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Special Article

Korean Practice Guidelines for Gastric Cancer 2022: An Evidence-based, Multidisciplinary Approach

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ABSTRACT

Gastric cancer is one of the most common cancers in Korea and the world. Since 2004, this is the 4th gastric cancer guideline published in Korea which is the revised version of previous evidence-based approach in 2018. Current guideline is a collaborative work of the interdisciplinary working group including experts in the field of gastric surgery, gastroenterology, endoscopy, medical oncology, abdominal radiology, pathology, nuclear medicine, radiation oncology and guideline development methodology. Total of 33 key questions were updated or proposed after a collaborative review by the working group and 40 statements were developed according to the systematic review using the MEDLINE, Embase, Cochrane Library and KoreaMed database. The level of evidence and the grading of recommendations were categorized according to the Grading of Recommendations, Assessment, Development and Evaluation proposition. Evidence level, benefit, harm, and clinical applicability was considered as the significant factors for recommendation. The working group reviewed recommendations and discussed for consensus. In the earlier part, general consideration discusses screening, diagnosis and staging of endoscopy, pathology, radiology, and nuclear medicine. Flowchart is depicted with statements which is supported by meta-analysis and references. Since clinical trial and systematic review was not suitable for postoperative oncologic and nutritional follow-up, working group agreed to conduct a nationwide survey investigating the clinical practice of all tertiary or general hospitals in Korea. The purpose of this survey was to provide baseline information on follow up. Herein we present a multidisciplinary-evidence based gastric cancer guideline.

Keywords: Stomach neoplasms; Chemotherapy; Endoscopy; Surgery; Guidelines

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Endorsements

The present guidelines were endorsed by the Korean Society of Medical Oncology, the Korean Society of Gastroenterology, the Korean College of Helicobacter and Upper Gastrointestinal Research, the Korean Society of Gastrointestinal Endoscopy, the Korean Society of Pathologists, the Korean Society of Abdominal Radiology, the Korean Society of Radiation Oncology, the Korean Society of Nuclear Medicine, and the Korean Gastric Cancer Association.

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Conflict of Interest

Seong-Ho Kong has received research funding from Stryker Co., Ltd. and Medtronic Inc. as the principal investigator and is the CEO of VITCAL, Co., Ltd. No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Background

Gastric cancer is one of the most common cancers in Korea and the world, which is ranks 5th in incidence and was the 4th leading cause of death among all solid cancers, excluding nonmelanoma skin cancer, globally in 2020 [1]. In Korea, new cases of gastric cancer (26,662) ranked 4th (10.8%), followed by thyroid cancer (11.8%), lung cancer (11.7%), and colon cancer (11.2%), with small differences in 2020, according to the report of the Korea Central Cancer Registry [2-4]. Early detection through national and public screening programs and advancements in treatment resulted in the proportion of surgically treated early gastric cancer (EGC) to increase from 28.6% in 1995 to 63.6% in 2019, and the 5-year survival increased from 43.9% (1993–1995) to 77.5% (2015–2019) [5]. Environmental factors, local dietary factors, socioeconomic factors, and *Helicobacter pylori* infections are considered important in the development of gastric cancer [6-9].

Chronology

Since 2004, 3 guidelines have been published and this is the 4th gastric cancer guideline published in Korea which is the revised version of previous evidence-based approach in 2018 [10-12]. It is the third guideline directed by the Korean gastric cancer association and prepared as a designated project assignment (No. 1020440) under the Research and Development Program for Cancer Control, conducted by the Ministry of Health and Welfare, South Korea. This is a collaborative work of the interdisciplinary working group that was nominated by the Korean Society of Medical Oncology, the Korean Society of Gastroenterology, the Korean College of Helicobacter and Upper Gastrointestinal Research, the Korean Society of Gastrointestinal Endoscopy, the Korean Society of Pathologists, the Korean Society of Abdominal Radiology, the Korean Society of Radiation Oncology, the Korean Society of Nuclear Medicine and the Korean Gastric Cancer Association along with the participation of experts in guideline development methodology (National Evidence-based Healthcare Collaborating Agency).

Methodology

After a collaborative review by the working group, key questions (KQs) were either updated or proposed (de novo). For the updated KQs, published literature was systematically searched using the MEDLINE, Embase, Cochrane Library and KoreaMed database, between January 2018 and December 2021, followed by a previous systematic search [10]. For de Novo KQ, a comprehensive search was performed up to December 2021, and starting date was not limited. Manual-searching was also performed for complementary results, and some literature published in 2022 and unpublished results from completed studies were also included. Screening and selection were performed by 2 reviewers. Criteria for selection and exclusion were predefined by the KQs. Initial screening of the articles was performed by title and abstract, and secondary screening was done by full-text review. Each panel independently selected the articles and compared the results for inconsistency. When disagreements occurred during the review process, a final agreement was reached through consensus with the involvement of a third review panel.

For quality assessments, the Cochrane Risk of Bias 2.0 (ROB) was used for randomized controlled trials (RCTs), the Risk of Bias for Nonrandomized Studies (RoBANS) was used for non-RCTs, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was used for diagnostic studies, and AMSTAR 2 was used for systematic reviews/meta-analyses.

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Table 1. Level of evidence (Grading of Recommendations, Assessment, Development and Evaluation approach)

Level	Definition
High	We are very confident that the true effect lies close to that of the estimated effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimated effect.
Very low	We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

Table 2. Grading of recommendations

Grade	Definition
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.
Conditional 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.
Conditional 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.
Investigational	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.

In this revised edition, the level of evidence and grading of recommendation were redefined based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology review [13]. The level of evidence was classified into 4 levels (**Table 1**) and the recommendation grading was categorized into 5 levels following the GRADE methodology (**Table 2**). We considered evidence level, benefit, harm, and clinical applicability as recommendation factors. The development working group reviewed the draft simultaneously and discussed for consensus.

Meta-analysis output and forest plots were computed from Review Manager (RevMan; Cochrane, London, UK) software. Evidence tables were summarized according to KQs, and the evidence-to-decision table was applied using GRADEpro (https://gradepro.org) software.

STATEMENT LIST

No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S1	1	Acquisition of multiplanar reformation (MPR) images in addition to axial images should be performed for gastric cancer staging using multidetector row computed tomography (MDCT).	Low	Strong for
S2	1	F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) can be considered an additional supplementary diagnostic tool during staging workup.	Moderate	Conditional for
S3	-	FDG PET/CT can be considered for the differential diagnosis of suspected recurrence in patients with gastric cancer after curative surgery.	Low	Conditional for
S4	1, 2	Endoscopic resection is recommended for well or moderately differentiated tubular or papillary EGCs meeting the following endoscopic findings: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor.	Moderate	Strong for
S5	1, 2	Endoscopic submucosal dissection (ESD) as well as gastrectomy with lymph node (LN) dissection can be indicated for well or moderately differentiated tubular or papillary EGCs 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.	Moderate	Strong for
S6	1, 2	Endoscopic resection could be cautiously considered for poorly differentiated tubular or poorly cohesive (including signet-ring cell) EGCs meeting the following endoscopic findings after sufficient discussion: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor.	Low	Conditional for
S7	2	Additional surgery is recommended when the result of endoscopic resection for EGC does not meet the criteria for curative resection or when there is lymphovascular invasion or positive vertical margin.	Low	Strong for
S8	2	After endoscopic resection in EGC, endoscopic treatment such as ESD and argon plasma coagulation (APC) could be considered for EGCs that have only positive lateral margin and meet all other criteria for curative resection.	Low	Conditional for

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STATEMENT LIST

(Continued)

No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S9	2	H. pylori eradication is recommended for the prevention of metachronous gastric cancer in patients successfully treated by endoscopic resection of EGC with H. pylori infection.	Moderate	Strong for
S10	-	There are no differences in functional outcomes or nutritional outcomes (weight loss, albumin) between Billroth I (BI), Billroth II (BII), and Roux-en-Y (RY) reconstruction methods after distal gastrectomy (DG). Each reconstruction method has advantages and disadvantages, and surgeons may make case-specific decisions.	High	Conditional for
S11-1	4	Various efforts to achieve negative margins are recommended for better survival outcomes in EGC patients. Reresection or reoperation should be considered when patient condition is favorable and technically feasible.	Low	Strong for
S11-2	4	Efforts should be made to obtain negative margins in advanced or infiltrative gastric cancer surgery. If the final postoperative pathologic margin shows involvement of the margin, reoperation to achieve R0 should be chosen cautiously, considering the possibility of limited survival benefits and the risk of postoperative complications in advanced-stage cancer.	Low	Conditional for
S12	3	Proximal gastrectomy (PG) with double tract reconstruction (DTR) as well as total gastrectomy (TG) can be considered for EGC in the upper third of the stomach in terms of less vitamin B12 deficiency and similar survival and reflux symptoms compared to TG.	Low	Conditional for
S13	3	For EGC located ≥5 cm proximal from the pylorus, pylorus-preserving gastrectomy (PPG) as well as DG could be performed. PPG has the benefits of less gallstone formation and protein preservation; however, delayed gastric emptying should be considered when making decisions.	Moderate	Conditional for
S14	1	Prophylactic splenectomy for splenic hilar LN dissection is not recommended in curative resection for advanced gastric cancer (AGC) in the proximal stomach without greater curvature invasion.	High	Strong against
S15	5	PG may be performed in AGC with adenocarcinoma histology located in the gastroesophageal junction (GEJ; Siewert II/III) without serosal invasion, due to low rate of LN metastasis to the distal part of the stomach.	Low	Conditional for
S16-1	5	Lower mediastinal LN dissection could be performed to remove possible metastatic LNs in advanced cancer invading the GEJ.	Low	Conditional for
S16-2	5	The transhiatal (TH) approach rather than the transthoracic (TT) approach is recommended to acquire negative resection margin and perform lower mediastinal LN dissection in resectable adenocarcinoma invading the GEJ.	Moderate	Strong for
S17	3	D1+ dissection can be performed during surgery for EGC (cT1N0) patients in terms of survival.	Low	Strong for
S18	3	Sentinel node navigation surgery (SNNS) implemented by well-designed protocols and follow-up plans could be considered as a treatment option for cT1N0 and ≤3 cm gastric cancers in terms of better nutritional outcomes and quality of life (QOL). Treatment decisions should be made after sufficient discussion with the patient regarding the possibility of metachronous cancer and rescue surgery.	Moderate	Conditional for
S19-1	3	Laparoscopic DG (LDG) is recommended for c-Stage I gastric cancer in terms of better short-term surgical outcomes and comparable long-term survival compared to open DG (ODG).	High	Strong for
S19-2	3	LDG as well as ODG can be recommended for locally AGCs for comparable survival outcomes.	High	Strong for
S20	3	Robotic gastrectomy (RG) can be considered a treatment option for gastric cancer in terms of noninferior survival and fewer complications than laparoscopic gastrectomy (LG). However, disadvantages such as additional cost and longer operation time should also be considered for patient shared decision-making.	Moderate	Conditional for
S21	3	Partial omentectomy (PO) could be considered for AGC patients.	Low	Conditional for
S22	-	Administration of ursodeoxycholic acid (UDCA) for one year can be recommended to reduce gallstone formation after gastrectomy.	Moderate	Conditional for
S23	4	Adjuvant chemotherapy (S-1 or capecitabine plus oxaliplatin [XELOX]) is recommended in patients with pathological stage II or III gastric cancer.	High	Strong for
S24-1	6	Palliative first-line platinum/fluoropyrimidine-based chemotherapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer.	Moderate	Strong for
S24-2	6	Palliative first-line trastuzumab combined with capecitabine or fluorouracil (FU) 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 AGC.	High	Strong for
S24-3	6	Palliative first-line nivolumab combined with capecitabine or FU plus oxaliplatin (XELOX or FOLFOX) is recommended in patients with programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ≥5 and HER2-negative AGC.	High	Strong for
S25	6	Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer. Ramucirumab plus paclitaxel is preferentially recommended, but other agents could also be considered.	High	Strong for
S26	6	Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer.	High	Strong for
S27	1	Neoadjuvant chemotherapy (NCT) as part of perioperative chemotherapy can be considered for patients with resectable locally advanced gastric cancer.	High	Conditional for
S28	4	Adjuvant chemoradiation (CRT) is not usually recommended in patients with pathological stage II or III gastric cancer who have undergone curative gastrectomy.	High	Conditional against
S29	1	The evidence for adding radiation to NCT is not conclusive in patients with locally advanced gastric cancer.	Moderate	Investigational

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STATEMENT LIST

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No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S30	1	In patients with gastric outlet obstruction (GOO) caused by unresectable gastric cancer, either endoscopic stenting (ES) or surgical gastrojejunostomy (GJ) for palliative treatment can be performed. The decision should be based on a multidisciplinary assessment of the patient's performance status, projected clinical course, and preferences.	Low	Conditional for
S31-1	1	Reduction gastrectomy (or upfront debulking gastrectomy without systemic LN dissection) should not be considered as initial treatment options for stage IV gastric cancer patients who are susceptible to chemotherapy.	High	Strong against
S31-2	1	In stage IV gastric cancer patients with limited metastasis, conversion surgery might be considered as a treatment option for those with a good response to chemotherapy.	Low	Investigational
S32-1	1	Radical gastrectomy, metastasectomy and perioperative chemotherapy may be considered for selected gastric cancer patients with oligometastases in the liver.	Very low	Investigational
S32-2	1	Radical gastrectomy, oophorectomy and perioperative chemotherapy could be considered for selected gastric cancer patients with oligometastases in the ovary.	Very low	Conditional for
S33	1	For gastric cancer patients, intraperitoneal (IP) chemotherapy should only be applied for investigational purposes.	Low	Investigational

GENERAL CONSIDERATIONS

Endoscopy

Screening

Korea has shown the highest age-standardized incidence rates of gastric cancer worldwide, but the ratio of gastric cancer–related mortality to cancer incidence is much lower than that of other countries [14]. The Korean National Cancer Screening Program (KNCSP) for gastric cancer seems to have played a pivotal role in increasing the number of curable cancers by early detection and eventually improving overall survival (OS) [15]. The KNCSP for gastric cancer, launched in Korea in 2002, invites any Korean individual who is 40 years old or older to undergo endoscopy or upper gastrointestinal series (UGIS) every 2 years. A recent study showed that the screening group had a 41% decreased hazard ratio (HR) for gastric cancer mortality compared with the nonscreening group [16]. However, the reduction in gastric cancer mortality was only significant in the group that received endoscopic screening and was not in the group that received UGIS [17].

Diagnosis and classification of EGC

In the Japanese classification of gastric carcinoma, superficial gastric carcinoma is categorized according to morphologic features; polypoid lesions are classified as type I (protruding), flat lesions as type II (superficial), and ulcerated lesions as type III (excavated) [18]. Type II lesions are subdivided into 3 groups according to the elevation or depression of the lesion compared to the surrounding mucosa: IIa (superficial elevated), IIb (superficial flat) and IIc (superficial depressed). Tumors elevated by more than 3 mm are classified as type I [18].

Staging by endoscopic ultrasound (EUS)

EUS can be helpful for assessing the depth of local tumor invasion (T stage) as well as regional LN metastasis [19]. According to the results of the Cochrane review, the summary for sensitivity and specificity of EUS in discriminating T1 and T2 (superficial) vs. T3 and T4 (advanced) gastric carcinomas were 86% (95% confidence interval [CI], 81% to 90%) and 90 (95% CI, 87% to 93%), respectively [20] (**Table 3**). For the diagnostic capacity of EUS to distinguish T1 vs. T2 tumors, a meta-analysis of 46 studies (n=2,742) showed that the summary sensitivity and specificity were 85% (95% CI, 78% to 91%) and 90% (95% CI, 85% to 93%), respectively. For the capacity of EUS to distinguish between T1a (mucosal) vs. T1b

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Table 3. Diagnostic accuracy of endoscopic ultrasound (Cochrane review)

Test	Study No.	Patient No.	Sensitivity (%)	Specificity (%)
T1a vs. T1b	20	3,321	87 (81 to 92)	75 (62 to 84)
T1 vs. T2	46	2,742	85 (78 to 91)	90 (85 to 93)
T1–2 vs. T3–4	50	4,397	86 (81 to 90)	90 (87 to 93)
N– vs. N+	44	3,573	83 (79 to 87)	67 (61 to 72)

Values are presented as number of percentage (95% confidence interval).

(submucosal) cancers, the meta-analysis of 20 studies (n=3,321) showed that sensitivity and specificity were 87% (95% CI, 81% to 92%) and 75% (95% CI, 62% to 84%), respectively. Finally, for the metastatic involvement of LNs (N-stage), the meta-analysis of 44 studies (n=3,573) showed that sensitivity and specificity were 83% (95% CI, 79% to 87%) and 67% (95% CI, 61% to 72%), respectively. However, the heterogeneity between studies was high, reflecting that the diagnostic accuracy of EUS depends on the operator.

Radiology

UGIS

The UGIS has been used for screening and evaluation for postoperative complications in gastric cancer. Recently, the percentage of participants of the KNCSP who undergo UGIS for screening of gastric cancer has decreased [21,22]. Studies comparing UGIS and endoscopy using the KNCSP database reported that UGIS showed lower detection sensitivity and disadvantage in long-term survival compared to endoscopy [17,23]. Although its role as screening method has been reduced, UGIS is still a valuable tool where endoscopy is not available or when the examinee cannot tolerate endoscopy.

CT

CT has been widely used to detect and diagnose gastric cancers, to determine the optimal treatment method via accurate staging (cTNM) and to identify therapeutic effects after surgery or anticancer treatments. MDCT with multiple parallel rows of X-ray detectors in the craniocaudal direction (z-direction) enables various high-quality MPR imaging. After the introduction of MDCT, the accuracy of gastric cancer staging and the detection of EGCs or small metastatic lesions have improved. Although isolated lung metastasis is not common in gastric cancer, chest CT can be helpful in case of esophageal involvement in GEJ cancer [24-27].

Protocol

An MDCT unit with 16 or more channels is recommended to acquire isotropic imaging with less than 1.25-mm collimation [28]. The patient needs to fast for at least 6 hours. Optimal gastric distension is critical for successful CT gastrography. Stomach distension is achieved using a negative contrast agent (effervescent gas-producing agent) or a neutral contrast agent (water). Anti-peristaltic drugs can reduce motion artifacts. Patient positioning is determined according to the location of the suspected lesion and the choice of oral contrast (e.g., supine/prone, right decubitus/left posterior oblique). Obtaining images from appropriate positions helps to evaluate the entire stomach in its distended state. Portal venous phase images usually provide information on the depth of the tumor, regional LN metastasis, and distant metastasis. Arterial phase images are useful to detect abnormal gastric wall enhancement and assess possible anatomic variation in the surgically relevant vasculature, such as replacing left hepatic artery arising from the left gastric artery.

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KQ 1: Is acquisition of additional MPR images better than axial images alone in terms of T and N staging accuracy for gastric cancer patients?

Statement 1: Acquisition of MPR images in addition to axial images should be performed for gastric cancer staging using MDCT (evidence: low, recommendation: strong for).

The staging accuracy of MDCT has been reported to be 67.1% to 89.1% (median, 78.6%) for T staging and 49.3% to 79.5% (median, 68.8%) for N staging [29-42]. MDCT, which allows faster scanning with thinner slice thicknesses, can generate excellent reformation images, such as MPR images, CT gastrography, or virtual gastroscopy. In a meta-analysis, acquisition of MPR images in addition to axial images improved staging accuracy, especially in T staging (accuracy difference [95% CI], 0.10 [0.02 to 0.18] for T staging [P=0.01] and 0.04 [−0.04 to 0.13] for N staging [P=0.33]) [30,32,33] (**Fig. 1**). The 3D reformation images, such as CT gastrography or virtual gastroscopy, can improve the detection rate of EGCs, possibly allowing for more accurate T staging [29,30,39]. Ability to detect peritoneal metastases, it has been reported that MDCT has high specificity 57.1% to 100% (median, 96.5%) but low sensitivity 25.0% to 90.0% (median, 57.6%) [43-48].

Magnetic resonance imaging (MRI)

Evaluation of liver metastases is one of the most potent applications of MRI in gastric cancer. Many studies on gastrointestinal malignancies, especially colorectal cancer, have shown that liver-specific contrast-enhanced MRI with diffusion-weighted imaging (DWI) is the most sensitive imaging method for the diagnosis of liver metastases [49]. Although no study has been restricted to gastric cancer patients, liver-specific contrast agent-enhanced MRI with

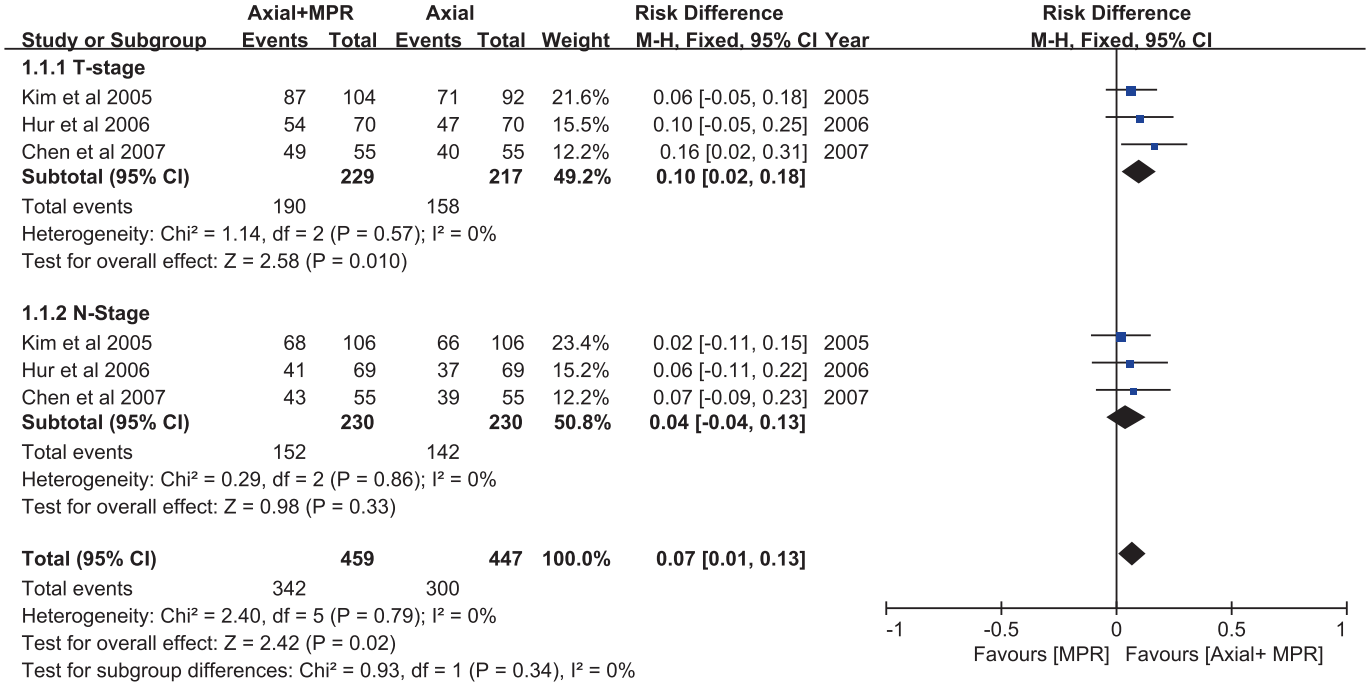

Fig. 1. Forest plot comparing staging accuracy between axial plane plus MPR vs. axial plane only in multidetector row computed tomography.
MPR = multiplanar reformation; CI = confidence interval.

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DWI is expected to also be useful in diagnosing liver metastases in gastric cancer given its high contrast resolution. A meta-analysis showed the applicability of MRI in the evaluation of T stage and peritoneal metastases [50,51]. However, further investigation is needed to confirm these results due to the small number of patients included in these analyses.

FDG PET/CT

FDG PET/CT can reflect the degree of glucose uptake and metabolism in many cancer lesions [52]. FDG PET/CT can also provide good evidence to differentiate cancer recurrence from inflammatory and postoperative changes [53,54]. The degree of FDG uptake is known to be related to the biological characteristics of cancer cells, and the possibility of false negative results should be considered. High FDG uptake has been shown to be correlated with tumor hypoxia, increased Ki-67 index, and aggressive biological features, whereas low FDG uptake has been correlated with small tumor size, diffuse type Lauren classification, mucin predominant pathology, and HER2 negative expression in gastric cancer [55-57].

Diagnostic accuracy of FDG PET/CT for staging

> KQ 2: Is additional FDG PET/CT helpful for accurate diagnosis in detecting LN and distant metastases during staging work-up for gastric cancer patients?
>
> Statement 2: FDG PET/CT can be considered an additional supplementary diagnostic tool during staging workup (evidence: moderate, recommendation: conditional for).

A total of 20 studies were reviewed, 19 studies with 2,195 patients were included in the meta-analysis of the diagnostic ability of FDG PET/CT for detecting LN metastasis [44,58-69] or distant metastasis [64,66,70-75] in gastric cancer patients during staging. The pooled sensitivity and specificity of FDG PET/CT for detecting LN metastasis were 45% (95% CI, 34% to 57%) and 87% (95% CI, 80% to 92%), respectively. In the evaluation of distant metastasis, the pooled sensitivity and specificity were 61% (95% CI, 42% to 78%) and 97% (95% CI, 82% to 99%), respectively.

One possible factor for the low sensitivity of FDG PET/CT in detecting LN or distant metastasis could be the inclusion of diffuse (Lauren classification) or signet ring cell type cancers, which generally have lower FDG uptake. However, FDG PET/CT has a higher tendency for accurate diagnosis in intestinal-type pathology.

FDG PET/CT showed high specificity in detecting LN metastasis and distant metastasis and can be considered a supplementary diagnostic tool with diagnostic CT for staging the work-up of gastric cancer.

Diagnostic accuracy of FDG PET/CT for cancer recurrence

> KQ 3: Can PET/CT be more accurate in diagnosing recurrence when recurrence is suspicious for gastric cancer patients who underwent curative surgery?
>
> Statement 3: FDG PET/CT can be considered for the differential diagnosis of suspected recurrence in patients with gastric cancer after curative surgery (evidence: low, recommendation: conditional for).

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A total of 13 studies with 1,567 patients were included in the meta-analysis [76-87]. The pooled sensitivity and specificity of FDG PET/CT for detecting the recurrence of gastric cancer were 81% (95% CI, 71% to 88%) and 88% (95% CI, 80% to 93%), respectively, with an area under the summarized receiver operating characteristic curve (AUC) of 0.91 (95% CI, 0.89 to 0.93). Of the 13 studies, 5 studies with 438 patients compared the diagnostic ability in detecting recurrence between FDG PET/CT and contrast-enhanced CT [76,78,80,86,88].

In the meta-analysis of these 5 studies, FDG PET/CT showed a pooled sensitivity of 72% (95% CI, 50% to 87%) and specificity of 89% (95% CI, 69% to 97%) with an AUC of 0.88 (95% CI, 0.85 to 0.90), whereas contrast-enhanced CT revealed a pooled sensitivity of 88% (95% CI, 74% to 95%) and specificity of 83% (95% CI, 65% to 93%) with an AUC of 0.92 (95% CI, 0.90 to 0.94). There was no statistically significant difference in diagnostic accuracy between FDG PET/CT and contrast-enhanced CT (P>0.05).

While FDG PET/CT showed higher sensitivity for detecting bone metastasis than contrast-enhanced CT, contrast-enhanced CT showed higher sensitivity for detecting peritoneal metastasis than FDG PET/CT. Because of the high specificity, PET/CT could be helpful for the differential diagnosis of equivocal lesions on contrast-enhanced CT.

Regarding recurrence, 2 studies assessed the diagnostic value of FDG PET/CT for detecting recurrence in 29 patients with elevated levels of serum tumor markers and negative results on conventional radiological imaging [83]. Among these 29 patients, FDG PET/CT detected cancer recurrence in 17 patients (59%). FDG PET/CT could be useful for detecting recurrence in patients who showed equivocal results on contrast-enhanced CT and elevated serum tumor marker levels but negative findings on conventional imaging.

Pathology

Preparation of the specimens

For resected gastric cancer specimens, the stomach is opened along the greater curvature, unless the tumor is located on the greater curvature (in which case, it is opened along the lesser curvature). For endoscopic mucosal resection (EMR)/ESD specimens, the specimen is spread out with the mucosal side up and pinned on a flat board. The proximal and distal directions are marked for orientation.

Specimen fixation

After completing the preparation process, the specimens are immediately immersed in 10% buffered formalin solution (as quickly as possible). The volume of fixative solution should be more than ten times that of the specimen [89]. Proper fixation time (between 24 and 48 hours) at average room temperature is recommended for additional immunohistochemical or genomic evaluation [18,90].

Macroscopic types

Superficial gastric cancer can be subclassified into 5 categories. Protruding (EGC type I), superficial elevated (EGC type IIa), superficial flat (EGC type IIb), superficial depressed (EGC type IIc), and excavated (EGC type III) [18].

Based on Borrmann's classification, the gross type of AGC can be divided into polypoid (type 1), ulcerofungating (type 2), ulceroinfiltrative (type 3), diffuse infiltrative (type 4) and unclassifiable (type 5) [91,92].

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Inspection and sectioning of the specimens

For resected specimens, the location, size (maximum diameter), number, macroscopic types, appearance of the tumor and length of the closest proximal and distal resection margins should be measured and recorded. The deepest part of the tumor invasion should be noted. It is also necessary to assess whether there are findings other than the tumor lesion, such as congestion, hemorrhage, ulcer, and perforation. For EMR/ESD samples, all specimens are collected and embedded in blocks. The lateral and basal resection margins should be marked with ink, which helps with proper evaluation of the margins.

For sectioning, EMR/ESD specimens should be sectioned serially at 2-mm intervals parallel to a line that includes the closest lateral margin of the specimen. If the lesion is grossly AGC, at least 4 representative sections should be taken, including the deepest part of the tumor invasion. If the lesion is grossly EGC, grid mapping should be performed at a width of 4 to 5 mm. If there is suspicion of resection margin involvement with the tumor lesion, additional sections should be taken. In postchemotherapy gastrectomy specimens, representative sections are sufficient if the lesion is grossly obvious. However, the entire tumor bed must be microscopically examined when there are no residual cancer cells in the representative section, residual lesion is small or grossly inconspicuous. For multiple tumors or lesions with unusual configurations, suitable sectioning should be implemented for proper evaluation on a case-by-case basis.

Histologic classification

The World Health Organization (WHO) classification system of digestive tumors, 5th edition, is used for the pathologic classification of gastric carcinoma [93,94]. In addition, the Lauren classification can be applied in resected specimens, including ESD specimens [95].

A. WHO classification

a. Tubular adenocarcinoma

Tubular adenocarcinoma is the most common histologic subtype of gastric carcinoma and is characterized by irregularly distended, fused, or branching tubules of various sizes. Tumors with solid structures and rare tubule formation, corresponding to "poorly 1 (solid type): por1" in the Japanese Gastric Cancer Association classification, are included in this group [18]. Prominent intraluminal mucus and inflammatory debris can be observed.

b. Papillary adenocarcinoma

This relatively rare subtype usually shows an exophytic growth pattern and papillary tumor structure with a central fibrovascular core with columnar or cuboidal tumor cells. The tumor is classified as papillary adenocarcinoma when more than 50% of the tumor area shows papillary structures [96]. Papillary adenocarcinoma is frequently associated with liver metastasis, a higher rate of LN involvement and poor outcome [96-98].

c. Poorly cohesive carcinoma (PCC), including signet-ring cell carcinoma (SRCC)

PCCs are composed of poorly cohesive neoplastic cells that are isolated or form small aggregates without gland formation. This type includes SRCC and nonsignet-ring cell variants (PCC-NOS). SRCC is diagnosed when the tumor cells were predominantly or exclusively an SRC component [94]. Recent studies have revealed that the clinical behavior may differ in SRCC and PCC-NOS, with a relatively poor prognosis of PCC-NOS compared to SRCC and different mutational profiles between SRCC and PCC-NOS [99-101].

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d. Mucinous adenocarcinoma

This subtype is defined by malignant epithelial cells and extracellular mucin pools, which comprise more than 50% of the tumor volume. The tumor cells can show glandular architecture and irregular cell clusters, with occasional single scattered tumor cells, including floating SRCs. Mucinous adenocarcinoma tends to be diagnosed at a more advanced stage, which correlates with deeper invasion depth and poorer survival outcomes compared with nonmucinous gastric cancer [102,103].

e. Mixed adenocarcinoma

This type of tumor refers to carcinomas having a discrete mixture of both glandular (tubular/papillary) and signet ring/poorly cohesive components. It is recommended that any distinct histological component be reported. Recent data suggest that patients with mixed adenocarcinomas have a poorer clinical outcome than those with a pure subtype of carcinoma, especially in EGC [104-106]. However, there are still no clear diagnostic criteria for the minimum ratio of glandular to signet ring/poorly cohesive components for the definition of mixed adenocarcinoma.

f. Other histological subtypes

According to the WHO classification, other rare subtypes include gastric (adeno)carcinoma with lymphoid stroma, hepatoid adenocarcinoma, micropapillary adenocarcinoma, gastric adenocarcinoma of fundic-gland type, mucoepidermoid carcinoma, Paneth cell carcinoma and parietal cell carcinoma.

B. Grading

The grading of adenocarcinoma can be applied to tubular and papillary carcinomas but not to other subtypes. Well-differentiated adenocarcinoma is composed of a tumor with well-formed glands, whereas poorly differentiated adenocarcinoma shows poorly formed glands or no luminal structures (solid cluster). Although the WHO classification recommends a 2-tier grading system, low grade (well or moderately differentiated) vs. high grade (poorly differentiated), considering that most pathologists and clinicians are more familiar with a 3-tier grading system, we have agreed to use the current 3-tier grading system (well/moderately/poorly differentiated) to avoid confusion.

C. Lauren classification

The Lauren classification divides gastric cancers into intestinal, diffuse, and mixed types [95]. According to the recent WHO classification, well or moderately differentiated papillary and tubular adenocarcinomas are classified as intestinal type, whereas PCCs, including SRCC, are classified as diffuse type. In addition, poorly differentiated adenocarcinomas forming solid areas are classified as indeterminate type. Mucinous adenocarcinoma can be classified as intestinal, diffuse or indeterminate according to the differentiation of the main tumor components [94]. The mixed type is used for tumors containing approximately equal proportions of intestinal and diffuse components.

Addendum: To determine the feasibility of EMR/ESD specimens in gastric cancer, many studies use the 2-tier categories (differentiated or undifferentiated types) of the Japanese guidelines [107]. In this classification, tumors with solid structures correspond to the undifferentiated type. To avoid confusion with undifferentiated carcinoma in the WHO classification, it is not recommended to use the term 'differentiated/undifferentiated type' in pathology reports.

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Tumor size

Tumor size describes the largest dimension (cm) of the tumor.

Depth of invasion

pT1a	Invades lamina propria/Invades muscularis mucosa
pT1b	Invades submucosa (sm1/sm2/sm3)
pT2	Invades proper muscle
pT3	Invades subserosa
pT4a	Invades serosa (visceral peritoneum)
pT4b	Directly invades adjacent structure

In the staging of gastric cancer, the pT category is determined according to the depth of invasion of the tumor. Tumors with invasion beyond the proper muscle layer are classified as AGC, and tumors with mucosal or submucosal layer invasion are classified as EGC. The submucosal invasion depth is divided into the upper third (sm1), middle third (sm2), and lower third (sm3). When the proper muscle layer is lost at the ulcer site and there is a tumor in that area, it is considered subserosal invasion. Even if there is no tumor cell invasion of the muscle, if the tumor invades below the soft imaginary line connecting the proper muscle layers, it is staged as proper muscle invasion.

For endoscopic resection specimens, submucosal invasion depth is measured from the lowest surface of the muscularis mucosa. When the muscularis mucosa is lost in the area of deepest invasion, the invasion depth is measured from the virtual line that smoothly connects adjacent normal layers.

Lymph node

LN	
pN0	No regional LN metastasis
pN1	Metastasis in 1–2 regional LNs
pN2	Metastasis in 3–6 regional LNs
pN3a	Metastasis in 7–15 regional LNs
pN3b	Metastasis in 16 or more regional LNs

A sufficient number of regional LN dissections and pathological evaluations are important to ensure the proper diagnosis of stage N. The pathologic assessment should contain the number of nodes and the number of positive nodes. It is necessary to assess at least 16 local nodes to evaluate N3a staging; however, some studies suggest that it is desirable to remove/assess 30 or more nodes [108,109].

A tumor deposit is defined as a discrete tumor nodule within the lymphatic drainage zone of primary carcinoma without identifiable LN tissue, blood vessels or neural structures [108]. Tumor deposits, in which metastatic tumor lesions in the subserosal fat separate from adjacent primary gastric cancer are observed without evidence of LN tissue, are considered to be local LN metastases.

Resection margin

In gastric cancer, the proximal and distal margin status are described, and where applicable, the circumferential margin status is additionally described in GEJ cancer. The safety margin describes the distance between the resection margin and the tumor. If the distance of the

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safety margin in gross description is different from that of microscopic observation, the findings of microscopic observation are described.

For mucosal resection margins of endoscopic resection specimens, the direction close to the resection margin and the distance from the resection margin are described. The deep resection margin is also measured at the nearest point from the tumor and described.

Lymphatic invasion, vascular invasion, and perineural invasion

The presence or absence of lymphovascular invasion and perineural invasion should be described. For endoscopic resection specimens, it is recommended to separately mention lymphatic invasion and vascular invasion. The use of immunohistochemical staining (D2-40) could be helpful in identifying lymphatic invasion.

Regression grade

For the grading of primary tumor regression after neoadjuvant therapy, the modified Ryan system is recommended [110] (**Table 4**).

Peritoneal washing

Positive cancer cells in peritoneal washing cytology are classified as metastatic disease (pM1). There is evidence that positive cancer cells in the washing cytology of AGC patients are correlated with poor prognosis. Peritoneal washing cytology could be helpful in the staging of AGC.

Biomarkers

A. HER2

Because HER2 positivity is an indication for anti-HER2 targeted therapy, the HER2 status should be evaluated before systemic therapy and re-evaluated for recurrent and metastatic lesions. IHC tests should first be performed for the evaluation of HER2 status [111,112]. IHC 3+ is considered positive for HER2 overexpression, while IHC 0–1+ is considered negative [113]. 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 criterion for HER2 amplification was 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.

B. Microsatellite instability (MSI)

MSI status can be assessed by either polymerase chain reaction (PCR) or IHC for the 4 DNA mismatch repair (MMR) proteins [114]. Instability is examined by PCR of a representative panel of microsatellites [115]. The grade of the instability is determined by the numbers of unstable microsatellites: MSI-high (MSI-H), MSI-low (MSI-L), or microsatellite stable (MSS) [116]. In the IHC method, IHC staining is performed for the 4 MMR proteins MLH1, MSH2,

Table 4. Regression grade

Grade	Definition
Grade 0	Complete response (no viable cancer cells)
Grade 1	Near-complete response (single cells or rare small groups of cancer cells)
Grade 2	Partial response (residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells)
Grade 3	Poor or no response (extensive residual cancer with no evident tumor regression)

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PMS2, and MSH6 [117]. When the expression of any of the MMR proteins is lost, the case is considered MMR deficient (dMMR).

MSI-H/dMMR gastric cancer is classified as a separate subtype in the molecular classifications of gastric cancer and shows elevated mutation rates (high tumor mutation burden) and distinctive patterns of methylation [118]. This subtype has unique clinical characteristics, including distal location, high frequency of intestinal-type histology, lower stage, and favorable prognosis. In the palliative setting, MSI-H/dMMR is well known predictive biomarker to identify patients with gastric cancer who are most likely to benefit from immune checkpoint inhibitor (ICI) therapy [119].

C. Epstein–Barr virus (EBV)

The presence of the EBV genome can be examined by ISH to EBV-encoded RNA [120,121]. When signals in the tumor cell nuclei are observed, the case is considered EBV-positive. 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 [118]. This subtype is distinct in its proximal location, relation to poorly differentiated histology, lower stage, and good prognosis.

D. PD-L1 IHC

The PD-L1 interpretation method and cutoff value depend on the antibody clones and the predefined settings of approved clinical trials. However, most anti-programmed cell death protein 1 (PD-1)/PD-L1 therapies require the CPS interpretation system [122,123]. The CPS enumerator includes the number of PD-L1-stained tumor cells showing partial or complete membrane staining intensity and the number of PD-L1-stained mononuclear immune cells (lymphocytes and macrophages) within tumor nests and adjacent stroma.

There have been 2 different PD-L1 assays coupled to clinical trials for gastric cancer patients. The PD-L1 IHC 22C3 pharmDx assay uses CPS ≥1 as a criterion for PD-L1 positivity, and the 28-8 pharmDx assay uses a cutoff of CPS ≥5 [124,125].

For reliable PD-L1 interpretation, different cutoff values should be applied depending on the antibody used. It is also recommended to re-evaluate PD-L1 staining in cases of recurrent or metastatic tumors.

E. Next-generation sequencing (NGS)

Biomarkers associated with advanced gastric cancer management include HER2, MSI, PD-L1, tumor mutational burden (TMB) status, and *NTRK* gene fusion according to recent National Comprehensive Cancer Network (NCCN) guidelines [111]. For biomarker testing, IHC, ISH, or target PCR methods should be preferentially considered; however, validated NGS assay performed in an appropriate environment could be used for the identification of the biomarkers mentioned above. Additionally, there are some targets that could be tested by NGS assay and have shown promising clinical results in AGC, such as *FGFR2* amplification, epidermal growth factor receptor (*EGFR*) amplification, *MET* amplification, and alteration of homologous recombination deficiency-related genes [126-129].

TMB, which can be quantified by NGS assays, has been suggested as a potent biomarker for first line pembrolizumab-based therapy in patients with AGC [130]. While whole-exome sequencing is considered the gold standard for TMB, recent targeted gene panels also

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provide fairly accurate quantification of TMB [131]. However, the lack of cutoffs and different quantification methods across different panels is one of the main limitations to adopting TMB as a biomarker in clinical practice.

For accurate and reliable NGS assays, tissue preparation is one of the most important factors [132]. Most targeted NGS assays require total DNA and RNA amounts ranging from 10 to 300 ng, which can be obtained from both formalin-fixed, paraffin-embedded tissue and cytology specimens. In addition, a sufficient tumor fraction of the sample (surface area >10%–20% and 5 mm^2, respectively) could also affect reliable NGS results.

For further detailed information about the pathology for gastric cancer, please refer to the Guideline for Standardized Pathology Report for Gastric Cancer, first edition and the upcoming revised version [133,134].

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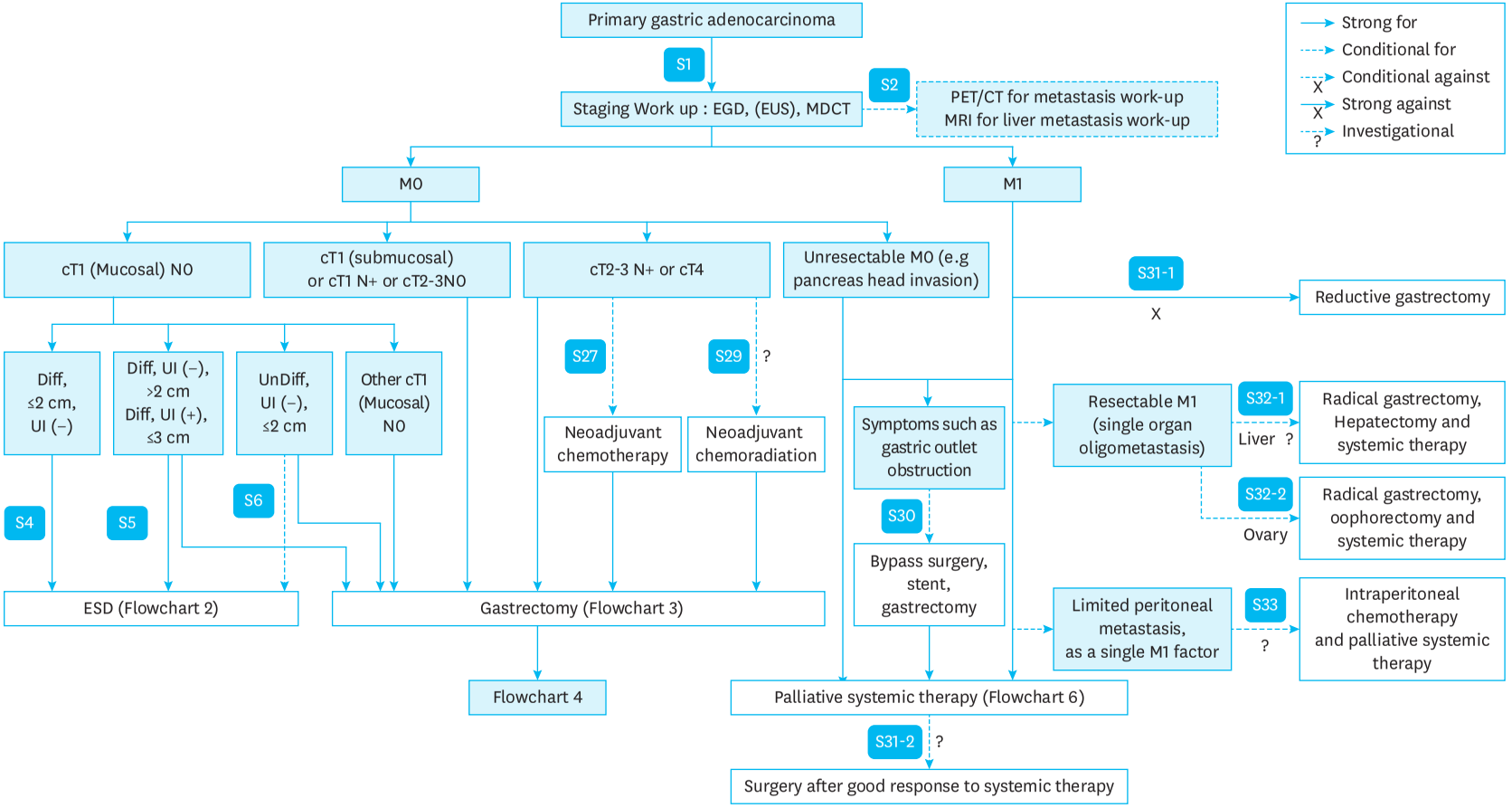
OVERALL TREATMENT ALGORITHM (Flowchart 1)



Flowchart 1. Overall treatment algorithm.
EGD = esophagogastroduodenoscopy; EUS = endoscopic ultrasound; MDCT = multidetector row computed tomography; PET = positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; Diff = well or moderately differentiated; UI = ulcer lesion; UnDiff = poorly differentiated/poorly cohesive (including signet-ring cell); ESD = endoscopic submucosal dissection.

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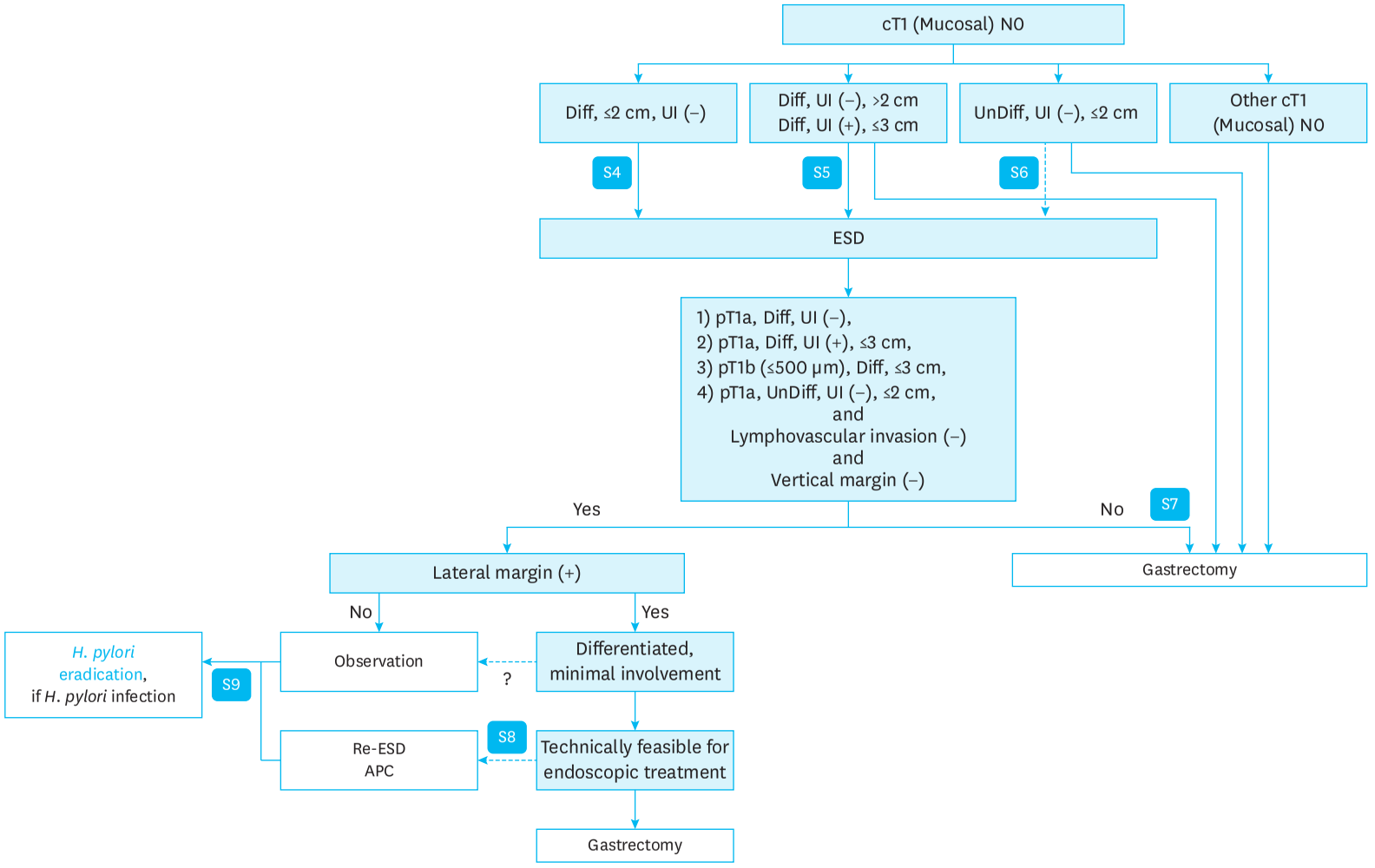
ENDOSCOPIC TREATMENT (Flowchart 2)



Flowchart 2. Endoscopic treatment.
Diff = well or moderately differentiated; UI = ulcer lesion; UnDiff = poorly differentiated/poorly cohesive (including signet-ring cell); ESD = endoscopic submucosal dissection; APC = argon plasma coagulation.

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KQ 4: Can endoscopic resection for EGC that meets classical absolute indications result in comparable survival to that of gastrectomy?

Statement 4: Endoscopic resection is recommended for well or moderately differentiated tubular or papillary EGCs 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).

ESD has been used as a minimally invasive therapy modality for EGC since the early 2000s in Korea [135,136]. The data in Korean National Health Insurance Service System showed 23,828 cases of ESD for EGC between November 2011 and December 2014 [136]. Previous studies have suggested that ESD could be considered as the first-line therapy modality for mucosal confined EGC with well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma, with a tumor size ≤2 cm, and without ulcer in the tumor (classical absolute indication) because these findings indicated that the lesions had a very low risk of LN metastasis [137] and ESD allows high rates of en bloc curative resection with low adverse event rates [135,138-141]. A large retrospective Japanese study including 5,265 patients who had undergone gastrectomy with LN dissection for EGC showed that none of the 1,230 well differentiated intramucosal cancers with diameters less than 30 mm were associated with metastases, and none of the 929 lesions without ulceration were associated with LN metastasis regardless of tumor size [137]. For classical absolute indications, the en bloc resection rate was 97.1%–99%, the curative resection rate was 91.5%–96.4%, and the local recurrence rate was 0.2%–1.8% [138].

Studies comparing survival data between ESD and gastrectomy for the classical absolute indication have rarely been conducted. In most studies, ESD cases were mixed with classical absolute and expanded indications and were not separately analyzed.

In Korean retrospective cohort studies, when the patients met the classical absolute indications, the 5-year OS rates (ESD, 93.6%–96.4% vs. gastrectomy, 94.2%–97.2%) and 10-year OS rates (ESD, 81.9% vs. gastrectomy 84.9%) did not differ between treatment methods [139-141].

A small Korean study including 35 endoscopic resections and 20 gastrectomies with same settings, showed no difference in OS (months) (93.4±3.2 [endoscopic resection], 85.8±5.5 [gastrectomy]) or disease-free survival (DFS) (months) (89.7±3.6 [endoscopic resection], 90.4±3.5 [gastrectomy]) [142]. Similar results were reported in a Japanese study, where patients were divided in different age groups (<65 years, ≥65 years). When the cases met the classical absolute indications, there were no significant difference in OS between endoscopic resection and gastrectomy in all age groups [143].

The 5-year metachronous recurrence rates were higher after endoscopic resection (5.8%–10.9%), compared to gastrectomy (0.9%–1.1%) [139-141]. Close endoscopic surveillance should be performed after ESD for early detection of metachronous cancer.

After endoscopic resection, preservation of the stomach may be associated with higher incidence of metachronous cancer, however, better QOL, shorter hospital stay, lower costs and lower treatment-related complication rates may be more anticipated compared to gastrectomy [139-142,144].

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KQ 5: Is there any difference in survival rate between ESD and surgery in the treatment of well or moderately differentiated, tubular or papillary, EGC meets 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?

Statement 5: ESD as well as gastrectomy with LN dissection can be indicated for well or moderately differentiated tubular or papillary EGCs 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: strong for).

Endoscopic resection for EGC is limited in that LN dissection cannot be included during the procedure. Therefore, in order to achieve curative resection with comparable survival to that of surgery by endoscopic resection, early cancers with very low risk of LN metastasis should be carefully selected. The clinically acceptable threshold of LN metastasis might be equivalent to the context of perioperative mortality following radical gastrectomy (0.1%–0.3% in high-volume centers in Korea and Japan) [145-147]. In addition, with endoscopic resection, it is technically feasible to achieve en bloc resection which is important to avoid remnant tumors or local recurrence after the procedure.

When the following criteria were met in the pathologic review of endoscopic resection specimens, the extragastric recurrence (nodal or distant metastasis) rate after endoscopic resection was between 0% and 0.21%, which was comparable to that of radical gastrectomy: well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma, en bloc resection, negative lateral resection margins, negative vertical resection margin, no lymphovascular invasion, and 1) tumor size >2 cm, mucosal cancer, and no ulcer in the tumor or 2) tumor size ≤3 cm, mucosal cancer, and ulcer in the tumor [148-150]. The OS was also comparable between patients undergoing endoscopic resection and those treated with radical surgery (93.3%–96.4%. vs. 92.0%–97.2%) [139,144,151-161].

Although a number of retrospective cohort studies support ESD, no prospective trial has compared the outcomes with those of standard operations based on these criteria where concerns for node metastases may still be present [149,162-164]. Thus, gastrectomy with LND may also be considered a valid treatment option, especially in cases of ESD with technical difficulty or where periodic endoscopic follow-up may not be feasible or affordable.

KQ 6: Is there any difference in the survival rate between surgery and ESD for poorly differentiated tubular or poorly cohesive (including signet-ring cell) EGCs meeting the following endoscopic findings: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor?

Statement 6: Endoscopic resection could be cautiously considered for poorly differentiated tubular or poorly cohesive (including signet-ring cell) EGCs meeting the following endoscopic findings after sufficient discussion: endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor (evidence: low, recommendation: conditional for).

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EGCs with poorly differentiated tubular and PCC (including SRCC) are associated with a higher risk of LN metastasis than well and moderately differentiated tubular EGCs. Thus, endoscopic resection can be considered very cautiously.

In previous Japanese Gastric Cancer guidelines, through a literature review of previous studies, endoscopic resection could be considered in poorly differentiated tubular adenocarcinoma or PCC (including SRCC) histologic confirmation from forceps biopsy specimens, endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor [107]. When the criteria were fulfilled, the risk of LN metastasis was reported to be 0%–2.3% [165-167].

Under the mentioned endoscopic findings, endoscopic resection could be considered for initial treatment. However, when risk factors for node metastasis (tumor size >2 cm, submucosal invasion, ulcer in the tumor, and lymphovascular invasion) are confirmed in pathologic reports, additional gastrectomy may be required [168].

In this guideline, we reviewed papers published after the previous edition. To date, there has been no prospective RCT comparing the long-term OS of endoscopic resection with that of gastrectomy with LN dissection, the standard treatment for these indications [169]. According to retrospective studies, there was no difference between gastrectomy and endoscopic resection in terms of OS, but endoscopic resection had a higher local recurrence rate in terms of recurrence-free survival (RFS), which is consistent with the findings of previous studies [144,170,171]. In a prospective, single-arm, phase III observational study in Japan (JCOG 1009/1010), the curative resection rate of the endoscopic resection group in undifferentiated EGC was 71% (195/275), and during the median follow-up period of 69.9 months, the 5-year OS rate was 99.3% (95% CI, 97.1% to 99.8%) and 5-year RFS rate was 98.9% (95% CI, 96.5% to 99.6%) [172]. In Korea, a study on Comparison of Endoscopic Resection And Surgery for Early Gastric Cancer with undifferentiated histological type: a multicenter randomized controlled trial (ERASE-GC trial, NCT04890171), is under way; the results of this study should be followed-up.

To date, the standard treatment for these criteria has been gastrectomy with LN dissection. Only retrospective cohort studies support these criteria for endoscopic resection, and the results of prospective trials are still lacking. A significant portion of these criteria estimated by pre-endoscopic resection work-up is confirmed to be out of criteria by the pathologic examination of endoscopic resection specimens. Thus, standard operation (gastrectomy with LN dissection) can also be considered for cases meeting these criteria. Therefore, it is advisable to decide on a treatment method after sufficient discussion with the patient about the possibility of LN metastasis and complications of the endoscopic procedure and surgery.

KQ 7: When the results of endoscopic resection for EGC do not meet the criteria for curative resection, can additional surgery improve survival outcome compared to observation?

Statement 7: Additional surgery is recommended when the result of endoscopic resection for EGC does not meet the criteria for curative resection or when there is lymphovascular invasion or positive vertical margin (evidence: low, recommendation: strong for).

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The results of endoscopic resection of EGC could be revealed as being beyond the criteria for curative resection based on pathological evaluation of resected specimens. Resected tumor characteristics that do not meet the following criteria are considered noncurative: 1) differentiated type (well or moderately differentiated tubular or papillary adenocarcinoma) mucosal cancer of any size without ulcer, 2) differentiated type mucosal cancer measuring ≤3 cm with ulcer, 3) differentiated type cancer with minute submucosal invasion (invasion depth ≤500 μm) measuring ≤3 cm, or 4) undifferentiated type (poorly differentiated tubular adenocarcinoma or PCC) mucosal cancer measuring ≤2 cm without ulcer. Lymphovascular invasion and positive vertical margins are also important conditions that require additional surgical treatment.

As a result of a literature search for reinforcement of the up-to-date guidelines, a total of 17 studies that compared additional surgery and observation were included in the final table of evidence [149,163,173-185]. Most studies appeared to have a high risk of bias in terms of participant comparability. Patients who did not undergo surgery were older and tended to have a higher incidence of comorbidities than those who underwent additional curative surgery [149,163,173-176,178,181,183,185]. In addition, there was a significant difference in tumor-related characteristics [149,163,173,175-177,179,180,182-184].

The 5-year OS rate in 15 studies was significantly higher in the surgery group than in the observation group [149,163,175,176,180,181,183,185]. Regarding disease-specific survival in 12 studies, all except one study showed a survival benefit for additional surgery [163,182,183], although this difference was not statistically significant in several studies [173,175,176,178,180,184,185]. In a study that performed propensity score matching analysis, it was also found that 5-year overall and disease-specific survival rates were significantly higher in the surgery group than in the observation group (91.0% and 99.0% in the surgery group and 75.5% and 96.8% in the observation group) [180].

Among patients who underwent additional surgery after noncurative endoscopic resection, LN metastasis was found in 2.0%–20.0% of patients [149,163,173,175-177,179-185]. Given the high incidence of LN metastasis and survival benefit associated with curative surgery, additional gastrectomy with LN dissection is recommended when the result of endoscopic resection for EGC does not meet the criteria for curative resection.

The survival benefit of additional surgery in older patients (>75 years) is controversial [164,178,179,183,186]. In addition, curative surgery may not be feasible in some patients because of underlying diseases or poor general conditions. In these patients, observation with regular follow-up could be a valid option when they give informed consent after receiving an explanation of the risk of recurrence.

KQ 8: When the results of endoscopic resection for EGC have only a positive horizontal margin and meet all other criteria for curative resection, are re-ESD or APC, or close observation acceptable options in terms of recurrence, mortality and survival rate compared to gastrectomy?

Statement 8: After endoscopic resection in EGC, endoscopic treatment such as ESD and APC could be considered for EGCs that have only positive lateral margins and meet all other criteria for curative resection (evidence: low, recommendation: conditional for).

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It has been reported that there is little risk of LN metastasis with en bloc resection, when only the lateral margin is positive and other criteria for complete resection are met. In the case of differentiated-type EGC with lateral margin positivity after ESD, when only close observation was performed, the 5-year local recurrence rate was 11.9% and there was no gastric cancer related mortality [187]. Therefore, close observation, endoscopic treatment (ESD or APC) and gastrectomy are considered as possible treatment options in these cases.

Seven retrospective studies compared the recurrence rate of endoscopic treatments including re-ESD and APC, with gastrectomy or close observation [188-194]. The mean follow-up period for the 6 studies was 60 months, and these studies included both differentiated and undifferentiated cancers. Local recurrence rates were 0% (95% CI, 0% to 0.02%; 0/163) in the gastrectomy group, 1.9% (95% CI, 0.5% to 6.9%; 2/101) in the re-ESD group, 13.4% (95% CI, 7.2% to 23.6%; 9/67) in the APC group, and 23.5% (95% CI, 17.4% to 30.1%; 35/149) in the observation group. Overall, endoscopic treatments (including both re-ESD and APC) significantly lowered the recurrence rate compared to close observation (relative risk [RR], 0.22; 95% CI, 0.06 to 0.86; P=0.03) in the meta-analysis (**Fig. 2A**). The recurrence rate of the endoscopic treatment group was significantly higher than that of the gastrectomy group (RR, 6.45; 95% CI, 1.17 to 35.52; P=0.03) (**Fig. 2B**), and in the gastrectomy group, local residual cancer was found in 64.7% (95% CI, 56.8% to 71.9%; 97/150) and the LN metastasis rate was 0.6% (95% CI, 0.1% to 1.9%; 1/150). However, all local recurrence cases can be

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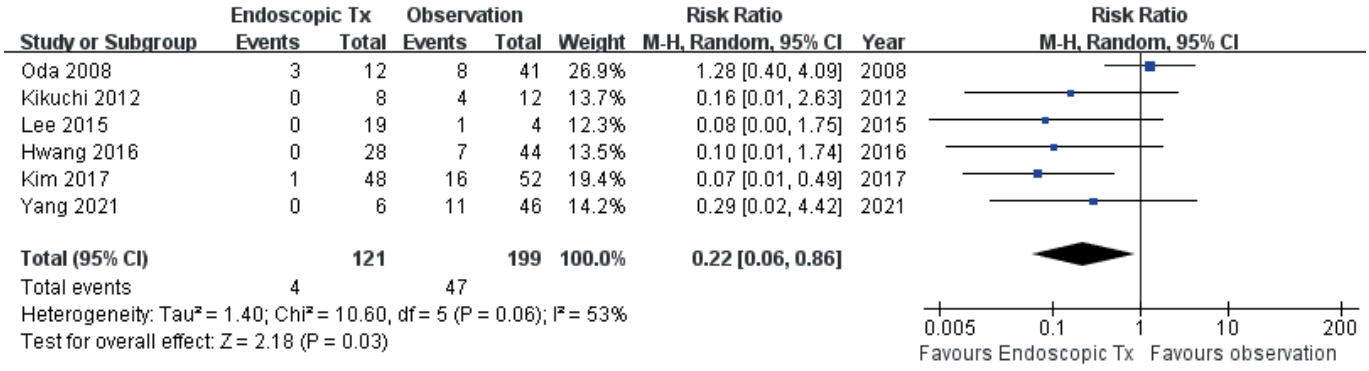

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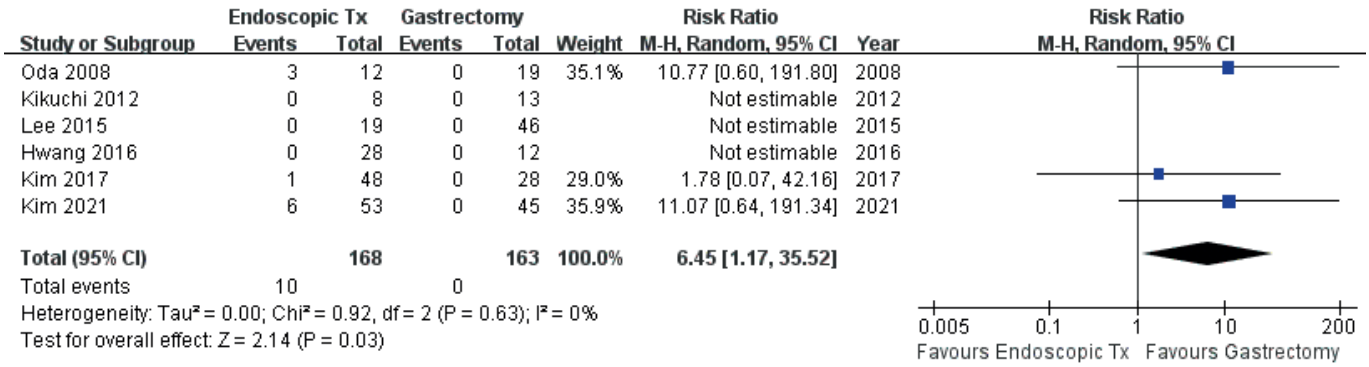

Fig. 2. Forest plot for comparison of local recurrence. (A) Risk of local recurrence in endoscopic treatment group vs. follow-up without therapy group. (B) Risk of local recurrence in endoscopic treatment group vs. gastrectomy.
Tx = treatment; CI = confidence interval.

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successfully managed with further endoscopic treatment or surgery. Gastric cancer mortality was reported in 3 studies, and there was no gastric cancer-related death in the endoscopic treatment group or the observation and gastrectomy group [188,189,192]. Thus, considering QOL after endoscopic treatment and mortality related to gastrectomy, endoscopic treatment could be considered in patients with a positive lateral margin after ESD in EGC. Considering the recurrence rate of endoscopic treatment (5.8%; 95% CI, 2.29% to 9.21%; 10/174), close follow-up after endoscopic treatment is necessary. Although no deaths related to gastric cancer were reported in any of the 3 groups, the study population of each study was not large, and the baseline characteristics were different due to the observational study design. Further research is needed to compare the mortality and survival outcomes of close observation, endoscopic treatment, and gastrectomy in a large population.

There were 3 retrospective studies comparing gastrectomy and close observation in patients with a positive lateral margin after ESD in differentiated type EGC [188,189,192]. The local recurrence rate of the gastrectomy group (0%; 95% CI, 0% to 0.1%; 0/44) was significantly lower than that of the close observation group (19.6%; 95% CI, 12.9% to 28.6%; 19/97), but cancer-related mortality was zero in both groups. All local recurrence cases in the observation group can also be managed with endoscopic treatment or surgery. In patients who underwent gastrectomy, local residual cancer was found in 51.6% (95% CI, 34.8% to 68.0%; 16/31), but the LN metastasis rate was 0% (95% CI, 0% to 0.1%; 0/44). In particular, long-term follow-up studies showed that a cancer-positive lateral margin length longer than 6 mm was significantly associated with local recurrence [187]. Therefore, close observation could be considered a selective treatment option in cases of positive lateral margins in differentiated-type EGC. Recently, a retrospective study comparing gastrectomy and nonsurgical treatments (endoscopic treatment [6/52] and close observation [46/52]) in undifferentiated-type EGC has also been published [194,195]. The local recurrence rate was 0% in the surgical group and 21.2% (11/52) in the nonsurgical group, and the 5-year survival rate was 87.8% in the nonsurgical group, lower than the 95.0% in the surgical group, but without statistical significance. Therefore, close observation may be considered in elderly patients or patients with high morbidity in undifferentiated-type EGC, but further studies are needed.

> KQ 9: Can *H. pylori* eradication prevent metachronous gastric cancer in patients who are successfully treated by endoscopic resection for EGC with *H. pylori*?
>
> Statement 9: *H. pylori* eradication is recommended for the prevention of metachronous gastric cancer in patients successfully treated by endoscopic resection of EGC with *H. pylori* infection (evidence: moderate, recommendation: strong for).

H. pylori was proposed as the first-class carcinogen for gastric cancer by the 1999 WHO. *H. pylori* infects approximately 50% of the world's population. Eradication provided a significant benefit for asymptomatic infected individuals (pooled incidence rate ratio, 0.62; 95% CI, 0.49 to 0.79) [196]. Therefore, eradication of *H. pylori* is considered an important strategy to prevent gastric cancer.

In addition, eradication of *H. pylori* would be an important issue for the prevention of metachronous gastric cancer in patients successfully treated by endoscopic resection of EGC with *H. pylori*. We identified 3 RCTs that observed metachronous gastric cancer and precancerous lesions in both the *H. pylori* eradication treatment and noneradication

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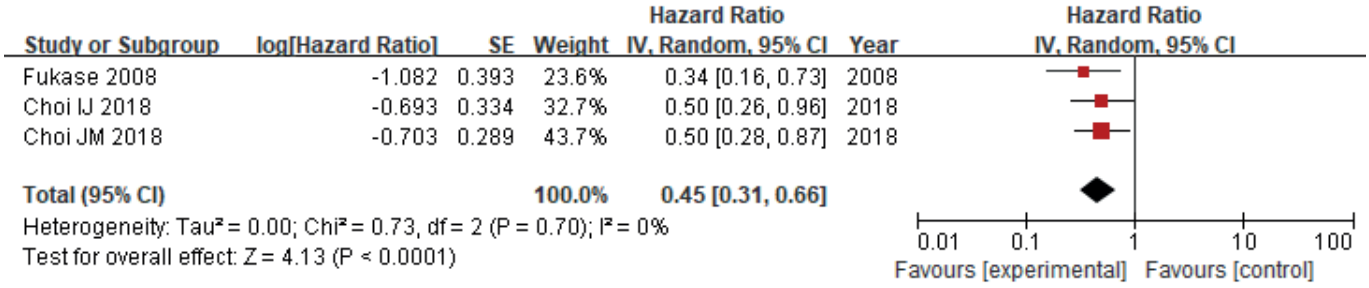

Fig. 3. Forest plot for a comparison of the risk of metachronous gastric cancer between *Helicobacter pylori* eradication (experimental) vs. no treatment (control).
SE = standard error; IV = interval variable; CI = confidence interval.

treatment groups in patients successfully treated by endoscopic resection for EGC with *H. pylori* [197,198]. The median follow-up periods were 3–5 years. The incidence rate of metachronous gastric cancer and precancerous lesions during the follow-up was 4.80% (41/856) in the *H. pylori* treatment group and 9.75% (87/892) in the non-*H. pylori* treatment group. The risk of metachronous gastric cancer and precancerous lesions among patients who underwent *H. pylori* eradication treatment was significantly lower than that among patients who did not undergo eradication treatment (HR, 0.45; 95% CI, 0.31 to 0.66). In addition, *H. pylori* eradication treatment had benefits for the risk of metachronous gastric cancer based on the study by Fukase et al. [197], which included only metachronous gastric cancer (HR 0.34; 95% CI 0.16-0.73) (**Fig. 3**). Therefore, *H. pylori* eradication is helpful for the prevention of metachronous gastric cancer in patients successfully treated by endoscopic resection of EGC with *H. pylori.*

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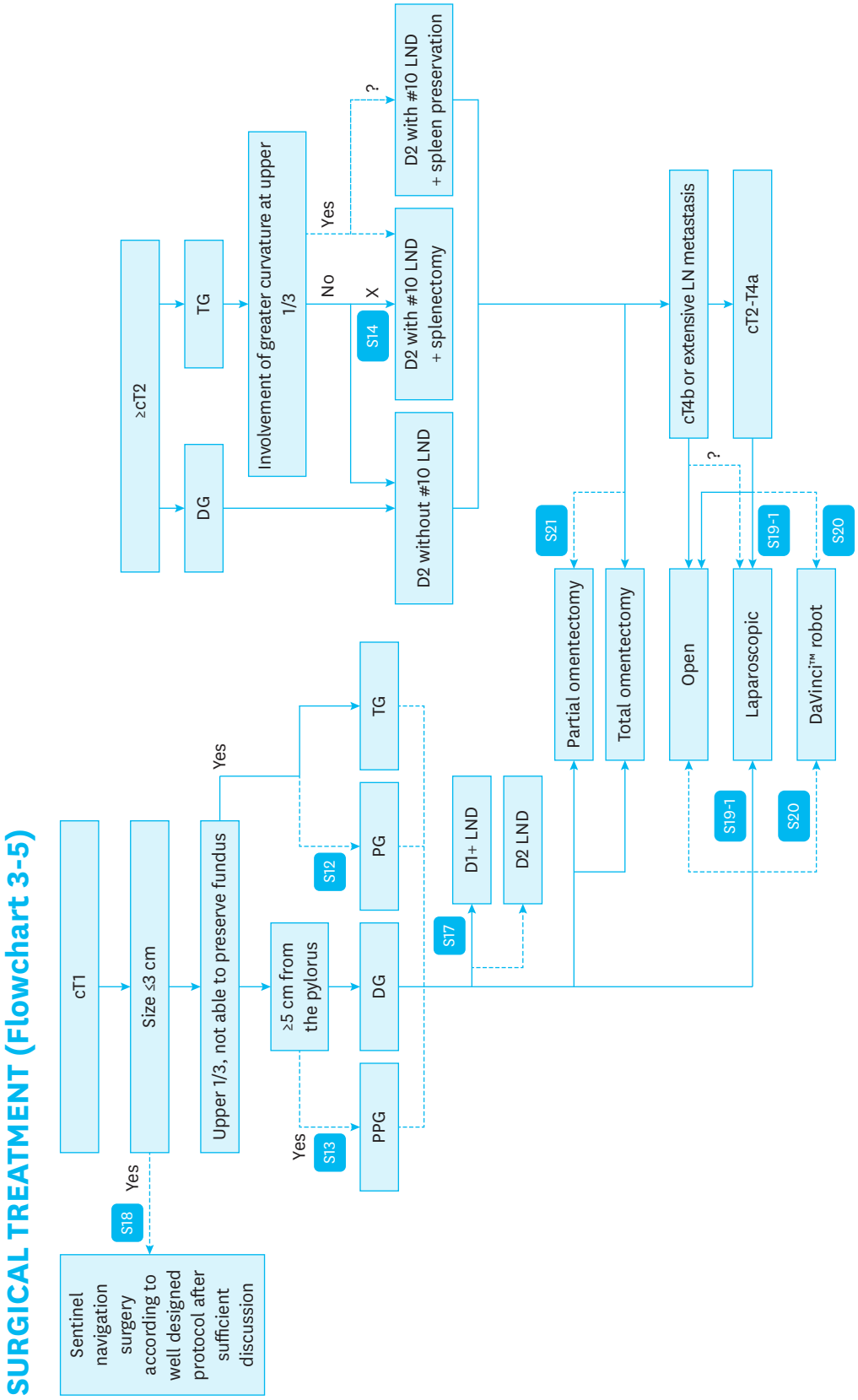

Flowchart 3. Approach and extent of gastrectomy.
DG = distal gastrectomy; TG = total gastrectomy; PPG = pylorus-preserving gastrectomy; PG = proximal gastrectomy; LND = lymph node dissection; LN = lymph node.

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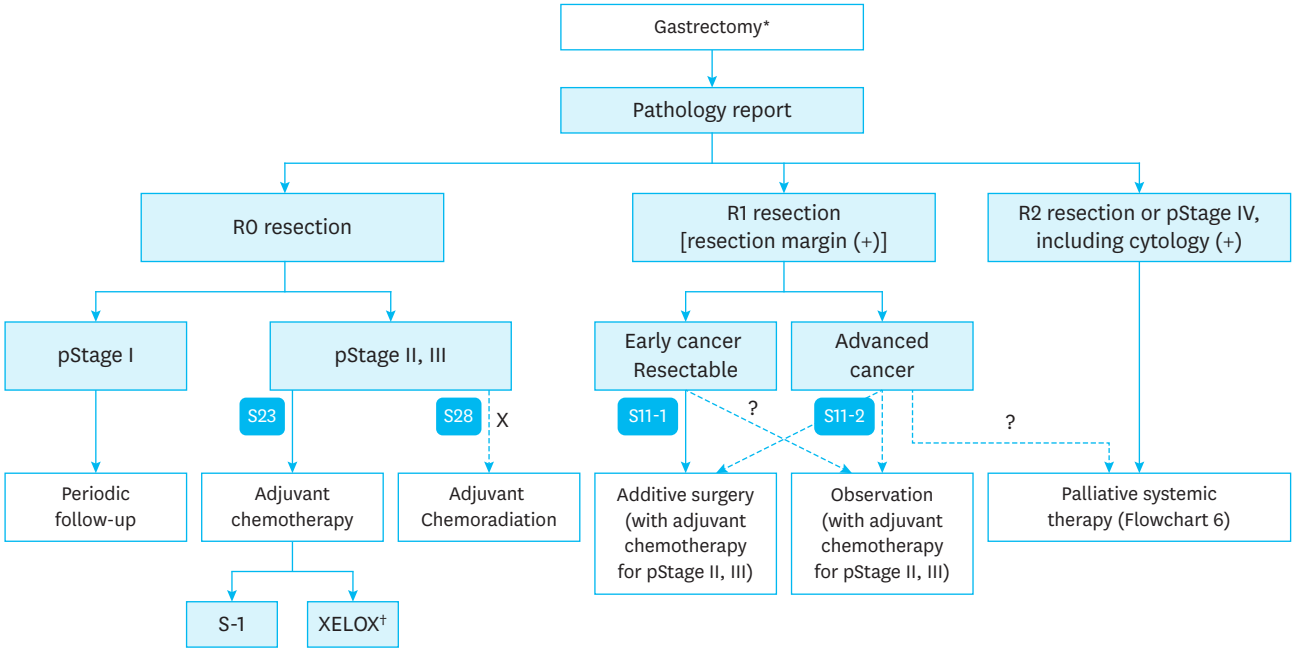
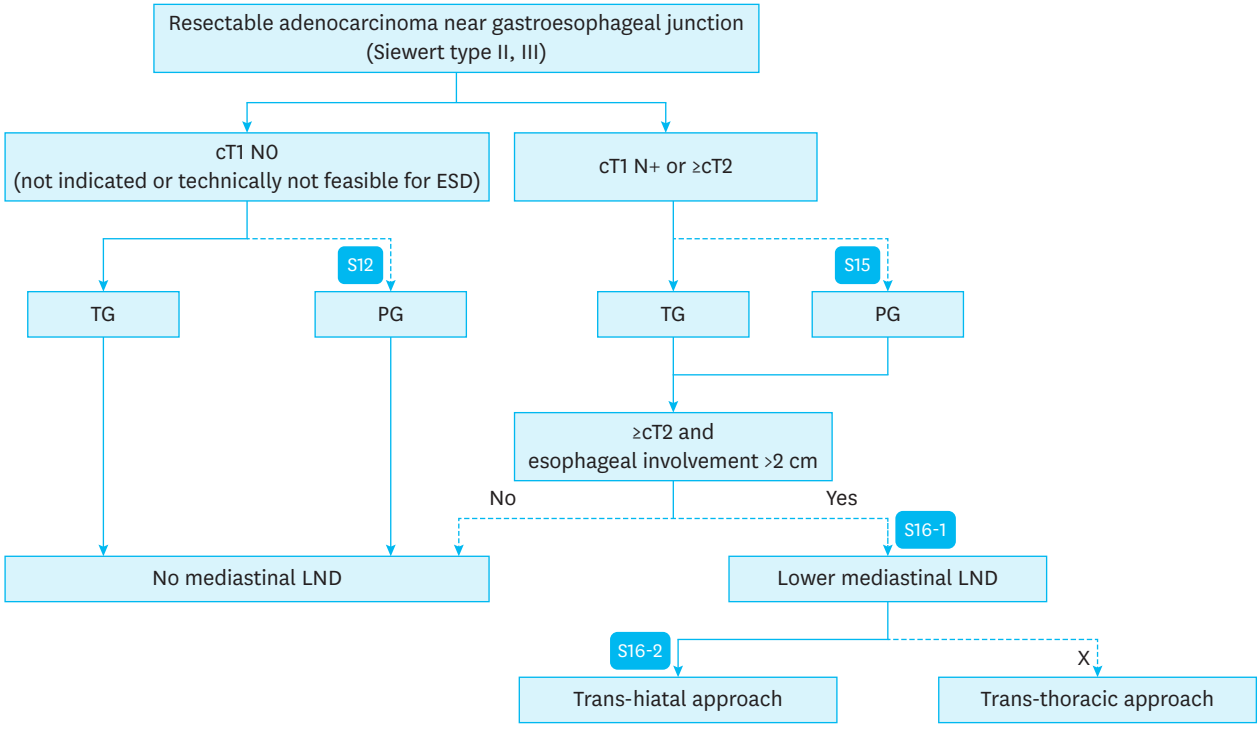


Flowchart 4. Treatment plans after gastrectomy.
LN = lymph node; XELOX = capecitabine and oxaliplatin.
*To obtain negative margin, single or combinations of various methods including intraoperative frozen section, perioperative gastroscopy, various preoperative clipping or dyeing, fluorescence imaging technique, ultrasonography, and simple X-ray, etc. can be applied.
†Preferred in pStage II with LN+ or pStage III.



Flowchart 5. Treatment guidelines in gastroesophageal junction adenocarcinoma.
ESD = endoscopic submucosal dissection; TG = total gastrectomy; PG = proximal gastrectomy; LND = lymph node dissection.

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KQ 10: Is RY and BI reconstruction better than BII reconstruction following DG in gastric cancer regarding functional or nutritional outcomes?

Statement 10: There are no differences in functional outcomes, or nutritional outcomes (weight loss, albumin) between BI, BII, and RY reconstruction methods after DG. Each reconstruction method has advantages and disadvantages, and surgeons may make case-specific decisions (evidence: high, recommendation: conditional for).

Functional and nutritional outcomes may differ according to the various reconstruction methods including BI, BII, and RY [199].

Well-designed studies comparing each reconstruction method are rare. In our meta-analysis with a limited number of studies, BI showed advantages in operation time (P<0.01), hospital stay (P<0.01), and bile reflux (P<0.03) over BII [200,201]. There was no difference in complications (P=0.10). BI was more favorable than RY in terms of operation time (P<0.01), complications (P=0.01) and hospital stay (P<0.01) [200,202-205]. Other merits of BI include decreased iron deficiency anemia, preservation of the continuity of the alimentary tract, no risk of Petersen hernia, less small bowel adhesion and easier access to the duodenum and biliary tract in cases of biliary diseases [206-209] (**Fig. 4**).

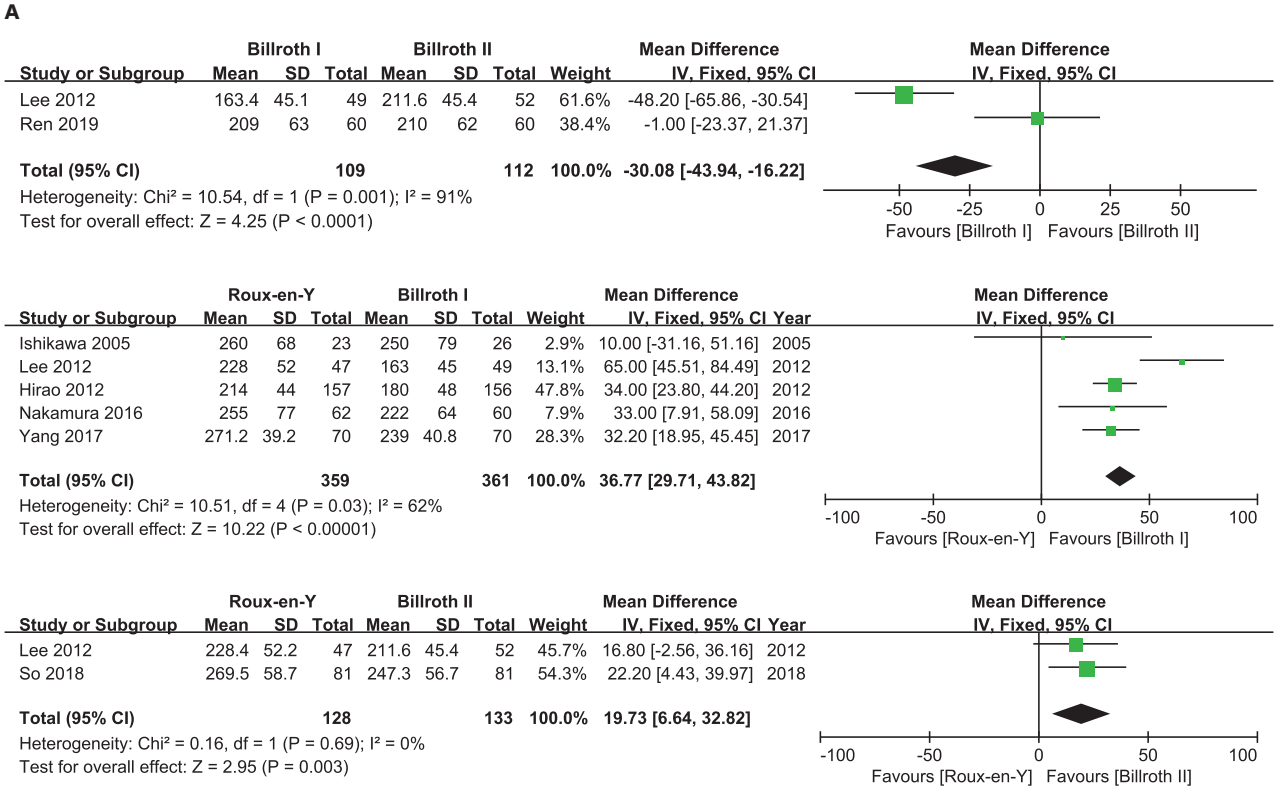

Fig. 4. Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stay. (D) Bile reflux. (E) Esophageal reflux.
SD = standard deviation; IV = interval variable; CI = confidence interval.
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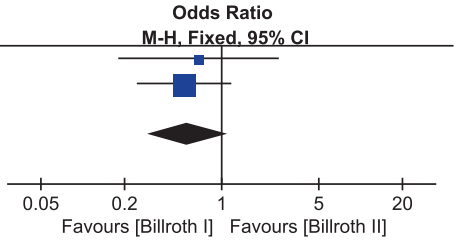
B

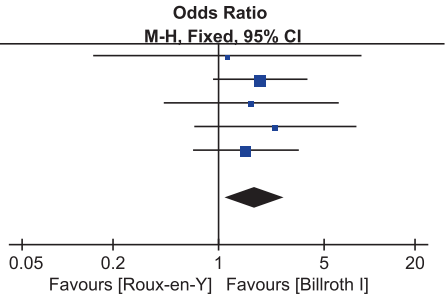
Study or Subgroup	Billroth I Events	Billroth I Total	Billroth II Events	Billroth II Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lee 2012	4	49	6	52	23.7%	0.68 [0.18, 2.58]
Ren 2019	37	60	45	60	76.3%	0.54 [0.25, 1.17]
Total (95% CI)		**109**		**112**	**100.0%**	**0.57 [0.29, 1.12]**
Total events	41		51			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)



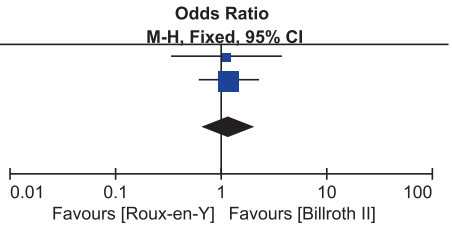
Study or Subgroup	Roux-en-Y Events	Roux-en-Y Total	Billroth I Events	Billroth I Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Ishikawa 2005	2	23	2	26	5.8%	1.14 [0.15, 8.84]	2005
Hirao 2012	23	157	13	156	37.9%	1.89 [0.92, 3.88]	2012
Lee 2012	6	47	4	49	11.6%	1.65 [0.43, 6.25]	2012
Nakamura 2016	9	62	4	60	11.8%	2.38 [0.69, 8.18]	2016
Yang 2017	18	70	13	70	32.9%	1.52 [0.68, 3.40]	2017
Total (95% CI)		**359**		**361**	**100.0%**	**1.75 [1.12, 2.75]**	
Total events	58		36				

Heterogeneity: Chi² = 0.57, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)



Study or Subgroup	Roux-en-Y Events	Roux-en-Y Total	Billroth II Events	Billroth II Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Lee 2012	6	47	6	52	23.3%	1.12 [0.34, 3.75]	2012
So 2018	28	81	25	81	76.7%	1.18 [0.61, 2.28]	2018
Total (95% CI)		**128**		**133**	**100.0%**	**1.17 [0.66, 2.08]**	
Total events	34		31				

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)



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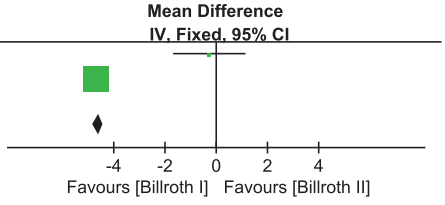
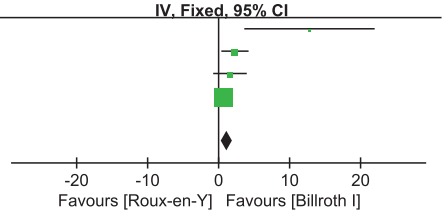
Study or Subgroup	Billroth I Mean	Billroth I SD	Billroth I Total	Billroth II Mean	Billroth II SD	Billroth II Total	Weight	Mean Difference IV, Fixed, 95% CI
Lee 2012	9.2	3.1	49	9.47	4.1	52	2.1%	-0.27 [-1.68, 1.14]
Ren 2019	7.16	0.48	60	11.85	0.66	60	97.9%	-4.69 [-4.90, -4.48]
Total (95% CI)			**109**			**112**	**100.0%**	**-4.60 [-4.80, -4.39]**

Heterogeneity: Chi² = 36.83, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 44.10 (P < 0.00001)



Study or Subgroup	Roux-en-Y Mean	Roux-en-Y SD	Roux-en-Y Total	Billroth I Mean	Billroth I SD	Billroth I Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Ishikawa 2005	31.8	21.7	23	19	6.2	26	0.7%	12.80 [3.62, 21.98]	2005
Hirao 2012	16.4	10.4	157	14.1	6.5	156	16.3%	2.30 [0.38, 4.22]	2012
Lee 2012	10.8	7.7	47	9.2	3.1	49	10.7%	1.60 [-0.77, 3.97]	2012
Yang 2017	10.3	3.7	70	9.6	1.2	70	72.3%	0.70 [-0.21, 1.61]	2017
Total (95% CI)			**297**			**301**	**100.0%**	**1.14 [0.37, 1.92]**	

Heterogeneity: Chi² = 8.64, df = 3 (P = 0.03); I² = 65%
Test for overall effect: Z = 2.89 (P = 0.004)



Study or Subgroup	Roux-en-Y Mean	Roux-en-Y SD	Roux-en-Y Total	Billroth II Mean	Billroth II SD	Billroth II Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Lee 2012	10.8	7.7	47	9.47	4.1	52	12.6%	1.33 [-1.14, 3.80]	2012
So 2018	8	3.5	81	9	2.5	81	87.4%	-1.00 [-1.94, -0.06]	2018
Total (95% CI)			**128**			**133**	**100.0%**	**-0.71 [-1.58, 0.17]**	

Heterogeneity: Chi² = 2.99, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.58 (P = 0.11)

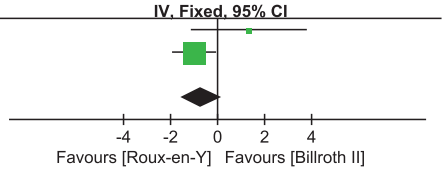


Fig. 4. (Continued) Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stay. (D) Bile reflux. (E) Esophageal reflux.
SD = standard deviation; IV = interval variable; CI = confidence interval.

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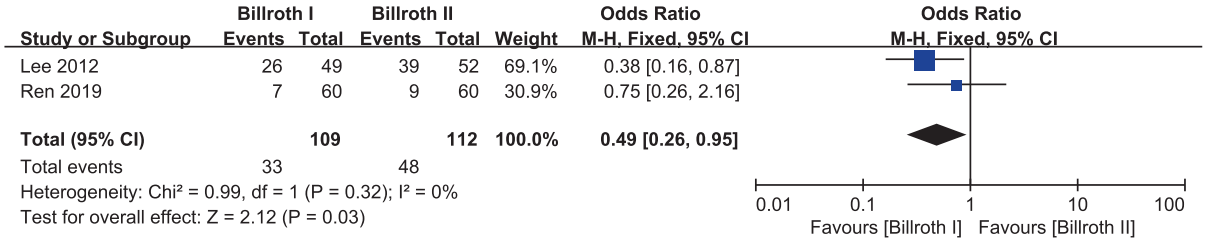

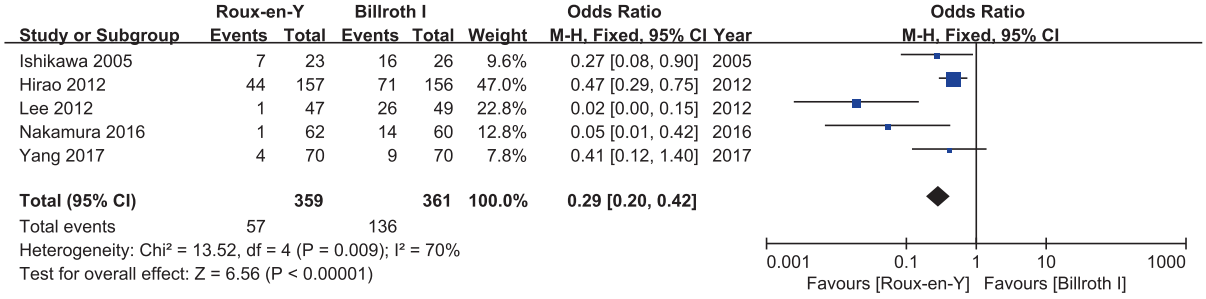

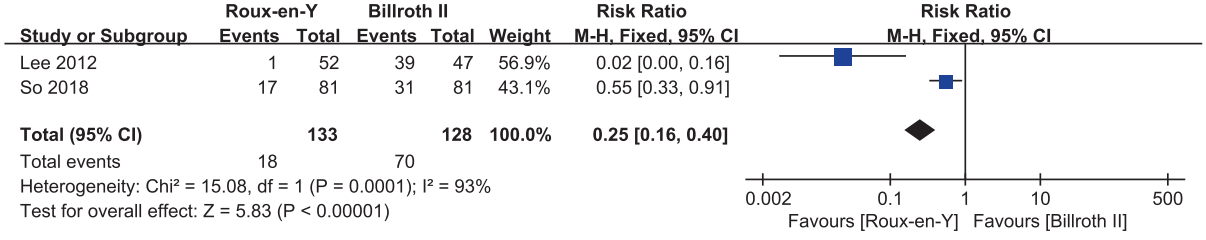

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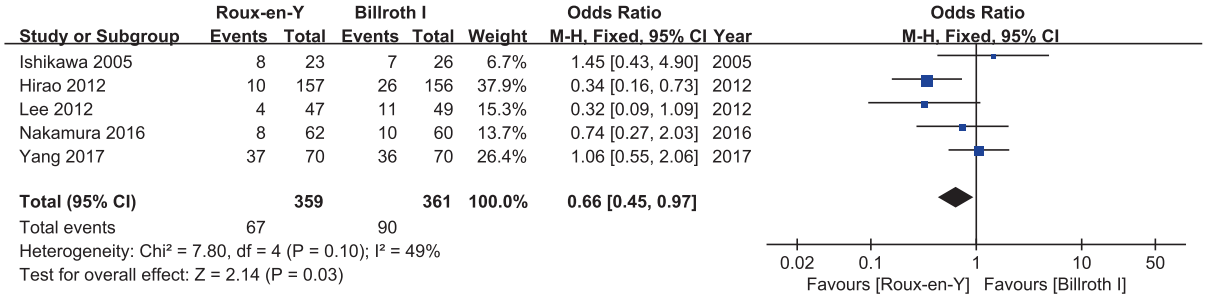

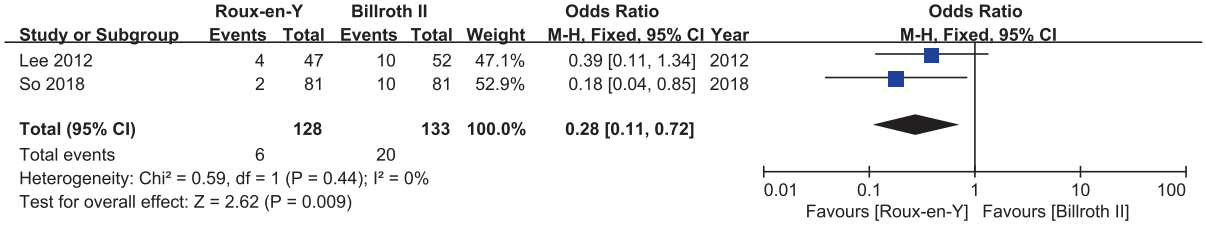

Fig. 4. (Continued) Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stay. (D) Bile reflux. (E) Esophageal reflux. SD = standard deviation; IV = interval variable; CI = confidence interval.

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RY showed advantages in preventing bile reflux and esophageal reflux under endoscopic findings [200-205,210]. However, to date, evidence regarding whether endoscopic bile reflux directly leads to superior QOL or the prevention of metachronous cancer is insufficient. In a retrospective series, RY with an increased length of limbs after gastrectomy showed favorable metabolic effects for gastric cancer patients with type II diabetes [208,211].

There was no difference in QOL (P=0.290–0.994) or nutritional aspects (weight loss, albumin) among the 3 reconstruction methods [200,212]. There is insufficient evidence to show differences in survival outcomes among reconstruction methods [213].

Taken together, the working group in the guideline could not recommend a specific reconstruction method as the best option for all cases due to the different advantages/disadvantages of each reconstruction method. We recommend that surgeons choose the best option according to the characteristics of the cancer and patients.

KQ 11: Can intraoperative evaluation of tumor margin, reresection or reoperation show improved outcome in margin positivity and survival outcome for gastric cancer patients who undergo gastrectomy?

Statement 11-1: Various efforts to achieve negative margins are recommended for better survival outcomes in EGC patients. Reresection or reoperation should be considered when patient condition is favorable and technically feasible (evidence: low, recommendation: strong for).

The impact of microscopically positive margin status was different according to the pathologic status of the cancer [214,215]. In our review, positive resection margins showed inferior survival outcomes compared to negative margins in pathologic T1 cancers ([68.6% vs. 97.4%, P<0.0001], [66.7% vs. 93.1%, P<0.04]) and T2 cancers ([21.5% vs. 55.2%, P<0.001], [8% vs. 64%, P<0.001]) [215-217].

There is a debate regarding whether securing an adequate length of margin may influence oncologic outcome in EGC [214,218-220]. However, most literature agrees that obtaining negative margin regardless of margin length shows better survival [219,221,222]. To obtain negative margin, single or combinations of various methods including intraoperative frozen section, perioperative gastroscopy, various preoperative clipping or dyeing, fluorescence imaging technique, ultrasonography, and simple X-ray, etc., were introduced [223-231].

In EGC, when pathologic results reveal tumor involvement of the resection margin, additional surgery to obtain R0 resection showed a survival benefit in several studies [221,222,232]. Therefore, development of this guideline made a consensus to recommend additional surgery when the patient condition is favorable and additional surgery is technically feasible.

There were also reports showing that R1 resection does not always lead to recurrence, partly due to lack of blood supply on the remnant transection line, discrepancy of true surgical margin from the use of surgical stapler or patients' immunity [214,216]. Watchful observation with frequent follow-up might be cautiously considered when the extent of the

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involved margin is minimal, or the anticipated risk of reoperation is high. However, further investigations are required to clarify the indications for no additional surgery.

Statement 11-2: Efforts should be made to obtain negative margins in advanced or infiltrative gastric cancer surgery. If the final postoperative pathologic margin shows involvement of the margin, reoperation to achieve R0 should be chosen cautiously, considering the possibility of limited survival benefits and the risk of postoperative complications in advanced-stage cancer (evidence: low, recommendation: conditional for).

In previous reports, various macroscopic margin lengths (3–8 cm) were recommended to secure pathologic negative resection margins in advanced or infiltrative cancer [230,233,234]. Intraoperative frozen section showed improved accuracy compared to macroscopic margin prediction to secure R0 resection [227,230,235-237]. The aforementioned methods to achieve negative margins can also benefit advanced cancer cases to obtain secure margins and tumor localization.

Unlike early-stage gastric cancer, many studies showed that a positive microscopic margin had no prognostic impact when staging was ≥ T3 or ≥ N2 or ≥ IIIa (American Joint Committee on Cancer [AJCC] 7th) [215,218,219,221,238-242]. In these situations, achievement of a negative margin showed limited survival benefits.

Therefore, utilizing various methods including intraoperative frozen section is advisable to achieve R0 resection in advanced cancer. However, in advanced diseases (≥ pT3 or ≥ pN2 or ≥ Stage IIIa (AJCC 7th) with R1 resection, reoperation should be decided cautiously considering pathologic stage, patient status, risk of postoperative complications and risk of delayed systemic therapy.

KQ 12: Can PG with DTR show better outcome than TG in terms of short-term surgical outcomes, nutritional status, QOL, and survival rate for EGC in the upper third of the stomach?

Statement 12: PG with DTR as well as TG can be considered for EGC in the upper third of the stomach in terms of less vitamin B12 deficiency and similar survival and reflux symptoms compared to TG (evidence: low, recommendation: conditional for).

TG has been a standard treatment for upper gastric cancer. Gastric cancer in the upper third of the stomach-has limited node metastasis to the lower part of the stomach, which makes PG acceptable and oncologically safe [243,244]. However, reconstruction has been a hurdle for PG due to the high incidence of reflux esophagitis and anastomosis stricture in esophagogastrostomy.

DTR was recently reported for its feasibility under laparoscopic settings. In our systematic review of retrospective studies, there were significantly fewer patients with vitamin B12 deficiency in the PG-DTR group than in the TG group (RR, 0.30; 95% CI, 0.23 to 0.40; P<0.01) [245-247]. Weight loss after surgery did not differ between the groups (RR, −4.89;

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95% CI, −11.75 to 1.97; P=0.16) [247,248]. There were no differences in reflux symptoms (RR, 1.28; 95% CI, 0.33 to 4.93) [246,249,250]. Complications were reported less frequently in the PG-DTR group (RR, 0.61; 95% CI, 0.45 to 0.83; P=0.002) (**Fig. 5**).

The Korean Laparoendoscopic Gastrointestinal Surgery Study Group conducted a prospective RCT on LPG-DTR vs. LTG (KLASS-05) and recently reported early results. The cumulative amount of intramuscular vitamin B12 supplementation required for patients during 2 postoperative years was significantly lower in the PG-DTR group than in the TG group (0.6±2.0 mg vs. 3.4±4.1 mg, P<0.001). The proportion of patients who required vitamin B12 supplementation was also significantly lower in the PG-DTR group (14.7% vs. 58.0%, P<0.001). However, the hemoglobin change after surgery, which was the co-first outcome, was not significantly different between the groups (5.6%±7.4% vs. 6.9%±8.3%, P=0.349).

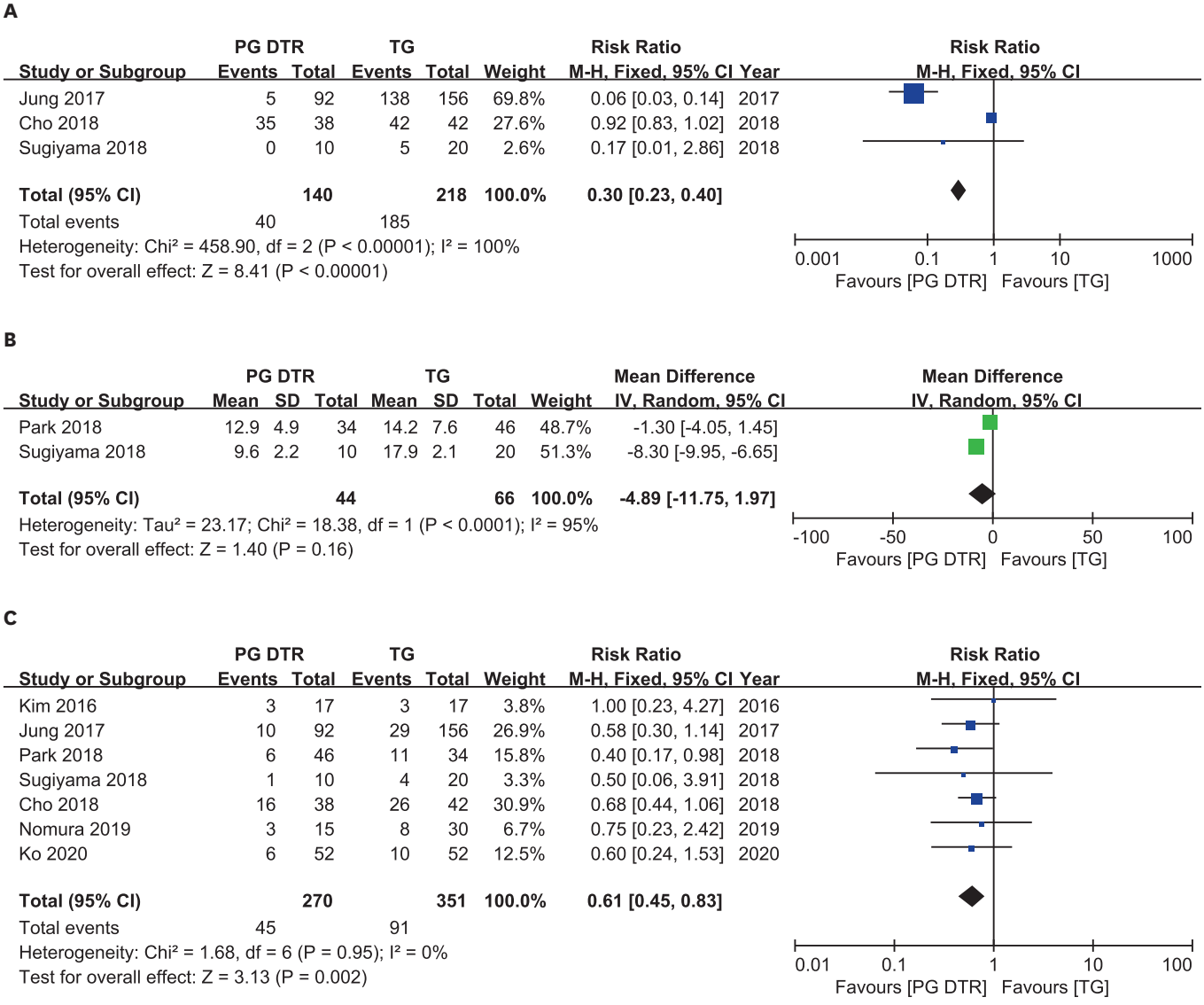

Fig. 5. Forest plots for comparison between proximal gastrectomy with double tract reconstruction vs. total gastrectomy in retrospective studies. (A) Vitamin B12 deficiency. (B) Weight loss. (C) Early complications. (D) Reflux symptom.
PG = proximal gastrectomy; DTR = double tract reconstruction; TG = total gastrectomy; IV = interval variable; CI = confidence interval. (continued to the next page)

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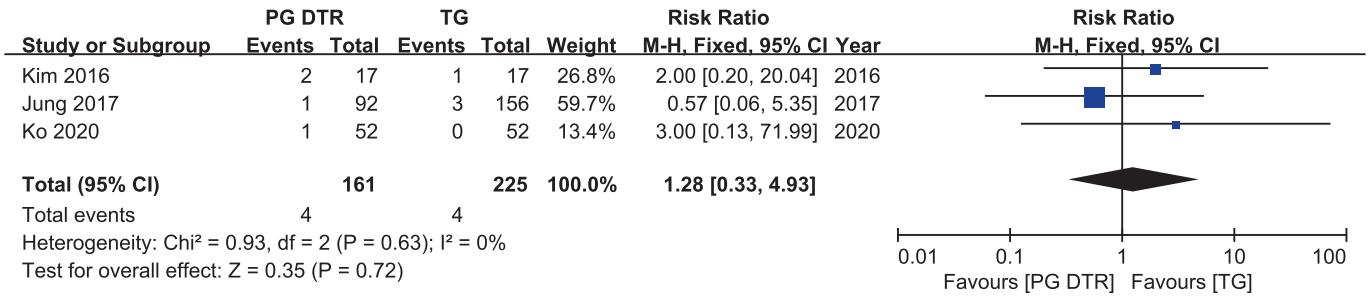

Fig. 5. (Continued) Forest plots for comparison between proximal gastrectomy with double tract reconstruction vs. total gastrectomy in retrospective studies. (A) Vitamin B12 deficiency. (B) Weight loss. (C) Early complications. (D) Reflux symptom.
PG = proximal gastrectomy; DTR = double tract reconstruction; TG = total gastrectomy; IV = interval variable; CI = confidence interval.

The Visick score for reflux symptoms at 2 weeks postoperatively (P=0.793) and postoperative complications were not different between the groups (23.5% vs. 17.4%, P=0.373) [251].

In the KLASS-05, the 2-year OS rates and DFS rates of the PG-DTR and TG groups were 98.5% vs. 100%, (P=0.330) and 98.5% vs. 97.1%, respectively (P=0.540) [251]. Regarding long-term QOL, the PG-DTR group showed better scores on the physical functioning (P=0.029) and social functioning (P=0.031) scales (European Organization for Research and Treatment of Cancer QOL Questionnaire [EORTC QLQ-C30]).

Recently, other methods such as side overlap esophagogastrostomy, double flap technique (DFT) reconstruction are being investigated for better functional outcomes [252-255]. Some studies show that DFT has better outcomes than TG in terms of morbidity, postoperative hospital stay, reflux esophagitis and postoperative nutritional status [252]. However, laparoscopic PG-DFT requires a more complex intracorporeal suturing technique and longer duration of surgery [253]. Further investigation is required for higher level of evidence [255].

KQ 13: Can PPG show improved outcomes than DG in terms of nutritional status, QOL, complications, and survival outcomes for patients with middle third gastric cancer?

Statement 13: For EGC located ≥5 cm proximal from the pylorus, PPG as well as DG could be performed. PPG has the benefits of less gallstone formation and protein preservation; however, delayed gastric emptying should be considered when making decisions (evidence: moderate, recommendation: conditional for).

PPG preserves the pylorus and distal antrum to prevent the rapid transit of food into the duodenum and the reflux of duodenal contents. Consequently, the postoperative incidence of dumping syndrome and reflux gastritis has been expected to show benefits in nutrition and QOL compared to DG.

Recently, a prospective RCT on laparoscopic PPG vs. laparoscopic DG (KLASS-04) was conducted and the results were reported [256,257].

In KLASS-04, there were no differences in survival outcomes or complications between the PPG group and the DG group. There was no difference in the incidence of dumping syndrome one year

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after surgery (13.2% vs. 15.8%, P=0.62). Reflux esophagitis (17.8% vs. 6.3%, P<0.01) and delayed gastric emptying (16.3% vs. 4.0%, P<0.01) were more frequent in the PPG group than in the DG group 3 years after surgery. However, bile reflux (13.2% vs. 24.4%, P=0.02) and the incidence of gallstone formation (2.3% vs. 8.7% P=0.03) were lower in the PPG group than in the DG group.

Although there was no difference in body weight change after surgery, the total protein level was preserved after PPG compared to DG (P<0.01). Regarding QOL after surgery, there was no difference between groups in terms of the EORTC QLQ-C30 and EORTC-QLQ-Gastric Cancer Module (STO22) questionnaires.

In our meta-analysis, most studies on PPG were retrospective. There were no differences in survival outcomes or postoperative complications [257-262]. The PPG group showed lower incidence of postoperative dumping syndrome and reflux [260,262,263]. Some studies reported reduced development of gallstones after PPG, probably due to preservation of the hepatic branch of the vagus nerve [258,260]. However, PPG was related to more frequent delayed gastric emptying than DG [258,260-263].

Regarding nutritional status, the decreases in serum protein and albumin from postoperative months 1 to 6 and abdominal fat area at postoperative year 1 were lower in the PPG group than in the DG group, and the PPG group showed more improvement in hemoglobin than the DG group [258,261,262,264].

PPG tended to present better improvement of QOL and fewer symptoms than DG with BI at 2 years after surgery [264]. The PPG group had a better physical functioning score (86.7 vs. 90.0, P=0.032) but also greater pain and reflux than the DG group (median score 8.3 vs. 16.7 in pain, 11.1 vs. 11.1 in reflux, P=0.034 and 0.001, respectively) at least 2 years after surgery [262].

In summary, PPG showed benefits in gallstone formation, bile reflux and preservation of serum total protein, while survival, postoperative complications and QOL were similar in comparison to DG in KLASS-04. Observational studies reported additional possible benefits in nutritional and functional aspects of PPG. For EGC located ≥5 cm proximal from the pylorus, PPG could be performed in this regard; however, delayed gastric emptying should be considered when making decisions.

KQ 14: Can splenectomy for prophylactic LN dissection of the splenic hilum provide better survival and complication outcomes than radical TG without splenectomy in advanced gastric cancer?

Statement 14: Prophylactic splenectomy for splenic hilar LN dissection is not recommended in curative resection for advanced gastric cancer in the proximal stomach without greater curvature invasion (evidence: high, recommendation: strong against).

The standard surgical procedure for proximal-third gastric carcinoma TG with proper LN dissection. Therapeutic splenectomy may be necessary if the tumor directly invades the spleen or if LN metastasis around the splenic hilum is suspected. However, there is debate regarding whether splenic resection with LN dissection of the splenic hilum for cancer should be performed in the absence of direct invasion of the spleen, splenic hilum, or greater curvature of the stomach.

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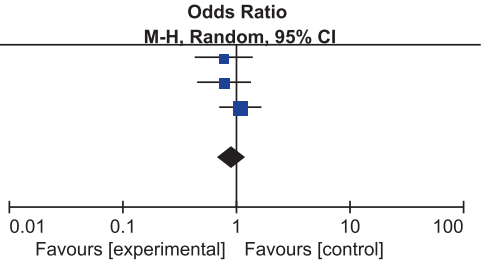
Study or Subgroup	non splenectomy Events	Total	splenectomy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Csendes 2002	35	97	38	90	24.7%	0.77 [0.43, 1.39]	2002
Yu 2006	50	103	57	104	28.7%	0.78 [0.45, 1.34]	2006
Sano 2017	171	224	173	231	46.7%	1.08 [0.70, 1.66]	2017
Total (95% CI)		**424**		**425**	**100.0%**	**0.91 [0.68, 1.21]**	
Total events	256		268				

Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)



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Study or Subgroup	non splenectomy Events	Total	splenectomy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Csendes 2002	39	97	61	90	33.2%	0.32 [0.18, 0.58]	2002
Yu 2006	9	103	16	104	12.8%	0.53 [0.22, 1.25]	2006
Sano 2017	42	224	77	231	54.0%	0.46 [0.30, 0.71]	2017
Total (95% CI)		**424**		**425**	**100.0%**	**0.42 [0.31, 0.59]**	
Total events	90		154				

Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 5.19 (P < 0.00001)

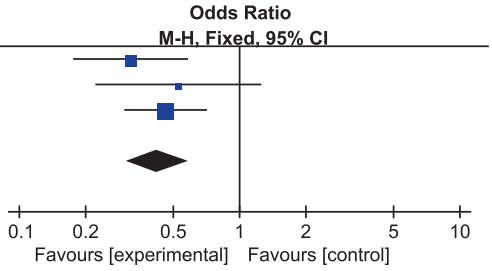

Fig. 6. Forest plot for a comparison between no splenectomy (experimental) vs. splenectomy (control). (A) Survival. (B) Complications.
CI = confidence interval.

Three prospective RCTs evaluated the survival advantage of prophylactic splenectomy in proximal-third gastric carcinoma [252,265,266]. Our meta-analysis showed no difference in survival (HR, 0.91; 95% CI, 0.68 to 1.21; P=0.51) but significantly fewer postoperative complications in the nonsplenectomy group (HR, 0.42; 95% CI, 0.31 to 0.59, P<0.01) (**Fig. 6**).

Studies in our meta-analysis did not include advanced cancer with gross involvement to the greater curvature or to gastrosplenic ligament, where the metastasis rate of LN#10 is relatively high and splenic hilar dissection with splenectomy is required to accomplish standard treatment [267-269].

In any circumstance, splenectomy increases postoperative complications and mortality rates. To overcome this, an operative technique for LN#10 dissection around the splenic hilum without splenectomy has been reported; however, its oncologic outcome is still under investigation [270-272].

KQ 15: Can PG without LN dissection at the distal stomach be recommended to treat advanced adenocarcinoma invading the GEJ compared to TG with standard LN dissection?

Statement 15: PG may be performed in advanced gastric cancer with adenocarcinoma histology located in the GEJ (Siewert II/III) without serosal invasion, due to low rate of LN metastasis to the distal part of the stomach (evidence: low, recommendation: conditional for).

TG is the standard treatment for AGC in the upper part of the stomach [10,111,234]. Some studies have raised suspicion that removing the entire stomach along with the perigastric tissues and LNs may be unnecessary in selected cases [243,273,274].

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In our meta-analysis, 5 retrospective studies that investigated the LN mapping of proximal gastric cancer after TG were included [273-277]. In the pooled data, the distal LN station #4d, #5 and #6 (distal LN) metastasis rates were analyzed. The metastasis rates in pT2 cancer were very low: #4d (0/359), #5 (1/425) and #6 (0/359) (distal LN). The risk ratio of metastasis in the distal LN for pT3 was 1.82 (CI, 0.77 to 4.29) compared to pT2 (P=0.17), and the risk ratio for pT4 was 9.89 (CI, 4.66 to 20.95) compared to pT2 (P<0.01) (**Fig. 7**).

In one retrospective study in Korea, 873 patients were reviewed [243]. In their multivariable analysis, a GEJ to tumor epicenter distance longer than 30 mm, tumor size >70 mm, macroscopic Bormann type IV tumor or serosa invasion were risk factors for LN metastasis to the distal stomach. In patients without any risk factors from above, the LN metastasis rates at stations 4d, 5, and 6 were 0.0%, 0.4%, and 0.4%, respectively, and the therapeutic value index (TVI) of LN #4d, #5, and #6 were low; 0, 0.4, and 0.4), respectively (TVI is calculated by incidence of LN metastasis and 5-year survival after removing corresponding LN and can be used for evaluating necessity of dissection of specific LN stations) [268].

A

Study or Subgroup	LN meta T3 Events	Total	LN meta T2 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
2.1.1 station #4d							
Isozaki 1995	0	23	0	16		Not estimable	1995
Haruta 2017	0	182	0	182		Not estimable	2017
Yura 2019	2	129	0	73	12.6%	2.85 [0.14, 58.49]	2019
Yun 2021	2	148	0	88	12.3%	2.99 [0.15, 61.50]	2021
Subtotal (95% CI)		**482**		**359**	**24.9%**	**2.92 [0.34, 24.74]**	
Total events	4		0				
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%							
Test for overall effect: Z = 0.98 (P = 0.33)							
2.1.2 station #5							
Isozaki 1995	5	23	0	16	11.5%	7.79 [0.46, 131.72]	1995
Haruta 2017	0	182	0	182		Not estimable	2017
Yura 2019	0	129	0	73		Not estimable	2019
Yun 2021	1	148	0	88	12.3%	1.79 [0.07, 43.52]	2021
Yang 2022	0	66	1	66	29.6%	0.33 [0.01, 8.04]	2022
Subtotal (95% CI)		**548**		**425**	**53.5%**	**2.28 [0.53, 9.89]**	
Total events	6		1				
Heterogeneity: Chi² = 2.15, df = 2 (P = 0.34); I² = 7%							
Test for overall effect: Z = 1.10 (P = 0.27)							
2.1.3 station #6							
Isozaki 1995	0	23	0	16		Not estimable	1995
Haruta 2017	0	182	0	182		Not estimable	2017
Yun 2021	1	148	0	73	13.2%	1.49 [0.06, 36.13]	2021
Yang 2022	1	66	0	88	8.5%	3.99 [0.16, 96.30]	2022
Subtotal (95% CI)		**419**		**359**	**21.6%**	**2.47 [0.28, 21.98]**	
Total events	2		0				
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%							
Test for overall effect: Z = 0.81 (P = 0.42)							
Total (95% CI)		**1449**		**1143**	**100.0%**	**2.48 [0.86, 7.15]**	
Total events	12		1				
Heterogeneity: Chi² = 2.40, df = 6 (P = 0.88); I² = 0%							
Test for overall effect: Z = 1.68 (P = 0.09)							
Test for subgroup differences: Chi² = 0.03, df = 2 (P = 0.98), I² = 0%							

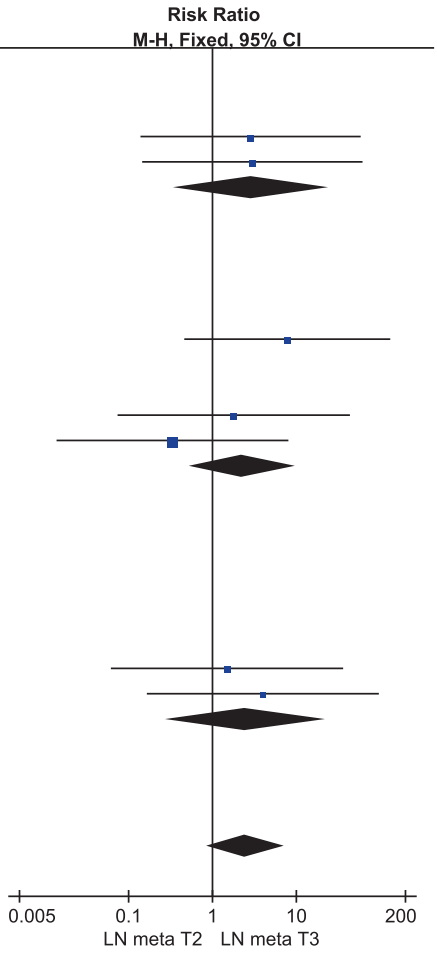

Fig. 7. Forest plot, LN metastasis rates of distal stomach according to the depth of tumor. (A) LN metastasis rate comparison T3 vs. T2 (P=0.17). (B) LN metastasis rate comparison T4 vs. T2 (P<0.01).
LN = lymph node; CI = confidence interval.

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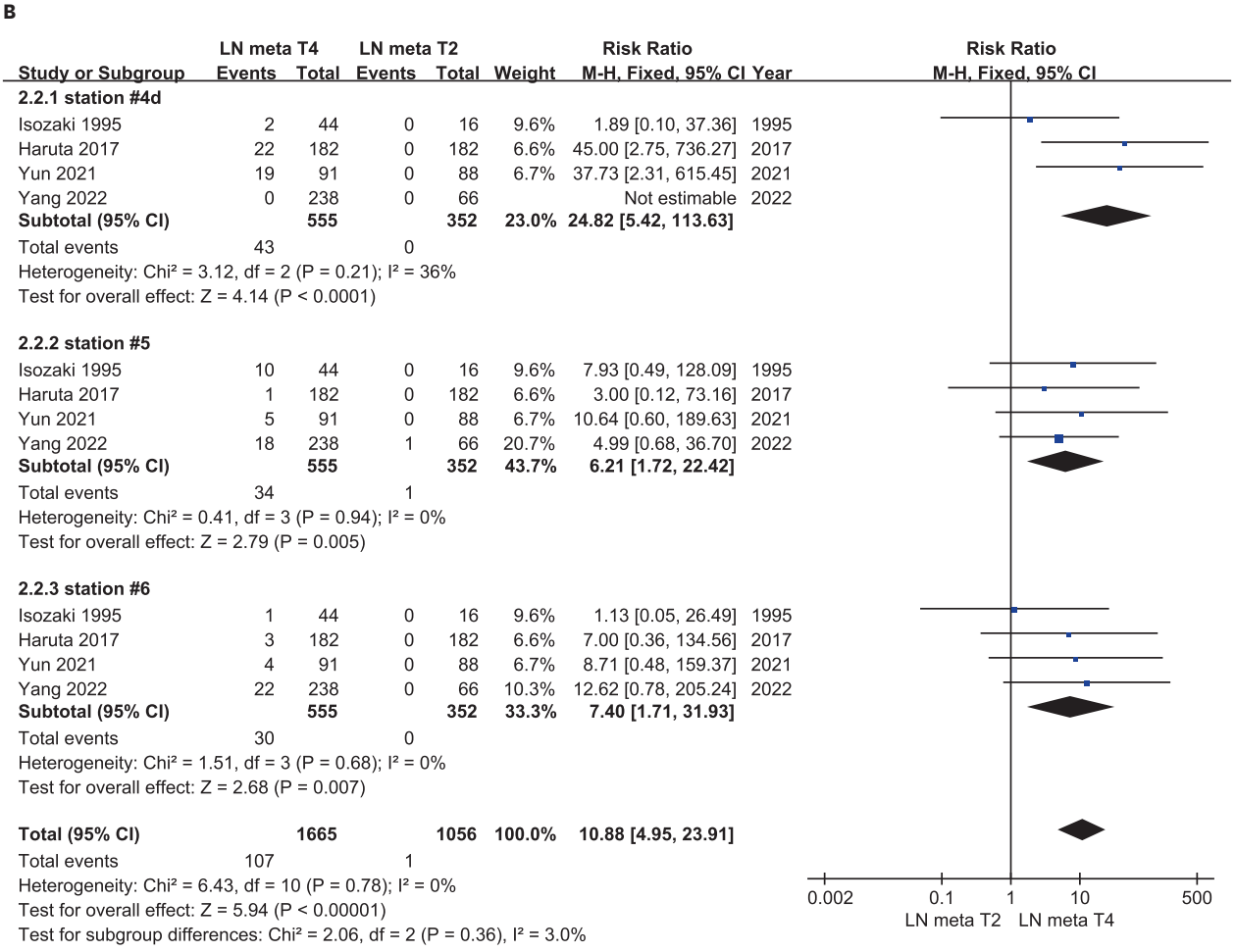

Fig. 7. (Continued) Forest plot, LN metastasis rates of distal stomach according to the depth of tumor. (A) LN metastasis rate comparison T3 vs. T2 (P=0.17). (B) LN metastasis rate comparison T4 vs. T2 (P<0.01).
LN = lymph node; CI = confidence interval.

From these results, PG without dissection of LN stations #4d, #5, and #6 could be considered in selected cases of advanced gastric cancer with adenocarcinoma histology located in the GEJ (Siewert II/III) without serosal invasion. However, more data are required to determine the detailed indications for PG and to evaluate the clinical outcomes of PG.

KQ 16: Can additional lower mediastinal LN dissection improve oncologic outcome for adenocarcinoma invading GEJ?

Statement 16-1: Lower mediastinal LN dissection could be performed to remove possible metastatic LNs for advanced cancer invading the GEJ (evidence: low, recommendation: conditional for).

The definition and extent of surgery around the GEJ have not been solidly established. The most frequently used classification is the Siewert classification, which defines GEJ carcinoma as a tumor with an epicenter within 5 cm proximal and distal of the anatomical cardia and

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categorizes it into 3 types: type 1 (lower esophageal cancer), type 2 (true GEJ cancer), and type 3 (subcardial cancer) [278]. In Japan, GEJ carcinoma is defined as a tumor according to the Japanese classification system, regardless of histological type, when its epicenter is located within 2 cm proximal or distal to the GEJ [18].

It is generally acknowledged that Siewert type I and type III carcinomas are usually treated as esophageal and gastric tumors, respectively [279,280]. Siewert type II adenocarcinoma, located 1 cm above to 2 cm below the GEJ, represents adenocarcinoma that arises from the epithelium of the cardia or short segments of intestinal metaplasia mostly in Western countries. There has been considerable controversy about whether Siewert type II carcinoma is esophageal or gastric cancer and about the extent of LN dissection.

In a retrospective analysis conducted in Korea, 672 patients who underwent radical TG with lymphadenectomy without lower mediastinal LN dissection for GEJ carcinoma type II, type III, or upper third of the stomach were reviewed [281]. They suggested that lower mediastinal LN dissection will not be essential for early-stage cancer based on excellent survival regardless of the location (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), which result implies the necessity of mediastinal LN dissection.

On the other hand, another retrospective analysis in Korea that reviewed 125 type II and 338 type III GEJ cancer patients demonstrated that there was no increase of recurrence in the mediastinal LNs without complete mediastinal LN dissection, regardless of the type. From this result, they suggested that TH approach without complete mediastinal LN dissection can be acceptable, at least for frequent types of GEJ cancer in Korea [282].

A prospective nationwide multicenter study in Japan reviewed the frequency of LN metastasis of GEJ tumors with cT2-T4 stages and recommended lower mediastinal LN dissection (especially station 110) if the length of esophageal invasion was more than 2 cm [26].

Taken together, lower mediastinal LN dissection seems to be not essential for early GEJ cancers. For advanced cancer, lower mediastinal LN dissection may be needed to sufficiently remove possible metastatic LNs in case esophageal involvement is more than 2 cm; however, further data in terms of local recurrence and survival gain remain to be needed.

> Statement 16-2: The TH approach rather than the TT approach is recommended to acquire negative resection margin and perform lower mediastinal LN dissection in resectable adenocarcinoma invading the GEJ (evidence: moderate, recommendation: strong for).

Two RCTs on optimal surgical approach for GEJ adenocarcinoma (Siewert type II, III) compared the surgical and oncological outcomes of TH and TT approaches (one left thoracoabdominal approach and one right thoracotomy). Our meta-analysis of RCTs demonstrated comparable in-hospital mortality (P=0.10) and anastomosis leakage (P=0.58) between the TT and TH approaches, but a higher incidence of pulmonary complication in the TT approach (P<0.0001) (**Fig. 8**). Although the Japanese RCT (JCOG9502) comparing the left thoracoabdominal and TH

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approaches was to be stopped after the interim analysis, the 5-year OS of TH approach were not inferior to that of the TT approach (HR, 0.90; CI, 0.73 to 1.10; P=0.31) in 2 RCTs [283,284].

In our meta-analysis with observational studies including right and left thoracotomy and right thoracoscopic approaches, the TT approach was associated with a higher incidence of pulmonary complications (P=0.0002), a higher in-hospital mortality rate (P=0.02) and similar anastomosis leakage (P=0.57) when compared to the TH approach. The TH approach was not inferior to the TT approach in 5-year OS (HR, 0.80; CI, 0.59 to 1.11; P=0.18) [26,285-291].

Regarding the high surgical complications of the TT approach and no difference in 5-year OS, the TH approach is recommended rather than the TT approach for resectable adenocarcinoma invading the GEJ.

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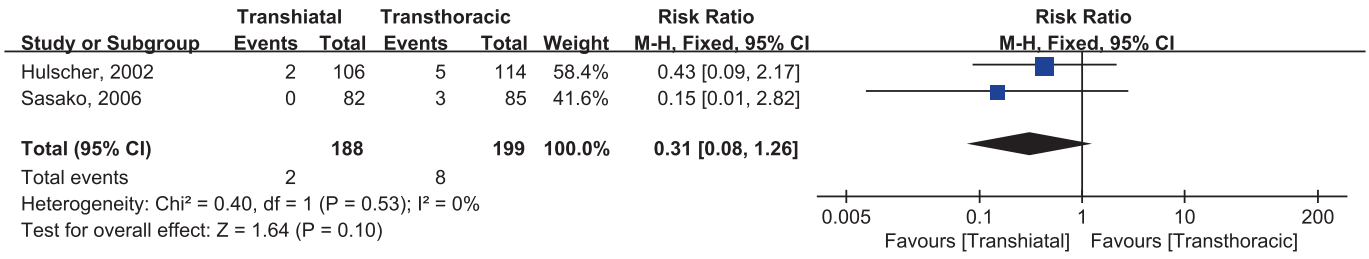

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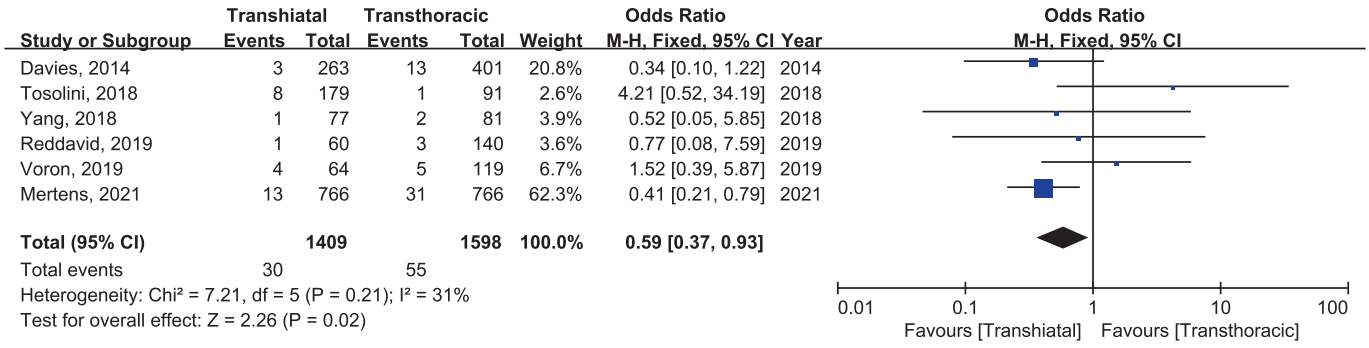

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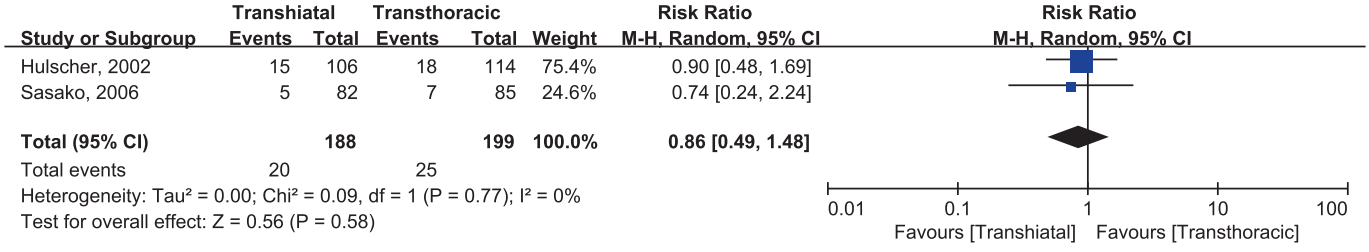

Fig. 8. Forest plots for comparisons between the TH abdominal approach vs. TT approach. TT approaches in the observational studies included. In-hospital mortality: (A) RCTs; (B) Observational studies. Pulmonary complications: (C) RCTs; (D) Observational studies. Five-year survival: (E) RCTs; (F) Observational studies.
TH = transhiatal; TT = transthoracic; CI = confidence interval; RCT = randomized controlled trial.

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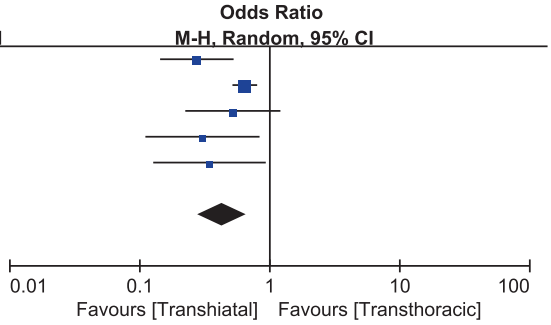
D

Study or Subgroup	Transhiatal Events	Transhiatal Total	Transthoracic Events	Transthoracic Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank, 2017	46	486	16	58	21.3%	0.27 [0.14, 0.53]
Mertens, 2021	200	766	272	766	37.2%	0.64 [0.52, 0.80]
Reddavid, 2019	8	60	32	140	16.0%	0.52 [0.22, 1.21]
Voron, 2019	5	64	26	119	12.6%	0.30 [0.11, 0.83]
Yang, 2018	6	77	16	81	12.9%	0.34 [0.13, 0.93]
Total (95% CI)		**1453**		**1164**	**100.0%**	**0.43 [0.28, 0.67]**
Total events	265		362			

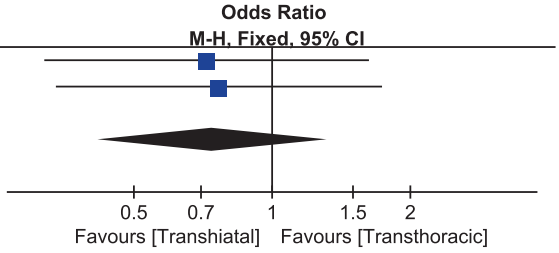
Heterogeneity: Tau² = 0.12; Chi² = 8.48, df = 4 (P = 0.08); I² = 53%
Test for overall effect: Z = 3.79 (P = 0.0002)



E

Study or Subgroup	Transhiatal Events	Transhiatal Total	Transthoracic Events	Transthoracic Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kurokawa, 2015	26	52	25	43	51.1%	0.72 [0.32, 1.62]
Omloo, 2007	36	52	47	63	48.9%	0.77 [0.34, 1.74]
Total (95% CI)		**104**		**106**	**100.0%**	**0.74 [0.42, 1.32]**
Total events	62		72			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



F

Study or Subgroup	Transhiatal Events	Transhiatal Total	Transthoracic Events	Transthoracic Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Blank, 2017	149	186	43	56	15.3%	1.22 [0.59, 2.49]
Reddavid, 2019	55	60	133	140	7.7%	0.58 [0.18, 1.90]
Tosolini, 2018	96	179	55	91	39.3%	0.76 [0.45, 1.26]
Voron, 2019	55	64	105	119	12.0%	0.81 [0.33, 2.00]
Yang, 2018	44	77	53	81	25.7%	0.70 [0.37, 1.34]
Total (95% CI)		**566**		**487**	**100.0%**	**0.81 [0.59, 1.11]**
Total events	399		389			

Heterogeneity: Chi² = 1.79, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)

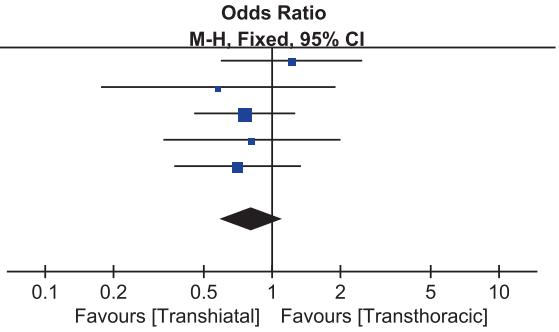


Fig. 8. (Continued) Forest plots for comparisons between the TH abdominal approach vs. TT approach. TT approaches in the observational studies included. In-hospital mortality: (A) RCTs; (B) Observational studies. Pulmonary complications: (C) RCTs; (D) Observational studies. Five-year survival: (E) RCTs; (F) Observational studies.
TH = transhiatal; TT = transthoracic; CI = confidence interval; RCT = randomized controlled trial.

KQ 17: Can D1+ dissection show comparable survival outcome for EGC (cT1N0) patients compared to D2 dissection?

Statement 17: D1+ dissection can be performed during surgery for EGC (cT1N0) patients in terms of survival (evidence: low, recommendation: Strong for).

D2 dissection was regarded as the standard LN dissection based on the long-term survival data of the Dutch trial [292]. However, application of standard D2 dissection has been questioned for EGC, especially in laparoscopic surgery. There have been no studies comparing D2 dissection and less dissection in EGC patients, but D1+ dissection has been widely accepted by surgeons in Korea and Japan considering the spatial information about

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LN metastasis, TVI calculated by the frequency of LN metastasis and 5-year survival rate after removing each LN station, and the Maruyama index, which evaluates the adequacy of LN dissection [268,293,294].

An Italian study suggested D2 dissection considering significant LN metastasis [295]. Others reported 10-year survival rates of 95% and 87.5% after standard D2 and D1 dissection, respectively, in EGC patients without statistical significance (P=0.80) [296]. In a report from Japan, the 5- and 10-year survival rates were 97% and 91% in patients after standard D2 dissection and 98% and 91% after modified D2 (D1+) dissection. There were no cases with metastasis to second-tier LNs in patients with cT1N0 or cT1N1 disease [297].

Although evidence for comparing D1+ and D2 dissection is insufficient, we referred to the excellent survival results of the RCTs for EGC that compared laparoscopic and open gastrectomy, in which less than D2 dissection was performed, and strongly suggested that D1+ dissection can be performed for EGC [298-300].

KQ 18: Can SNNS be considered a treatment option compared to conventional LG regarding survival, nutritional outcomes and QOL?

Statement 18: SNNS implemented by well-designed protocols and follow-up plans could be considered as a treatment option for cT1N0 and ≤3 cm gastric cancers in terms of better nutritional outcomes and QOL. Treatment decisions should be made after sufficient discussion with the patient regarding the possibility of metachronous cancer and rescue surgery (evidence: moderate, recommendation: conditional for).

To date, numerous feasibility studies for the sentinel node concept have shown a high detection rate and acceptable sensitivity of sentinel node mapping [301,302]. In previous meta-analyses, pooled detection rate and sensitivity rate were 93.7%–97% and 80.8%–89%, respectively. Clinical T1 tumors, dual tracers, submucosal injection, and IHC examinations were associated with higher sensitivity [301,302].

The oncologic safety and clinical benefits of SNNS have been evaluated only in few studies so far [303-308]. In these studies, SNNS was performed on small sized early lesion less than 3 cm in diameter. Two case-control studies and one RCT compared 5-year OS rates, and there was no significant difference between the SNNS and conventional LG groups [304,307,308]. In the RCT (SENORITA trial), 3-year DFS, the primary end point, did not show non-inferiority in SNNS compared to LG due to a higher incidence of metachronous cancer (91.8% vs. 95.5%, SNNS vs. LG) [308].

However, 5-year DFS, OS, and disease-specific survival, which were secondary end points, were not different after rescue surgery in cases of recurrence/metachronous gastric cancer; 88.9% vs. 80.7%, 97.3% vs. 88.3%, and 99.2% vs. 99.3% in SNNS vs LG, respectively (P=0.056, 0.74, and 0.959) [308].

Regarding nutritional outcomes, SNNS had less body weight loss and higher hemoglobin level than LG [303,305,308]. QOL was assessed using various tools in each study, and SNNS had better QOL in some subscales [303,305,306,308] (**Fig. 9**).

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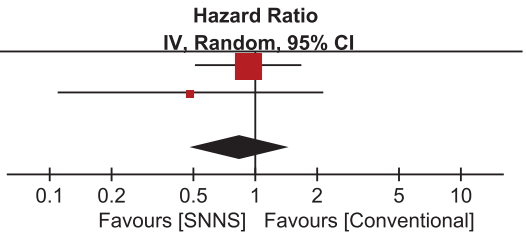
A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Liu 2015	-0.08	0.304	86.2%	0.92 [0.51, 1.68]	2015
Kinami 2021	-0.726	0.759	13.8%	0.48 [0.11, 2.14]	2021
Total (95% CI)			**100.0%**	**0.84 [0.49, 1.47]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



B

Study or Subgroup	SNNS Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.1.1 1month									
Yaguchi 2012	94.1	5.8	34	90.7	4.1	33	15.6%	3.40 [1.00, 5.80]	2012
Okubo 2020	94.2	0.007	25	94	0.007	44	18.8%	0.20 [0.20, 0.20]	2020
Subtotal (95% CI)			**59**			**77**	**34.4%**	**1.57 [-1.54, 4.67]**	
Heterogeneity: Tau² = 4.37; Chi² = 6.83, df = 1 (P = 0.009); I² = 85%									
Test for overall effect: Z = 0.99 (P = 0.32)									
1.1.2 6month									
Yaguchi 2012	94.5	6.4	34	91.9	6.1	33	14.3%	2.60 [-0.39, 5.59]	2012
Okubo 2020	97.3	0.017	25	93.2	0.012	44	18.8%	4.10 [4.09, 4.11]	2020
Subtotal (95% CI)			**59**			**77**	**33.1%**	**4.10 [4.09, 4.11]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%									
Test for overall effect: Z = 1064.57 (P < 0.00001)									
1.1.3 12month									
Yaguchi 2012	96.1	7.5	34	92.1	6	33	13.7%	4.00 [0.75, 7.25]	2012
Okubo 2020	97.4	0.012	25	93	0.009	44	18.8%	4.40 [4.39, 4.41]	2020
Subtotal (95% CI)			**59**			**77**	**32.5%**	**4.40 [4.39, 4.41]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%									
Test for overall effect: Z = 1595.95 (P < 0.00001)									
Total (95% CI)			**177**			**231**	**100.0%**	**3.09 [0.77, 5.40]**	
Heterogeneity: Tau² = 7.40; Chi² = 2077857.80, df = 5 (P < 0.00001); I² = 100%									
Test for overall effect: Z = 2.62 (P = 0.009)									
Test for subgroup differences: Chi² = 4015.06, df = 2 (P < 0.00001), I² = 100.0%									

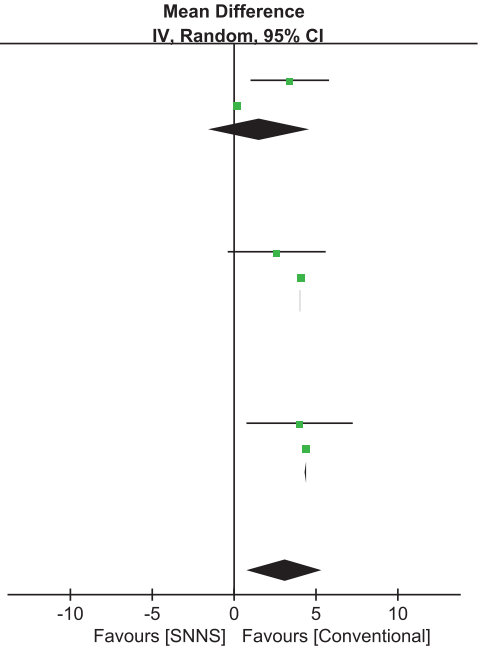


Fig. 9. Forest plots for comparison between the sentinel node navigation surgery vs. conventional surgery in observational studies. (A) Overall survival. (B) Body weight: percentages compared to preoperative body weight.
SE = standard error; SNNS = sentinel node navigation surgery; SD = standard deviation; IV = interval variable; CI = confidence interval.

There are still controversies over technical issue for sentinel node such as type of tracer, detection method, and practical pathological examination method. It should be noted that the SENORITA trial had a fastidious protocol including dual tracer composed of radioactive isotope (Technetium-99 m) and indocyanine green, sentinel basin dissection instead of pick-up biopsy, intraoperative frozen examination for sentinel LNs with 2 mm-interval cutting and 4-direction resection margins, and cytokeratin IHC for permanent histological evaluation. Therefore, SNNS should be performed under a strict protocol including indication criteria, detection method, and follow-up plan, and treatment decision should be made after sufficient discussion with the patient regarding the possibility of metachronous cancer and rescue surgery. Under these conditions, SNNS could be a treatment option for EGC in aspects of better nutritional outcomes and QOL.

KQ 19: Can LDG show comparable surgical and survival outcomes compared to ODG in the treatment of early or locally advanced gastric cancer?

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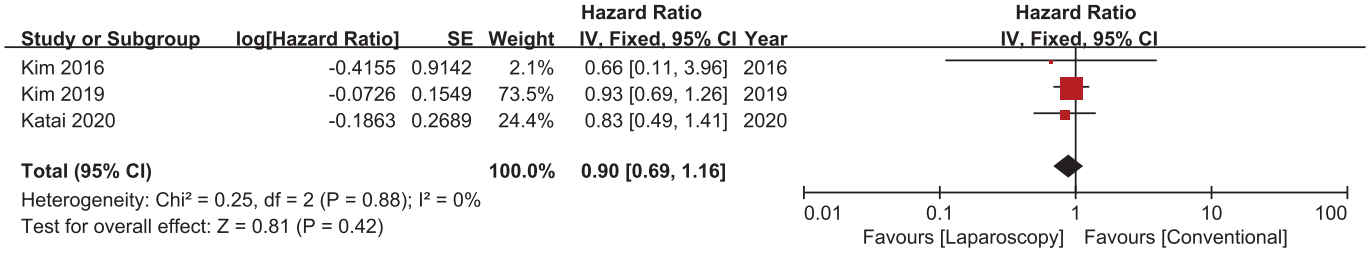
Statement 19-1: LDG is recommended for c-Stage I gastric cancer in terms of better short-term surgical outcomes and comparable long-term survival compared to ODG (evidence: high, recommendation: strong for).

Since the first clinical trial was reported in the early 2000s several pivotal trials comparing LDG and ODG for early or locally advanced gastric cancer have been published thus far [309].

Three prospective RCTs (KLASS-01, COACT 0301, JCOG0912) were conducted to evaluate the noninferiority of LDG for EGC [147,310,311]. Our meta-analysis demonstrated longer operation times of laparoscopic surgery (P<0.01) but better surgical outcomes, such as less operative blood loss (P<0.001), fewer postoperative complications (P<0.001), or reduced hospital stay (P<0.001), compared with ODG (**Fig. 10**). The long-term survival in LDG was not inferior to that of patients in the ODG group in all 3 trials (HR, 0.90; CI, 0.69 to 1.16; P=0.42) [298,299,310].

A



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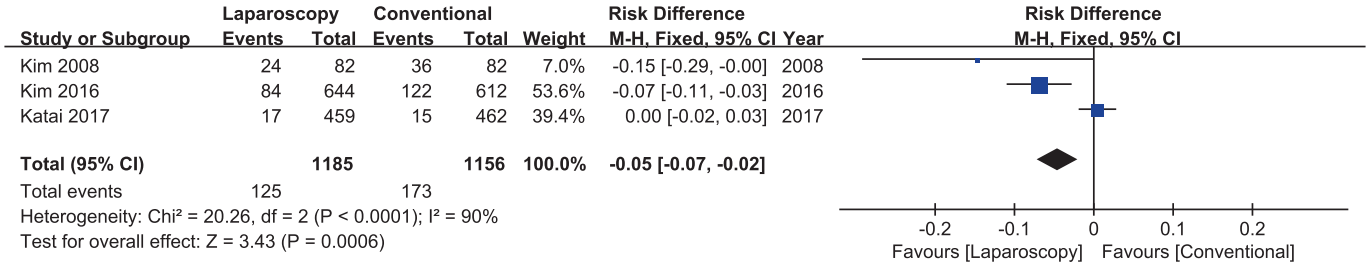

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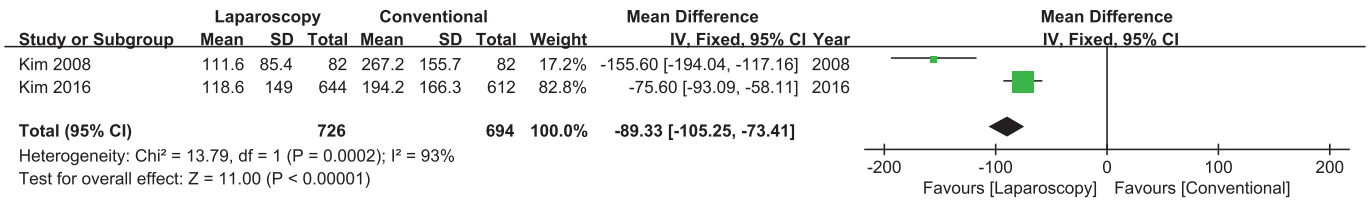

Fig. 10. Forest plots for comparisons between laparoscopic and open (conventional) distal gastrectomy in c-Stage I gastric cancer. (A)Overall survival. (B) Complications. (C) Intraoperative blood loss.
SE = standard error; SD = standard deviation; IV = interval variable; CI = confidence interval.

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Statement 19-2: LDG as well as ODG can be recommended for locally advanced gastric cancers for comparable survival outcomes (evidence: high, recommendation: strong for).

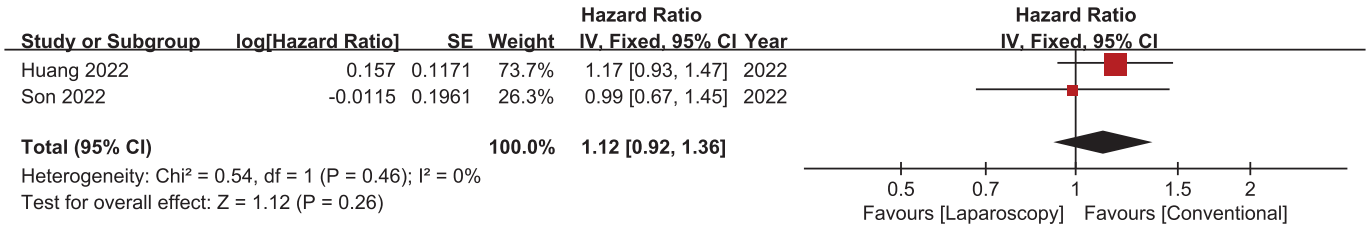
For AGC, 2 RCTs (KLASS-02, CLASS-01) were included in the meta-analysis [312,313]. In both trials, preoperatively diagnosed AGC cases of cT2-T4a were enrolled. The KLASS-02 trials included cases with no LN metastasis or limited metastasis to the left gastric artery or perigastric LNs, while the CLASS-01 trial recruited all cN0-3 cases.

The KLASS-02 study reported a lower complication rate in the laparoscopic group than in the open group (6.5% vs. 11.0%, P=0.01). The 5-year OS of LDG (88.9%) was not inferior to that of ODG (88.7%, P=0.30) [314,315] (**Fig. 11**).

The CLASS-01 study reported no significant difference in postoperative complications between LDG and ODG (15.2% vs. 12.9%, P=0.285) and noninferior 5-year OS (LDG, 72.6% vs. ODG, 76.3%, P=0.19) [316].

In our meta-analysis, LDG showed shorter hospital time (P=0.02), less intraoperative blood loss (P<0.01), and similar postoperative complications (P=0.27) but a longer operation time (P<0.01). For long-term outcomes, LDG was not inferior to ODG in the 5-year survival rate (HR, 1.12; CI, 0.92 to 1.36; P=0.26).

A



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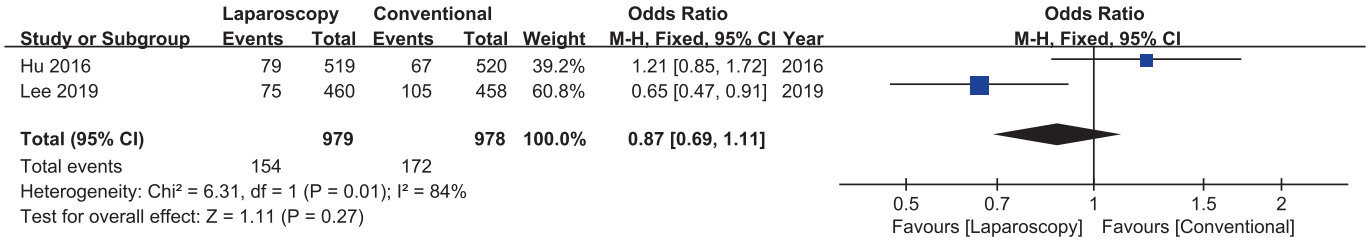

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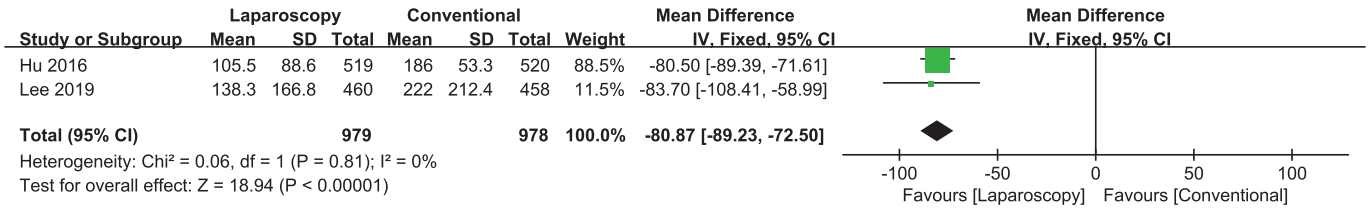

Fig. 11. Forest plots for comparisons between laparoscopic and open (conventional) distal gastrectomy in cT2-4a gastric cancer. (A) Overall survival. (B) Complications. (C) Intraoperative blood loss. (D) Operation time. (E) Hospital stay.
SE = standard error; SD = standard deviation; IV = interval variable; CI = confidence interval.

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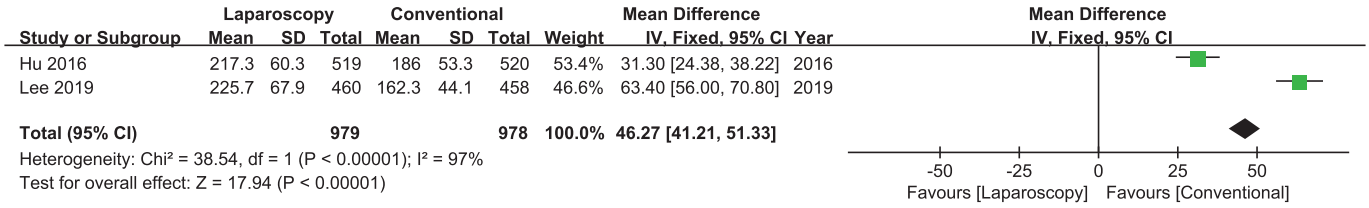

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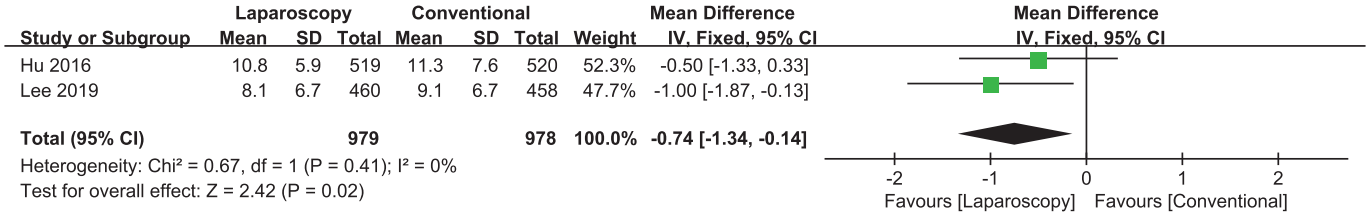

Fig. 11. (Continued) Forest plots for comparisons between laparoscopic and open (conventional) distal gastrectomy in cT2-4a gastric cancer. (A) Overall survival. (B) Complications. (C) Intraoperative blood loss. (D) Operation time. (E) Hospital stay.
SE = standard error; SD = standard deviation; IV = interval variable; CI = confidence interval.

LDG can be considered an optimal treatment option for AGC as well as ODG. However, since far advanced cases, such as cT4b cancer where multivisceral resection may be needed, were excluded from the studies, the application of LDG should not be interpreted beyond indications [317].

KQ 20: Can RG show better surgical, survival and economical outcome than LG for treating gastric cancer?

Statement 20: RG can be considered a treatment option for gastric cancer in terms of noninferior survival and fewer complications than LG. However, disadvantages such as additional cost and longer operation time should also be considered for patient shared decision-making (evidence: moderate, recommendation: conditional for).

RG has some technical advantages compared to LG, including surgeon-controlled vision, tremor filter and ergonomic wrist motion instruments [318,319]. Two RCTs and 8 retrospective studies were included in our systematic review to investigate RG vs. LG.

In our meta-analysis of 2 RCTs, RG was associated with fewer postoperative complications than LG (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.003). The incidence of pancreatic fistula was not different in the RCT (P=0.20) and non-RCT (P=0.58) analyses. The reoperation rate (P=0.25) and hospital stay (P=0.11) showed no difference. RG was associated with a longer operation time (mean difference [MD], 47.04 minutes; 95% CI, 30.67 to 63.41; P<0.01) compared to LG (**Fig. 12**).

In retrospective studies, there were no differences in either the 5-year OS (HR, 0.84; 95% CI, 0.57 to 1.24; P=0.38) or the 5-year RFS rate (HR, 0.98; 95% CI, 0.71 to 1.34, P=0.88) between the groups.

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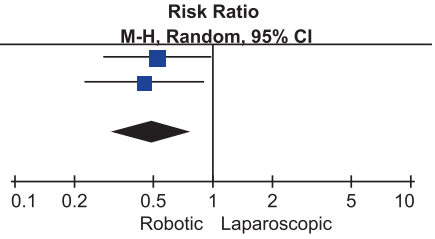
A

Study or Subgroup	Robotic Events	Robotic Total	Laparoscopic Events	Laparoscopic Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Huang 2021	13	141	25	142	55.1%	0.52 [0.28, 0.98]	2021
Ojima 2021	10	113	23	117	44.9%	0.45 [0.22, 0.90]	2021
Total (95% CI)		**254**		**259**	**100.0%**	**0.49 [0.31, 0.78]**	
Total events	23		48				

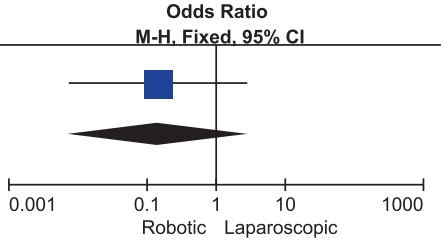
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)



B

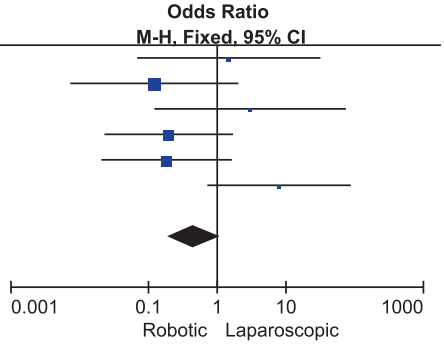
Study or Subgroup	Robotic Events	Robotic Total	Laparoscopic Events	Laparoscopic Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Huang 2021	0	141	0	142		Not estimable	2021
Ojima 2021	0	113	3	117	100.0%	0.14 [0.01, 2.82]	2021
Total (95% CI)		**254**		**259**	**100.0%**	**0.14 [0.01, 2.82]**	
Total events	0		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)



Study or Subgroup	Robotic Events	Robotic Total	Laparoscopic Events	Laparoscopic Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Noshiro 2014	0	21	2	160	3.3%	1.47 [0.07, 31.75]	2014
Suda 2015	0	88	19	438	36.5%	0.12 [0.01, 2.03]	2015
Kim 2016	1	185	0	185	2.8%	3.02 [0.12, 74.52]	2016
Ye 2020	1	285	5	285	27.8%	0.20 [0.02, 1.70]	2020
Isobe 2021	1	50	5	50	27.4%	0.18 [0.02, 1.63]	2021
Shin 2021	2	421	1	1663	2.2%	7.93 [0.72, 87.70]	2021
Total (95% CI)		**1050**		**2781**	**100.0%**	**0.46 [0.19, 1.10]**	
Total events	5		32				

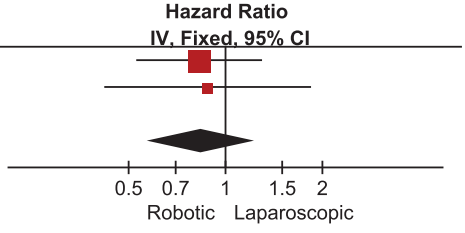
Heterogeneity: Chi² = 9.40, df = 5 (P = 0.09); I² = 47%
Test for overall effect: Z = 1.75 (P = 0.08)



C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Obama 2018	-0.1887	0.2296	73.0%	0.83 [0.53, 1.30]	2018
Shin 2021	-0.1278	0.3774	27.0%	0.88 [0.42, 1.84]	2021
Total (95% CI)			**100.0%**	**0.84 [0.57, 1.24]**	

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)



D

Study or Subgroup	Robotic Mean	Robotic SD	Robotic Total	Laparoscopic Mean	Laparoscopic SD	Laparoscopic Total	Weight	Mean Difference IV, Random, 95% CI	Year
Eom 2012	229.1	35.5	30	189.4	36.75	62	18.5%	39.70 [24.05, 55.35]	2012
Noshiro 2014	439	88	21	315	90	160	9.5%	124.00 [83.86, 164.14]	2014
Suda 2015	372	98	58	348	71.17	302	14.1%	24.00 [-2.47, 50.47]	2015
Kim 2016	248.4	40.1	87	230	55.8	288	20.4%	18.40 [7.79, 29.01]	2016
Ye 2020	186	12	285	147	9	285	22.3%	39.00 [37.26, 40.74]	2020
Isobe 2021	350	58.1	50	270.5	63.7	50	15.1%	79.50 [55.60, 103.40]	2021
Total (95% CI)			**531**			**1147**	**100.0%**	**47.04 [30.67, 63.41]**	

Heterogeneity: Tau² = 312.43; Chi² = 43.92, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.63 (P < 0.00001)

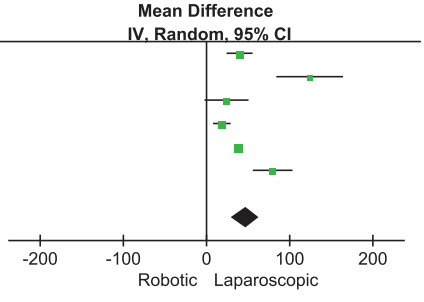


Fig. 12. Forest plots for comparisons between daVinci™ robot gastrectomy vs. laparoscopic gastrectomy. (A) Complications (RCTs). (B) Pancreatic fistula (RCTs and observational studies). (C) Overall survival (observational studies). (D) Operation time (observational studies).
SE = standard error; SD = standard deviation; IV = interval variable; CI = confidence interval; RCT = randomized controlled trial.

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In selected reports, the additional total hospital cost for RG ranged from $3,000 to $5,000 compared to LG [319,320].

Based on the current evidence, the guideline task force team decided the recommendation as "conditional for" because of noninferior perioperative and survival outcomes and fewer postoperative complications of RG compared to LG. Further investigation is required to identify the potential benefit of RG to justify longer operation time and higher cost, which should be discussed with the patient in the aspect of decision-making.

KQ 21: In patients with advanced gastric cancer, can PO show comparable survival, recurrence rates and complication rates compared to total omentectomy (TO)?

Statement 21: PO could be considered for advanced gastric cancer patients (evidence: low, recommendation: conditional for).

TO is regarded as a mandatory treatment for AGC without high-level evidence [107]. However, TO during LG is difficult and time-consuming [321]. PO is now widely adopted as a safe procedure for EGC based on excellent survival outcomes in randomized clinical trials in which PO was performed in the majority of cases; thus, we focused on its applicability to AGC in our meta-analysis [147,300].

In our meta-analysis, 5 retrospective studies were included to compare PO vs. TO [322-325]. Among all retrospective studies, 5 studies for meta-analysis regarding survival results were selected when propensity matching was performed to minimize selection bias. PO was not inferior to TO in relapse-free survival (RFS) (HR, 0.89; CI, 0.74 to 1.07; P=0.20) or OS (HR, 0.82; CI 0.67 to 1.00; P=0.06]. There was no difference in overall complications (P=0.10) or serious complications (P=0.92) between the procedures (**Fig. 13**).

Seven previous meta-analyses studied the oncologic feasibility of PO [326-330]. All the meta-analyses showed that PO was not inferior to TO regarding OS and relapse-free survival. Moreover, PO required less operation time and involved lower blood loss.

Although a significant proportion of patients with serosal invasion (T4a) were included in the studies, the working group of guidelines expressed concern about the possibly insufficient extent of resection in locally far advanced cancer, including cT4a cases and recommended cautious consideration in such cases while waiting for more confirmative results.

KQ 22: Can UDCA treatment reduce gallstone formation in patients after gastrectomy for gastric cancer treatment?

Statement 22: Administration of UDCA for one year can be recommended to reduce gallstone formation after gastrectomy (evidence: moderate, recommendation: conditional for).

Gallstone formation is known as one of the long-term complications following gastrectomy [207]. Denervation of the vagus nerve, obesity, rapid weight loss and TG precipitate the incidence and severity of gallstone [206,331,332]. Since prophylactic UDCA showed positive

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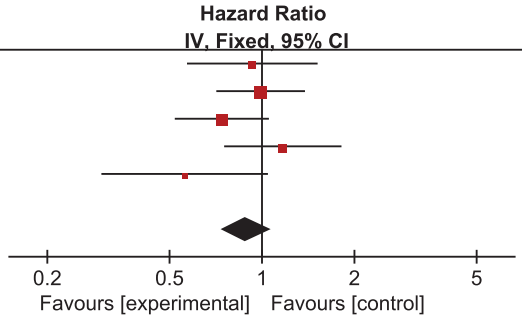
A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Hasegawa 2013	-0.0726	0.2498	14.4%	0.93 [0.57, 1.52]	2013
Ri 2020	-0.0101	0.1696	31.2%	0.99 [0.71, 1.38]	2020
Seo 2021	-0.3011	0.18	27.7%	0.74 [0.52, 1.05]	2021
Lee 2022(SNUBH)	0.1561	0.2244	17.8%	1.17 [0.75, 1.81]	2022
LeeKim2022	-0.5798	0.3185	8.9%	0.56 [0.30, 1.05]	2022
Total (95% CI)			**100.0%**	**0.89 [0.74, 1.07]**	

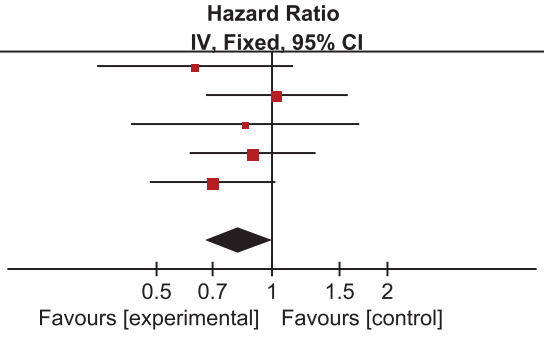
Heterogeneity: Chi² = 5.07, df = 4 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.27 (P = 0.20)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Hasegawa 2013	-0.462	0.2999	11.8%	0.63 [0.35, 1.13]
Lee 2022(SNUBH)	0.0296	0.2171	22.5%	1.03 [0.67, 1.58]
LeeKim2022	-0.1613	0.3495	8.7%	0.85 [0.43, 1.69]
Ri 2020	-0.1165	0.1927	28.5%	0.89 [0.61, 1.30]
Seo 2021	-0.3567	0.1925	28.6%	0.70 [0.48, 1.02]
Total (95% CI)			**100.0%**	**0.82 [0.67, 1.00]**

Heterogeneity: Chi² = 2.74, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)



C

Study or Subgroup	PO Events	PO Total	TO Events	TO Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hasegawa 2013	37	98	40	98	12.6%	0.88 [0.50, 1.56]
Lee 2022(SNUBH)	26	248	27	174	14.4%	0.64 [0.36, 1.14]
LeeKim2022	18	107	25	107	10.5%	0.66 [0.34, 1.30]
Ri 2020	18	263	29	263	13.7%	0.59 [0.32, 1.10]
Sakimura 2020	18	73	13	73	5.0%	1.51 [0.68, 3.37]
Seo 2021	70	225	67	225	23.4%	1.06 [0.71, 1.59]
Young 2020	182	381	48	90	20.5%	0.80 [0.51, 1.27]
Total (95% CI)		**1395**		**1030**	**100.0%**	**0.84 [0.68, 1.03]**
Total events	369		249			

Heterogeneity: Chi² = 6.04, df = 6 (P = 0.42); I² = 1%
Test for overall effect: Z = 1.65 (P = 0.10)

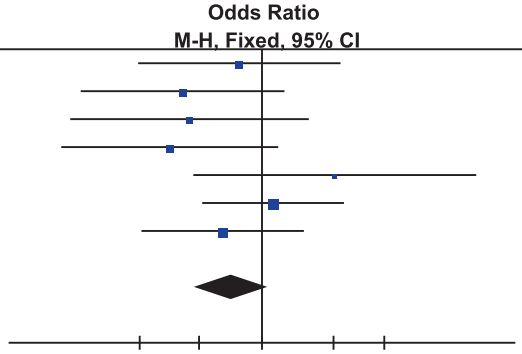


Fig. 13. Forest plots for comparisons between PO (experimental) vs. TO (control) in advanced gastric cancer in observational studies. (A) Overall survival (propensity score matched). (B) Relapse-free survival (propensity score matched). (C) Complications.
PO = partial omentectomy; TO = total omentectomy; SE = standard error; IV = interval variable; CI = confidence interval.

effect on reducing gallstones after bariatric surgery, UDCA can be as effective in gastric cancer patients.

One RCT studied the use of prophylactic UDCA after gastrectomy in patients with gastric cancer [208]. Patients were randomized into 3 groups: placebo, 300 mg or 600 mg group, and UDCA was administered as allocated for one year. Compared to placebo, 300 mg (odds ratio [OR], 0.27; 95% CI, 0.12 to 0.62; P<0.002) and 600 mg (OR, 0.20; 95% CI, 0.08 to 0.50; P<0.001) UDCA showed decreased gallstone formation. Daily 300 mg seems to be sufficient because the protective effect did not differ between 300 mg and 600 mg.

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Considering that there are some risk factors for gallstone formation and that the PPG or DG with preservation of the hepatic branch of vagus nerve rarely experiences gallstone formation, further studies may answer to question of who may especially benefit from UDCA prophylaxis, as well as long-term effect over 1 year postoperatively.

SYSTEMIC THERAPY

Adjuvant chemotherapy

KQ 23: Could adjuvant chemotherapy improve survival compared to surgery only in patients with pathological stage II or III disease who undergo curative gastrectomy?

Statement 23: Adjuvant chemotherapy (S-1 or XELOX) is recommended in patients with pathological stage II or III gastric cancer (evidence: high, recommendation: strong for).

Surgical resection with D2 LN dissection is the standard treatment for gastric cancer. However, the prognosis is usually poor in AGC [333,334]. Two randomized phase III trials conducted in Asia showed significant survival benefits for adjuvant chemotherapy over observation after curative gastrectomy with D2 LN dissection in patients with gastric cancer [335,336]. In the adjuvant chemotherapy trial of S-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) who underwent D2 gastrectomy received adjuvant S-1 for 1 year or were observed after surgery [336,337]. The 3-year DFS rates were 72.2% in the S-1 group and 59.6% in the surgery-only group (HR, 0.62; 95% CI, 0.50 to 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 to 0.87; P=0.003). In the capecitabine and oxaliplatin 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 [338]) who underwent D2 gastrectomy received either XELOX for 6 months or were observed [335]. The 3-year DFS rates were 74% in the chemotherapy and surgery groups and 59% in the surgery-only group (HR, 0.56; 95% CI, 0.44 to 0.72; P<0.001). The 5-year follow-up data in these 2 studies confirmed these findings [339,340]. In our present meta-analysis, adjuvant chemotherapy significantly improved OS and DFS compared to surgery alone (OS: HR, 0.66, 95% CI, 0.56 to 0.78; DFS: HR, 0.62, 95% CI, 0.54 to 0.72; P<0.001) (**Fig. 14**). Based on these results, both chemotherapy regimens (S-1 or XELOX) are currently accepted as standard treatments in patients with pathological stage II or III gastric cancer after curative gastrectomy. It should be noted that there is currently no evidence to support the use of adjuvant chemotherapy for patients who fall into the category of stage IB by the AJCC 6th edition but stage IIA by the AJCC 7th and 8th editions (pT1N2M0 and pT3N0M0) [341].

Although the survival benefit of adjuvant S-1 for 1 year in gastric cancer patients was demonstrated, the optimal duration of adjuvant S-1 for gastric cancer was unclear. In the randomized phase III noninferiority trial (OPAS-1) in Japan, 590 patients with stage II (excluding T1N2–3 and T3N0) gastric cancer (by Japanese classification, 3rd English edition) who underwent gastrectomy with D2 LN dissection (with D1 plus dissection being allowed for clinical stage IA) received 8 courses (12 months) or 4 courses (6 months) of S-1 [18,342]. At the first planned interim analysis, this study was terminated early because the HR for DFS of the 4-course group compared with the 8-course group exceeded 1.37 and met the

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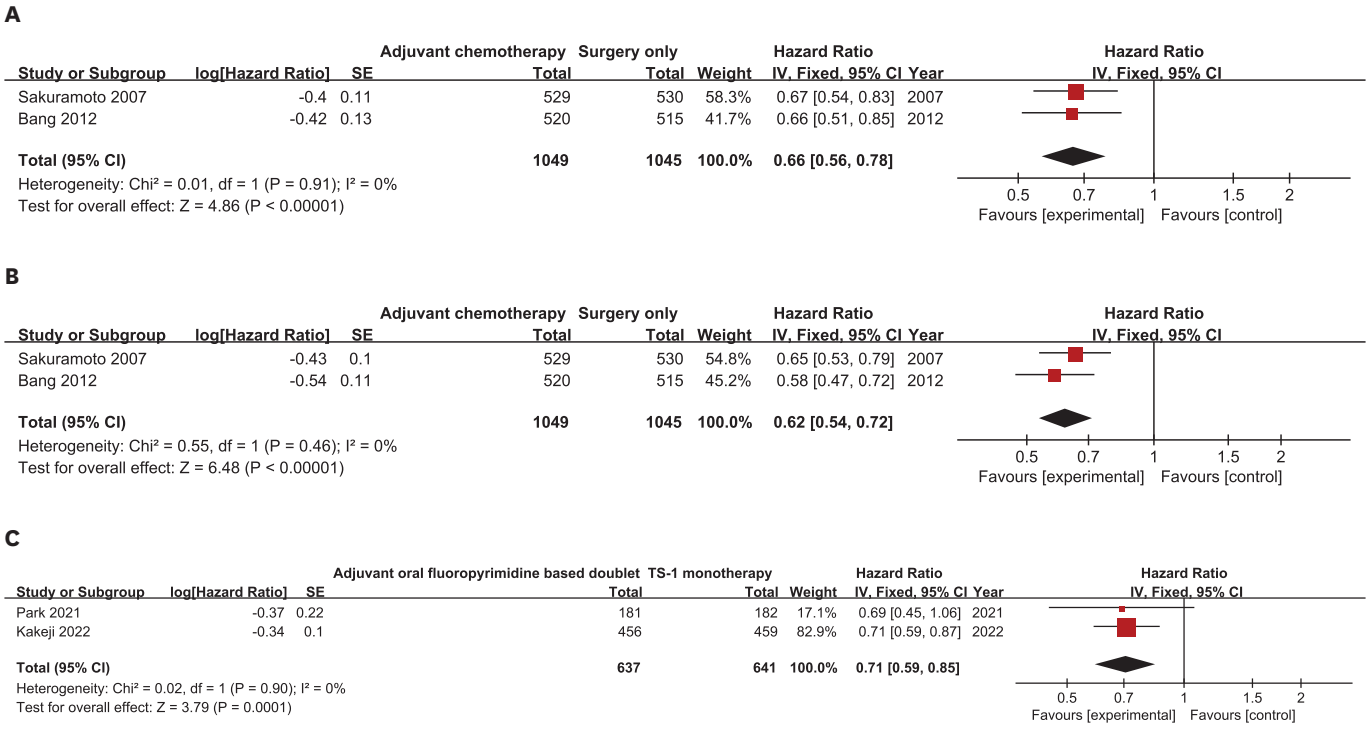

Fig. 14. Forest plots for comparisons between adjuvant chemotherapy vs. surgery only and doublet vs. S1 monotherapy. (A) Overall survival for adjuvant chemotherapy (experimental) vs. surgery only (control). (B) Disease-free survival for adjuvant chemotherapy (experimental) vs. surgery only (control). (C) Disease-free survival for oral fluoropyrimidine-based doublet (experimental) vs. S1 monotherapy (control).
SE = standard error; IV = interval variable; CI = confidence interval.

prespecified criteria for early termination. The 3-year DFS rate was 93.1% for the 8-course group and 89.8% for the 4-course group (HR, 1.84; 95% CI, 0.93 to 3.6; noninferiority margin for HR, 1.37), and the 3-year OS rates were 96.1% and 92.6%, respectively (HR, 3.37; 95% CI, 1.23 to 9.19). Therefore, S-1 for 1 year remains the standard adjuvant treatment for pathological stage II gastric cancer.

Despite the benefit of adjuvant S-1 for gastric cancer, as shown through the ACTS-GC trial, there was a question about a lack of efficacy in advanced stages [336,340]. In the randomized phase III trial (JACCRO GC-07), adjuvant chemotherapy of the S-1 plus docetaxel group was associated with survival benefits compared to the S-1 group in patients with stage III gastric cancer (by Japanese classification, 3rd English edition) who underwent D2 gastrectomy [18,343]. The 3-year DFS rates were 67.7% in the S-1 plus docetaxel group and 57.4% in the S-1 group (HR, 0.72; 95% CI, 0.59 to 0.87; P<0.001), and the 3-year OS rates were 77.7% and 71.2%, respectively (HR, 0.74; 95% CI, 0.60 to 0.92; P=0.008). The randomized phase III trial (ARTIST-2) for stage II or III gastric cancer with positive LNs (by AJCC 7th edition [344]) also showed the superiority of S-1 plus oxaliplatin (SOX; 74.3%) to S-1 monotherapy (64.8%) for the 3-year DFS rate (HR, 0.69; 95% CI, 0.41 to 0.99; P=0.042) [345]. When comparing the SOX and S-1 arms, the 3-year DFS rates were 74.3% and 64.8%, respectively (HR, 0.69; 95% CI, 0.41 to 0.99; P=0.042) [345]. In the present meta-analysis including JACCRO GC-07 and ARTIST-2, adjuvant oral pyrimidine-based doublet regimens improved DFS compared to S-1 monotherapy (HR, 0.71; 95% CI, 0.59 to 0.85, P=0.0001). Furthermore, the subgroup analysis of the CLASSIC trial [335] showed that the efficacy of XELOX was maintained even in a more advanced stage, which was not observed in the ACTS-GC trial. According to these

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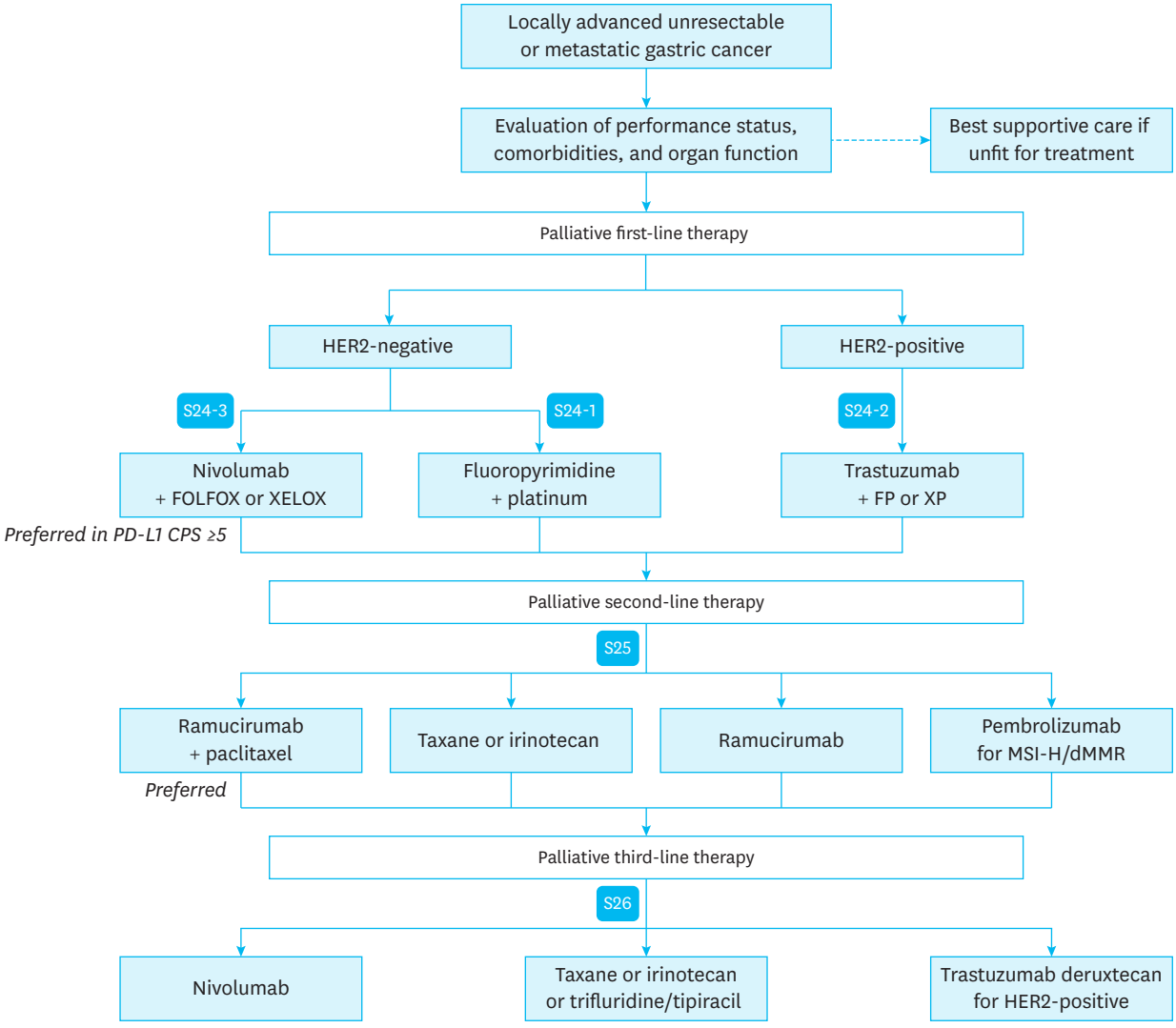
results, oral pyrimidine-based doublet regimens can be a more favorable treatment option than S-1 alone for pathological stage II with positive LN or stage III gastric cancer.

Palliative systemic therapy (Flowchart 6)



Flowchart 6. Treatment guideline for palliative systemic therapy.
HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death-ligand 1; CPS = combined positive score; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; XELOX = capecitabine and oxaliplatin; FP = 5-fluorouracil and cisplatin; XP = capecitabine plus cisplatin; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient.

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KQ 24: Could palliative first-line systemic therapy improve survival in patients with locally advanced unresectable or metastatic gastric cancer?

Statement 24-1: Palliative first-line platinum/fluoropyrimidine-based chemotherapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer (evidence: moderate, recommendation: strong for).

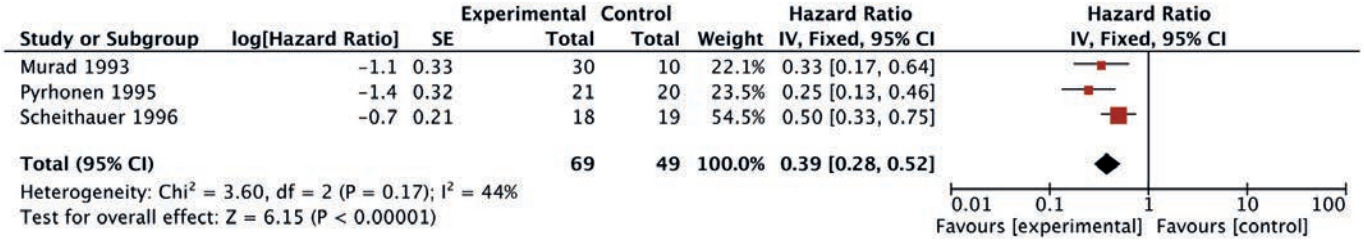
Chemotherapy vs. best supportive care

Several cytotoxic chemotherapeutic agents, including fluoropyrimidine, platinum, taxane, anthracycline, and irinotecan, have been shown to be active against AGC. In our present meta-analysis, chemotherapy significantly improved OS compared to best supportive care (HR, 0.39; 95% CI, 0.28 to 0.52, P<0.001) (**Fig. 15**). In a Cochrane meta-analysis, the efficacy of combination chemotherapy showed a statistically significant survival benefit over single-agent chemotherapy (HR, 0.82; 95% CI, 0.75 to 0.9; median survival, 8.3 vs. 6.7 months) [346].

Fluoropyrimidines: oral vs. intravenous

With oral fluoropyrimidines, patients can avoid complications and inconveniences associated with venous access for infusional 5-FU. Randomized phase III studies have demonstrated that the oral fluoropyrimidines capecitabine [347-349] and S-1 [350,351] are noninferior to infusional 5-FU. Therefore, oral fluoropyrimidines (capecitabine or S-1) are safe and have been widely used as an alternative to infusional 5-FU for combinations with platinum compounds in patients with AGC. Recently, TAS-118 was developed as a new oral drug containing S-1 and leucovorin. The SOLAR Phase III trial demonstrated clinically significant improvement in OS with manageable toxicity when TAS-118 plus oxaliplatin was administered compared to S-1 plus cisplatin in Asian patients with AGC (median OS, 16 vs. 15.1 months; HR, 0.83; 95% CI, 0.69 to 0.99; P=0.039) [352].

A



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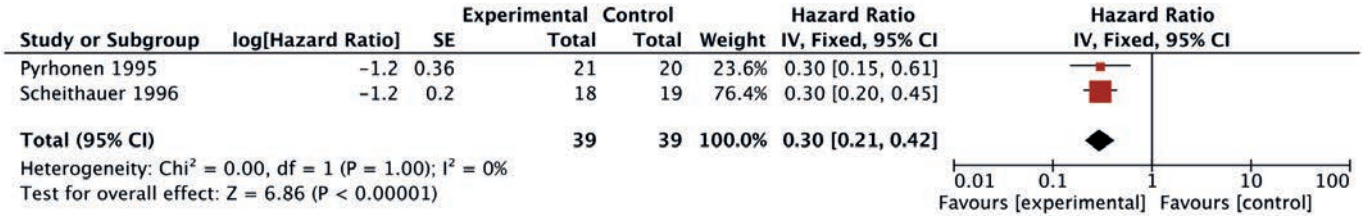

Fig. 15. Forest plots for comparisons between palliative first-line chemotherapy (experimental) vs. best supportive care (control). (A) Overall survival. (B) Progression-free survival.
SE = standard error; IV = interval variable; CI = confidence interval.

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Platinum (cisplatin vs. oxaliplatin)

Regarding avoidance of cisplatin-associated toxicity, several studies [347,353-355] have shown noninferior or better efficacy and less toxicity with oxaliplatin than with cisplatin in patients with AGC. Therefore, oxaliplatin was preferred over cisplatin with a favorable safety profile.

Triplet vs. doublet combination

The triplet regimens have been investigated, and it remains unclear whether triplet or doublet regimens are better. The phase III V325 trial showed that docetaxel, cisplatin, and FU improved survival outcomes compared with cisplatin and FU (median OS, 9.2 vs. 8.6 months) but also markedly increased severe toxicities, including hematological and gastrointestinal toxicity [356]. The JCOG1013 phase III trial showed that modified docetaxel, S-1, and cisplatin did not improve OS but increased toxicity, such as neutropenia and leukopenia, compared to S-1 and cisplatin in Japanese patients with AGC [357]. Triplet combinations can be considered in selected patients.

Statement 24-2: Palliative first-line trastuzumab combined with capecitabine or FU plus cisplatin is recommended in patients with HER2 IHC 3+ or IHC 2+ and ISH-positive advanced gastric cancer (evidence: high, recommendation: strong for).

The Trastuzumab for Gastric Cancer (ToGA) phase III trial demonstrated the efficacy of trastuzumab, which is a monoclonal antibody against HER2, plus fluoropyrimidine/cisplatin as the first-line treatment in patients with HER2-positive AGC [112]. The OS was improved with the addition of trastuzumab to capecitabine or FU/cisplatin (median, 13.8 vs. 11.1 months; HR, 0.74; 95% CI, 0.60 to 0.91; P<0.01). The survival benefit from trastuzumab was more pronounced in patients with IHC 3+ or IHC 2+ and FISH+ (median OS, 16 vs. 11.8 months; HR, 0.65; 95% CI, 0.51 to 0.83; P<0.01).

In terms of dual blockade of HER2, the JACOB phase III trial evaluated the efficacy of pertuzumab (which is a monoclonal antibody interfering with HER2 heterodimerization with other EGFR family members), plus trastuzumab and chemotherapy as first-line therapy compared to trastuzumab and chemotherapy [358]. Although PFS increased with the addition of pertuzumab to trastuzumab plus fluoropyrimidine/cisplatin (median, 8.5 vs. 7.2 months; HR, 0.73; 95% CI, 0.62 to 0.85; P<0.01), there was no statistically significant improvement in OS for the primary endpoint in patients with HER2-positive AGC (median, 17.5 vs. 14.2; HR, 0.84; 95% CI, 0.71 to 1.00, P=0.057). Lapatinib is a small-molecule tyrosine kinase inhibitor of EGFR and HER2. In the LOGiC phase III trial, lapatinib plus capecitabine and oxaliplatin as first-line therapy did not significantly improve OS (median, 12.2 vs. 10.5 months; HR, 0.91; 95% CI, 0.73 to 1.12; P=0.349) compared to capecitabine and oxaliplatin in HER2-amplified AGC. Therefore, trastuzumab plus capecitabine or FU/cisplatin is recommended in patients with HER2-positive AGC [359].

Several targets, including EGFR [360,361], vascular endothelial growth factor/receptor-2 (VEGF/R2) [362,363], hepatocyte growth factor receptor/MET [364-366], and matrix metalloproteinase [367], have been evaluated as first-line treatments for AGC. However, none of these targeting agents demonstrated significant OS benefits in phase III trials.

Statement 24-3: Palliative first-line nivolumab combined with capecitabine or FU plus oxaliplatin (XELOX or FOLFOX) is recommended in patients with PD-L1 CPS ≥5 and HER2-negative advanced gastric cancer (evidence: high, recommendation: strong for).

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Nivolumab is a PD-1 inhibitor and the first successful ICI used in combination with platinum/fluoropyrimidine chemotherapy as first-line treatment in AGC. The CheckMate 649 global phase III trial demonstrated significant improvement in OS with the addition of nivolumab to capecitabine or FU/oxaliplatin in patients with PD-L1 CPS ≥5 and HER2-negative AGC (median OS, 14.1 vs. 11.1 months; HR, 0.71; 95% CI, 0.59 to 0.86; P<0.01) [125]. PD-L1 IHC was performed using a Dako PD-L1 IHC 28-8 pharmDx assay (Dako, Santa Clara, CA, USA). In the ATTRACTION-4 phase III trial, nivolumab plus capecitabine or S-1/oxaliplatin as the first-line treatment significantly improved PFS (10.5 vs. 8.3 months; HR, 0.68; 95% CI, 0.51 to 0.90; P<0.01) but not OS in Asian patients with HER2-negative AGC regardless of PD-L1 status [368]. In the KEYNOTE-062 global phase III trial, pembrolizumab, another PD-1 inhibitor, plus chemotherapy (FU or capecitabine and cisplatin) was not superior to chemotherapy for OS in patients with PD-L1 CPS ≥1 and HER2-negative AGC (median OS, 12.5 vs. 11.1 months; HR, 0.85; 95% CI, 0.70 to 1.03; P=0.05) [369]. PD-L1 IHC was performed using a PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). In our meta-analysis including CheckMate 649, ATTRACTION-4, and KEYNOTE-062, palliative first-line systemic therapy with anti-PD1 improved OS compared to chemotherapy alone (HR, 0.82; 95% CI, 0.74 to 0.92, P=0.004) (**Fig. 16**). The KEYNOTE-859 phase III trial evaluating pembrolizumab in combination with chemotherapy (FU/cisplatin or capecitabine/oxaliplatin) as first-line treatment for patients with HER2-negative AGC is ongoing [367]. The KEYNOTE-859 trial will use a different chemotherapy backbone than the KEYNOTE-062 trial and a modified statistical design to better identify the underlying clinical benefit. Based on the aforementioned results, nivolumab plus XELOX or FOLFOX is currently approved as the first-line treatment in Korea.

There are some issues according to different PD-L1 IHC assays and a lack of evidence for the addition of ICIs for low PD-L1-expressing AGC. A recent analysis of pivotal trials of ICI with chemotherapy showed that there were no significant benefits from nivolumab on OS in patients with PD-L1 CPS 1-4 from the CheckMate 649 trial [370]. Therefore, nivolumab combined with XELOX or FOLFOX is recommended in patients with PD-L1 CPS ≥5 and HER2-negative AGC. Meanwhile, the KEYNOTE-811 phase III trial evaluating pembrolizumab plus trastuzumab and chemotherapy for HER2-positive AGC is ongoing with promising tumor reduction (objective response rate, 74.4% vs. 51.9%; P<0.01) [367]. The dual blockade of PD-1/PD-L1 and HER2 needs to be further investigated in the future.

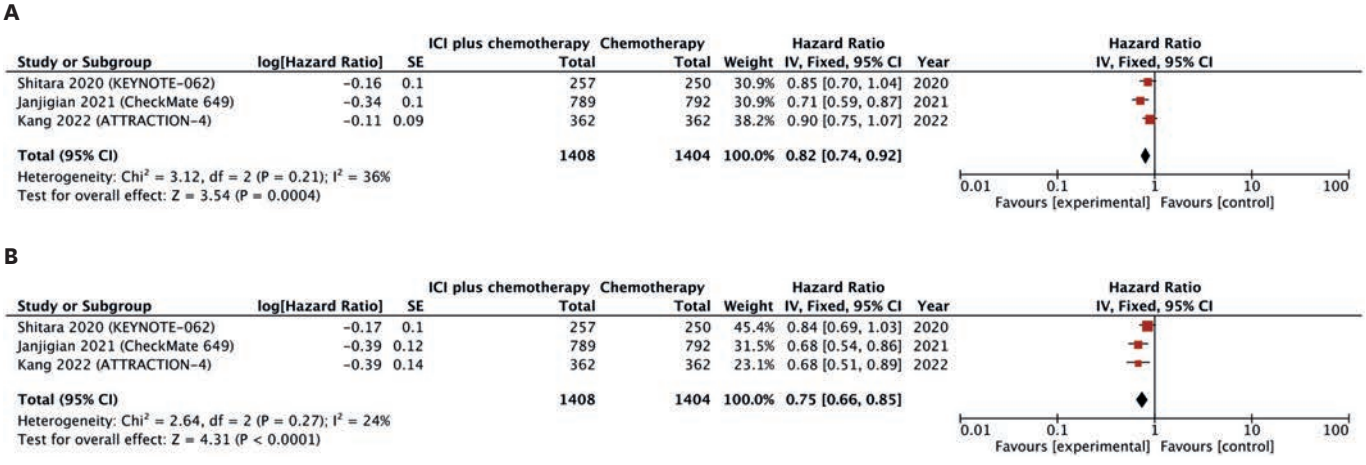

Fig. 16. Forest plots for comparisons between palliative first-line chemotherapy with immune checkpoint inhibitor (experimental) vs. chemotherapy (control).
(A) Overall survival. (B) Progression-free survival.
ICI = immune checkpoint inhibitor; SE = standard error; IV = interval variable; CI = confidence interval.

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KQ 25: Could palliative second-line systemic therapy improve survival in patients with locally advanced unresectable or metastatic gastric cancer who progress after or fail palliative first-line systemic therapy?

Statement 25: Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer. Ramucirumab plus paclitaxel is preferentially recommended, but other agents could also be considered (evidence: high, recommendation: strong for).

RCTs and previous meta-analyses 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 [371-374]. In the present meta-analysis, second-line systemic therapy significantly improved OS compared to best supportive care (HR, 0.69; 95% CI, 0.59 to 0.82, P<0.001) (**Fig. 17**). Weekly paclitaxel treatment was associated with similar survival outcomes to biweekly irinotecan treatment in previous phase III trials [375,376]. Meanwhile, ramucirumab monotherapy, involving a monoclonal antibody that targets VEGFR2, significantly improved OS and PFS compared to placebo in the REGARD trial [377]. Furthermore, the addition of ramucirumab to weekly paclitaxel significantly prolonged OS (median, 9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.678 to 0.962; P=0.017) and PFS (median, 4.4 vs. 2.9 months, HR, 0.635; 95% CI, 0.536 to 0.752; P<0.0001) compared to paclitaxel plus placebo in the RAINBOW trial [378].

Based on previous trials, ramucirumab in combination with paclitaxel is recommended as the most preferred second-line treatment. Other agents, including irinotecan, docetaxel, paclitaxel, or ramucirumab monotherapy, can also be considered second-line options if not previously administered in the first-line treatment.

Pembrolizumab, an anti-PD-1 antibody, failed to provide a significant survival benefit compared to paclitaxel [379-381], whereas it was efficacious in patients with solid tumors

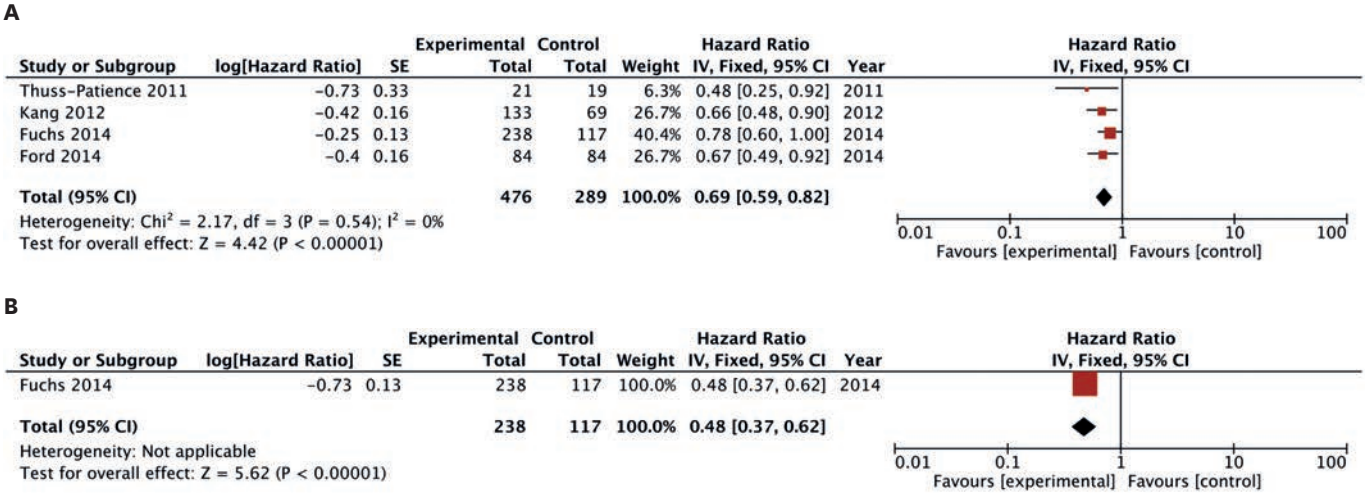

Fig. 17. Forest plots for comparisons between palliative second-line systemic therapy (experimental) vs. best supportive care or placebo (control). (A) Overall survival. (B) Progression-free survival.
SE = standard error; IV = interval variable; CI = confidence interval.

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characterized as MSI-H, dMMR, or TMB-H (≥10 mutations/megabase) [382,383]. In Korea, pembrolizumab was approved in patients with several inoperable or metastatic solid tumors, including gastric cancer with MSI-H or dMMR, who have progressed following prior treatment and who have no satisfactory alternative treatment options.

Trastuzumab deruxtecan, a HER2-directed antibody and topoisomerase inhibitor conjugate, was recently approved by the Food and Drug Administration for the treatment of patients with HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen. The phase 2 trial of trastuzumab deruxtecan as second-line treatment provided clinical evidence only in the Western population [384]. Therefore, further phase 3 trials comparing the survival outcomes of trastuzumab deruxtecan to ramucirumab plus paclitaxel, the current standard second-line treatment, are needed in Asian patients with HER2-positive gastric cancer.

KQ 26: Could palliative third-line systemic therapy improve survival in patients with locally advanced unresectable or metastatic gastric cancer who progress after 2 previous palliative systemic therapies?

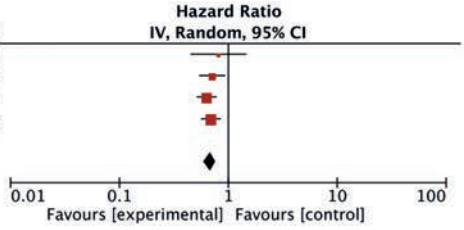
Statement 26: Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer (evidence: high, recommendation: strong for).

For patients with preserved performance status who have disease progression after second-line systemic therapy, palliative third-line systemic therapy is recommended. In our present meta-analysis, third-line systemic therapy significantly improved OS compared to best supportive care (HR, 0.68; 95% CI, 0.60 to 0.77, P<0.001) (**Fig. 18**).

A

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Kang 2012	−0.2107	0.3002	33	21	4.7%	0.81 [0.45, 1.46]	2012
Li 2016	−0.3425	0.1414	176	91	21.3%	0.71 [0.54, 0.94]	2016
Kang 2017	−0.462	0.1084	330	163	36.3%	0.63 [0.51, 0.78]	2017
Shitara 2018	−0.3711	0.1065	337	170	37.6%	0.69 [0.56, 0.85]	2018
Total (95% CI)			**876**	**445**	**100.0%**	**0.68 [0.60, 0.77]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.94$, df = 3 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 5.98 (P < 0.00001)



B

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Li 2016	−0.8119	0.1496	176	91	22.9%	0.44 [0.33, 0.60]	2016
Kang 2017	−0.5108	0.1086	330	163	36.8%	0.60 [0.48, 0.74]	2017
Shitara 2018	−0.5621	0.1016	337	170	40.3%	0.57 [0.47, 0.70]	2018
Total (95% CI)			**843**	**424**	**100.0%**	**0.55 [0.47, 0.64]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.81$, df = 2 (P = 0.25); $I^2 = 29\%$
Test for overall effect: Z = 7.50 (P < 0.00001)

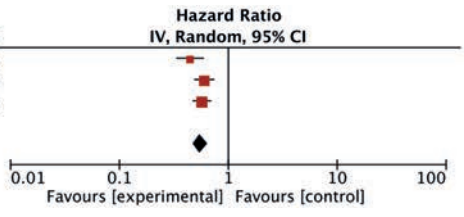


Fig. 18. Forest plots for comparisons between palliative third-line systemic therapy (experimental) vs. best supportive care (control). (A) Overall survival. (B) Progression-free survival.
SE = standard error; IV = interval variable; CI = confidence interval.

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Cytotoxic agents can be recommended as palliative third-line therapy. Docetaxel and irinotecan, as a randomized phase III trial (median OS, 5.3 vs. 3.8 months; HR, 0.66; 95% CI, 0.49 to 0.89; P=0.007) [371]. Several phase II and retrospective studies investigating taxane- or irinotecan-based chemotherapy as third-line treatment also showed consistent results [385-387]. In a randomized phase III trial, trifluridine/tipiracil significantly improved OS vs. placebo (median OS, 5.7 vs. 3.6 months; HR, 0.69; 95% CI, 0.56 to 0.85; P=0.00058) in AGC patients who had received at least 2 previous systemic treatments [388].

Nivolumab showed a survival benefit over placebo in heavily treated patients who received 2 or more previous systemic therapies in a randomized phase 3 ATTRACTION-2 trial (median OS, 5.3 vs. 4.1 months; HR, 0.63; 95% CI, 0.51 to 0.78; P<0.0001) [389]. Two-year updated data from the ATTRACTION-2 trial confirmed the long-term survival benefit of nivolumab regardless of PD-L1 expression status [390]. Based on the ATTRACTION-2 trial, nivolumab is recommended as a palliative third-line therapy for AGC patients who are naïve to ICI therapy.

In the phase 2 DESTINY-Gastric01 trial conducted in Japan and South Korea, trastuzumab deruxtecan was compared to the physician's choice of irinotecan or paclitaxel in patients with HER2-positive gastric cancer who received at least 2 previous palliative systemic treatments including trastuzumab [391]. In this trial, trastuzumab deruxtecan was associated with significant improvements in the objective response rate (51% vs. 14%, P<0.001) and OS (median OS, 12.5 vs. 8.4 months; HR, 0.59; 95% CI, 0.39 to 0.88; P=0.01) compared to the physician's choice of irinotecan or paclitaxel. The positive results from the DESTINY-Gastric01 trial led to approval for prescription of trastuzumab deruxtecan in patients with HER2-positive gastric or GEJ adenocarcinoma who received a prior trastuzumab-based regimen as second-line or later treatment in the US and third-line or later treatment in Korea.

Neoadjuvant chemotherapy (NCT)

KQ 27: Could NCT as part of perioperative chemotherapy improve survival in patients with resectable locally advanced gastric cancer compared to upfront surgery followed by adjuvant chemotherapy?

Statement 27: NCT as part of perioperative chemotherapy can be considered for patients with resectable locally advanced gastric cancer (evidence: high, recommendation: conditional for).

Adjuvant chemotherapy following D2 gastrectomy has been the standard treatment for pathological stage II or III gastric cancer in Asia. However, survival outcomes with adjuvant chemotherapy are still disappointing, especially for those with stage III disease. Moreover, adjuvant chemotherapy is often delayed following surgical resection due to surgical morbidities, and chemotherapy after gastrectomy is associated with more frequent adverse events. In this regard, NCT may be considered for the advantages of intensifying chemotherapy and commencing chemotherapy at an earlier time when patients are more medically fit.

Three prospective randomized phase 3 clinical trials have evaluated the clinical benefit of NCT as part of perioperative chemotherapy in Asia. The PRODIGY study performed in Korea investigated whether neoadjuvant docetaxel, oxaliplatin, and S-1 (DOS) followed by

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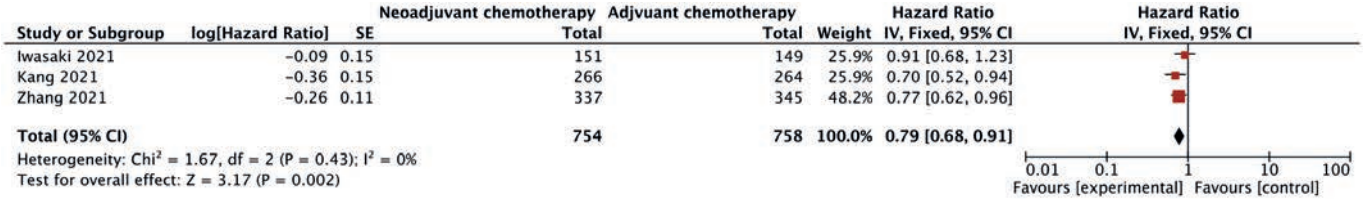

Fig. 19. Forest plot for a comparison of disease-free survival between neoadjuvant chemotherapy as part of perioperative chemotherapy (experimental) vs. adjuvant chemotherapy only (control).
SE = standard error; IV = interval variable; CI = confidence interval.

surgery and adjuvant S-1 could improve outcomes vs. upfront surgery followed by adjuvant S-1 in locally AGC patients with clinical T2/3 N+ or cT4 N-any disease [392]. NCT led to a higher rate of complete resection (R0 resection) than upfront surgery (95% vs. 84%, P<0.001). Neoadjuvant DOS followed by surgery and adjuvant S-1 significantly improved PFS compared to upfront surgery followed by adjuvant S-1 (adjusted HR, 0.70; 95% CI, 0.52 to 0.95; stratified log-rank P=0.023). The RESOLVE study evaluated perioperative SOX vs. upfront surgery followed by adjuvant CapOx [393]. Perioperative SOX significantly improved DFS compared with adjuvant XELOX in patients (HR, 0.77; 95% CI, 0.61 to 0.97; P=0.027). The JCOG0501 study evaluated the efficacy of neoadjuvant S-1 plus cisplatin followed by gastrectomy and adjuvant chemotherapy vs. upfront surgery and adjuvant S-1 in patients with Borrmann type 4 or large (≥8 cm) type 3 gastric cancer [394]. However, NCT with S-1 plus cisplatin failed to demonstrate a survival benefit. In our meta-analysis of Asian neoadjuvant trials, NCT showed clinical benefit compared to upfront surgery (DFS: HR, 0.79; 95% CI, 0.68 to 0.91) (**Fig. 19**).

On the other hand, it should be noted that the efficacy and safety of perioperative chemotherapy regimens used in Western countries including FU plus leucovorin, oxaliplatin, and docetaxel (FLOT) have never been reported in Asian populations.

Because NCT is commenced based on clinical radiological staging, which can be frequently inaccurate, inadvertent inclusion of early-stage disease may be an issue. In the exploratory analysis of the PRODIGY study, radiological criteria involving cT4 disease exhibited a lower percentage of pathologic stage I disease (5%) while preserving sensitivity for pathologic stage III disease (80.1%) [395]. Accordingly, RR reduction by NCT was most prominent in patients meeting this cT4N-any criterion, suggesting that patients meeting this criterion may be preferentially considered for NCT.

Considering its clinical benefit for DFS, NCT as part of perioperative chemotherapy can be considered one of the viable therapeutic options for patients with resectable locally advanced gastric cancer in Korea. The clinical decision to proceed with NCT should be made based on a careful discussion considering various factors, including the clinical stage as well as potential advantages and limitations of NCT over upfront surgery (either followed by adjuvant chemotherapy or not according to the pathological stage). A multidisciplinary team approach is recommended to make such treatment decisions. Long-term follow-up studies reporting OS outcomes with NCT, which may further help to make clinical decisions, are awaited.

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RADIATION THERAPY

Adjuvant radiation therapy

KQ 28: Could adjuvant CRT improve treatment outcomes compared to adjuvant chemotherapy alone in patients with pathological stage II or III disease who have undergone curative gastrectomy?

Statement 28: Adjuvant CRT is not usually recommended in patients with pathological stage II or III gastric cancer who have undergone curative gastrectomy (evidence: high, recommendation: conditional against).

A total of 6 RCTs were included in the present meta-analysis, including 2 recent RCTs published after the Korean Practice Guideline for Gastric Cancer 2018: An Evidence-based, Multidisciplinary Approach [345,396-399]. The target volume of radiation therapy was generally similar in these trials, including the tumor bed, anastomotic site and/or stump, and regional LN stations.

In the meta-analysis, the addition of adjuvant CRT reduced locoregional recurrence compared to chemotherapy alone (HR, 0.62; 95% CI, 0.48 to 0.81; P=0.0004) with no significant difference in grade 3 or higher toxicities (HR, 0.85; 95% CI, 0.63 to 1.13; P=0.26). Adjuvant CRT showed superior outcomes compared to adjuvant chemotherapy alone in terms of DFS (HR, 0.85; 95% CI, 0.713 to 0.98; P=0.03). However, when compared to platinum-based combination chemotherapy, there was no benefit in terms of DFS (HR, 0.91; 95% CI, 0.78 to 1.07, P=0.24) and OS (HR, 1.03; 95% CI, 0.87 to 1.23; P=0.70) (**Fig. 20**).

Based on these studies, the addition of adjuvant CRT is not usually recommended in gastric cancer patients after complete resection with D2 lymphadenectomy. Further prospective trials should be focus on identifying potential candidates who might benefit from adjuvant CRT.

Neoadjuvant radiation therapy

KQ 29: Could neoadjuvant CRT improve treatment outcomes compared to NCT alone in patients with locally advanced gastric cancer?

Statement 29: The evidence for adding radiation to NCT is not conclusive in patients with locally advanced gastric cancer (evidence: moderate, recommendation: investigational).

Neoadjuvant chemoradiation (NCRT) is mainly studied for cancer of the esophagus, GEJ, and/or gastric cardia, where obtaining a complete R0 resection is challenging, and thus, there is a higher probability of locoregional relapse. The MAGIC trial showed that perioperative chemotherapy significantly improved OS over surgery alone for distal esophageal and gastric cardia adenocarcinoma [400]. Studies have focused on determining whether adding radiation therapy to NCT would have a benefit for gastric cancer. Two RCTs have been conducted, and 1 RCT is ongoing to compare the outcomes of NCRT vs. NCT alone in resectable cancer of the GEJ or stomach [401-405].

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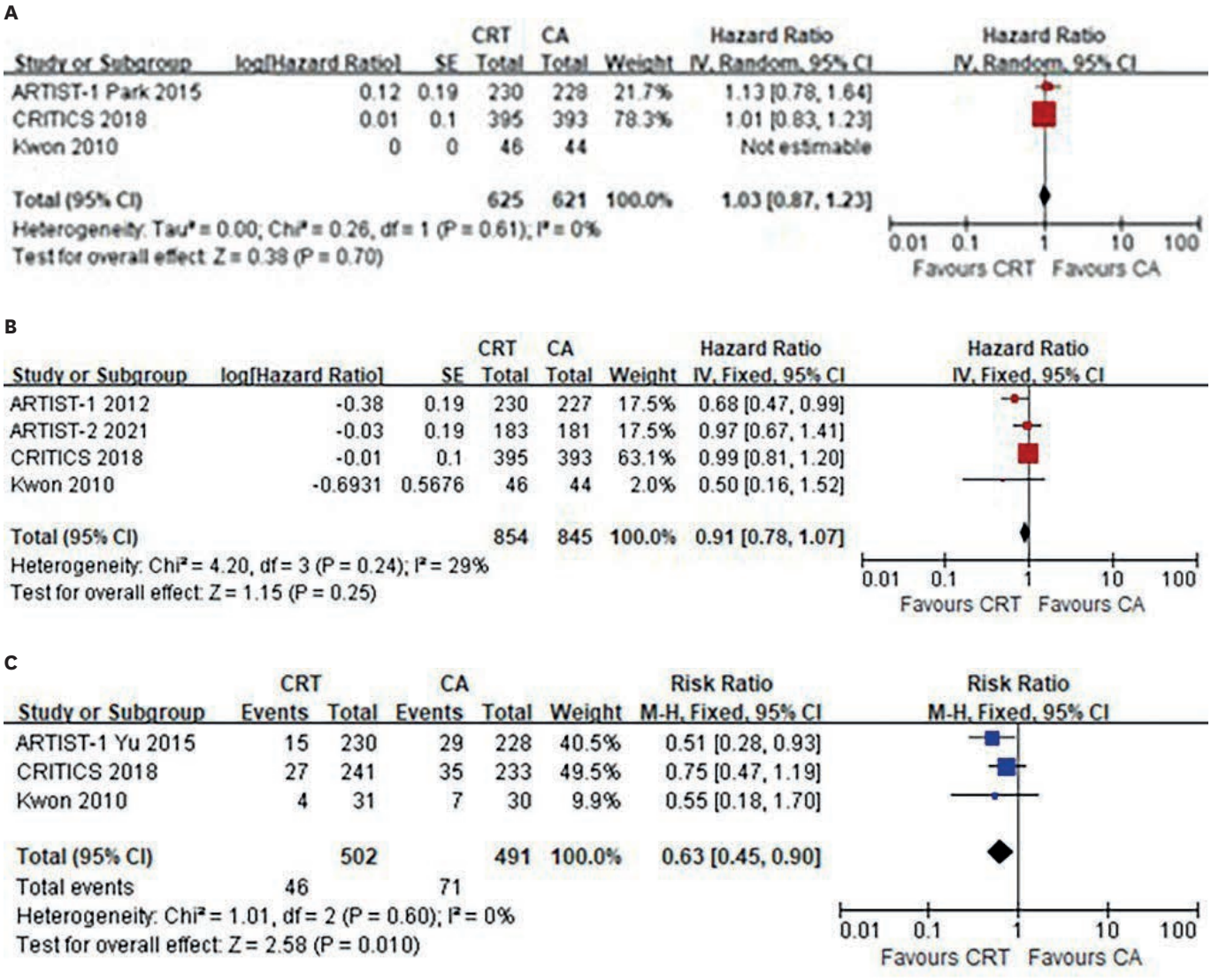

Fig. 20. Forest plots for comparison between adjuvant concurrent CRT vs. adjuvant platinum-based combination CA. (A) Overall survival. (B) Disease-free survival. (C) Locoregional recurrence.
CRT = chemoradiation therapy; CA = chemotherapy alone; SE = standard error; IV = interval variable; CI = confidence interval.

Final treatment outcomes were reported in the POET trial and the NeoRes [401,403]. In the pooled analysis, the pathologic complete remission rate (23.6% in NCRT vs. 6.3% in NCT) and pathologic N0 rate (69.9% in NCRT vs. 45.7% in NCT) were significantly improved in the NCRT group. Local PFS was reported only in the POET trial and showed a significant improvement with NCRT in the long-term follow-up data (HR, 0.37; 95% CI, 0.16 to 0.85). However, the improved pathologic responses did not lead to a significant improvement in OS (HR, 0.85; 95% CI, 0.63 to 1.15). In addition, there were no significant differences in the R0 resection rate (74% in NCRT vs. 66% in NCT). PFS was reported only in the NeoRes trial, and there was no significant difference in the 3-year PFS rate (44% in NCRT vs. 44% in NCT). An interim analysis of the TOPGEAR study showed no significant difference in adverse events or surgical complications [402]. In the pooled analysis of the TOPGEAR and NeoRes studies, there was no significant difference in severe gastrointestinal toxicity (15.3% in NCRT vs. 13.2% in NCT) (**Fig. 21**).

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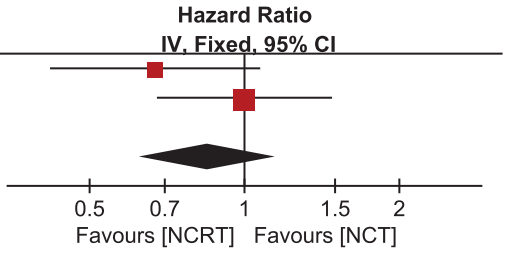
A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Stahl 2009	-0.4	0.24	41.0%	0.67 [0.42, 1.07]	2009
Klevebro 2015	0	0.2	59.0%	1.00 [0.68, 1.48]	2015
Total (95% CI)			**100.0%**	**0.85 [0.63, 1.15]**	

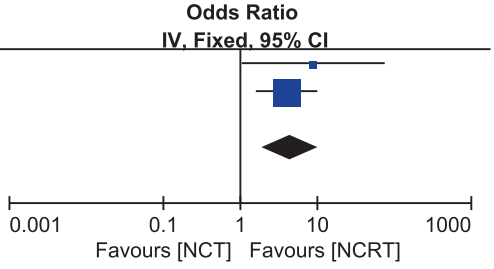
Heterogeneity: Chi² = 1.64, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 1.07 (P = 0.29)



B

Study or Subgroup	NCRT Events	NCRT Total	NCT Events	NCT Total	Weight	Odds Ratio IV, Fixed, 95% CI	Year
Stahl 2009	7	45	1	49	15.6%	8.84 [1.04, 75.01]	2009
Klevebro 2015	22	78	7	78	84.4%	3.98 [1.59, 10.00]	2015
Total (95% CI)		**123**		**127**	**100.0%**	**4.51 [1.94, 10.51]**	
Total events	29		8				

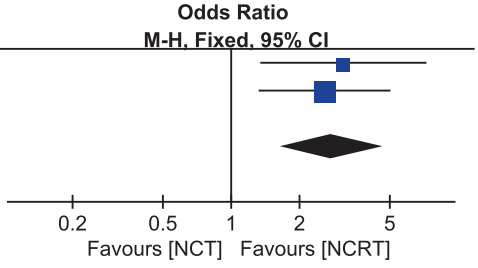
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.50 (P = 0.0005)



C

Study or Subgroup	NCRT Events	NCRT Total	NCT Events	NCT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Stahl 2009	29	45	18	49	36.3%	3.12 [1.34, 7.25]	2009
Klevebro 2015	57	78	40	78	63.7%	2.58 [1.32, 5.03]	2015
Total (95% CI)		**123**		**127**	**100.0%**	**2.78 [1.64, 4.69]**	
Total events	86		58				

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.82 (P = 0.0001)



D

Study or Subgroup	NCRT Events	NCRT Total	NCT Events	NCT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Stahl 2009	43	60	41	59	45.4%	1.11 [0.50, 2.44]	2009
Klevebro 2015	68	90	58	91	54.6%	1.76 [0.92, 3.35]	2015
Total (95% CI)		**150**		**150**	**100.0%**	**1.46 [0.89, 2.41]**	
Total events	111		99				

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)

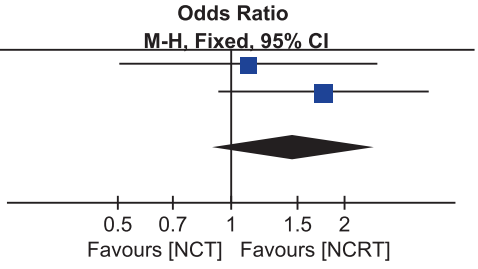


Fig. 21. Forest plots for comparisons between NCRT compared to NCT. (A) Overall survival. (B) Pathologic complete response. (C) Pathologic complete nodal regression. (D) R0 resection.
NCRT = neoadjuvant chemoradiation; NCT = neoadjuvant chemotherapy; SE = standard error; CI = confidence interval.

Notably, the mentioned studies were performed mainly in patients with esophageal and/or GEJ cancer. GEJ cancer is common in Western countries, and most studies evaluating the efficacy of NCRT for gastric cancer (mainly GEJ cancer) have also been performed in Western populations. In addition, in the NeoRes trial, some patients with squamous cell carcinoma at the esophagus were included. Evidence is still insufficient, and further prospective studies including Asian populations and nonjunction cancers are needed for better evidence.

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TREATMENT FOR FAR ADVANCED GASTRIC CANCER

KQ 30: Can endoscopic stent insertion as a palliative therapy improve oral intake with comparable complication rate for malignant GOO compared to surgical bypass?

Statement 30: In patients with GOO caused by unresectable gastric cancer, either ES or surgical GJ for palliative treatment can be performed. The decision should be based on a multidisciplinary assessment of patients' performance status, projected clinical course, and preferences (evidence: low, recommendation: conditional for).

In patients with advanced or metastatic gastric cancer, GOO commonly appears as a symptom, causing nausea, vomiting, dehydration, and malnutrition and leading to marked deteriorations in patients' QOL. Given that radical surgery is not indicated in patients with incurable gastric cancer, palliative treatment is required to relieve symptoms of GOO and restore the ability to tolerate an oral diet.

Surgical GJ and ES are palliative treatments for GOO caused by unresectable gastric cancer. GJ is the standard palliative treatment for GOO and adequately relieves symptoms of GOO. However, early major complications and procedure-related mortality have been reported to be substantial [406,407]. ES is increasingly being performed for malignant GOO. With a shorter procedure time, faster resumption of oral intake, and shorter duration of hospital stay than GJ, ES presents an effective and less invasive therapeutic option for the palliative treatment of GOO [406,407]. Nevertheless, compared with GJ, a higher rate of complications, reintervention, and recurrent obstruction has also been reported [406,407].

In this clinical guideline, we compared the outcomes of ES with GJ by conducting a meta-analysis. Our literature search identified 1,637 articles, and a total of 15 studies were finally selected through the literature selection process [186,408-420]. These studies were included in the final table of evidence, i.e., 12 observational studies in addition to 3 RCTs. Of the 15 studies, 5 were Korean [186,413,416-418]. A total of 818 patients received ES, and 468 patients underwent GJ. The overall certainty for outcome results reported by the RCTs (low) and the observational studies (very low) was downgraded because of the small number of events and because of bias due to confounding and selection of participants. Regarding procedure outcomes, technical success (OR, 1.33; 95% CI, 0.37 to 4.73; P=0.66) and clinical success (OR, 0.68; 95% CI, 0.41 to 1.13; P=0.14) were not significantly different between the ES and GJ groups (**Fig. 22A and B**). There was no significant difference in procedure-related mortality (OR, 0.64; 95% CI, 0.26 to 1.63; P=0.35) (**Fig. 22C**). Regarding postoperative outcomes, patients in the ES group had faster resumption of oral intake (MD, −3.94 days; 95% CI, −4.01 to −3.88; P<0.001) and a shorter duration of hospital stay (MD, −6.56 days; 95% CI, −7.20 to −5.92; P<0.001) (**Fig. 23A and B**). The rate of minor complications was not significantly different between the 2 groups (OR, 0.52; 95% CI, 0.25 to 1.10; P=0.09) (**Fig. 23C**). However, the rates of major complications (OR, 1.81; 95% CI, 1.10 to 2.96; P=0.02) and reintervention (OR, 3.83; 95% CI, 2.40 to 6.12; P<0.001) were significantly higher in the ES group than in the GJ group (**Fig. 23D and E**). Moreover, ES was significantly associated with a shorter patency duration (MD, −4.97 months; 95% CI, −6.42 to −3.51; P<0.001) (**Fig. 23F**). However, OS was not significantly different between the ES and GJ groups (MD, 0.12 months; 95% CI, −0.48 to 0.72, P=0.69) (**Fig. 23G**).

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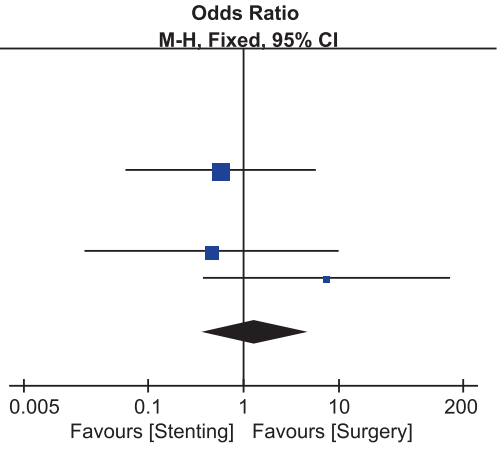
A

Study or Subgroup	Stenting Events	Stenting Total	Surgery Events	Surgery Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fiori 2004	9	9	9	9		Not estimable	2004
Maetani 2005	22	22	22	22		Not estimable	2005
Alonso-Larraga 2012	19	19	20	20		Not estimable	2012
Fiori 2013	9	9	9	9		Not estimable	2013
No 2013	69	72	40	41	52.3%	0.57 [0.06, 5.71]	2013
Park 2015	217	217	39	39		Not estimable	2015
Park 2015	0	0	0	0		Not estimable	2015
Fiori 2016	70	72	30	30	36.1%	0.46 [0.02, 9.92]	2016
Park 2016	74	74	70	73	11.6%	7.40 [0.38, 145.78]	2016
Total (95% CI)		**494**		**243**	**100.0%**	**1.33 [0.37, 4.73]**	
Total events	489		239				

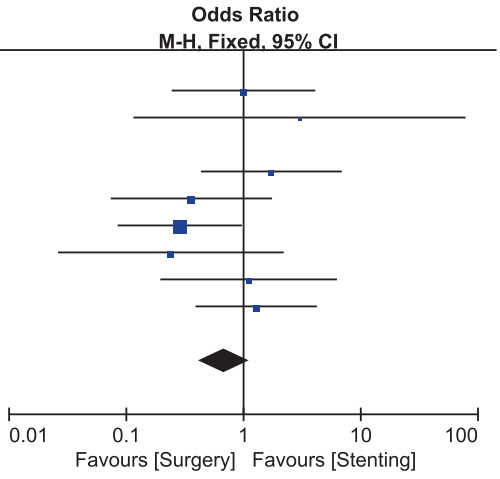
Heterogeneity: Chi² = 2.24, df = 2 (P = 0.33); I² = 11%
Test for overall effect: Z = 0.44 (P = 0.66)



B

Study or Subgroup	Stenting Events	Stenting Total	Surgery Events	Surgery Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fiori 2004	9	9	9	9		Not estimable	2004
Maetani 2005	17	22	17	22	10.1%	1.00 [0.24, 4.10]	2005
Alonso-Larraga 2012	19	19	19	20	1.2%	3.00 [0.11, 78.27]	2012
Fiori 2013	9	9	9	9		Not estimable	2013
Keranen 2013	44	50	17	21	7.5%	1.73 [0.43, 6.88]	2013
No 2013	63	72	39	41	16.2%	0.36 [0.07, 1.75]	2013
Park 2015	168	217	36	39	35.9%	0.29 [0.08, 0.97]	2015
Park 2016	70	74	73	74	10.3%	0.24 [0.03, 2.20]	2016
Jang 2017	95	99	43	45	6.2%	1.10 [0.19, 6.26]	2017
Haga 2020	25	31	26	34	12.5%	1.28 [0.39, 4.22]	2020
Total (95% CI)		**602**		**314**	**100.0%**	**0.68 [0.41, 1.13]**	
Total events	519		288				

Heterogeneity: Chi² = 7.62, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.48 (P = 0.14)



C

Study or Subgroup	Stenting Events	Stenting Total	Surgery Events	Surgery Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fiori 2004	0	9	0	9		Not estimable	2004
Maetani 2005	0	22	0	22		Not estimable	2005
No 2013	1	72	1	41	11.5%	0.56 [0.03, 9.25]	2013
Fiori 2013	0	9	0	9		Not estimable	2013
Keranen 2013	12	50	5	21	49.1%	1.01 [0.31, 3.34]	2013
Park 2015	1	217	0	39	7.7%	0.55 [0.02, 13.68]	2015
Fiori 2016	0	70	0	30		Not estimable	2016
Haga 2020	0	34	3	34	31.7%	0.13 [0.01, 2.63]	2020
Fiori 2021	0	13	0	14		Not estimable	2021
Total (95% CI)		**496**		**219**	**100.0%**	**0.64 [0.26, 1.63]**	
Total events	14		9				

Heterogeneity: Chi² = 1.65, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)

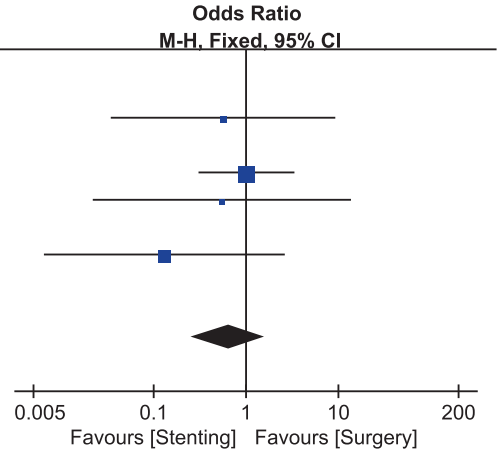


Fig. 22. Forest plot results of meta-analysis of procedure outcomes. (A) Technical success. (B) Clinical success. (C) Procedure related mortality.
CI = confidence interval.

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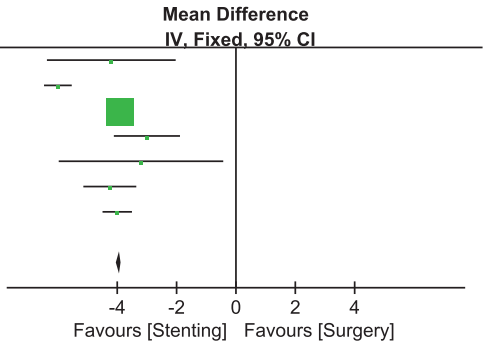
A

Study or Subgroup	Stenting Mean	SD	Total	Surgery Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Fiori 2004	2.1	1.05	9	6.3	3.15	9	0.1%	-4.20 [-6.37, -2.03]	2004
Maetani 2005	2	0.5	22	8	1	22	1.9%	-6.00 [-6.47, -5.53]	2005
Alonso-Larraga 2012	1	0.11	19	4.9	0.1	20	95.4%	-3.90 [-3.97, -3.83]	2012
No 2013	2	1.33	72	5	3.5	41	0.3%	-3.00 [-4.11, -1.89]	2013
Fiori 2013	3.1	3	9	6.3	3	9	0.1%	-3.20 [-5.97, -0.43]	2013
Keranen 2013	1	1.75	50	5.25	1.75	21	0.5%	-4.25 [-5.14, -3.36]	2013
Park 2015	1	1.17	217	5	1.5	39	1.7%	-4.00 [-4.50, -3.50]	2015
Total (95% CI)			**398**			**161**	**100.0%**	**-3.94 [-4.01, -3.88]**	

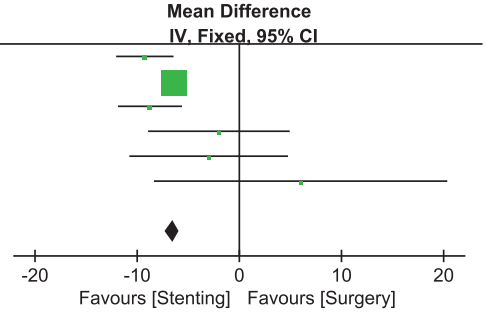
Heterogeneity: Chi² = 79.68, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 119.66 (P < 0.00001)



B

Study or Subgroup	Stenting Mean	SD	Total	Surgery Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Maetani 2005	19.13	4.63	22	28.38	4.88	22	5.2%	-9.25 [-12.06, -6.44]	2005
Alonso-Larraga 2012	1.4	0.85	19	7.8	1.28	20	88.9%	-6.40 [-7.08, -5.72]	2012
Keranen 2013	3	7	50	11.75	5.75	21	4.2%	-8.75 [-11.88, -5.62]	2013
No 2013	16	8.33	72	18	21.75	41	0.9%	-2.00 [-8.93, 4.93]	2013
Park 2015	6	8	217	9	24.5	39	0.7%	-3.00 [-10.76, 4.76]	2015
Haga 2020	27	35.5	34	21	23.75	34	0.2%	6.00 [-8.36, 20.36]	2020
Total (95% CI)			**414**			**177**	**100.0%**	**-6.56 [-7.20, -5.92]**	

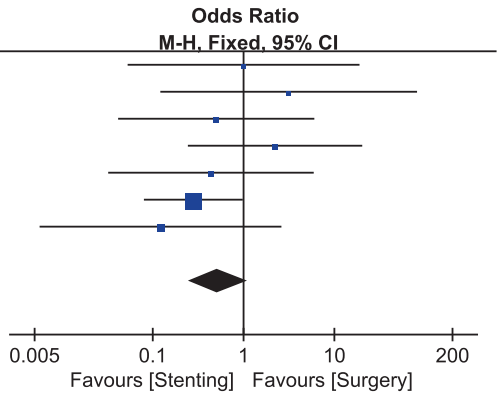
Heterogeneity: Chi² = 11.02, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 20.09 (P < 0.00001)



C

Study or Subgroup	Stenting Events	Total	Surgery Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fiori 2004	1	9	1	9	4.6%	1.00 [0.05, 18.91]	2004
Maetani 2005	1	22	0	22	2.4%	3.14 [0.12, 81.35]	2005
Alonso-Larraga 2012	1	19	2	20	9.7%	0.50 [0.04, 6.02]	2012
Keranen 2013	5	50	1	21	6.6%	2.22 [0.24, 20.27]	2013
Fiori 2013	1	9	2	9	9.3%	0.44 [0.03, 5.93]	2013
Min 2017	4	58	9	43	50.3%	0.28 [0.08, 0.98]	2017
Fiori 2021	0	13	3	14	17.0%	0.12 [0.01, 2.61]	2021
Total (95% CI)		**180**		**138**	**100.0%**	**0.52 [0.25, 1.10]**	
Total events	13		18				

Heterogeneity: Chi² = 4.84, df = 6 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)



D

Study or Subgroup	Stenting Events	Total	Surgery Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fiori 2004	1	9	1	9	3.7%	1.00 [0.05, 18.91]	2004
Maetani 2005	1	22	0	22	1.9%	3.14 [0.12, 81.35]	2005
Alonso-Larraga 2012	2	19	4	20	14.5%	0.47 [0.08, 2.93]	2012
Fiori 2013	4	9	1	9	2.3%	6.40 [0.55, 74.89]	2013
Keranen 2013	8	50	1	21	4.9%	3.81 [0.45, 32.57]	2013
Park 2016	24	74	19	74	53.3%	1.39 [0.68, 2.84]	2016
Min 2017	17	58	4	43	13.5%	4.04 [1.25, 13.08]	2017
Fiori 2021	0	13	1	14	5.8%	0.33 [0.01, 8.93]	2021
Total (95% CI)		**254**		**212**	**100.0%**	**1.81 [1.10, 2.96]**	
Total events	57		31				

Heterogeneity: Chi² = 7.17, df = 7 (P = 0.41); I² = 2%
Test for overall effect: Z = 2.35 (P = 0.02)

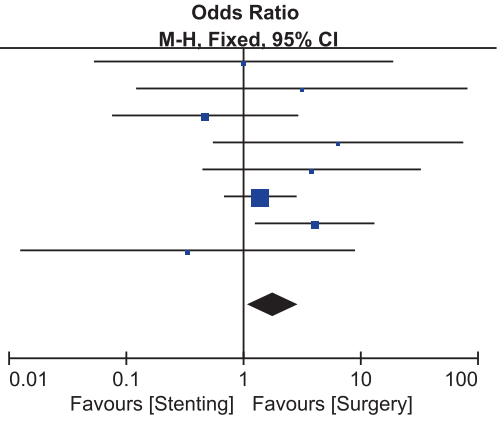


Fig. 23. Forest plot results of meta-analysis of postoperative outcomes. (A) Resumption of oral intake. (B) Duration of hospital stay. (C) Minor complications. (D) Major complications. (E) Re-intervention. (F) Patency duration. (G) Overall survival.
SD = standard deviation; IV = interval variable; CI = confidence interval.

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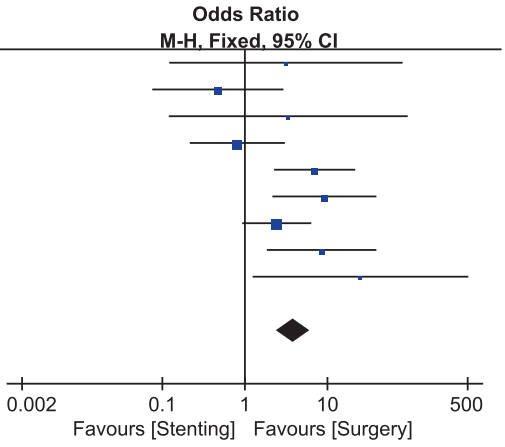
E

Study or Subgroup	Stenting Events	Stenting Total	Surgery Events	Surgery Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Maetani 2005	1	22	0	22	2.1%	3.14 [0.12, 81.35]	2005
Alonso-Larraga 2012	2	19	4	20	16.0%	0.47 [0.08, 2.93]	2012
Fiori 2013	1	9	0	9	2.0%	3.35 [0.12, 93.83]	2013
Keranen 2013	8	50	4	21	21.8%	0.81 [0.21, 3.05]	2013
No 2013	31	72	4	41	13.3%	6.99 [2.25, 21.70]	2013
Park 2015	72	217	2	39	10.4%	9.19 [2.15, 39.19]	2015
Park 2016	15	74	7	74	25.7%	2.43 [0.93, 6.37]	2016
Min 2017	17	58	2	43	7.5%	8.50 [1.84, 39.17]	2017
Fiori 2021	6	13	0	14	1.2%	25.13 [1.24, 509.12]	2021
Total (95% CI)		**534**		**283**	**100.0%**	**3.83 [2.40, 6.12]**	
Total events	153		23				

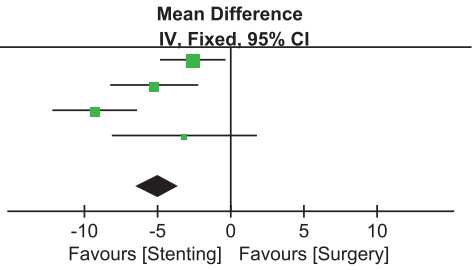
Heterogeneity: Chi² = 16.23, df = 8 (P = 0.04); I² = 51%
Test for overall effect: Z = 5.63 (P < 0.00001)



F

Study or Subgroup	Stenting Mean	Stenting SD	Stenting Total	Surgery Mean	Surgery SD	Surgery Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Keranen 2013	1.43	3.77	50	4.03	4.62	21	42.5%	-2.60 [-4.84, -0.36]	2013
No 2013	4.17	1.65	72	9.4	9.75	41	23.5%	-5.23 [-8.24, -2.22]	2013
Park 2015	3.1	3.76	217	12.4	9.08	39	25.4%	-9.30 [-12.19, -6.41]	2015
Park 2016	4.33	9.28	74	7.5	19.68	74	8.6%	-3.17 [-8.13, 1.79]	2016
Total (95% CI)			**413**			**175**	**100.0%**	**-4.97 [-6.42, -3.51]**	

Heterogeneity: Chi² = 13.46, df = 3 (P = 0.004); I² = 78%
Test for overall effect: Z = 6.68 (P < 0.00001)



G

Study or Subgroup	Stenting Mean	Stenting SD	Stenting Total	Surgery Mean	Surgery SD	Surgery Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Fiori 2013	8.6	15.42	9	9.43	16.57	9	0.2%	-0.83 [-15.62, 13.96]	2013
Keranen 2013	1.67	3.77	50	7.91	5.38	21	5.7%	-6.24 [-8.77, -3.71]	2013
No 2013	6.3	5.15	72	9.77	9.12	41	3.9%	-3.47 [-6.50, -0.44]	2013
Park 2016	5.83	9.59	217	6.87	9.09	39	3.7%	-1.04 [-4.17, 2.09]	2016
Haga 2020	7.8	3	34	4	2.05	33	24.1%	3.80 [2.57, 5.03]	2020
Fiori 2021	14.45	0.93	13	14.87	1.09	14	62.4%	-0.42 [-1.18, 0.34]	2021
Total (95% CI)			**395**			**157**	**100.0%**	**0.12 [-0.48, 0.72]**	

Heterogeneity: Chi² = 66.72, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 0.40 (P = 0.69)

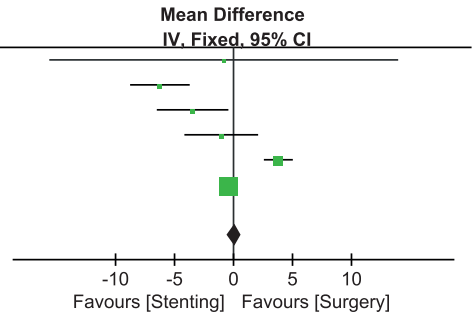


Fig. 23. (Continued) Forest plot results of meta-analysis of postoperative outcomes. (A) Resumption of oral intake. (B) Duration of hospital stay. (C) Minor complications. (D) Major complications. (E) Re-intervention. (F) Patency duration. (G) Overall survival.
SD = standard deviation; IV = interval variable; CI = confidence interval.

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Both GJ and ES are effective palliative treatments for GOO caused by unresectable gastric cancer. Our results suggest that ES may be associated with more favorable results in patients who are poor surgical candidates with relatively short life expectancy and those who place a high value on resumption of oral diet and being discharged early, while GJ is preferable in patients with more prolonged prognosis and good performance status. Stent insertion by radiologic intervention showed similar efficacy to endoscopic stent insertion in a single-center study [418]. When available, radiologic stent insertion can also be considered for GOO.

KQ 31: Can surgery plus chemotherapy improve survival outcomes for stage IV gastric cancer patients compared to chemotherapy only?

Statement 31-1: Reduction gastrectomy (or upfront debulking gastrectomy without systemic LN dissection) should not be considered as initial treatment options for stage IV gastric cancer patients who are susceptible to chemotherapy (evidence: high, recommendation: strong against).

The REGATTA trial, the only phase III RCT comparing gastrectomy with D1 dissection followed by chemotherapy vs. chemotherapy alone, focused on pure reduction surgery without metastasectomy [418]. Gastric cancer patients with a single noncurable factor were enrolled. Reduction surgery showed no survival benefit compared to chemotherapy alone, and the trial was terminated after the first interim analysis owing to no benefit in the surgery group (HR, 1.08; 95% CI, 0.74 to 1.58; P=0.06). Based on these findings, it was concluded that in patients with metastatic gastric cancer, reductive gastrectomy cannot be justified.

Statement 31-2: In stage IV gastric cancer patients with limited metastasis, conversion surgery might be considered as a treatment option for those with a good response to chemotherapy (evidence: low, recommendation: investigational).

Three retrospective studies and one prospective study were included in our meta-analysis. The data regarding OS showed better survival in stage IV gastric cancer patients who underwent systemic chemotherapy (SC) followed by radical surgery than in patients who received chemotherapy alone (HR, 0.58; 95% CI, 0.42 to 0.80; P<0.01) (**Fig. 24**).

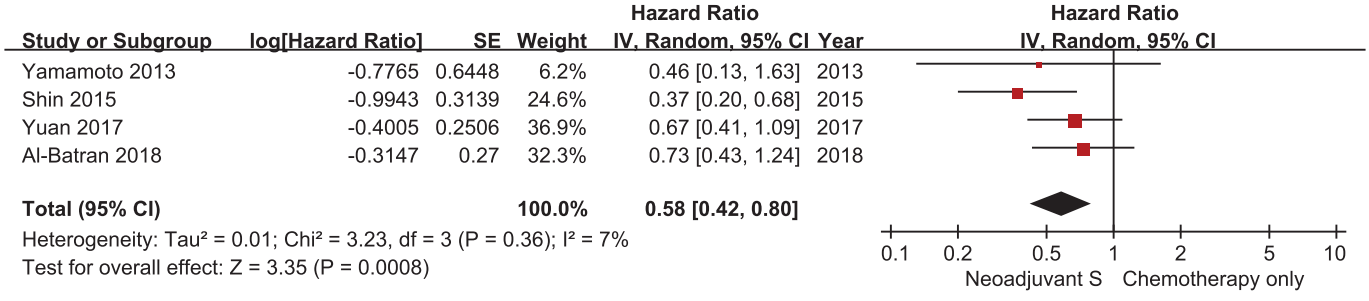

Fig. 24. Forest plot for a comparison of overall survival between surgery after chemotherapy vs. chemotherapy alone in metastatic gastric cancer.
SE = standard error; IV = interval variable; CI = confidence interval.

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In a large retrospective review, patients with stage IV cancer who were responsive to chemotherapy and underwent R0 resection following chemotherapy experienced better survival than patients in the R1 and R2 resection groups [421]. In one prospective nonrandomized trial, surgery after chemotherapy, especially in R0 resection, was associated with a survival benefit for gastric cancer patients with limited distant metastasis [422]. However, since collected studies are retrospective and thus may be influenced by selection bias in nature, evidence is limited for stronger recommendations. A prospective multicenter randomized trial, RENAISSANCE (AIO-FLOT5), is being conducted to elucidate the effects of surgical resection after chemotherapy on the survival and QOL of patients with limited metastatic adenocarcinoma of the stomach and esophagogastric junction, and its results are anticipated for a higher level of evidence [422].

Despite possible benefits from the meta-analysis, the role of conversion surgery and detailed indications are inconclusive as of now because of inevitable selection bias in the observational studies comparing surgery and systemic therapy for stage IV gastric cancer as well as uncertainty regarding whether the development of new systemic therapy will increase or decrease the clinical meaning of conversion surgery.

KQ 32: Can radical gastrectomy with local treatment plus SC improve survival outcomes compared to chemotherapy alone for gastric cancer patients with single organ oligometastasis?

Statement 32-1: Radical gastrectomy, metastasectomy and perioperative chemotherapy may be considered for selected gastric cancer patients with oligometastases in the liver (evidence: very low, recommendation: investigational).

Traditionally, oligometastasis has been defined as an intermediate state between localized and widespread systemic disease with the presence of fewer than 5 metastases [423]. However, the definition is still not clear, and oligometastasis is generally defined as fewer than 3 or 5 metastatic lesions involving 1 or 2 organs [424,425].

For hepatic oligometastasis in gastric cancer, 2 retrospective studies were included in our meta-analysis (**Fig. 25**) [426,427]. The meta-analysis showed that radical gastrectomy with hepatectomy plus SC provided a survival benefit compared to chemotherapy alone (HR, 0.27; 95% CI, 0.12 to 0.62; P<0.001). Local treatments, such as transarterial chemoembolization (TACE), radiofrequency ablation, and hepatic arterial infusion, have also been reported to provide potential survival benefits [428-431]. However, because most of the related studies were single-arm studies or compared with hepatectomy, they could not be included in the meta-analysis. Liu et al. [431] retrospectively compared radical gastrectomy with TACE plus SC with chemotherapy alone. Although all types of liver metastasis (H1, H2, H3) were included in this study, the median OS was 14 and 8 months, respectively, between the surgery and chemotherapy groups (P<0.001).

There is some optimistic evidence that resection of liver oligometastasis may provide survival benefit. However, because of the small sample size and retrospective nature, the evidence of the included study is weak. Therefore, candidates for liver resection should be selected cautiously. Further evidence is required for generalization.

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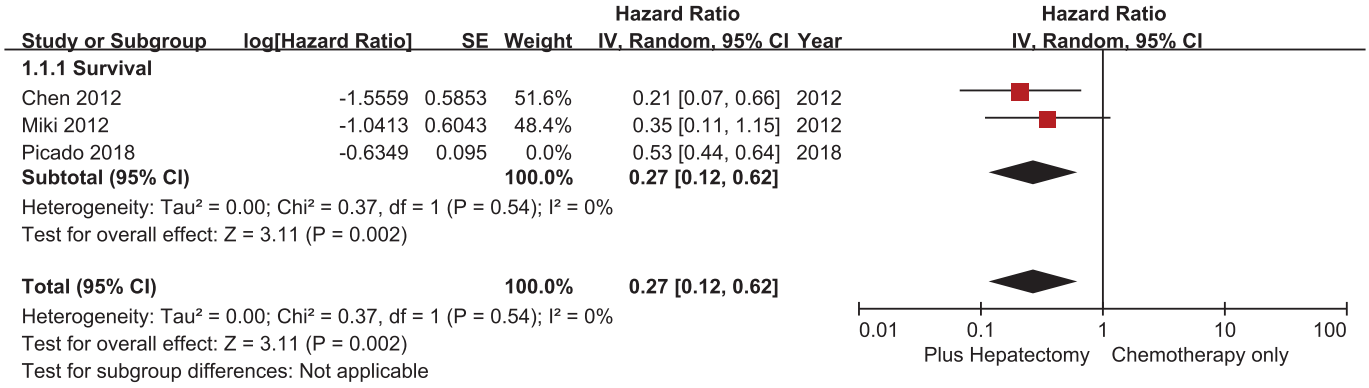

Fig. 25. Forest plot for comparison of overall survival between (hepatectomy and gastrectomy with chemotherapy) vs. (chemotherapy only) in gastric cancer with oligometastasis confined to liver from observational studies.
SE = standard error; IV = interval variable; CI = confidence interval.

> Statement 32-2: Radical gastrectomy, oophorectomy and perioperative chemotherapy could be considered for selected gastric cancer patients with oligometastases in the ovary (evidence: very low, recommendation: conditional for).

For ovarian metastasis, 3 retrospective studies were analyzed in the meta-analysis, and there was better survival in the metastasectomy group (HR, 0.45; 95% CI, 0.34 to 0.59; P<0.001) [432-434] (**Fig. 26**). Cheong et al. [435] reported that Krukenberg tumors were frequently accompanied by peritoneal dissemination with a significantly worse prognosis (HR, 1.74; 95% CI, 1.28 to 2.36; P<0.001), and only when curative resection was obtained was the median OS time longer in the resection group than in the nonresection group (17 vs. 3 months, P<0.001).

Regarding para-aortic LNs, only 3 prospective nonrandomized studies evaluated the response rate of preoperative chemotherapy and the efficacy of subsequent D2 LND plus para-aortic LN dissection; they did not show favorable survival outcomes [436-438].

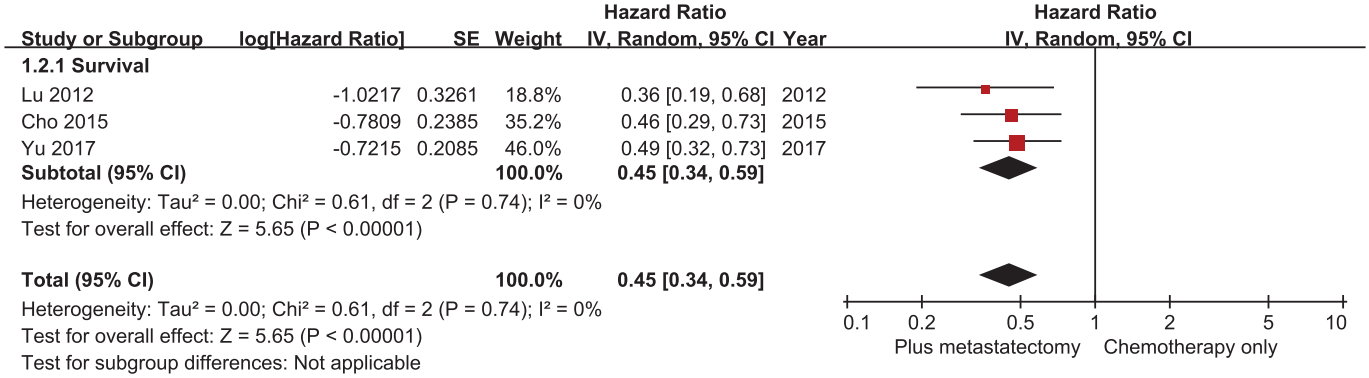

Fig. 26. Forest plot for comparison of overall survival between (oophorectomy and gastrectomy with chemotherapy) vs. (chemotherapy only) in gastric cancer with oligometastasis confined to ovary in observational studies.
SE = standard error; IV = interval variable; CI = confidence interval.

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KQ 33: Can additional IP chemotherapy improve survival outcome for gastric cancer patients with peritoneal carcinomatosis compared to SC alone?

Statement 33: For gastric cancer patients with peritoneal carcinomatosis, additional IP chemotherapy should be applied for investigational purposes (evidence: low, recommendation: investigational).

Peritoneal metastasis is known to be less responsive to SC and offer worse prognosis than hematogenous or lymphatic metastasis (mean survival time [MST]: 5.2–18 months) [439,440]. One of the causes is the limited delivery of anticancer drugs to the peritoneum due to the peritoneum-plasma barrier. For direct application to cancer cells on the peritoneum, IP infusion using anticancer drugs with lower absorption and systemic toxicity, such as paclitaxel and docetaxel, has been studied in various cancers. It is considered effective and safe in treating peritoneal cancer dissemination from ovarian cancer [441-447].

In gastric cancer patients with peritoneal metastasis, phase 1 and 2 studies showed that patients in the IP (paclitaxel + docetaxel) plus SC group had improved survival compared to patients in the SC alone group in terms of MST (24.6 vs. 15.1 months) and 1-year survival time (78% vs. 70.4%) [440].

However, the phase 3 trial of the IP plus SC study conducted by Ishigami et al. [448] did not show significant improvement in survival outcome compared to SC alone (HR, 0.72; 95% CI, 0.49 to 1.04; stratified log-rank P=0.080). In their study, the authors claim that patient withdrawal and protocol violation caused the true effect of IP therapy to be underestimated.

Currently, phase 1, 2, and 3 studies are underway in Korea. Further investigation is required for recommendation, and until trial outcome data become available, IP chemotherapy should only be applied for investigational purposes.

FOLLOW UP AND NUTRITIONAL CONSIDERATIONS

Oncologic follow-up

Patients are regularly followed-up after curative gastrectomy for gastric cancer. The primary goal of regular follow-up is early detection of recurrence or secondary cancer followed by timely treatment. Other important goals are to manage postgastrectomy symptoms, receive nutritional support, and improve QOL. However, there is a lack of high-level evidence on which examination or how often the examination should be performed. Although the NCCN, Japanese, and Chinese guidelines for gastric cancer recommend some follow-up schedules, they were based on expert opinions [89,92,111]. Because lack of evidence, we conducted a nationwide survey targeting all tertiary or general hospitals. The purpose of presenting this survey was only to provide baseline information regarding current practices and not to recommend, force, or limit practices. We hope to encourage further discussion and study on this issue.

A total of 71 representative clinicians from each hospital responded to the questionnaire via e-mail. **Table 5** shows the main intervals (months) for the physical examination, blood test, tumor markers, abdomen pelvis CT, chest X-ray, and endoscopy. For patients with

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Table 5. Investigations of oncologic follow up period in 71 hospitals

Stage	Examinations	Within 1 yr	1–2 yr	2–3 yr	3–5 yr	After 5 yr
Stage I	Physical examination, blood test, tumor makers	6 mo (65%)	12 mo (10%)	12 mo (40%)	12 mo (60%)	24 mo (5%)
		3 mo (34%)	6 mo (80%)	6 mo (58%)	6 mo (38%)	12 mo (35%)
			3 mo (10%)	3 mo (2%)	3 mo (2%)	None (60%)
	Abdomen pelvis CT, chest X-ray	12 mo (58%)	12 mo (78%)	12 mo (90%)	12 mo (95%)	24 mo (5%)
		6 mo (40%)	6 mo (22%)	6 mo (10%)	6 mo (5%)	12 mo (35%)
		3 mo (2%)				None (60%)
	Endoscopy	12 mo (10%)	12 mo (78%)	12 mo (90%)	12 mo (95%)	24 mo (5%)
		6 mo (80%)	6 mo (22%)	6 mo (10%)	6 mo (5%)	12 mo (35%)
		3 mo (10%)				None (60%)
Stage II/III	Physical examination, blood test, tumor makers	6 mo (25%)	6 mo (70%)	12 mo (5%)	12 mo (20%)	24 mo (2%)
		3 mo (65%)	4 mo (10%)	6 mo (70%)	6 mo (75%)	12 mo (56%)
		Etc. (4, 2, 1 mo) (10%)	3 mo (20%)	4 mo (10%)	3 mo (5%)	6 mo (2%)
				3 mo (15%)		None (40%)
	Abdomen pelvis CT, chest X-ray	12 mo (5%)	12 mo (5%)	12 mo (10%)	12 mo (10%)	24 mo (5%)
		6 mo (65%)	6 mo (65%)	6 mo (80%)	6 mo (80%)	12 mo (35%)
		3 mo (30%)	4 mo (5%)	4 mo (5%)	4 mo (5%)	None (60%)
			3 mo (25%)	3 mo (5%)	3 mo (5%)	
	Endoscopy	12 mo (60%)	12 mo (80%)	12 mo (85%)	12 mo (85%)	12 mo (85%)
		6 mo (40%)	6 mo (20%)	6 mo (15%)	6 mo (10%)	None (10%)

Korea numbers in the parenthesis are proportions of the response from the participants.
CT = computed tomography.

pathological stage I tumors, physical examination, and blood tests, including tumor markers, were mainly conducted every 6 months for 3 years and then every 6–12 months until 5 years postoperatively. Abdomen pelvis CT and chest X-ray were mainly checked every 6 months for 2 years, 6 or 12 months in the third year, and then annually until 5 years postoperatively. For patients with pathological stage II or III tumors, physical examination, and blood tests, including tumor markers, were mainly conducted every 3 months for 1 year postoperatively and then every 6 months until 5 years postoperatively. Abdomen pelvis CT and chest X-ray were mainly performed every 3 or 6 months for 1 year postoperatively, every 6 months in the second and third years, and then every 6 or 12 months until 5 years postoperatively. Esophagogastroduodenoscopy (EGD) was conducted once or twice within 1 year and then annually until 5 years postoperatively regardless of stage. After 5 years, annual EGD was recommended for all patients. In addition, a few hospitals checked chest CT as a routine examination annually during the follow-up period.

Nutritional follow-up

Gastrectomy can be accompanied by not only short-term but also long-term nutritional deterioration. Therefore, nutritional status must be monitored after surgery, and nutritional supplements may be given accordingly. **Table 6** shows the main interval (months) for body weight, nutritional parameters, anemia study, and bone related study.

Patients lose a significant amount of body weight after gastric cancer surgery. Lower preoperative body mass index (BMI), female sex, and TG or PG were significant risk factors for malnutrition (BMI <18.5 kg/m^2) 6 months after surgery [449]. Postoperative sarcopenia could serve as a prognostic factor for survival in gastric cancer patients [449]. Some have suggested that postoperative oral nutritional supplementation could improve nutritional outcomes in high-risk patients, but concrete evidence is still lacking [450,451].

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Table 6. Investigations of nutritional follow up period

Resection type	Examinations	Within 1 yr	1–2 yr	2–3 yr	3–5 yr	After 5 yr
Total gastrectomy	Body weight	6 mo (40%)	12 mo (5%)	12 mo (20%)	12 mo (60%)	12 mo (50%)
		3 mo (50%)	6 mo (80%)	6 mo (80%)	6 mo (38%)	None (50%)
		1–2 mo (10%)	3 mo (15%)		3 mo (2%)	
	Nutritional parameters (total protein, albumin, total cholesterol)	6 mo (40%)	6 mo (80%)	12 mo (15%)	12 mo (40%)	12 mo (50%)
		3 mo (60%)	3 mo (20%)	6 mo (80%)	6 mo (60%)	None (50%)
				3 mo (5%)		
	Anemia study (hemoglobin, iron, ferritin, vitamin B12, folate)	6 mo (50%)	6 mo (70%)	12 mo (50%)	12 mo (60%)	12 mo (50%)
		3 mo (50%)	3 mo (25%)	6 mo (50%)	6 mo (40%)	6 mo (10%)
						None (40%)
	Bone related	6 mo (40%)	6 mo (60%)	12 mo (20%)	12 mo (40%)	12 mo (40%)
		3 mo (40%)	3 mo (20%)	6 mo (60%)	6 mo (40%)	6 mo (10%)
		None (20%)	None (20%)	None (20%)	None (20%)	None (50%)
Partial gastrectomy	Body weight	6 mo (40%)	12 mo (5%)	12 mo (20%)	12 mo (60%)	12 mo (50%)
		3 mo (60%)	6 mo (80%)	6 mo (80%)	6 mo (38%)	None (50%)
			3 mo (15%)		3 mo (2%)	
	Nutritional parameters (total protein, albumin, total cholesterol)	6 mo (40%)	6 mo (80%)	12 mo (15%)	12 mo (40%)	12 mo (50%)
		3 mo (60%)	3 mo (20%)	6 mo (80%)	6 mo (60%)	None (50%)
				3 mo (5%)		
	Anemia study (hemoglobin, iron, ferritin, vitamin B12, folate)	6 mo (40%)	6 mo (80%)	12 mo (40%)	12 mo (40%)	24 mo (5%)
		3 mo (50%)	3 mo (20%)	6 mo (30%)	6 mo (30%)	12 mo (35%)
		1–2 mo (10%)		None (30%)	None (30%)	None (60%)
	Bone related	6 mo (40%)	6 mo (60%)	12 mo (20%)	12 mo (40%)	12 mo (40%)
		3 mo (40%)	3 mo (20%)	6 mo (60%)	6 mo (40%)	6 mo (10%)
		None (20%)	None (20%)	None (20%)	None (20%)	None (50%)

Numbers in the parenthesis are proportions of the response from the participants.

Iron deficiency is one of the most common nutritional problems after gastric cancer surgery, and the incidence gradually increases with time after gastrectomy. The prevalence of iron deficiency at 3 years was reported to be 64.8% and 90.5% after DG and TG, respectively, and overt anemia was observed in 31.9% of patients after gastric cancer surgery at 3 years [452]. Female sex and TG have been consistently identified as independent risk factors for iron deficiency in the literature [452-454]. Oral iron supplementation should be given in patients with iron deficiency to correct anemia and replenish body reserve. Intravenous iron can be used when oral preparations are not tolerated or are ineffective. Intravenous iron (ferric carboxymaltose) was proven effective in managing isovolemic anemia that occurred within a week after radical gastrectomy and significantly reduced the need for additional treatments for anemia [455]. Transfusion is reserved for patients with an urgent need or risks of cardiovascular decompensation [456].

Vitamin B12 deficiency can occur from the reduction in intrinsic factors and gastric acidity after gastric cancer surgery. The cumulative incidence was reported at 100% at 4 years after TG with a median time to deficiency of 15 months, while a significantly lower rate of 15.7% was seen after DG [452]. Elderly patients with low preoperative vitamin B12 levels can be predisposed to vitamin B12 deficiency even after DG. Prolonged vitamin B12 deficiency is associated with anemia and with irreversible neuropathy. Nationwide studies in Korea demonstrated that vitamin B12 deficiency after TG could also be related to the pathogenesis of Alzheimer's dementia and Parkinson's disease [457,458]. Therefore, periodic monitoring of serum vitamin B12 levels and adequate supplementation for therapeutic or prophylactic purposes are warranted for patients undergoing gastric cancer surgery. Intramuscular injection of vitamin B12 is generally suggested as the treatment of choice in TG patients deprived of intrinsic factors. At the same time, daily oral vitamin B12 supplementation at a high dosage (1,500 μg once daily) can be an alternative option with similar efficacy [459-461].

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Postgastrectomy patients can suffer from metabolic bone disorders demonstrating significantly decreased bone mineral density [462-464]. A decrease in oral calcium intake and generalized malabsorption induced by rapid gut transit in the early postoperative period and vitamin D deficiency and secondary hyperparathyroidism in the longer term are suggested as common mechanisms underlying bone mineral density impairment after gastric cancer surgery [463,465]. A Korean nationwide cohort study demonstrated that gastric cancer survivors had an elevated risk of osteoporotic fracture (HR, 1.61; 95% CI, 1.53 to 1.70) [466]. Older age, female sex, and marked weight loss (≥20%) were independently associated with an increased risk of osteoporosis [467]. There is currently little evidence on the optimal strategies for monitoring bone health and fracture in patients undergoing gastric cancer surgery. Dual-energy X-ray absorptiometry can be used for quantitative assessment of bone mineral content and screening osteoporosis in gastrectomy patients. Currently, no universal guidelines are available for the prevention or management of metabolic bone disorders related to gastrectomy. Generally, oral calcium and vitamin D supplementation is recommended in populations with an increased risk of osteoporosis. A few recent RCTs demonstrated that alendronate therapy effectively reduced bone loss and bone resorption in gastrectomy patients [468].

According to a nationwide survey in 2022, the postoperative nutritional monitoring schedule was not significantly different between total and partial gastrectomy. During the first year after surgery, the majority of the respondents followed their patients either every 3 months (50%–51%) or every 6 months (41.7%–43.7%). The interval increased to every 6 months (73.6%–80.0%) in the following 2nd and 3rd years and then to either every 6 months (43.7%–48.6%) or 12 months (41.7%–49.3%) up to the 5th year. After 5 years, half of the respondents continued nutritional monitoring mostly every year, while the other half discontinued surveillance. Body weight, hemoglobin, total protein, albumin, and total cholesterol were evaluated every visit in most of the centers. Other commonly monitored nutritional indices included the following: iron (76.6%–81.9%), ferritin (73.2%–81.9%), vitamin B12 (86.1%–93.1%), folate (62.0%–73.6%), and calcium (80.3%–81.6%) levels. Other indices, such as vitamin D (30%), parathyroid hormones (5%), prealbumin (15%), and thiamine (5%), were selectively evaluated by a smaller number of respondents, and micronutrients, such as copper or zinc, were rarely monitored. Annual bone densitometry was utilized to evaluate bone health at approximately 10% of the centers.

MULTIDISCIPLINARY TREATMENT (MDT)

Although treatment plans for gastric cancer patients can be made straightforward in many routine cases, there are also numerous cases requiring multidisciplinary considerations to arrive at the best treatment option. The advantages of MDT may include correct diagnosis, change into better treatment plan, shorter decision-making time and survival benefit [469-472]. For these reasons, health services in several countries have implemented MDT as the preferred system in cancer treatment [111,469,470,473]. The MDT team in gastric cancer treatment can include surgeons, gastroenterologists, medical and radiation oncologists, radiologists, pathologists, nuclear medicine experts, and other members, such as nutritional services, social workers, nurses, and palliative care specialists [474-477].

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Several studies have shown the advantages of MDT in gastrointestinal malignancies. After the MDT meeting, changes in diagnosis occurred for 18.4%–26.9% of the evaluated patients [478,479], and the treatment plan was changed in 23.0%–76.81% of cancer patients [479-481].

From the caregivers' perspective, MDT meetings may provide an interprofessional opportunity for feedback on various diagnostic imaging, operative findings, and pathologic results, which is beneficial for all parties [482]. MDT meetings can be a good opportunity to record specialists' opinions on complex cases and improve diagnosis accuracy, treatment quality and accurate communication [482,483].

However, regardless of the potential benefits of MDT, there is little evidence to support its advantage and scarce information about how and for whom MDT activities should be conducted in gastric cancer. Considering cost and time effectiveness, how to select patients and how to organize the MDT meeting can be one of the issues because many patients without substantial comorbidities can follow routine decision-making processes without MDT team discussion [484]. However, the number of cases requiring MDT team discussion may increase according to the development of diverse treatment options and increasing proportions of patients with very old ages and comorbidities. Allum et al. [485] recommended that MDT team activities should also involve discussing treatment decisions with patients. However, there is no evidence that the treatment discussion with patients is better than the conference type of MDT discussion. All reports regarding the benefit of MDT were about professional consensus meetings followed by private interviews of the designated caregiver with the patient [485-491]. We may wait for further research on which MDT discussion type is better in terms of treatment outcome and cost effectiveness.

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