine. In addition, Allum et al. [61] recommended that MDTs should discuss treatment decisions with patients. The MDT members for gastric cancer treatment are recommended to include surgeons, gastroenterologist, medical and radiation oncologists, radiologists and pathologists, and other members such as those from nutritional services, social workers, nurses, and palliative care specialists [62,276,278,279].

In conclusion, MDT treatment has a benefit in the treatment of gastric cancer patients regarding patient satisfaction, change to better treatment plans, and more correct diagnosis; however, stronger evidence is required.

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SUPPLEMENTARY MATERIALS

Supplement Data 1

Flowcharts of the literature search and study selection

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Supplement Data 2

Selected literature lists

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Supplement Data 3

Quality assessment tables

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Supplement Data 4

Evidence tables

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