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Special Article

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Korean Practice Guidelines for Gastric Cancer 2024: An Evidence-based, Multidisciplinary Approach (Update of 2022 Guideline)

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ABSTRACT

Gastric cancer is one of the most common cancers in both Korea and worldwide. Since 2004, the Korean Practice Guidelines for Gastric Cancer have been regularly updated, with the 4th edition published in 2022. The 4th edition was the result of a collaborative work by an interdisciplinary team, including experts in gastric surgery, gastroenterology, endoscopy, medical oncology, abdominal radiology, pathology, nuclear medicine, radiation oncology, and guideline development methodology. The current guideline is the 5th version, an updated version of the 4th edition. In this guideline, 6 key questions (KQs) were updated or proposed after a collaborative review by the working group, and 7 statements were developed, or revised, or discussed based on a systematic review using the MEDLINE, Embase, Cochrane Library, and KoreaMed database. Over the past 2 years, there have been significant changes in systemic treatment, leading to major updates and revisions focused on this area. Additionally, minor modifications have been made in other sections, incorporating recent research findings. The level of evidence and grading of recommendations were categorized according to the Grading of Recommendations, Assessment, Development and Evaluation system. Key factors for recommendation included the level of evidence, benefit, harm, and clinical applicability. The working group reviewed and discussed the recommendations to reach a consensus. The structure of this guideline remains similar to the 2022 version. Earlier sections cover general considerations, such as screening, diagnosis, and staging of endoscopy, pathology, radiology, and nuclear medicine. In the latter sections, statements are provided for each KQ based on clinical evidence, with flowcharts supporting these statements through meta-analysis and references. This multidisciplinary, evidence-based gastric cancer guideline aims to support clinicians in providing optimal care for gastric cancer patients.

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

INTRODUCTION

Background

Gastric cancer is one of the most common cancers in Korea and the world, ranking 5th in incidence and 4th in mortality among all solid cancers, excluding nonmelanoma skin cancer, globally in 2020 [1]. In Korea, new cases of gastric cancer (29,361 cases) ranked 4th (10.6%) in 2021, following thyroid cancer (12.7%), colorectal cancer (11.8%) and lung cancer

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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

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

(11.4%), according to the Korea Central Cancer Registry [2,3]. Early detection through national and public screening programs and advancements in treatment has led to increase in the proportion of surgically treated early gastric cancer (EGC) cases, from 28.6% in 1995 to 63.6% in 2019, and the 5-year survival has improved from 43.9% (1993–1995) to 77.5% (2015–2019) [4]. Environmental factors, local dietary factors, socioeconomic factors, and *Helicobacter pylori* infections are considered significant contributors to the development of gastric cancer [5-8].

Chronology

Since 2004, this is the 5th gastric cancer guideline published in Korea, a revised version of the previous evidence-based approach in 2022 [9], and this work was developed by the Korean Gastric Cancer Association (KGCA) and supported by the Research Fund of the National Cancer Center, Republic of Korea (NCC-2112570). The Korean Practice Guidelines for Gastric Cancer are intended for patients diagnosed with gastric or gastroesophageal junction (GEJ) adenocarcinoma. These guidelines are primarily designed to be used by healthcare professionals who specialize in the diagnosis and management of gastric cancer, including surgeons, medical oncologists, gastroenterologists, and other members of the multidisciplinary care team. The recommendations aim to provide evidence-based guidance to optimize patient outcomes and ensure consistent standards of care. This guideline represents a collaborative work by an interdisciplinary working group 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 KGCA, with the participation of experts in guideline development methodology from the National Evidence-based Healthcare Collaborating Agency.

The Korean Practice Guidelines for Gastric Cancer will be regularly updated to reflect the latest evidence and advancements in the field. Comprehensive reviews of the guideline content will be performed at least every 2 to 4 years.

Methodology

The Korean Practice Guidelines for Gastric Cancer were developed based on a comprehensive and systematic review of the literature. Evidence selection followed predefined criteria, emphasizing relevance to key clinical questions, study design, sample size, and methodological rigor. Priority was given to high-quality randomized controlled trials (RCTs), meta-analyses, and systematic reviews. In the absence of such evidence, well-conducted observational studies, cohort studies, and expert consensus were considered. The working group also evaluated clinical applicability, balance between benefits and harms, and relevance to the Korean clinical setting to ensure that recommendations are both evidence-based and practical.

After a collaborative review by the working group, 6 key questions (KQs) were either updated or newly proposed (de novo). For the updated KQs, published literatures were systematically searched using the MEDLINE, Embase, Cochrane Library, and KoreaMed database, covering the period from January 2022 to January 2024, following a previous systematic search [9]. Screening and selection were performed by 2 reviewers, with predefined selection and exclusion criteria based on the KQs. Initial screening of articles was conducted by title and abstract, followed by secondary screening through full-text review. Each panel independently

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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.

selected articles and compared results to check for inconsistencies. When disagreements occurred during the review process, consensus was reached with the involvement of a third review panel.

For quality assessments, the Cochrane Risk of Bias 1.0 (ROB) was used for RCTs, the Risk of Bias for Nonrandomized Studies (RoBANS) for non-RCTs, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic studies, and AMSTAR 2 for systematic reviews/meta-analyses.

In this edition, the level of evidence and grading of recommendation were defined based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology review [10]. 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 it to reach a consensus.

Meta-analysis outputs and forest plots were generated using 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.

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STATEMENT LIST

No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S1	1	Acquisition of multiplanar reformation images in addition to axial images should be performed for gastric cancer staging using multidetector row computed tomography.	Low	Strong for
S2	1	F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) can be considered an additional supplementary diagnostic tool during staging workup.	Low	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 early gastric cancers (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 results of endoscopic resection for EGC do not meet the criteria for curative resection or when lymphovascular invasion or positive vertical margin is present.	Low	Strong for
S8	2	After endoscopic resection in EGC, endoscopic treatment such as ESD and argon plasma coagulation could be considered for EGCs that have only positive lateral margins and meet all other criteria for curative resection.	Low	Conditional for
S9	2	*Helicobacter pylori* eradication is recommended for the prevention of metachronous gastric cancer in patients successfully treated with 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, Billroth II, and Roux-en-Y 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	Efforts to achieve negative margins are recommended to improve survival outcomes in EGC patients. Reresection or reoperation should be considered when the patient's condition is favorable and the procedure is technically feasible.	Low	Strong for
S11-2	4	Efforts should be made to achieve negative margins in surgery for advanced or infiltrative gastric cancer. If the final postoperative pathologic margin shows involvement of the margin, reoperation to achieve R0 resection 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 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 at least 5 cm proximal to the pylorus, pylorus-preserving gastrectomy (PPG) as well as DG could be performed. PPG has the benefits of reduced gallstone formation and better protein preservation; however, delayed gastric emptying should be considered when making decisions.	Moderate	Conditional for

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No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S14	3	Prophylactic splenectomy for splenic hilar LN dissection is not recommended in curative resection for advanced gastric cancer (AGC) in the proximal stomach without invasion of the 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 for advanced cancer invading the GEJ.	Low	Conditional for
S16-2	5	The transhiatal approach rather than the transthoracic approach is recommended to achieve a 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 outcomes.	Low	Strong for
S18	3	Sentinel node navigation surgery 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. 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 cStage 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 outcomes and fewer complications than laparoscopic gastrectomy. However, disadvantages including additional cost and longer operation times should be discussed with the patient to facilitate shared decision-making.	Moderate	Conditional for
S21	3	Partial omentectomy could be considered for AGC patients.	Low	Conditional for
S22	-	Administration of ursodeoxycholic acid 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 [CAPOX]) is recommended in patients with pathological stage II or III gastric cancer.	High	Strong for
S24*	1	Neoadjuvant chemotherapy as part of perioperative chemotherapy can be considered for patients with resectable locally AGC.*	High	Conditional for
S25-1*	6	Palliative first-line systemic therapy with anti-programmed cell death protein-1 antibody combined with fluoropyrimidine/platinum-based chemotherapy is recommended in patients with human epidermal growth factor receptor 2 (HER2)-negative and programmed cell death-ligand 1 (PD-L1)-positive locally advanced unresectable or metastatic gastric cancer. Nivolumab combined with chemotherapy is recommended for tumors with PD-L1 combined positive score (CPS) ≥5, and pembrolizumab combined with chemotherapy is recommended for tumors with PD-L1 CPS ≥1.*	High	Strong for
S25-2*	6	Palliative first-line systemic therapy with zolbetuximab combined with capecitabine or fluorouracil plus oxaliplatin (CAPOX or FOLFOX) is recommended in patients with HER2-negative and claudin 18.2-positive and locally advanced unresectable or metastatic gastric cancer.*	High	Strong for
S26*	6	Palliative first-line systemic therapy with trastuzumab combined with fluoropyrimidine/platinum-based chemotherapy is recommended in patients with HER2-positive locally advanced unresectable or metastatic gastric cancer. Pembrolizumab and trastuzumab combined with chemotherapy is recommended for patients with HER2-positive and PD-L1 CPS ≥1.*	High	Strong for

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No.	Flowchart No.	Statement	Level of evidence	Grade of recommendation
S27*	6	Palliative second-line systemic therapy with ramucirumab combined with paclitaxel is recommended in patients with locally advanced unresectable or metastatic gastric cancer; however, other agents may also be considered.*	High	Strong for
S28*	6	Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer. Trastuzumab-deruxtecan is preferentially recommended in patients with HER2-positive gastric cancer.*	High	Strong for
S29	4	Adjuvant chemoradiation is not recommended in patients with pathological stage II or III gastric cancer who have undergone curative gastrectomy.	High	Conditional against
S30	1	The evidence for adding radiation to neoadjuvant chemotherapy is not conclusive in patients with locally AGC.	Moderate	Investigational
S31	1	In patients with gastric outlet obstruction caused by unresectable gastric cancer, either endoscopic stenting or surgical gastrojejunostomy for palliative treatment can be performed. The decision should be based on a multidisciplinary assessment of the patients' performance status, projected clinical course, and individual preferences.	Low	Conditional for
S32-1	1	Reduction gastrectomy (or upfront debulking gastrectomy without systemic LN dissection) should not be considered as an initial treatment option for stage IV gastric cancer patients who are susceptible to systemic therapy.	High	Strong against
S32-2	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 systemic therapy.	Low	Investigational
S33-1	1	Radical gastrectomy, metastatectomy and systemic therapy may be considered for selected gastric cancer patients with oligometastases in the liver.	Very low	Investigational
S33-2	1	Radical gastrectomy, oophorectomy, and systemic therapy could be considered for selected gastric cancer patients with oligometastases in the ovary.	Very low	Conditional for
S34	1	For gastric cancer patients with peritoneal carcinomatosis, additional intraperitoneal chemotherapy should be applied for investigational purposes.	Low	Investigational

*These statements were developed or revised or discussed in the current guideline.

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GENERAL CONSIDERATIONS

Endoscopy

Screening

Korea has 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 [11]. The Korean National Cancer Screening Program (KNCSP) for gastric cancer appears to have played a crucial role in increasing the number of curable cancers through early detection, and thereby improving overall survival (OS) [12]. The KNCSP for gastric cancer, launched in Korea in 2002, invites all Korean individuals aged 40 or older to undergo endoscopy or upper gastrointestinal series (UGIS) every 2 years. A recent study showed that the screening group had a 41% lower hazard ratio (HR) for gastric cancer mortality compared with the non-screening group [13]. However, the reduction in gastric cancer mortality was significant only in the group that received endoscopic screening, not in the group that received UGIS [14].

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) [15]. Type II lesions are further subdivided into 3 groups according to the elevation or depression of the lesion relative 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 [15].

Staging by endoscopic ultrasound (EUS)

EUS can be helpful for assessing the depth of local tumor invasion (T stage) and regional lymph node (LN) metastasis [16]. According to the results of a Cochrane review, the summary sensitivity and specificity of EUS in distinguishing T1 and T2 (superficial) vs. T3 and T4 (advanced) gastric carcinomas were 86% (95% confidence interval [CI], 81% to 0.90%) and 90% (95% CI, 87% to 93%), respectively (**Table 3**) [17]. For the diagnostic capacity of EUS in distinguishing T1 vs. T2 tumors, a meta-analysis of 46 studies (n=2,742) showed that the 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 (submucosal) cancers, a 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 assessing metastatic involvement of LNs (N stage), a 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 high heterogeneity between studies indicates that the diagnostic accuracy of EUS depends on the operator.

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

Test	No. of study	No. of patient	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).

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Radiology

UGIS

The UGIS has been used for screening and for evaluating postoperative complications in gastric cancer. Recently, the percentage of participants of the KNCSP who undergo UGIS for gastric cancer screening has decreased [18,19]. Studies using a large general population cohort participating in hte KNCSP reported that screening by endoscopy reduced gastric cancer mortality, but the effect was not significant in the UGIS group [14,20]. Therefore, starting in 2018, the program was changed to perform endoscopy as the basic examination, with UGIS being performed optionally in cases where it is difficult to perform endoscopy.

Computed tomography (CT)

CT has been widely used to detect and diagnose gastric cancers, determine the optimal treatment method through accurate staging (cTNM), and assess therapeutic effects after anticancer treatments. Multidetector row CT (MDCT), which has multiple parallel rows of X-ray detectors in the craniocaudal direction (z-direction), enables various high-quality multiplanar reformation (MPR) imaging. Since 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 uncommon in gastric cancer, chest CT can be helpful in case of esophageal involvement in GEJ cancer [21-24]. For the CT protocol, an MDCT unit with 16 or more channels is recommended to acquire isotropic imaging with collimation of less than 1.25-mm [25]. The patient should fast for at least 6 hours. Optimal gastric distension is critical for successful CT gastrography and is achieved using either a negative contrast agent (effervescent gas-producing agent) or a neutral contrast agent (water). Anti-peristaltic drugs can help reduce motion artifacts. Patient positioning is determined based on the location of the suspected lesion and the type of oral contrast used (e.g., supine/prone, right decubitus/left posterior oblique). Obtaining images from appropriate positions facilitates evaluation of the entire stomach in a distended state. Portal venous phase images typically provide information on tumor depth, regional LN metastasis, and distant metastasis. Arterial phase images are useful for detecting abnormal gastric wall enhancement and assessing possible anatomic variations in surgically relevant vasculature, such as a replaced left hepatic artery arising from the left gastric artery.

S1. MPR imaging with MDCT in gastric cancer staging accuracy

KQ 1: Is acquisition of additional MPR images improve T and N staging accuracy compared to axial images alone 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 range from 67.1% to 89.1% (median, 78.6%) for T staging and from 49.3% to 79.5% (median, 68.8%) for N staging [26-39]. MDCT, which enables faster scanning with thinner slice thicknesses, can generate high-quality reformation images, such as MPR images, CT gastrography, or virtual gastroscopy.
In a meta-analysis, the addition of MPR images to axial images improved staging accuracy, particularly for 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]) (**Fig. 1**) [27,29,30]. Three-dimensional reformation images, such as CT gastrography or virtual gastroscopy, can improve the detection

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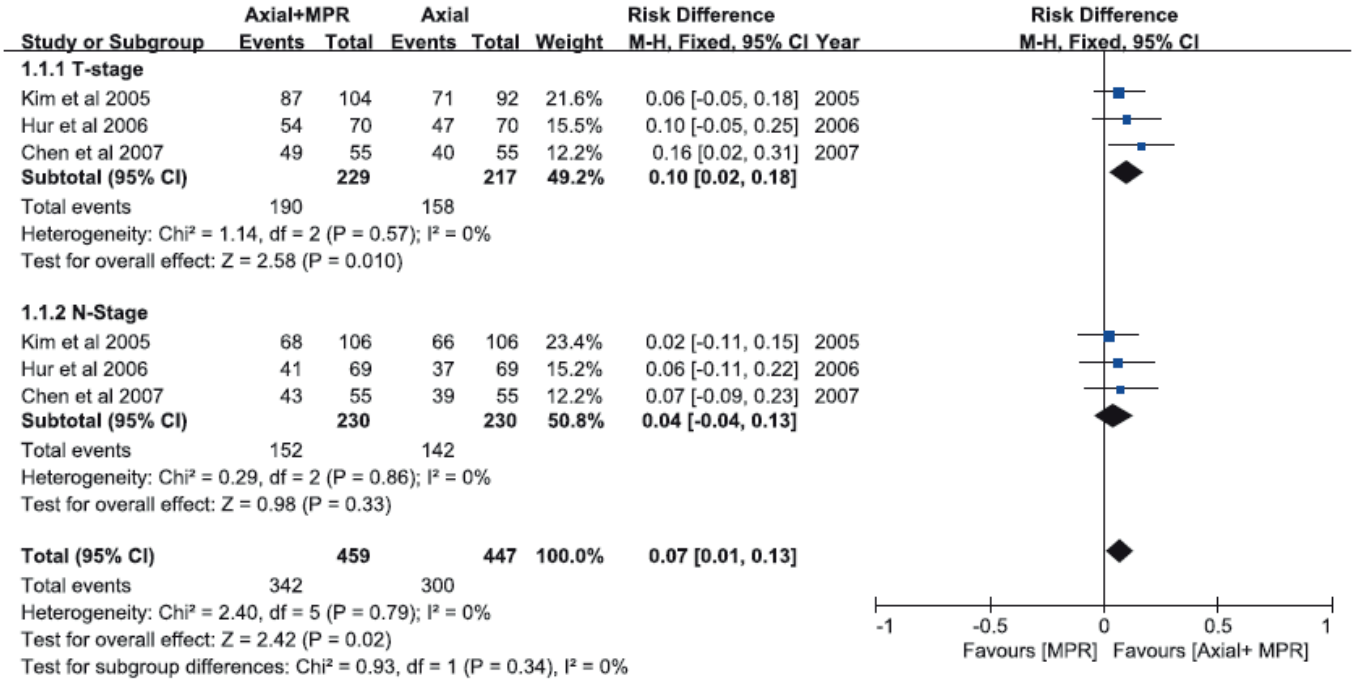

Fig. 1. Forest plot comparing staging accuracy between MPR plus axial plane vs. axial plane only in multidetector row computed tomography.
MPR = multiplanar reformation; CI = confidence interval.

rate of EGCs, potentially allowing for more accurate T staging [26,27,36]. Regarding the detection of peritoneal metastases, MDCT has been reported to have high specificity, ranging from 57.1% to 100% (median, 96.5%), but low sensitivity, ranging from 25.0% to 90.0% (median, 57.6%) [40-45].

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 demonstrated that liver-specific contrast-enhanced MRI with diffusion-weighted imaging (DWI) is the most sensitive imaging method for the diagnosis of liver metastases [46]. Although no studies have focused exclusively on gastric cancer patients, liver-specific contrast agent-enhanced MRI with DWI is expected to be useful for diagnosing liver metastases in gastric cancer due to its high contrast resolution. A meta-analysis has shown the applicability of MRI in evaluating T stage and peritoneal metastases [47,48]. However, further investigation is needed to confirm these findings due to the small number of patients included in these analyses.

Nuclear medicine

F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) can reflect the degree of glucose uptake and metabolism in many cancer lesions [49]. FDG PET/CT can also provide good evidence to differentiate malignant lesions from inflammatory and postoperative changes [50,51]. 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 associated with small tumor size, diffuse-type Lauren classification, mucin-predominant

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pathology, and human epidermal growth factor receptor 2 (HER2)-negative expression in gastric cancer [52-54].

S2. FDG PET/CT for staging workup

KQ 2: Is additional FDG PET/CT helpful for accurate diagnosis in detecting LN and distant metastases during staging workup for gastric cancer patients?

Statement 2: FDG PET/CT can be considered an additional supplementary diagnostic tool during staging workup (evidence: low, recommendation: conditional for).

A total of 20 studies were reviewed, 19 studies with 2,195 patients were included in the meta-analysis assessing the diagnostic ability of FDG PET/CT for detecting LN metastasis [55-67] or distant metastasis [60,62,64,68-73] 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. For 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 reason for the low sensitivity of FDG PET/CT in detecting LN or distant metastasis could be the inclusion of diffuse-type (Lauren classification) or signet ring cell type cancers, which generally exhibit lower FDG uptake. However, FDG PET/CT tends to provide more accurate diagnoses for intestinal-type tumors.

FDG PET/CT showed high specificity in detecting LN and distant metastases and can be considered a supplementary diagnostic tool with diagnostic CT for staging the workup in gastric cancer.

S3. FDG PET/CT for the diagnosis of cancer recurrence

KQ 3: Is PET/CT more accurate for diagnosing recurrence in gastric cancer patients with suspected recurrence after 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).

A total of 13 studies with 1,567 patients were included in the meta-analysis [74-86]. 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 these 13 studies, 5 studies with 438 patients compared the diagnostic ability in detecting recurrence between FDG PET/CT and contrast-enhanced CT [74,76,78,84,86]. In the meta-analysis of these 5 studies, FDG PET/CT showed a pooled sensitivity of 72% (95% CI, 50%

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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. Due to its 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 [74,81]. 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 with equivocal findings on contrast-enhanced CT, 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)/endoscopic submucosal dissection (ESD) specimens, the specimen is spread out with the mucosal side up and pinned to a flat board. The proximal and distal directions are marked for orientation.

Specimen fixation

After completing the preparation process, the specimens should be 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 [87]. A proper fixation time (between 24 and 48 hours) at average room temperature is recommended for additional immunohistochemical or genomic evaluation [15,88].

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) [15].

Based on Borrmann's classification, the gross type of advanced gastric cancer (AGC) can be divided into polypoid (type 1), ulcerofungating (type 2), ulceroinfiltrative (type 3), diffuse infiltrative (type 4), and unclassifiable (type 5) [89,90].

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 also be noted. Additionally, any findings other than the tumor lesion, such as congestion, hemorrhage, ulcer, and perforation, should be assessed. For EMR/ESD samples, all specimens

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should be collected and embedded in blocks. The lateral and basal resection margins should be marked with ink to aid in accurate 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. For grossly EGC lesions, 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 examined microscopically when no residual cancer cells are found in representative section, or when the residual lesion is small or grossly inconspicuous. For multiple tumors or lesions with unusual configurations, appropriate 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 [91,92]. In addition, the Lauren classification can be applied in resected specimens, including ESD specimens [93].

A. WHO classification

a. Tubular adenocarcinoma

Tubular adenocarcinoma is the most common histologic subtype of gastric carcinoma, and 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 [15]. Prominent intraluminal mucus and inflammatory debris can be observed.

b. Papillary adenocarcinoma

This relatively rare subtype usually shows an exophytic growth pattern and a 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 [94]. Papillary adenocarcinoma is often associated with liver metastasis, a higher rate of LN involvement, and poor outcome [94-96].

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

PCCs consist of poorly cohesive neoplastic cells that are isolated or form small aggregates without gland formation. This type includes SRCC and non-signet-ring cell variants (PCC-NOS). SRCC is diagnosed when the tumor cells were predominantly or exclusively of the SRC component [92]. Recent studies have revealed that the clinical behavior of SRCC and PCC-NOS may differ, with a relatively poor prognosis for PCC-NOS and different mutational profiles between SRCC and PCC-NOS [97-99].

d. Mucinous adenocarcinoma

This subtype is defined by malignant epithelial cells and extracellular mucin pools comprising more than 50% of the tumor volume. The tumor cells may exhibit glandular architecture and irregular cell clusters, with occasional single scattered tumor cells, including floating SRCs. Mucinous adenocarcinoma tends to be diagnosed at a more

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advanced stage, which correlates with deeper invasion depth and poorer survival outcomes compared to non-mucinous gastric cancer [100,101].

e. Mixed adenocarcinoma

This type of tumor contains a distinct 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 [102-104]. However, no clear diagnostic criteria currently exist 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 applied to tubular and papillary carcinomas but not to other subtypes. Well-differentiated adenocarcinoma consists of tumors 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 [93]. 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. Poorly differentiated adenocarcinomas forming solid areas are classified as indeterminate type. Mucinous adenocarcinoma can be classified as intestinal, diffuse or indeterminate based on the differentiation of the main tumor components [92]. 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 [105]. 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.

Tumor size

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

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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 by the depth of tumor invasion. Tumors with invasion beyond the proper muscle layer are classified as AGC, while tumors with invasion limited to the mucosal or submucosal layers are classified as EGC. Submucosal invasion depth is further 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 extends below an imaginary line connecting the proper muscle layers, it is classified as invasion of the proper muscle.

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

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 essential for the accurate diagnosis of N staging. The pathologic assessment should include both the total number of nodes and the number of positive nodes. At least 16 local nodes should be assessed to evaluate N3a staging; however, some studies suggest that it is desirable to remove and assess 30 or more nodes [106,107].

A tumor deposit is defined as a discrete tumor nodule within the lymphatic drainage zone of the primary carcinoma without identifiable LN tissue, blood vessels, or neural structures [106]. Tumor deposits, where metastatic tumor lesions in the subserosal fat are separated from the adjacent primary gastric cancer 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.

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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).

If there is a discrepancy between the grossly observed safety margin and that observed microscopically, the microscopic findings are reported.

For endoscopic resection specimens, the mucosal resection margins are described by indicating the direction closest to the resection margin and the distance from the resection margin. The deep resection margin is also measured at the closest 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 report lymphatic invasion and vascular invasion. Immunohistochemical staining (D2-40) could be helpful for identifying lymphatic invasion.

Regression grade

For the grading of primary tumor regression after neoadjuvant therapy, the modified Ryan system is recommended (**Table 4**) [108].

Peritoneal washing

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

Biomarkers

A. HER2

HER2 positivity is an indication for anti-HER2 targeted therapy, so HER2 status should be evaluated before systemic therapy and re-evaluated for recurrent and metastatic lesions. Immunohistochemistry (IHC) should first be performed for the evaluation of HER2 status [109,110]. HER2 overexpression is considered positive with IHC 3+, while IHC 0–1+ is negative [111]. IHC 2+ is regarded as equivocal and should be followed by in situ hybridization (ISH). 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 with a ratio is <2, an average HER2 signal of >6 is interpreted as a positive. IHC 3+ or IHC 2+ and ISH positivity are considered HER2-positive.

B. Microsatellite instability (MSI)

MSI status can be assessed via polymerase chain reaction (PCR) or IHC for the 4 DNA mismatch repair (MMR) proteins [112]. Instability is evaluated by PCR of a representative panel of microsatellites [113], with grades determined by the numbers of unstable

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microsatellites: MSI-high (MSI-H), MSI-low, or microsatellite stable [114]. In IHC, staining is performed for the MMR proteins MLH1, MSH2, PMS2, and MSH6 [115]. When the expression of any MMR protein is lost, the case is considered MMR deficient (dMMR).

MSI-H/dMMR gastric cancer is a distinct subtype in the molecular classifications of gastric cancer, showing high mutation rates (high tumor mutation burden) and distinctive patterns of methylation [116]. 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 a well-known predictive biomarker to identify patients with gastric cancer most likely to benefit from immune checkpoint inhibitor (ICI) therapy [117].

C. Epstein–Barr virus (EBV)

The presence of the EBV genome can be detected by ISH for EBV-encoded RNA [118,119]. Cases showing signals in the tumor cell nuclei are considered EBV-positive. EBV-positive gastric cancer is classified as a separate subtype in molecular classification of gastric cancer and shows hypermethylation distinct from MSI subtype [116]. This subtype is distinct in its proximal location, relation to poorly differentiated histology, lower stage, and good prognosis.

D. Programmed cell death-ligand 1 (PD-L1) expression

The method and cutoff value for PD-L1 interpretation depend on antibody clones and predefined settings of approved clinical trials. Most anti-programmed cell death protein 1 (PD-1)/PD-L1 therapies require the combined positive score (CPS) interpretation system [120,121], which 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.

Two PD-L1 assays have been linked to clinical trials for gastric cancer patients: the PD-L1 IHC 22C3 pharmDx assay with a CPS ≥1 for PD-L1 positivity and the 28-8 pharmDx assay with a cutoff of CPS ≥5 [122,123].

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. Claudin 18.2 (CLDN18.2)

CLDN18.2 has emerged as a promising target for gastric cancer and is expected to be integrated into routine practice. This tight-junction molecule predominantly found in the non-tumor gastric epithelium, becomes accessible on tumor cell surface during malignant transformation [124]. Recent phase III trials (SPOTLIGHT and GLOW) demonstrated that zolbetuximab, an anti-CLDN18.2 monoclonal antibody, improved OS when combined with chemotherapy in previously untreated HER2-negative AGC with high level of CLDN18.2 [125,126]. CLDN18.2 positivity is defined as ≥75% of tumor cells showing moderate-to-strong membranous staining using the VENTANA® CLDN18 (43-14A) Assay. CLDN18.2 positivity was observed in 38.4% and 38.5% of patients in the GLOW and SPOTLIGHT trials, respectively.

F. Next-generation sequencing (NGS)

Biomarkers associated with AGC management include HER2, MSI, PD-L1, tumor mutational burden (TMB) status, and *NTRK* gene fusion according to recent National Comprehensive

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Cancer Network (NCCN) guidelines [109]. For biomarker testing, IHC, ISH, or target PCR methods should be preferentially considered; however, validated NGS assay performed in an appropriate setting could be used for the identification of the biomarkers mentioned above. Additionally, NGS assay can test for other clinically relevant targets in AGC, such as *FGFR2* amplification, epidermal growth factor receptor (*EGFR*) amplification, *MET* amplification, and alterations of homologous recombination deficiency-related genes [127-130].

TMB, quantifiable by NGS, has been proposed as a potent biomarker for pembrolizumab-based therapy in patients with AGC [131]. Although whole-exome sequencing is the gold standard for TMB, recent targeted gene panels also provide fairly accurate TMB quantification [132]. However, a lack of standard cutoffs and variations in 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 [133]. Most targeted NGS assays require total DNA and RNA amounts ranging from 10 to 300 ng, which can be obtained from formalin-fixed, paraffin-embedded tissue or cytology specimens. A sufficient tumor fraction of the sample (surface area >10%–20% and 5 mm^2) 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, second edition [134,135].

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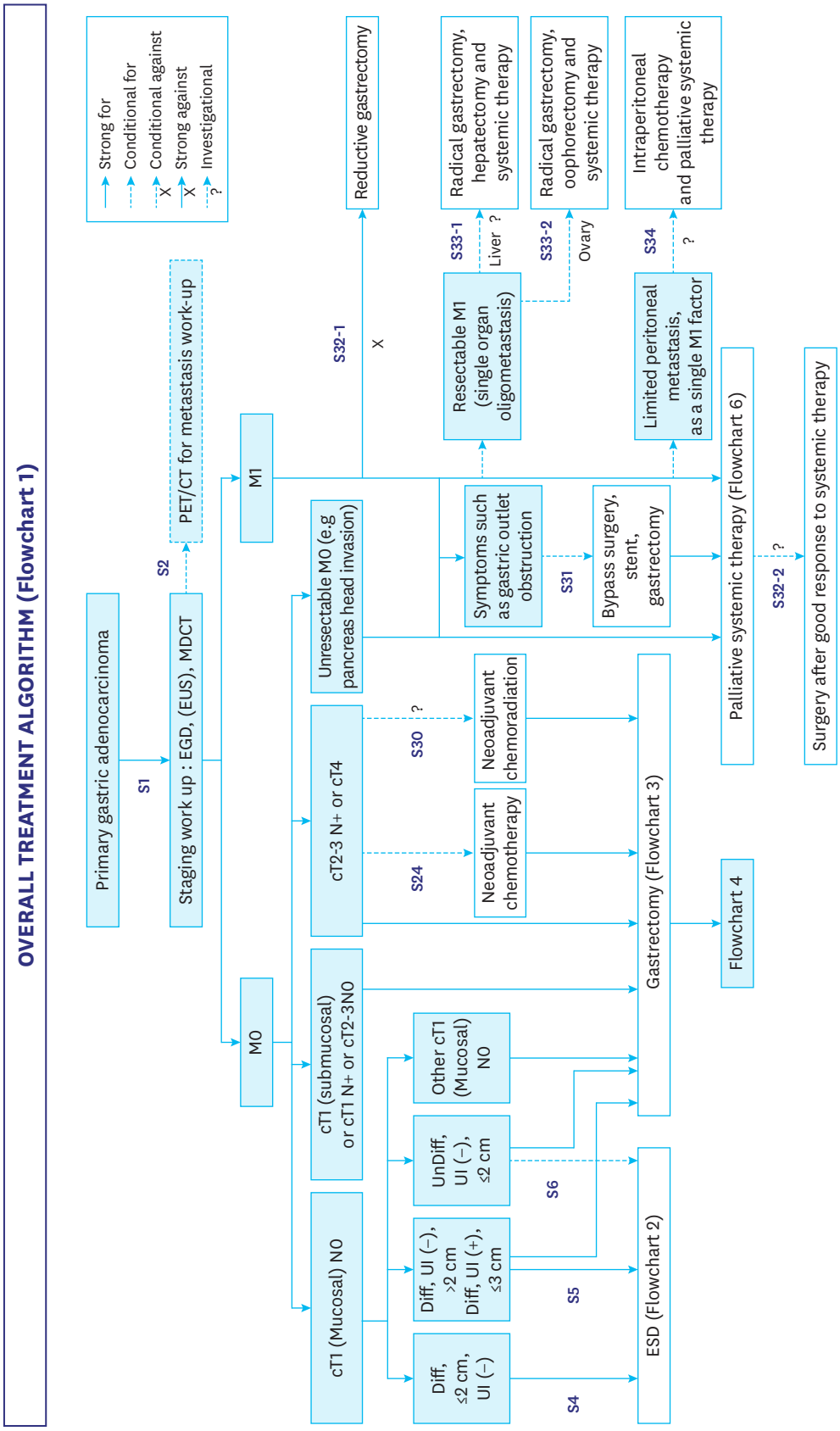

Flowchart 1. Overall treatment algorithm.
PET = positron emission tomography; CT = computed tomography; EGD = esophagogastroduodenoscopy; EUS = endoscopic ultrasound; MDCT = multidetector row computed tomography; MRI = magnetic resonance imaging; Diff = well or moderately differentiated; UI = ulcer lesion;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

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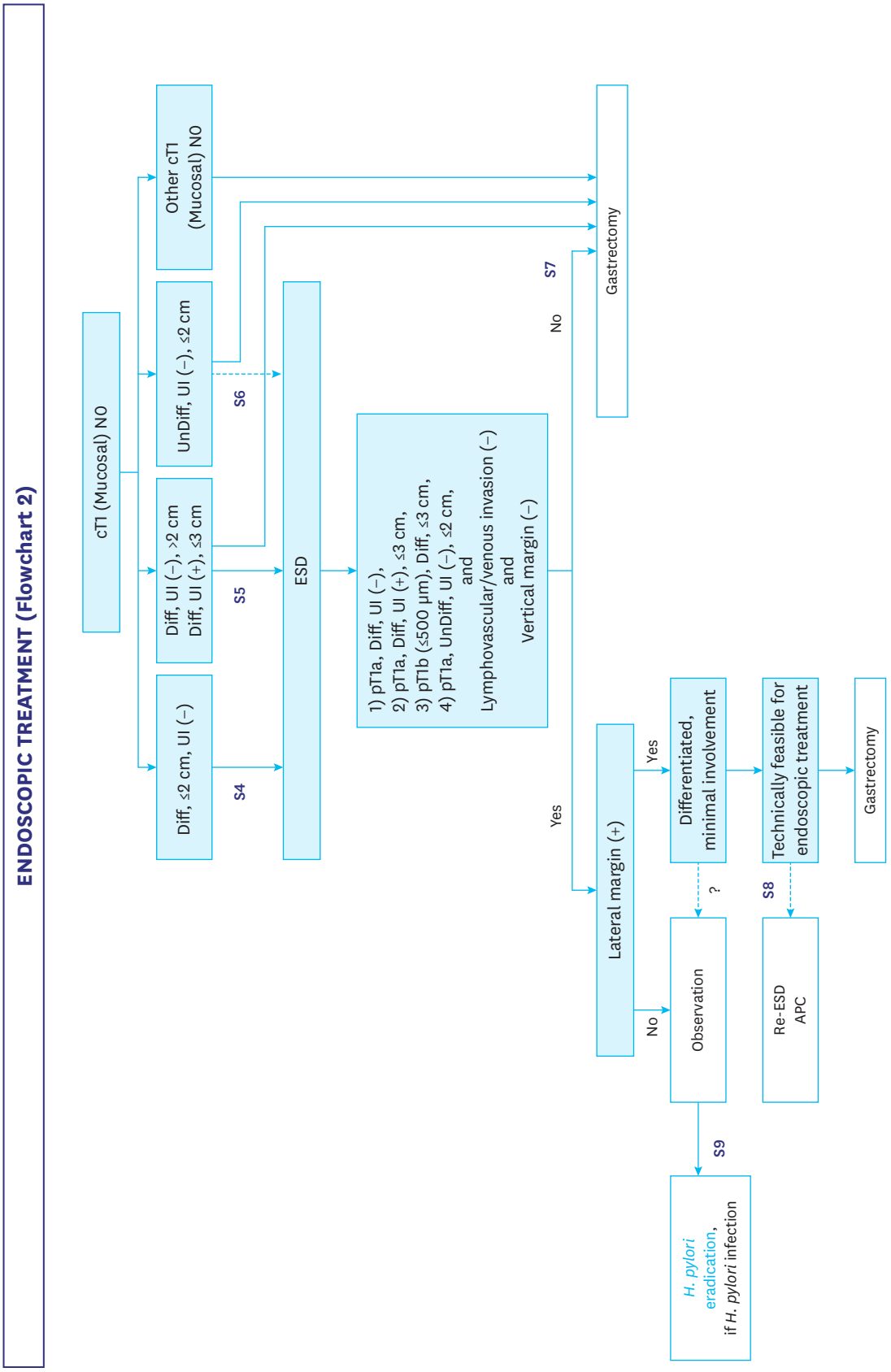

Flowchart 2. Endoscopic treatment.
Diff = well or moderately differentiated; UI = ulcer lesion; UnDiff = poorly differentiated/poorly cohesive (including signet-ring cell); ESD = endoscopic submucosal dissection; APC = argon plasma coagulation.

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S4. Endoscopic resection for EGC meeting classical absolute indications

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).

Since the early 2000s, ESD has been used in Korea as a minimally invasive therapy modality for EGC [136,137]. Data from the Korean National Health Insurance Service System showed 23,828 cases of ESD for EGC between November 2011 and December 2014 [137]. Previous studies have suggested that ESD could be considered as the first-line therapy for mucosal-confined EGC with well or moderately differentiated tubular or papillary adenocarcinoma, with a tumor size ≤2 cm, and no ulcer in the tumor (classical absolute indication) as these characteristics indicate a very low risk of LN metastasis [138]. ESD allows high rates of en bloc curative resection with low adverse event rates [136,139-142]. A large Japanese retrospective study including 5,265 patients who underwent 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 [138]. For lesions meeting 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% [139].

Few studies have directly compared survival between ESD and gastrectomy for classical absolute indications, as many combine cases with classical absolute and expanded indications. In Korean retrospective cohort studies, patients meeting classical absolute indications showed no significant differences in 5-year OS rates (ESD, 93.6%–96.4% vs. gastrectomy, 94.2%–97.2%) or 10-year OS rates (ESD, 81.9% vs. gastrectomy, 84.9%) between treatment methods [140-142].

A small Korean study of 35 endoscopic resections and 20 gastrectomies with classical absolute indications, showed no differences in OS (months) (93.4±3.2 [endoscopic resection], 85.8±5.5 [gastrectomy]) or disease-free survival (DFS) (89.7±3.6 [endoscopic resection], 90.4±3.5 [gastrectomy]) [143]. Similar results were reported in a Japanese study, which found no significant OS difference between endoscopic resection and gastrectomy across age groups (<65 years, ≥65 years) for cases meeting classical absolute indications [144].

Five-year metachronous recurrence rates were higher after endoscopic resection (5.8%–10.9%) compared to gastrectomy (0.9%–1.1%) [140-142]. Close endoscopic surveillance should be performed following ESD for early detection of metachronous cancer.

While endoscopic resection may increase the incidence of metachronous cancer due to preservation of the stomach, it may also offer better quality of life (QOL), shorter hospital stay, lower costs, and fewer treatment-related complication rates compared to gastrectomy [140-143,145].

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S5. Endoscopic resection for EGC meeting expanded indications

KQ 5: Is there a difference in survival rates 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 by the inability to perform LN dissection during the procedure. Therefore, to achieve curative resection with survival outcomes comparable to surgery, EGC cases with a very low risk of LN metastasis should be carefully selected. The clinically acceptable threshold of LN metastasis risk may be equivalent to perioperative mortality rates following radical gastrectomy (0.1%–0.3% in high-volume centers in Korea and Japan) [146-148]. 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%, comparable to that of radical gastrectomy: well or moderately differentiated tubular or papillary adenocarcinoma, en bloc resection, negative lateral and vertical resection margins, no lymphovascular invasion, and either 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 [149-151]. OS was also comparable between patients undergoing endoscopic resection and those treated with radical surgery (93.3%–96.4% vs. 92.0%–97.2%) [140,145,152-162].

Although a number of retrospective cohort studies support ESD, no prospective trials have compared outcomes with those of standard operations based on these criteria, where concerns for node metastases may still exist [150,163-165]. Consequently, gastrectomy with LN dissection may also be a valid treatment option, especially in cases of ESD with technical difficulty or when periodic endoscopic follow-up is not be feasible or affordable.

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S6. Endoscopic resection for EGC meeting relative indications

KQ 6: Is there a difference in the survival rates 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).

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, making endoscopic resection very cautious consideration.

In previous Japanese Gastric Cancer Guidelines, a literature review of the literature that endoscopic resection could be considered for poorly differentiated tubular adenocarcinoma or PCC (including SRCC) in cases with histologic confirmation from forceps biopsy specimens, endoscopically estimated tumor size ≤2 cm, endoscopically mucosal cancer, and no ulcer in the tumor [105]. When these criteria were met, the risk of LN metastasis was reported to range from 0% to 2.3% [166-168].

Under the mentioned endoscopic findings, endoscopic resection could be considered for initial treatment. However, when risk factors for LN metastasis (tumor size >2 cm, submucosal invasion, ulcer in the tumor, and lymphovascular invasion) are revealed in pathologic reports, additional gastrectomy may be necessary [169].

In this guideline, we reviewed recent literature published since the previous edition. Currently, no prospective RCTs have compared the long-term OS of endoscopic resection with that of gastrectomy with LN dissection, which is the standard treatment for these indications [170]. Retrospective studies have shown no difference in OS between gastrectomy and endoscopic resection, though endoscopic resection had a higher local recurrence rate in terms of recurrence-free survival (RFS), which is consistent with the findings of previous studies [145,171,172]. In a prospective, single-arm, phase III observational study in Japan (JCOG1009/1010), the curative resection rate of the endoscopic resection group in undifferentiated EGC was 71% (195/275). Over a 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%) [173]. In Korea, a study on the Comparison of Endoscopic Resection And Surgery for Early Gastric Cancer with undifferentiated histological type: a multicenter RCT (ERASE-GC trial, NCT04890171), is currently ongoing, and its results 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 data from prospective trials are still lacking. Additionally, a significant portion of cases estimated to meet these criteria in the pre-endoscopic resection workup are found to be out these criteria upon pathologic examination of endoscopic resection specimens. Therefore,

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standard surgery (gastrectomy with LN dissection) can also be considered for cases meeting these criteria. It is advisable to choose a treatment method after sufficient discussion with the patient about the possibility of LN metastasis, and complications associated with endoscopic procedure and surgery.

S7. Additional surgery after noncurative endoscopic resection for EGC

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 results of endoscopic resection for EGC do not meet the criteria for curative resection or when lymphovascular invasion or positive vertical margin is present (evidence: low, recommendation: strong for).

Endoscopic resection of EGC could be revealed pathologic characteristics that do not meet the criteria for curative resection. 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 factors indicating the need for further surgical treatment.

As a result of a literature search for reinforcement of the up-to-date guidelines, a total of 17 studies comparing additional surgery to observation for noncurative endoscopic resection were included in the final table of evidence [150,164,174-186]. Most studies indicated a high risk of bias in terms of participant comparability, as those who did not undergo surgery tended to be older and had higher rates of comorbidities compared to those who underwent additional curative surgery [150,164,174-177,179,182,184,186]. In addition, there was a significant difference in tumor-related characteristics between groups [150,164,174,176-178, 180,181,183-185].

The 5-year OS rate across 15 studies was significantly higher in the surgery group than in the observation group [150,164,176,177,181,182,184,186]. Among 12 studies examining disease-specific survival, all but one study showed a survival benefit for additional surgery [164,183,184], although this difference was not statistically significant in several studies [174,176,177,179,181,185,186]. A propensity score matching analysis also showed significantly higher 5-year OS and disease-specific survival rates in the surgery group compared to the observation group (91.0% and 99.0% in the surgery group vs. 75.5% and 96.8% in the observation group) [181].

LN metastasis was found in 2.0%–20.0% of patients who underwent additional surgery following noncurative endoscopic resection [150,164,174,176-178,180-186]. Given the high risk of LN metastasis and the survival benefit associated with curative surgery, additional gastrectomy with LN dissection is recommended when endoscopic resection for EGC does not meet the criteria for curative resection.

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However, the survival benefit of additional surgery in older patients (>75 years) remains controversial [165,179,180,184,187]. For patients with comorbidities or poor general conditions, where curative surgery may not be feasible, observation with regular follow-up could be a valid option, provided the patient gives informed consent after an explanation of the risk of recurrence.

S8. Endoscopic treatment of positive lateral margins after ESD in EGC

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 argon plasma coagulation (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).

It has been reported that there is a minimal risk of LN metastasis with en bloc resection, when only the lateral margin is positive and other criteria for complete resection are met. For differentiated-type EGC with positive lateral margin following ESD, when only close observation was performed, the 5-year local recurrence rate was 11.9% and there was no gastric cancer related mortality [188]. Therefore, close observation, endoscopic treatment (ESD or APC) and gastrectomy are considered as possible treatment options in these cases.

Seven retrospective studies compared recurrence rates among endoscopic treatments (re-ESD and APC), gastrectomy, and close observation [189-195]. In 6 studies with an average follow-up of 60 months (including both differentiated and undifferentiated cancers), local recurrence rates were as follows: 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. In a meta-analysis, endoscopic treatments (re-ESD and APC) significantly reduced recurrence rates compared to close observation (relative risk [RR], 0.22; 95% CI, 0.06 to 0.86; P=0.03) (**Fig. 2A**), but had higher recurrence rates than gastrectomy (RR, 6.45; 95% CI, 1.17 to 35.52; P=0.03) (**Fig. 2B**). Local residual cancer was found in 64.7% of gastrectomy cases (95% CI, 56.8% to 71.9%; 97/150), while LN metastasis rate was 0.6% (95% CI, 0.1% to 1.9%; 1/150). However, all local recurrence cases can be successfully managed with further endoscopic treatment or surgery. Gastric cancer-related mortality was reported in 3 studies, and there was no gastric cancer-related death in the endoscopic treatment group or the observation and gastrectomy groups [189,190,193]. Therefore, considering QOL and mortality associated with 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 gastric cancer-related deaths were reported in any of the 3 groups, the study populations in each study were relatively small, and baseline characteristics differed 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 larger population.

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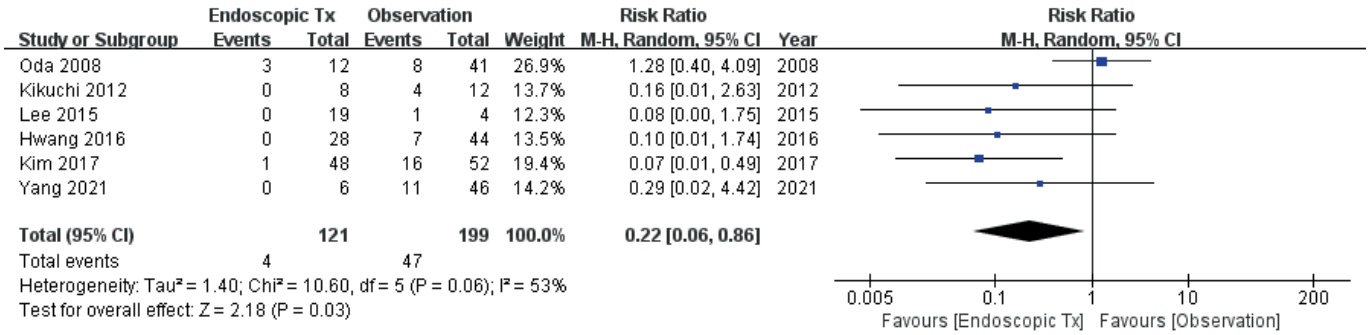

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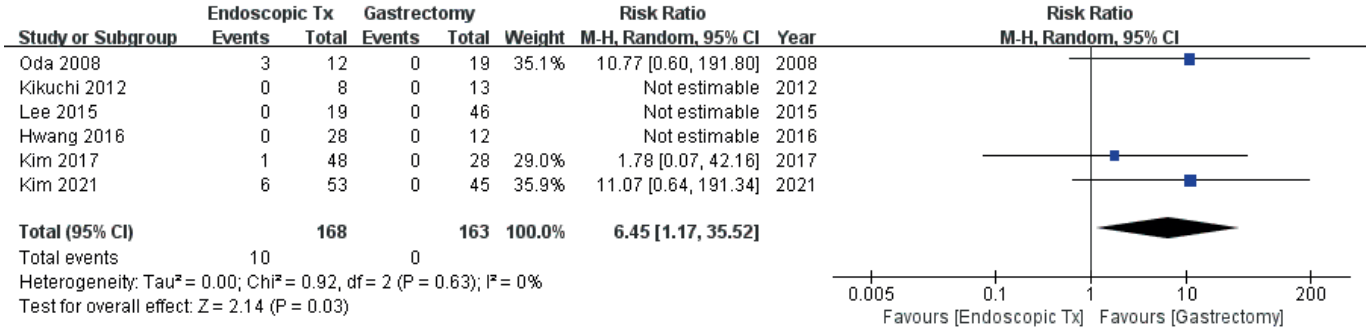

Fig. 2. Forest plot for comparison of local recurrence. (A) Risk of local recurrence in endoscopic treatment group vs. follow-up without therapy group. (B) Risk of local recurrence in endoscopic treatment group vs. gastrectomy.
Tx = treatment; CI = confidence interval; M-H = Mantel-Haenszel.

Three retrospective studies compared gastrectomy and close observation in patients with a positive lateral margin after ESD in differentiated type EGC [189,190,193]. The local recurrence rate in 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). However, cancer-related mortality was zero in both groups. All cases of local recurrence in the observation group can also be managed with additional endoscopic treatment or surgery. Among patients who underwent gastrectomy, local residual cancer was identified in 51.6% of cases (95% CI, 34.8% to 68.0%; 16/31), but the LN metastasis rate was 0% (95% CI, 0% to 0.1%; 0/44). Long-term follow-up studies showed that a cancer-positive lateral margin length longer than 6 mm was significantly associated with local recurrence [188]. Consequently, close observation could be considered a selective treatment option in cases of positive lateral margins in differentiated-type EGC. Recently, a retrospective study was published comparing gastrectomy and non-surgical treatments (endoscopic treatment [6/52] and close observation [46/52]) in undifferentiated-type EGC [195,196]. The local recurrence rate was 0% in the surgical group and 21.2% (11/52) in the non-surgical group. The 5-year survival rate was 87.8% in the non-surgical group, lower than the 95.0% in the surgical group, though the difference was not statistically significant. Therefore, close observation may be considered in elderly patients or those with high morbidity in undifferentiated-type EGC, but additional studies are needed to confirm these findings.

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S9. H. pylori eradication after endoscopic resection for EGC

KQ 9: Can *H. pylori* eradication prevent metachronous gastric cancer in patients successfully treated with endoscopic resection for EGC with *H. pylori* infection?

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

In 1999, the WHO classified *H. pylori* as the first-class carcinogen for gastric cancer, and it infects approximately 50% of the global population. Eradication *H. pylori* has shown significant benefits for asymptomatic infected individuals (pooled incidence rate ratio, 0.62; 95% CI, 0.49 to 0.79) [197], making eradication of *H. pylori* an important strategy to prevent gastric cancer.

Eradication of *H. pylori* is also crucial for the prevention of metachronous gastric cancer in patients who have been successfully treated by endoscopic resection of EGC with *H. pylori* infection. We identified 3 RCTs that observed the incidence of metachronous gastric cancer and precancerous lesions in patients treated with *H. pylori* eradication vs. those who did not receive eradication treatment following successful endoscopic resection for EGC [198,199]. The median follow-up periods were 3–5 years. During follow-up, the incidence of metachronous gastric cancer and precancerous lesions was 4.80% (41/856) in the *H. pylori* eradiation group and 9.75% (87/892) in the non-eradiation group. The risk of developing metachronous gastric cancer and precancerous lesions was significantly lower in the eradication group (HR, 0.45; 95% CI, 0.31 to 0.66) (**Fig. 3**). Additionally, the study by Fukase et al. [198], which focused solely on metachronous gastric cancer, showed a significant benefit from *H. pylori* eradication (HR, 0.34; 95% CI, 0.16 to 0.73). Therefore, *H. pylori* eradication is helpful for the prevention of metachronous gastric cancer in patients who have been successfully treated by endoscopic resection of EGC with *H. pylori* infection.

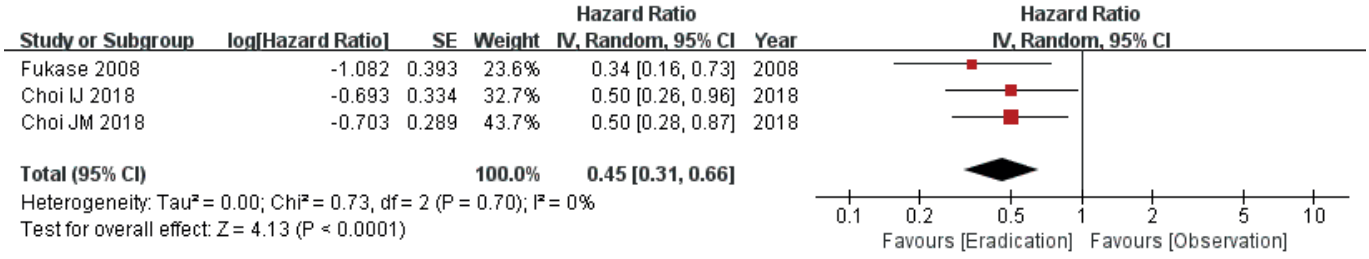

Fig. 3. Forest plot for a comparison of the risk of metachronous gastric cancer between *Helicobacter pylori* eradication vs. no treatment.
SE = standard error; IV = interval variable; CI = confidence interval.

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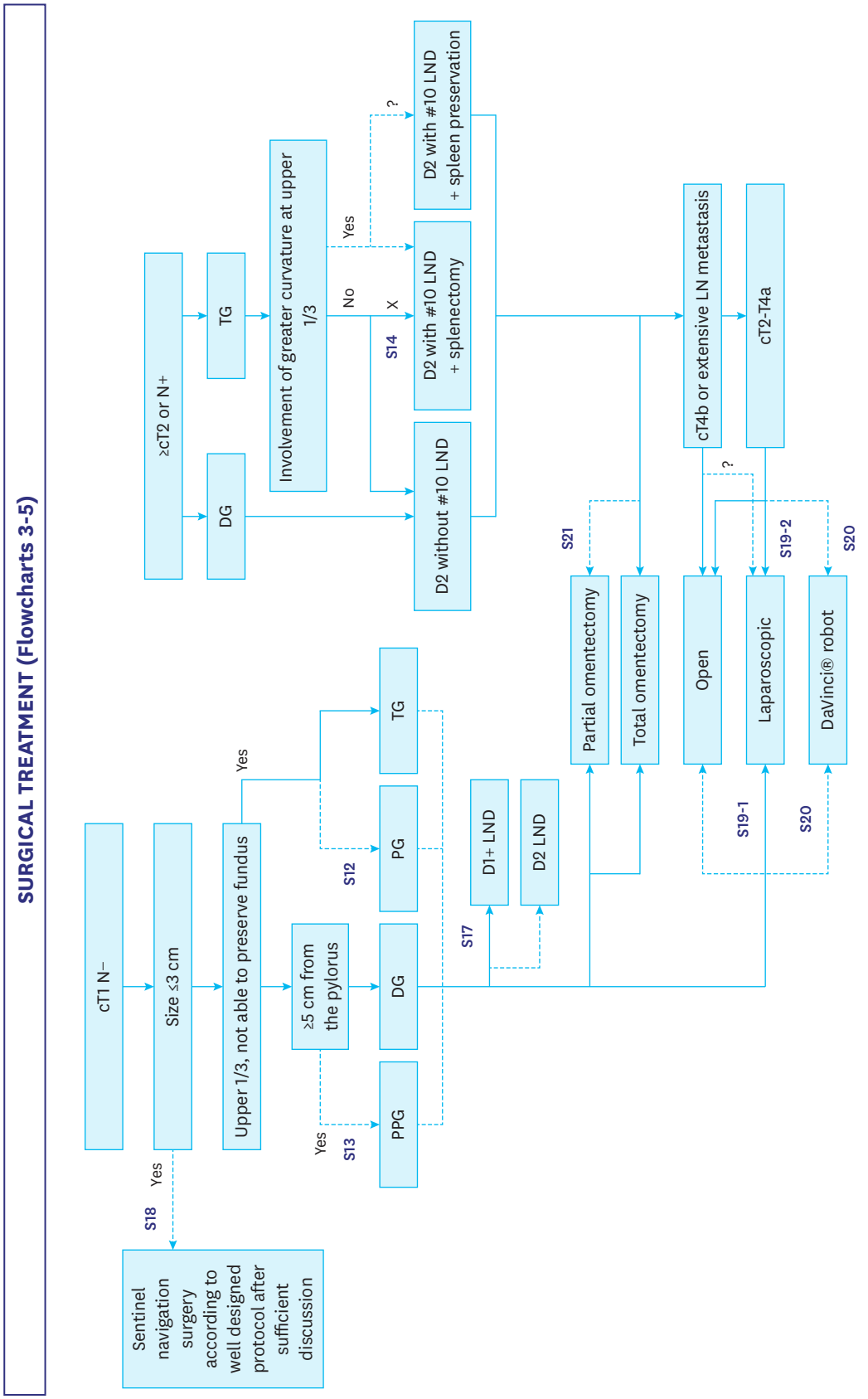

Flowchart 3. Approach and extent of gastrectomy.
DG = distal gastrectomy; TG = total gastrectomy; PPG = pylorus-preserving gastrectomy; PG = proximal gastrectomy; LND = lymph node dissection; LN = lymph node.

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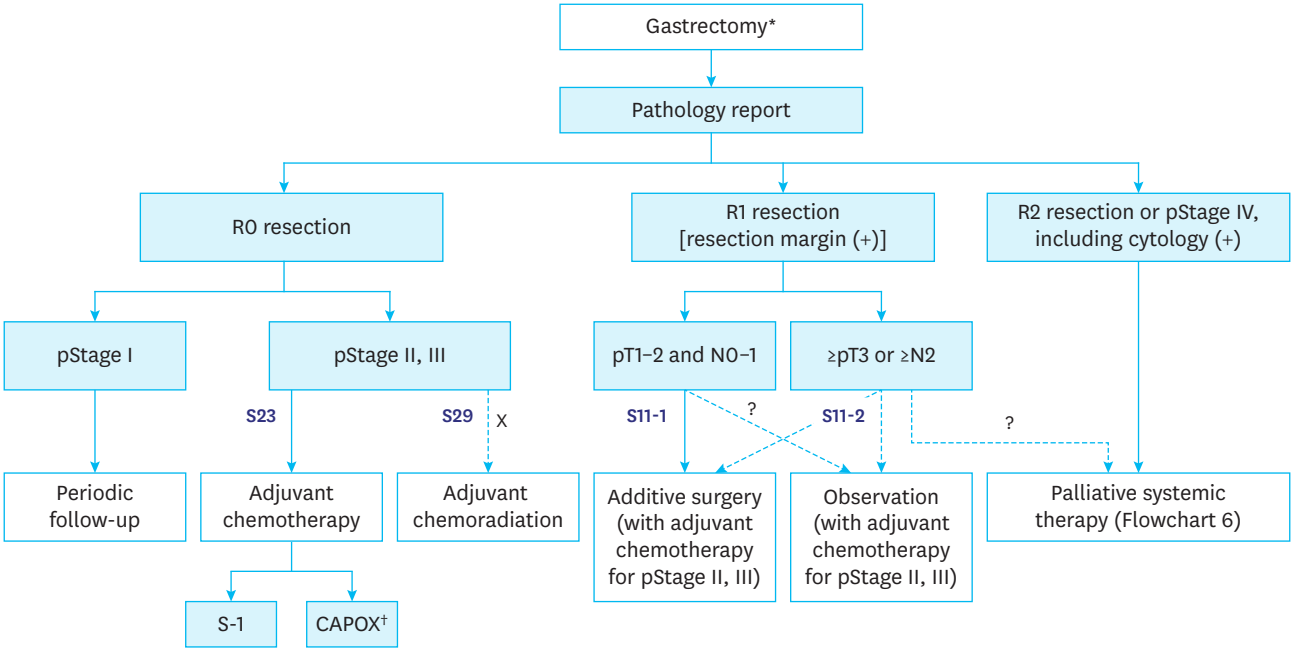
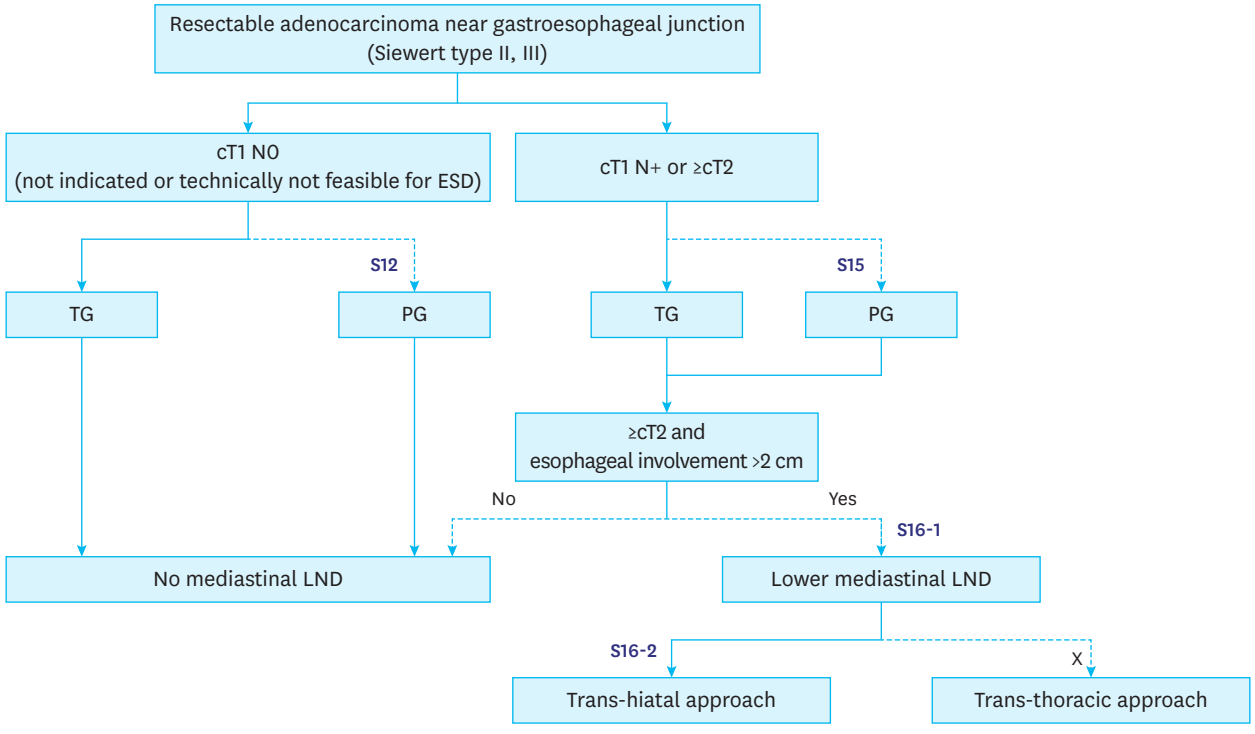


Flowchart 4. Treatment plans after gastrectomy.
LN = lymph node; CAPOX = capecitabine and oxaliplatin.
*To obtain negative margin, single or combinations of various methods including intraoperative frozen section, perioperative gastroscopy, various preoperative clipping or dyeing, fluorescence imaging 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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S10. Reconstruction methods following distal gastrectomy (DG)

KQ 10: Is Roux-en-Y (RY) and Billroth I (BI) reconstruction better than Billroth II (BII) reconstruction following DG in gastric cancer in terms of 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 vary depending on the reconstruction method including BI, BII, and RY [200].

Well-designed studies directly comparing each reconstruction method are rare. In our meta-analysis, which included 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 [201,202]. There was no significant difference in complications (P=0.10). BI was also more favorable than RY in terms of operation time (P<0.01), complications (P=0.01), and hospital stay (P<0.01) [201,203-206]. Other benefits of BI include decreased risk of iron deficiency anemia, preservation of alimentary tract continuity, no risk of Petersen hernia, reduced small bowel adhesions, and easier access to the duodenum and biliary tract in cases of biliary diseases [207-210] (**Fig. 4**).

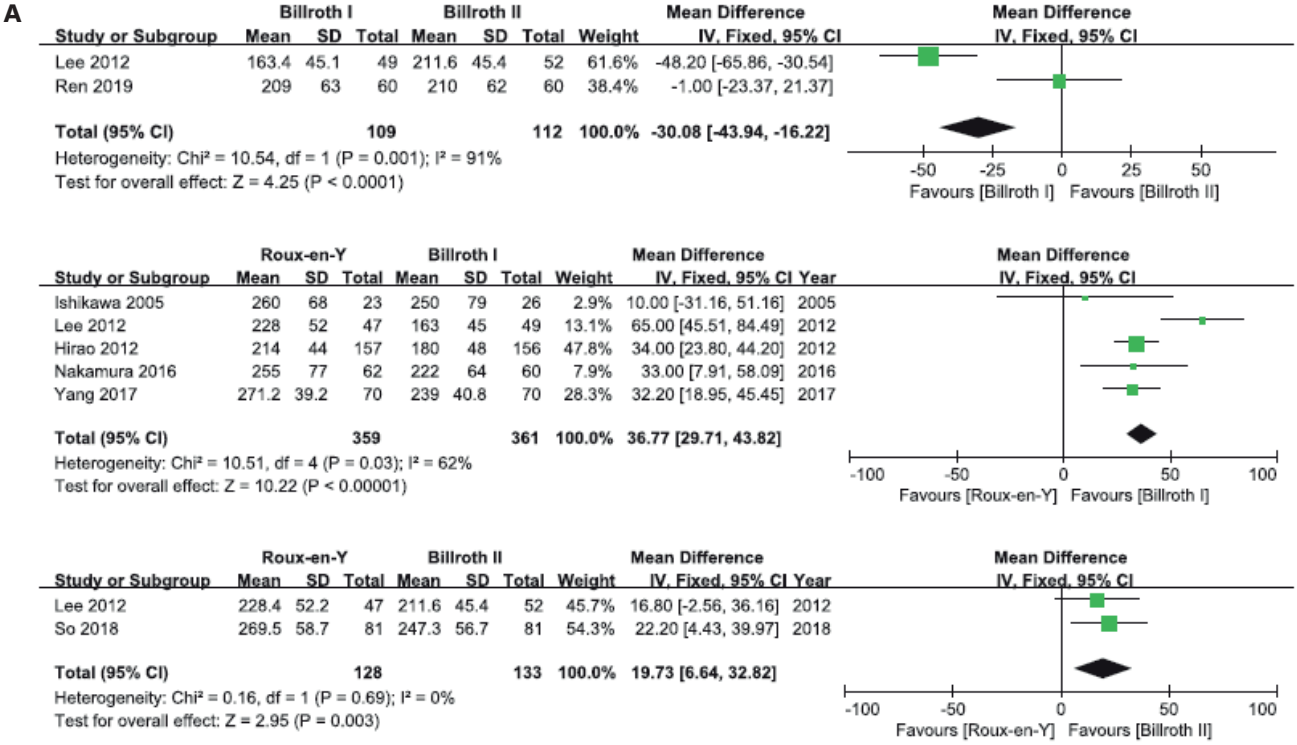

Fig. 4. Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stays. (D) Bile reflux. (E) Esophageal reflux.
SD = standard deviation; IV = interval variable; M-H = Mantel-Haenszel; CI = confidence interval.
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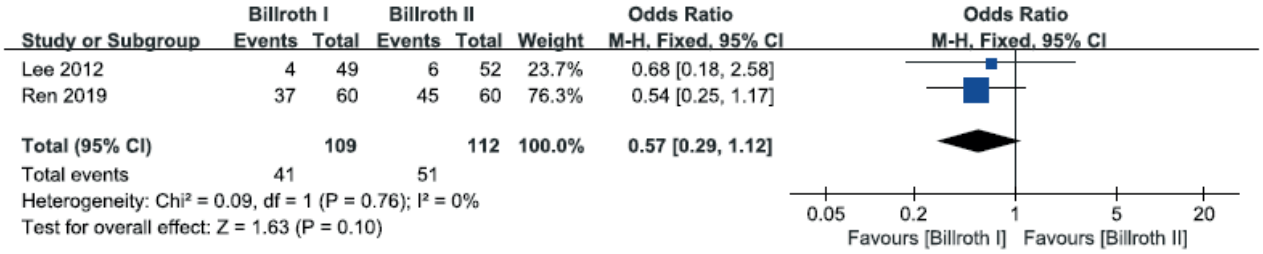

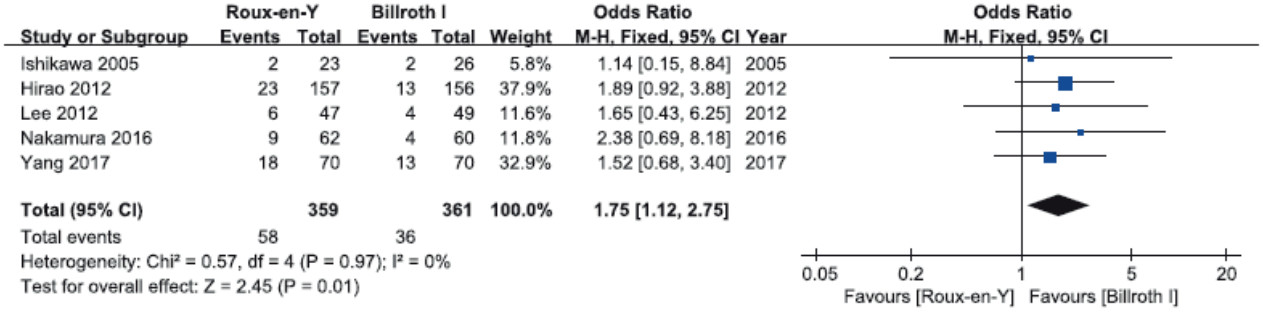

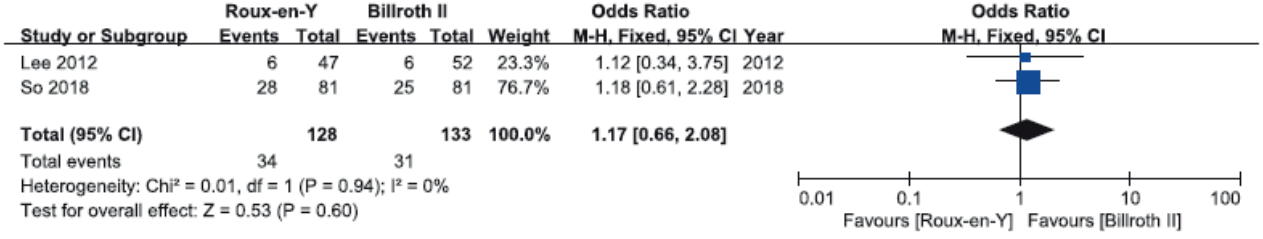

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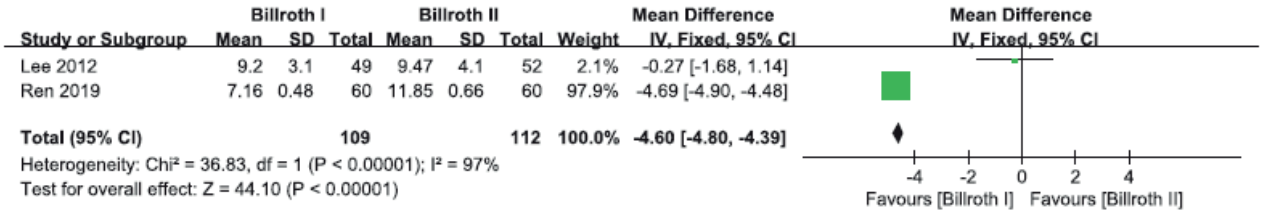

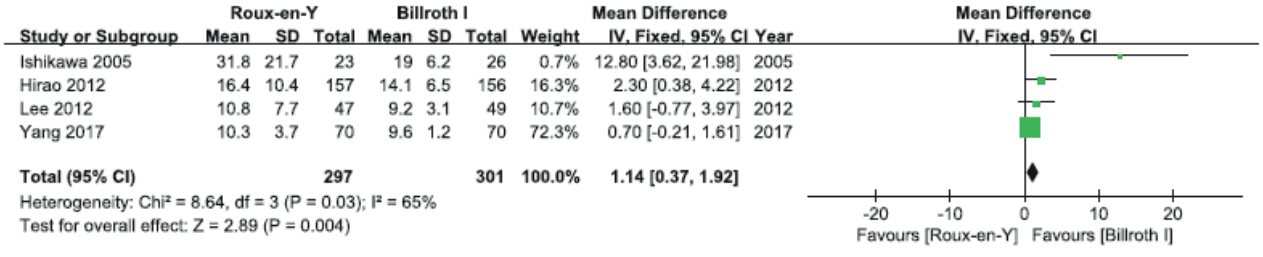

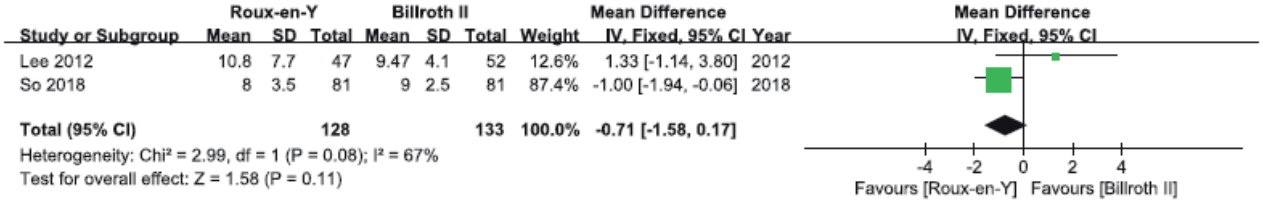

Fig. 4. (Continued) Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stays. (D) Bile reflux. (E) Esophageal reflux. SD = standard deviation; IV = interval variable; M-H = Mantel-Haenszel; CI = confidence interval.

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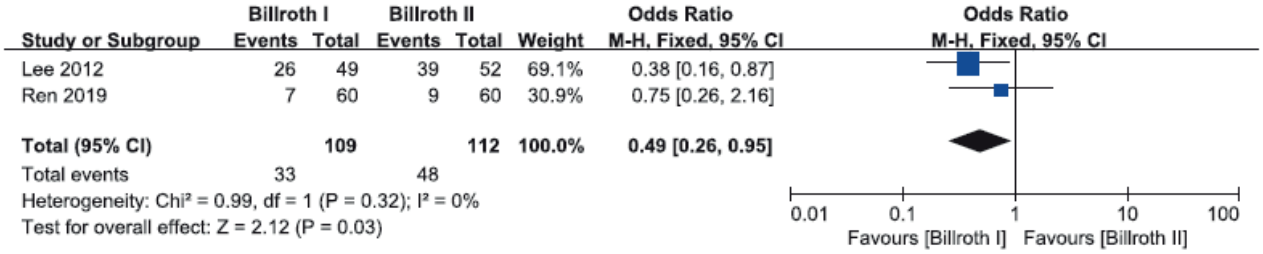

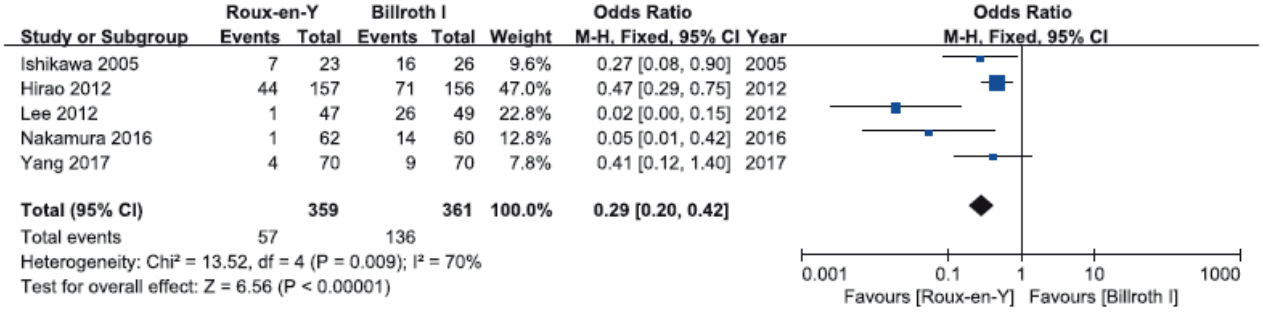

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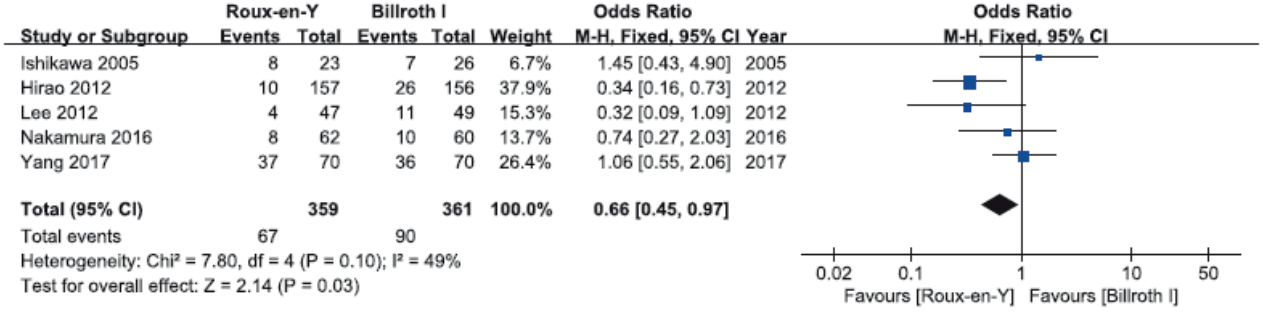

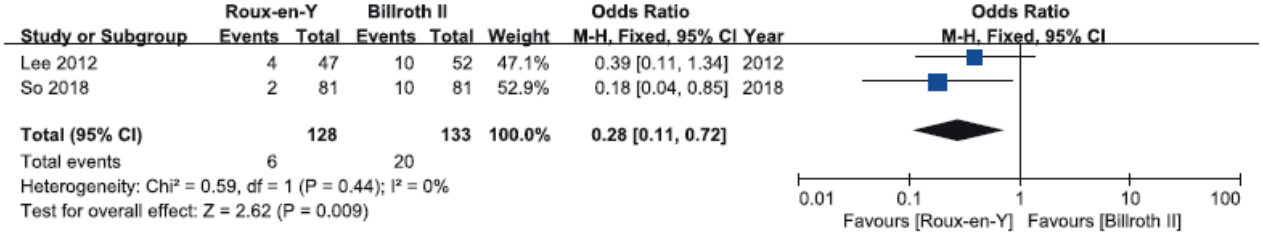

Fig. 4. (Continued) Forest plots comparing reconstruction methods. (A) Operation time. (B) Complications. (C) Hospital stays. (D) Bile reflux. (E) Esophageal reflux. SD = standard deviation; IV = interval variable; M-H = Mantel-Haenszel; CI = confidence interval.

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RY reconstruction showed advantages in preventing bile and esophageal reflux on endoscopic findings [201,203-206,211]. However, current evidence is insufficient to confirm whether endoscopic bile reflux directly leads to superior QOL or the prevention of metachronous cancer. 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 [209,212].

There was no significant difference in QOL (P=0.290–0.994) or nutritional parameters (e.g., weight loss, albumin) among the 3 reconstruction methods [201,213]. Additionally, there is insufficient evidence to suggest differences in survival outcomes among reconstruction methods [214].

In summary, the experts in the guideline task force team could not recommend a specific reconstruction method as the best option for all cases, given the unique advantages and disadvantages of each reconstruction method. We recommend that surgeons select the optimal method according to the characteristics of the cancer and the patients.

S11. Resection margin

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

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

The impact of microscopically positive margin status varies according to the pathologic status of the cancer [215,216]. In our review, positive resection margins correlated with inferior survival outcomes compared to negative margins in pathologic T1 cancers (Nagata et al. [217] [68.6% vs. 97.4%, P<0.0001], Sun et al. [216] [66.7% vs. 93.1%, P<0.04]) and T2 cancers (Sun et al. [216] [21.5% vs. 55.2%, P<0.001], Morgagni et al. [218] [8% vs. 64%, P<0.001]).

There is a debate regarding whether achieving an adequate length of margin may influence oncologic outcome in EGC [215,219-221]. However, most literature agrees that attaining a negative margin regardless of margin length, is associated with improved survival [220,222,223]. Various methods, used alone or in combination, have been introduced to achieve negative margin, including intraoperative frozen section, perioperative gastroscopy, preoperative clipping or dyeing, fluorescence imaging techniques, ultrasonography, and simple X-ray, among others [224-232].

In cases of EGC, when pathologic results reveal tumor involvement at the resection margin, several studies showed a survival benefit with additional surgery to obtain R0 resection [222,223,233]. Therefore, development of this guideline made a consensus to recommend additional surgery when the patient's condition is favorable and additional surgery is technically feasible.

However, there were reports showing that R1 resection does not always lead to recurrence, potentially due to lack of blood supply on the remnant transection line, discrepancy of true

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surgical margin from the use of surgical stapler or patients' immunity [215,217]. Careful observation with frequent follow-up might be cautiously considered when the extent of the involved margin is minimal or the anticipated risk of reoperation is high. Further investigations are needed to clarify the indications for cases where additional surgery may not be required.

> Statement 11-2: Efforts should be made to achieve negative margins in surgery for advanced or infiltrative gastric cancer. If the final postoperative pathologic margin shows involvement of the margin, reoperation to achieve R0 resection 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).

Previous reports have recommended various macroscopic margin lengths (3–8 cm) to ensure pathologic negative resection margins in advanced or infiltrative cancer [231,234,235]. Intraoperative frozen section has shown improved accuracy compared to macroscopic margin prediction in achieving R0 resection [228,231,236-238]. The methods mentioned earlier to achieve negative margins can also benefit advanced cancer cases to obtain secure margins and tumor localization.

Unlike in early-stage gastric cancer, many studies have shown that a positive microscopic margin had no prognostic impact when staging was ≥T3 or ≥N2 or ≥IIIa (American Joint Committee on Cancer [AJCC] 7th) [216,219,220,222,239-243]. In these cases, achievement of a negative margin has shown limited survival benefits.

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

S12. Proximal gastrectomy (PG) with double tract reconstruction (DTR)

KQ 12: Can PG with DTR show better outcomes than total gastrectomy (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 the 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, making PG an acceptable and oncologically safe option [244,245]. However, reconstruction after PG has posed challenges due to the high incidence of reflux esophagitis and anastomosis stricture in esophagogastrostomy.

DTR has recently been shown to be feasible in laparoscopic settings. In our systematic review of retrospective studies, significantly fewer patients in the PG-DTR group experienced

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vitamin B12 deficiency compared to those in the TG group (RR, 0.30; 95% CI, 0.23 to 0.40; P<0.01) [246-248]. Weight loss after surgery did not differ between the groups (RR, −4.89; 95% CI, −11.75 to 1.97; P=0.16) [248,249]. Reflux symptoms were also comparable (RR, 1.28; 95% CI, 0.33 to 4.93, P=0.72) [247,250,251]. 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**).

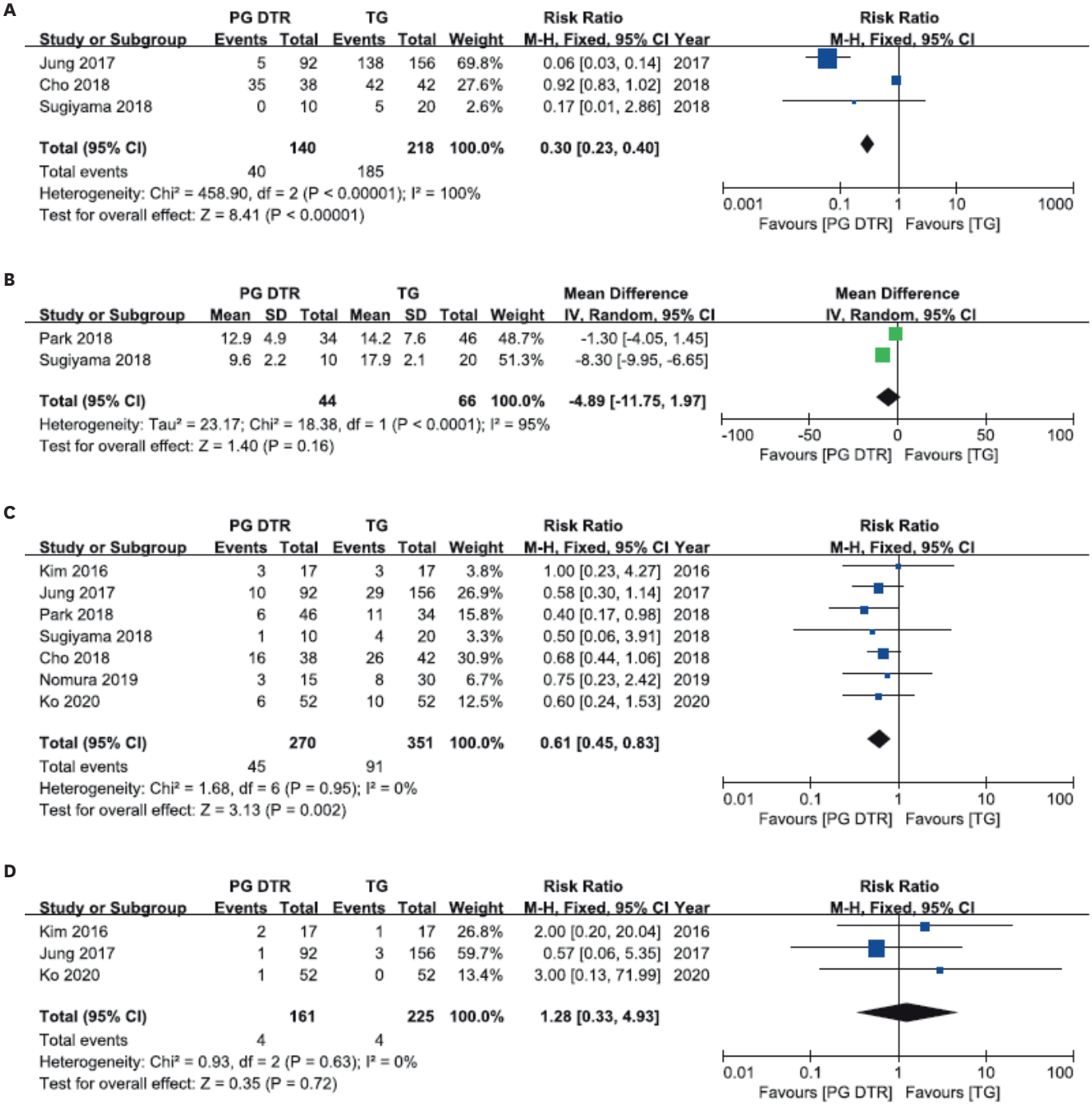

Fig. 5. Forest plots for comparison between PG DTR vs. TG in retrospective studies. (A) Vitamin B12 deficiency. (B) Weight loss. (C) Early complications. (D) Reflux symptom. PG = proximal gastrectomy; DTR = double tract reconstruction; TG = total gastrectomy; IV = interval variable; M-H = Mantel-Haenszel;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

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The Korean Laparoendoscopic Gastrointestinal Surgery Study Group conducted a prospective RCT comparing LPG-DTR and laparoscopic TG (KLASS-05) and recently reported early results. The cumulative amount of intramuscular vitamin B12 supplementation required over 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%, P<0.001). However, hemoglobin changes after surgery, one of the primary outcomes, were not significantly different between the groups (5.6%±7.4% vs. 6.9%±8.3, P=0.349). Additionally, the Visick score for reflux symptoms at 2 weeks postoperatively (P=0.793) and postoperative complications (23.5% vs. 17.4%, P=0.373) were not different between the groups [252].

In 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) [252]. Regarding long-term QOL, the PG-DTR group showed better on the physical functioning (P=0.029) and social functioning (P=0.031) scales of the European Organization for Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30).

Recently, alternative reconstruction techniques such as side overlap esophagogastrostomy, double flap technique (DFT) reconstruction are being explored for better functional outcomes. Some studies show that DFT has better outcomes than TG in terms of morbidity, postoperative hospital stay, reflux esophagitis, and postoperative nutritional status [253]. However, laparoscopic PG with DFT requires more complex intracorporeal suturing technique and longer operation time [254]. Further studies are needed to provide higher level of evidence [255,256].

S13. Pylorus-preserving gastrectomy (PPG) vs. DG for middle third gastric cancer

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

Statement 13: For EGC located at least 5 cm proximal to the pylorus, PPG as well as DG could be performed. PPG has the benefits of reduced gallstone formation and better 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 rapid food transit into the duodenum and reduce reflux of duodenal contents. Consequently, the reduced 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 comparing laparoscopic PPG and laparoscopic DG (KLASS-04) reported its findings [257,258].

The study found no significant differences in survival outcomes or complications between the PPG and the DG groups [257]. Additionally, the incidence of dumping syndrome one year after surgery was similar between the groups (13.2% vs. 15.8%, P=0.62). However, 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 postoperatively.

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Conversely, bile reflux (13.2% vs. 24.4%, P=0.02) and gallstone formation (2.3% vs. 8.7% P=0.03) were less frequent in the PPG group than in the DG group.

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

In several studies, there were no differences in survival outcomes or postoperative complications between PPG and DG [258-263]. The PPG group experienced a lower incidence of postoperative dumping syndrome and reflux [261,263,264]. Some studies also reported reduced development of gallstones after PPG, probably due to the preservation of the hepatic branch of the vagus nerve [259,261]. However, delayed gastric emptying was reported more frequently with PPG than DG [259,261-264].

Regarding nutritional status, decreases in serum protein and albumin levels during the first 6 months postoperatively and reductions in abdominal fat area at one year, were lower in the PPG group than in the DG group. Additionally, hemoglobin levels improved more in the PPG group than in the DG group [259,262,263,265].

Two years after surgery, PPG showed trends toward better improvement of QOL and fewer symptoms than DG with BI reconstruction [265]. The PPG group had a better physical functioning score (86.7 vs. 90.0, P=0.032) but reported more 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) [263].

In summary, PPG showed benefits in reducing gallstone formation, bile reflux and preserving serum total protein, while survival, postoperative complications and QOL were similar to DG as shown in KLASS-04. Observational studies further reported possible nutritional and functional benefits of PPG. For EGC located at least 5 cm proximal to the pylorus, PPG could be a viable option; however, delayed gastric emptying should be carefully considered in decision-making.

S14. Prophylactic splenectomy for splenic hilar LN dissection in proximal-third AGC

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

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

The standard surgical procedure for proximal-third gastric carcinoma is TG with appropriate 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 should be performed in the absence of direct invasion of the spleen, splenic hilum, or greater curvature of the stomach.

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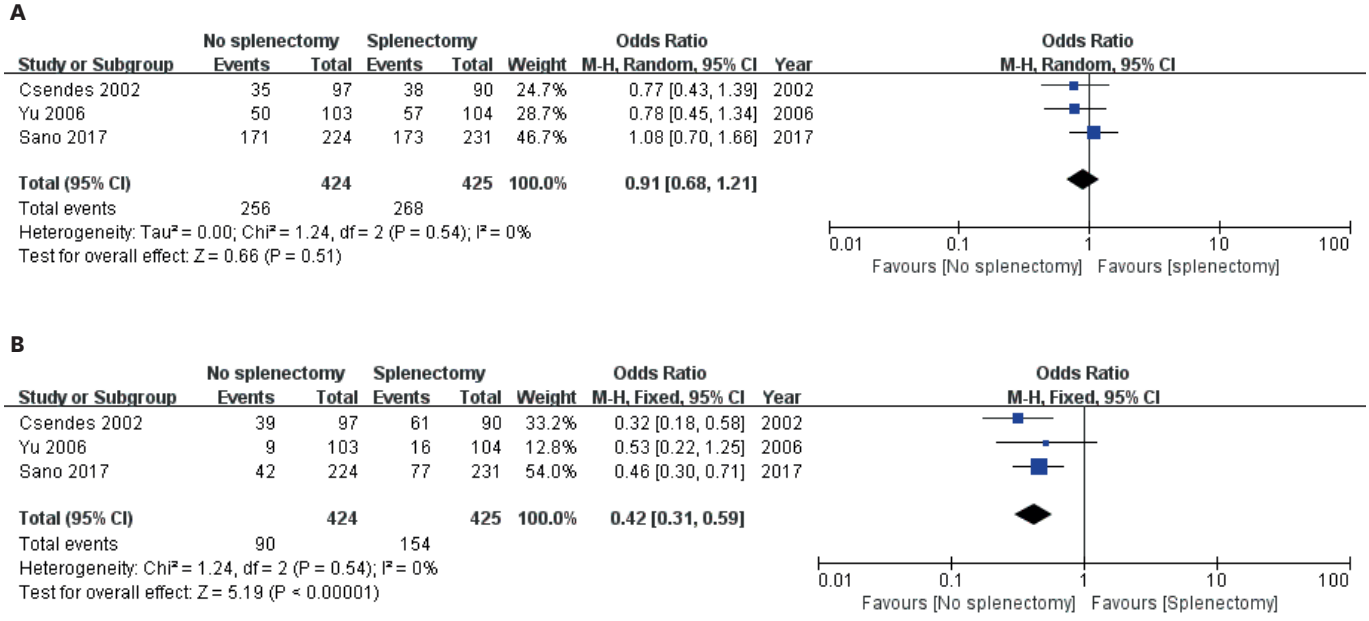

Fig. 6. Forest plot for a comparison between no splenectomy vs. splenectomy. (A) Survival. (B) Complications.
M-H = Mantel-Haenszel; CI = confidence interval.

Three prospective RCTs have evaluated the survival benefit of prophylactic splenectomy in proximal-third gastric carcinoma [266-268]. Our meta-analysis showed no survival difference between groups (HR, 0.91; 95% CI, 0.68 to 1.21; P=0.51), but significantly fewer postoperative complications in the group without splenectomy (HR, 0.42; 95% CI, 0.31 to 0.59; P<0.01) (**Fig. 6**).

The studies included in our meta-analysis excluded cases of advanced cancer with gross involvement of the greater curvature or the gastrosplenic ligament, where the metastasis rate of LN#10 is relatively high, and splenic hilar dissection with splenectomy is necessary for standard treatment [269-271].

In all situations, splenectomy is associated with increased postoperative complications and mortalities. To address this, operative techniques for LN#10 dissection around the splenic hilum without splenectomy has been reported; however, its oncologic outcomes are still under investigation [272-274].

S15. PG for GEJ adenocarcinoma

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 AGC 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).

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TG is the standard treatment for AGC in the upper part of the stomach [109,235,275]. However, some studies have questioned whether removing the entire stomach along with the perigastric tissues and LNs may be unnecessary in selected cases [244,276,277].

Our meta-analysis included 5 retrospective studies that investigated LN mapping of proximal gastric cancer following TG [276-280]. In the pooled data, the metastasis rates to distal LN station #4d, #5, and #6 (distal LN) 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 2.48 (CI, 0.86 to 7.15) compared to pT2 (P=0.09), and the risk ratio for pT4 was 10.88 (CI, 4.95 to 23.91) compared to pT2 (P<0.01) (**Fig. 7**).

In a retrospective study in Korea involving 873 patients [244], multivariable analysis identified a distance greater than 30 mm from the GEJ to the tumor epicenter, tumor size >70 mm, macroscopic Bormann type IV tumor, and serosa invasion as risk factors for LN metastasis to the distal stomach. In patients without these risk factors, the LN metastasis rates at stations

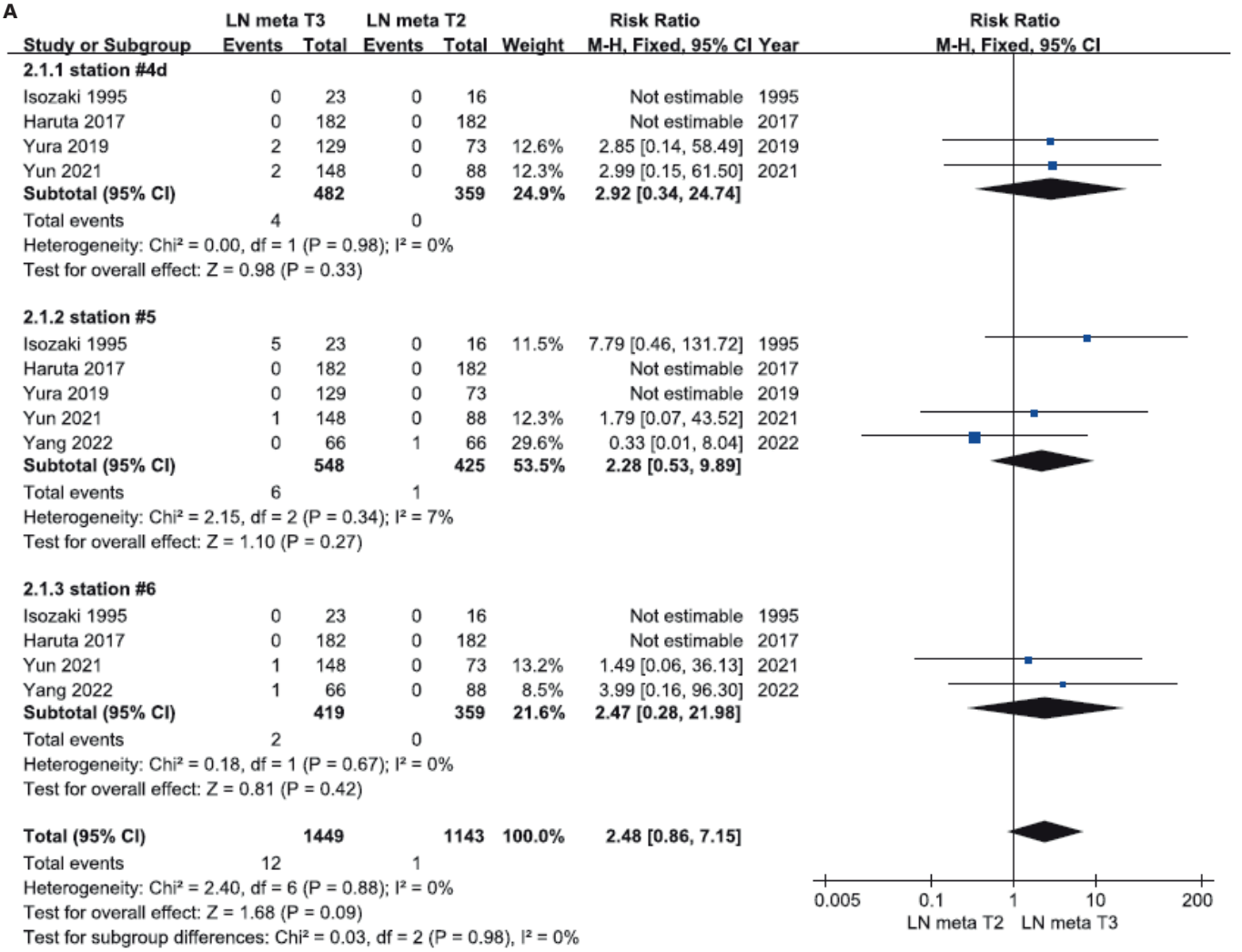

Fig. 7. Forest plot, LN metastasis rates of distal stomach according to the depth of tumor. (A) T2 vs. T3. (B) T2 vs. T4.
M-H = Mantel-Haenszel; LN = lymph node; CI = confidence interval.

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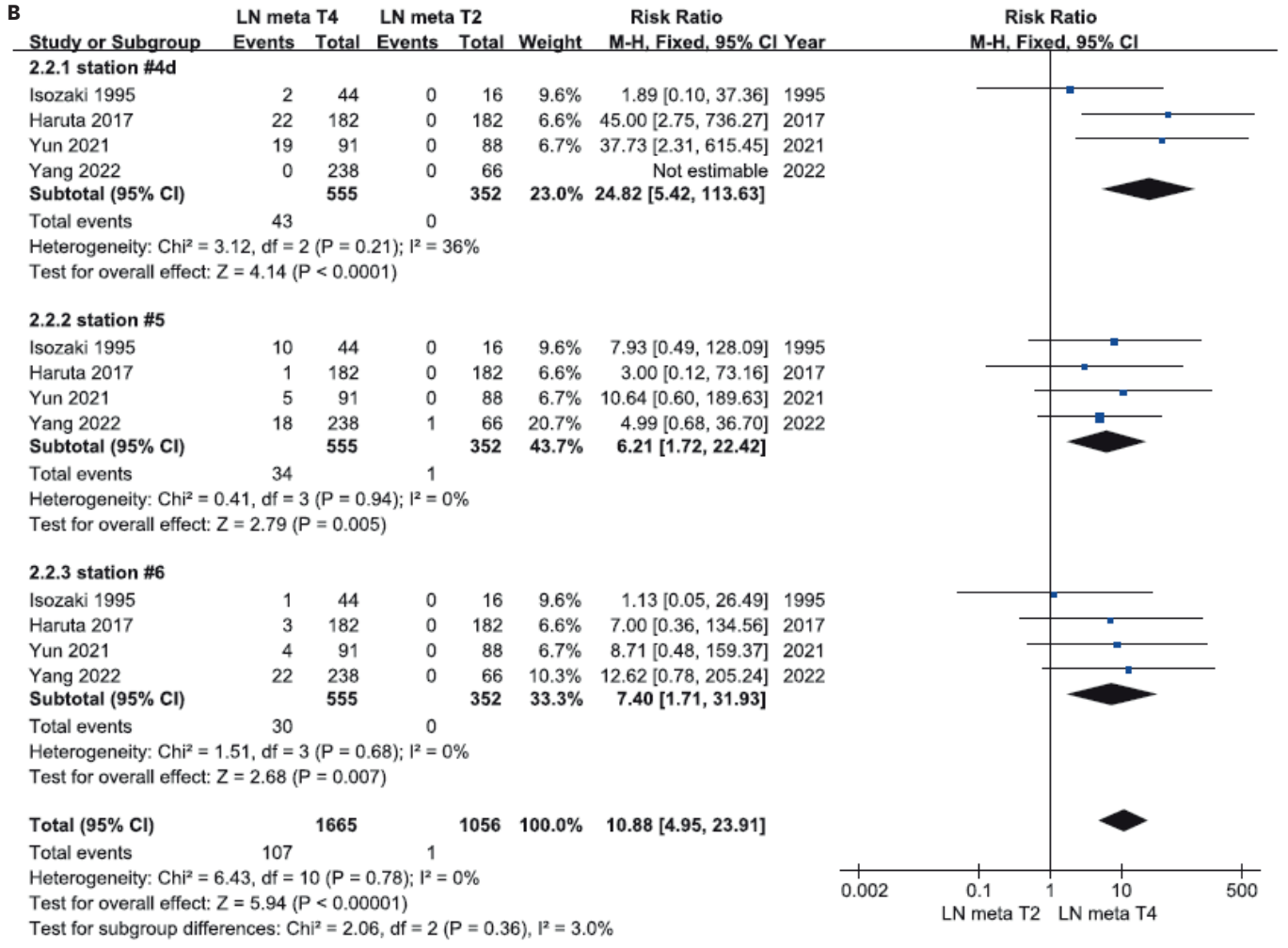

Fig. 7. (Continued) Forest plot, LN metastasis rates of distal stomach according to the depth of tumor. (A) T2 vs. T3. (B) T2 vs. T4.
M-H = Mantel-Haenszel; LN = lymph node; CI = confidence interval.

#4d, #5, and #6 were 0.0%, 0.4%, and 0.4%, respectively. The therapeutic value index (TVI) of LN #4d, #5, and #6 were 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) [270].

These results suggest that PG without dissection of LN stations #4d, #5, and #6 could be considered in selected cases of AGC with adenocarcinoma histology located in the GEJ (Siewert II/III) without serosal invasion. However, further data are needed to determine the detailed indications for PG and to evaluate the clinical outcomes of PG.

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S16. Lower mediastinal LN dissection and surgical approach for GEJ adenocarcinoma

KQ 16: Can additional lower mediastinal LN dissection improve oncologic outcomes for adenocarcinoma invading the 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 its epicenter within 5 cm proximal and distal of the anatomical cardia and categorizing it into 3 types: type 1 (lower esophageal cancer), type 2 (true GEJ cancer), and type 3 (subcardial cancer) [281]. 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 [15].

It is generally acknowledged that Siewert type I and type III carcinomas are usually treated as esophageal and gastric tumors, respectively [282,283]. 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, primarily seen 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 Korean retrospective analysis including 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 [284], suggested that lower mediastinal LN dissection may not be necessary 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.

Conversely, 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. This led to the suggestion that a TH approach without complete mediastinal LN dissection can be acceptable for common types of GEJ cancer in Korea [285].

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 [23].

In summary, lower mediastinal LN dissection seems to be not essential for early GEJ cancers. For advanced GEJ cancers, 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 are needed to determine its impact on local recurrence and survival benefits.

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

Two RCTs on the optimal surgical approach for GEJ adenocarcinoma (Siewert type II, III) compared the surgical and oncological outcomes between the TH and TT approaches (one left thoracoabdominal approach and one right thoracotomy) [286,287]. Our meta-analysis of these RCTs (**Fig. 8**) found comparable in-hospital mortality (P=0.10) and anastomosis leakage (P=0.57) between the TT and TH approaches. Although the Japanese RCT (JCOG9502) comparing the left thoracoabdominal and the TH approaches was stopped after interim analysis, the 5-year OS of the TH approach was not inferior to the TT approach (HR, 0.74; CI, 0.42 to 1.32; P=0.31) in both RCTs [286,287].

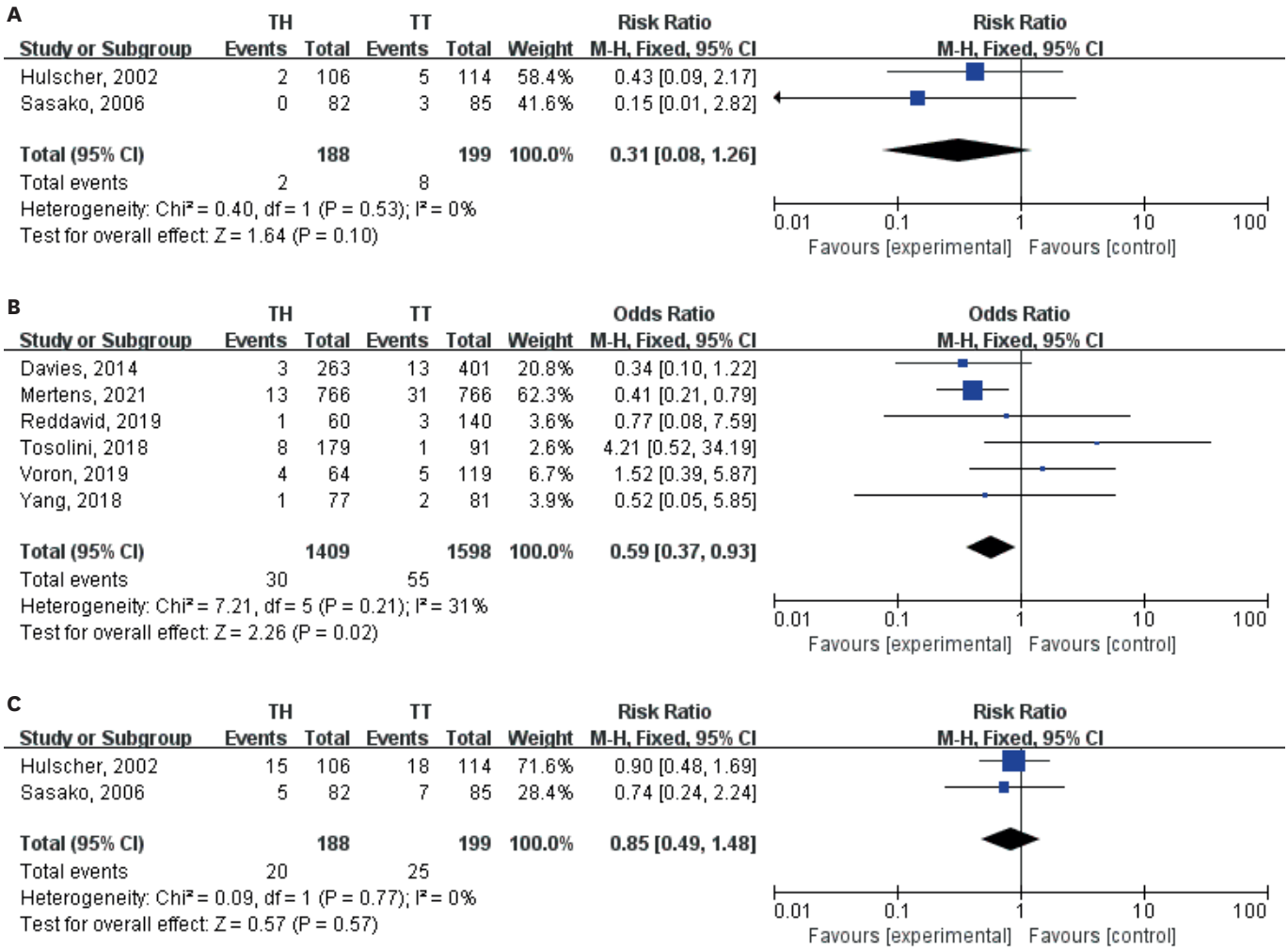

Fig. 8. Forest plots for comparisons between the TH abdominal approach (Experimental) vs. TT approach (Control). TT approaches in the observational studies included. In-hospital mortality: (A) RCTs, (B) Observational studies. Anastomosis leakage: (C) RCTs, (D) Observational studies. Pulmonary complications: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

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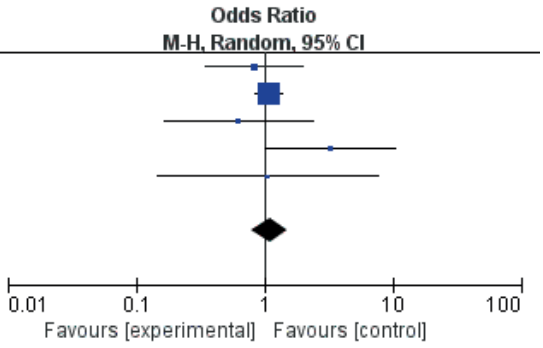
D

Study or Subgroup	TH Events	TH Total	TT Events	TT Total	Weight	Odds Ratio M-H, Random, 95% CI
Blank, 2017	22	186	8	58	12.7%	0.84 [0.35, 2.00]
Mertens, 2021	149	766	140	766	71.6%	1.08 [0.84, 1.39]
Tosolini, 2018	5	179	4	91	5.7%	0.63 [0.16, 2.39]
Voron, 2019	8	64	5	119	7.4%	3.26 [1.02, 10.41]
Yang, 2018	2	77	2	81	2.6%	1.05 [0.14, 7.67]
Total (95% CI)		**1272**		**1115**	**100.0%**	**1.10 [0.79, 1.52]**
Total events	186		159			

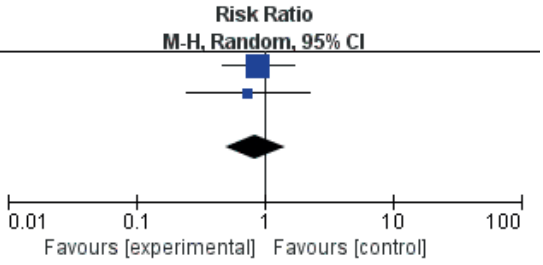
Heterogeneity: Tau² = 0.02; Chi² = 4.43, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.57 (P = 0.57)



E

Study or Subgroup	TH Events	TH Total	TT Events	TT Total	Weight	Risk Ratio M-H, Random, 95% CI
Hulscher, 2002	15	106	18	114	75.4%	0.90 [0.48, 1.69]
Sasako, 2006	5	82	7	85	24.6%	0.74 [0.24, 2.24]
Total (95% CI)		**188**		**199**	**100.0%**	**0.86 [0.49, 1.48]**
Total events	20		25			

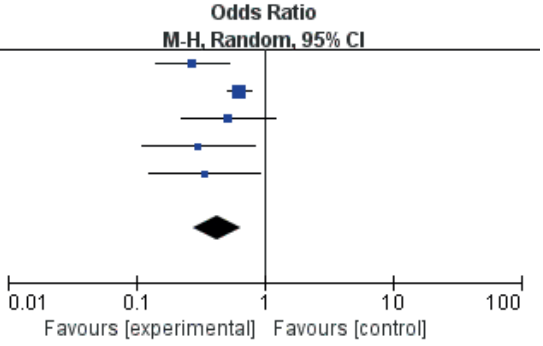
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)



F

Study or Subgroup	TH Events	TH Total	TT Events	TT 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)



G

Study or Subgroup	TH Events	TH Total	TT Events	TT 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)

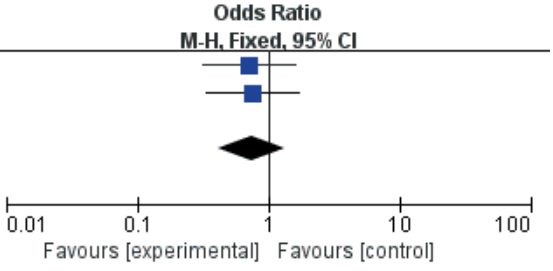


Fig. 8. (Continued) Forest plots for comparisons between the TH abdominal approach (Experimental) vs. TT approach (Control). TT approaches in the observational studies included. In-hospital mortality: (A) RCTs, (B) Observational studies. Anastomosis leakage: (C) RCTs, (D) Observational studies. Pulmonary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

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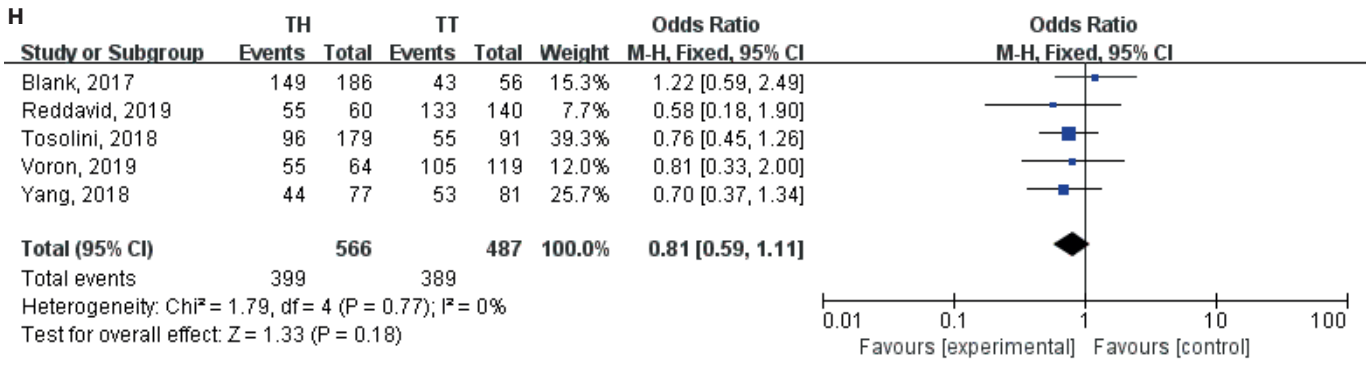

Fig. 8. (Continued) Forest plots for comparisons between the TH abdominal approach (Experimental) vs. TT approach (Control). TT approaches in the observational studies included. In-hospital mortality: (A) RCTs, (B) Observational studies. Anastomosis leakage: (C) RCTs, (D) Observational studies. Pulmonary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

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) compared to the TH approach. The TH approach was also not inferior to the TT approach in terms of 5-year OS (HR, 0.80; CI, 0.59 to 1.11; P=0.18) [23,288-294].

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

S17. D1+ dissection for EGC

KQ 17: Can D1+ dissection show comparable survival outcomes 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 outcomes (evidence: low, recommendation: strong for).

D2 dissection has been considered the standard LN dissection based on long-term survival data of the Dutch trial [295]. However, the necessity of standard D2 dissection for EGC has been questioned, especially in laparoscopic surgery. There have been no studies comparing D2 dissection and less extensive dissection in EGC patients, but D1+ dissection has been widely accepted by surgeons in Korea and Japan considering the spatial information about 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 [270,296,297].

An Italian study suggested D2 dissection due to the presence of significant LN metastasis [298]. Other studies reported 10-year survival rates of 95% and 87.5% following standard D2 and D1 dissection, respectively, in EGC patients, with no statistically significant difference (P=0.80) [299]. In a Japanese report, the 5- and 10-year survival rates were 97% and 91% for standard D2 dissection and 98% and 91% for modified D2 (D1+) dissection. There were no cases with metastasis to second-tier LNs in patients with cT1N0 or cT1N1 disease [300].

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Although evidence for comparing D1+ and D2 dissection is limited, we referenced the excellent survival outcomes from RCTs comparing laparoscopic and open gastrectomy in EGC, in which less than D2 dissection was performed, and strongly suggested that D1+ dissection can be performed for EGC [301-303].

S18. Sentinel node navigation surgery (SNNS)

KQ 18: Can SNNS be considered a treatment option compared to conventional laparoscopic gastrectomy (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 [304,305]. Previous meta-analyses reported pooled detection rates and sensitivity rates of 93.7%–97% and 80.8%–89%, respectively, with higher sensitivity associated with clinical T1 tumors, dual tracers, submucosal injection, and IHC examinations [304,305].

The oncologic safety and clinical benefits of SNNS have been evaluated only in a limited number of studies [306-311]. In these studies, SNNS was performed on small sized early lesions less than 3 cm in diameter. Two case-control studies and one RCT compared 5-year OS rates [307,310,311]. Our meta-analysis of 2 case-control studies showed that there is no significant difference of OS between the SNNS and conventional LG groups (**Fig. 9**). In the RCT (SENORITA trial), the primary endpoint of 3-year DFS did not show non-inferiority of SNNS compared to LG due to a higher incidence of metachronous cancer (91.8 vs. 95.5%, SNNS vs. LG) [311].

However, secondary endpoints including 5-year DFS, OS, and disease-specific survival, were not different after rescue surgery in cases of recurrence or metachronous gastric cancer; 88.9% vs. 80.7% for DFS, 97.3% vs. 88.3% for OS, and 99.2% vs. 99.3% for disease-specific survival in SNNS vs. LG, respectively (P=0.056, 0.74, and 0.959) [312].

In terms of nutritional outcomes, SNNS was associated with less body weight loss and higher hemoglobin levels than LG [306,308,311]. QOL, assessed using various tools, showed better QOL in some subscales for SNNS [306,308,309,311].

There are still controversies over technical issues 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 rigorous protocol including a dual tracer composed of radioactive isotope (Technetium-99 m) and indocyanine green, sentinel basin dissection rather than pick-up biopsy, intraoperative frozen examination for sentinel LNs with 2 mm-interval cutting, 4-direction resection margins, and cytokeratin IHC for permanent histological evaluation. Therefore, SNNS should be performed under a strict protocol including indication criteria, detection methods, and follow-up plans, and treatment decisions should be made after sufficient discussion with the patient regarding the possibility of metachronous

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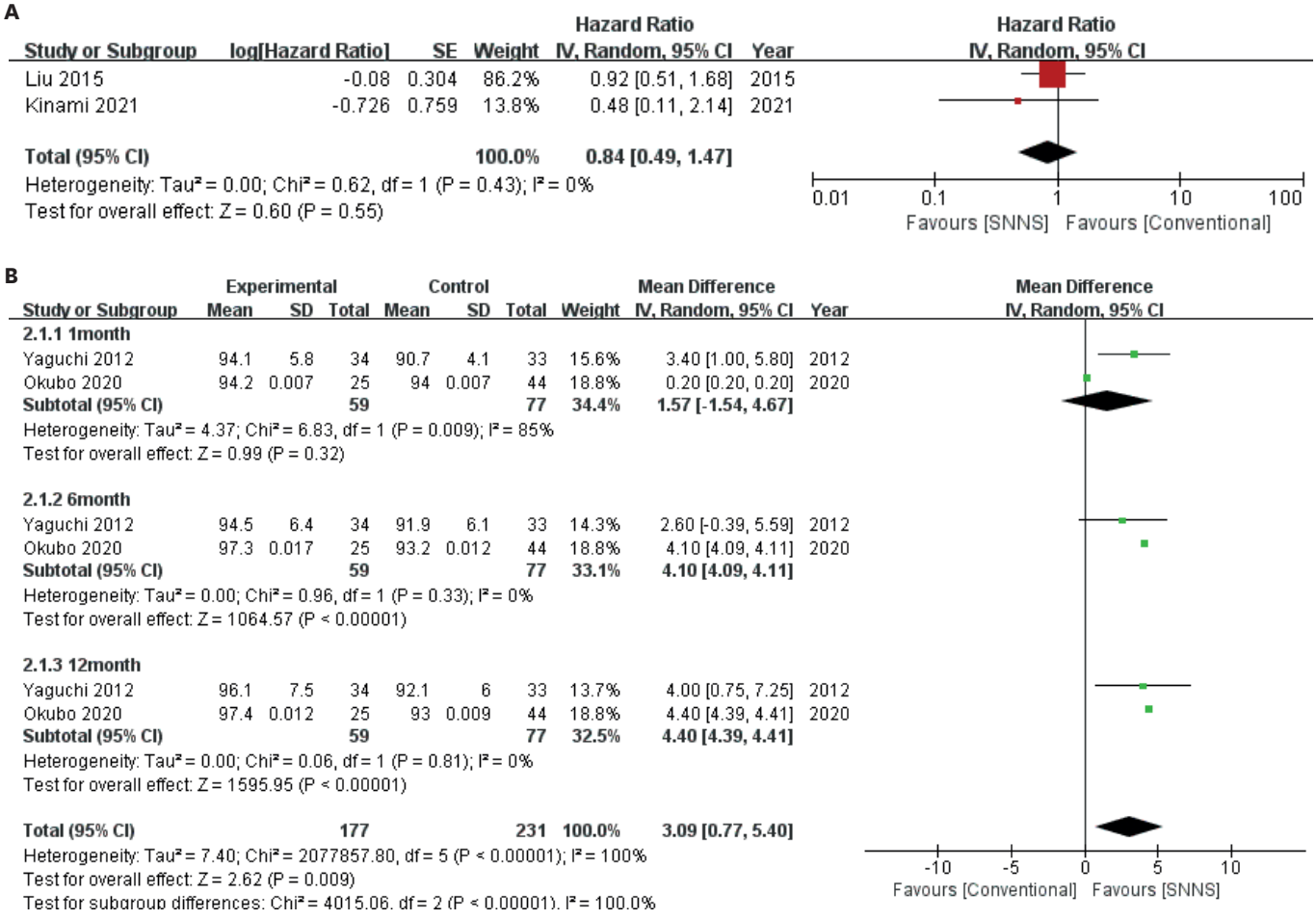

Fig. 9. Forest plots for comparison between the SNNS vs. conventional surgery (Conventional) in observational studies. (A) Overall survival. (B) Body weight: percentages compared to preoperative body weight.
SE = standard error; SNNS = sentinel node navigation surgery; SD = standard deviation; IV = interval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

cancer and rescue surgery. Under these conditions, SNNS could be a treatment option for EGC, offering potential benefits in nutritional outcomes and QOL.

S19. Laparoscopic vs. open approach in DG

KQ 19: Can laparoscopic DG (LDG) show comparable surgical and survival outcomes compared to open DG (ODG) in the treatment of early or locally AGC?

Statement 19-1: LDG is recommended for cStage 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 in the early 2000s, several pivotal trials comparing LDG and ODG for early or locally AGC have been published [313].

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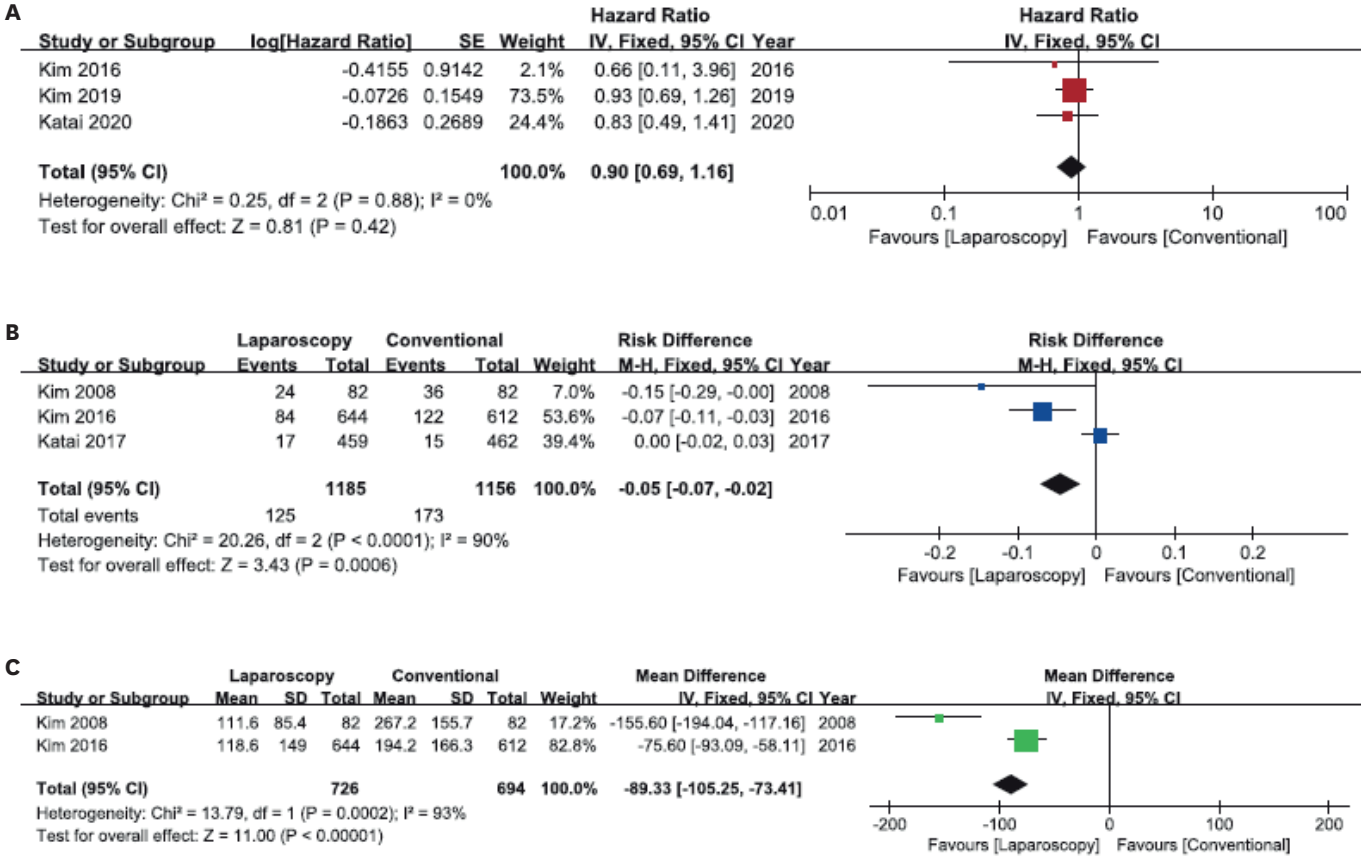

Fig. 10. Forest plots for comparisons between laparoscopic (Laparoscopy) and open (Conventional) distal gastrectomy in cStage I gastric cancer. (A) Overall survival. (B) Complications. (C) Intraoperative blood loss.
SE = standard error; SD = standard deviation; IV = interval variable; M-H = Mantel-Haenszel;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

Three prospective RCTs (KLASS-01, COACT 0301, and JCOG0912) were conducted to evaluate the noninferiority of LDG for EGC [148,314,315]. 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 shorter hospital stay (P<0.001), compared with ODG (**Fig. 10**). The long-term survival in LDG was not inferior to that of the ODG group in all 3 trials (HR, 0.90; CI, 0.69 to 1.16; P=0.42) [301,302,315].

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

Three prospective RCTs (KLASS-02, CLASS-01, and JLSSG0901) were conducted to evaluate the oncologic safety of LDG compared to ODG in the treatment of locally AGC [316-318]. These trials enrolled cases preoperatively diagnosed with AGC (cT2-T4a): KLASS-02 included cases without LN metastasis or with limited metastasis to the left gastric artery or perigastric LNs, CLASS-01 recruited all cN0-3 cases, and JLSSG0901 included cases with N0-2 without bulky node metastasis [319-321]. Surgical outcomes were reported in operation times, intraoperative blood loss, complications, hospital stays [320,322,323], and oncological outcomes were reported in 5-year OS rates [316-318].

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In our meta-analysis, LDG showed less intraoperative blood loss and longer operating time compared to ODG (both P<0.01, respectively). There were no significant differences in hospital stay (P=0.10) or complication rates (P=0.35). Five-year OS rate was also not different between the LDG and ODG groups (HR, 1.05; CI, 0.88–1.26, P=0.61) (**Fig. 11**).

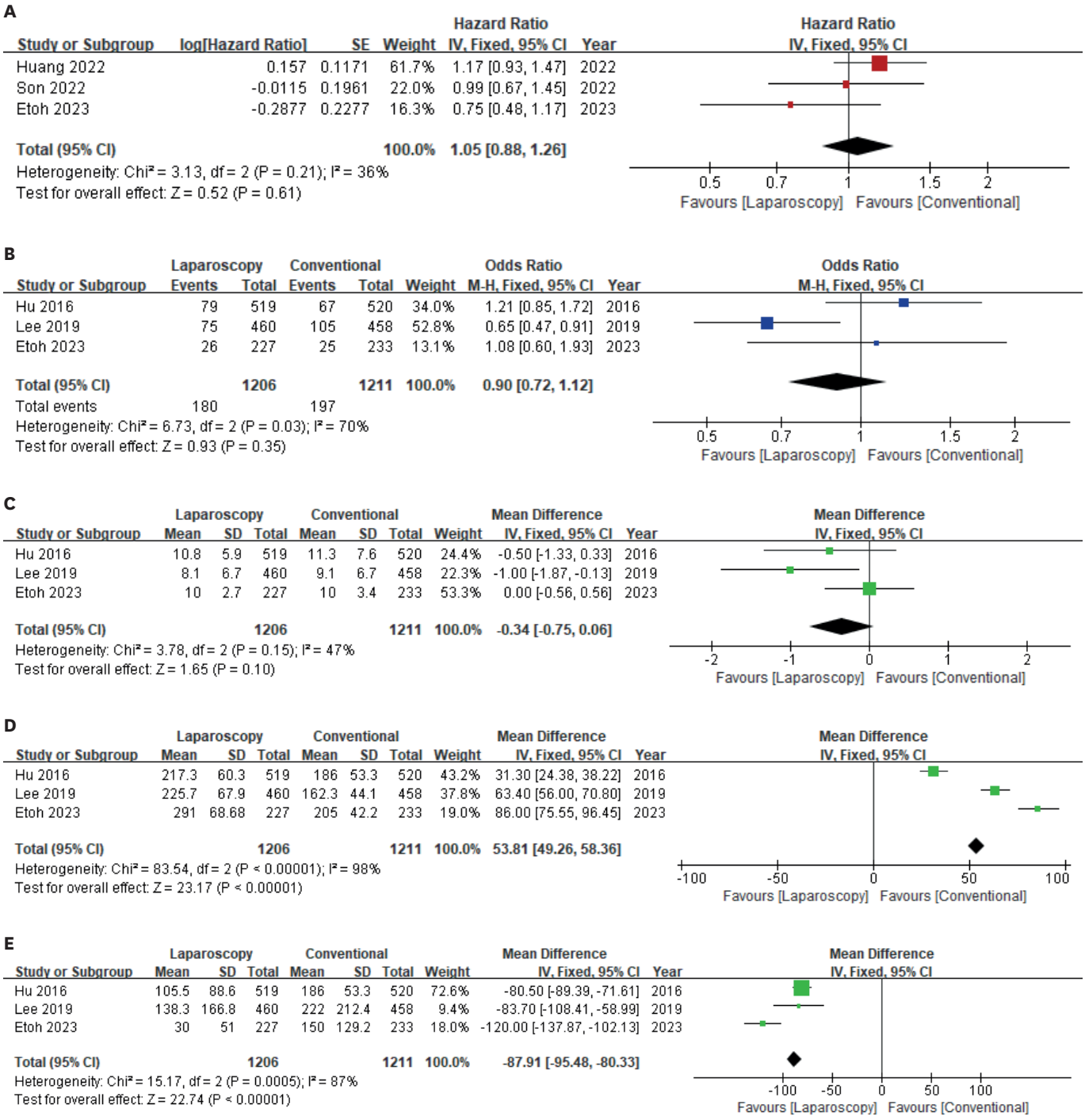

Fig. 11. Forest plots for comparisons between laparoscopic (Laparoscopy) and open (Conventional) distal gastrectomy in cT2-4a gastric cancer. (A) Overall survival. (B) Complications. (C) Hospital stays (day). (D) Operation time (minutes). (E) Intraoperative blood loss (mL).
SE = standard error; SD =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

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LDG can be an optimal treatment option for AGC as well as ODG. However, further studies are needed on application of laparoscopic approach to far-AGC such as cT4b cancers, which requires multivisceral resection.

S20. Robot gastrectomy (RG)

KQ 20: Can RG show better surgical, survival and economical outcomes than LG in the treatment of gastric cancer?

Statement 20: RG can be considered a treatment option for gastric cancer in terms of noninferior survival outcomes and fewer complications than LG. However, disadvantages including additional cost and longer operation times should be discussed with the patient to facilitate 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 [324-326]. Our meta-analysis included 2 RCTs and 8 retrospective to compare RG and LG [325,327-335].

In our meta-analysis of the 2 RCTs [327,328], 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 both RCT (P=0.20) and non-RCT (P=0.58) analyses. There was no significant difference in reoperation rates (P=0.25) and hospital stay duration (P=0.11) between RG and LG. However, RG was associated with a longer operation time (mean difference, 47.04 minutes; 95% CI, 30.67 minutes to 63.41 minutes; P<0.01) compared to LG (**Fig. 12**).

In the 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.

In selected reports, the additional total hospital cost for RG ranged from $3,000 to $5,000 compared to LG [325-327].

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. However, further investigation is needed to identify the potential benefit of RG to justify longer operation time and higher cost, which should be discussed with the patient as part of the shared decision-making process.

S21. Partial omentectomy (PO) for AGC

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

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

TO is regarded as a mandatory treatment for AGC, though high-level evidence to support this is lacking [105]. TO can be challenging and time-consuming during LG [336]. PO has been

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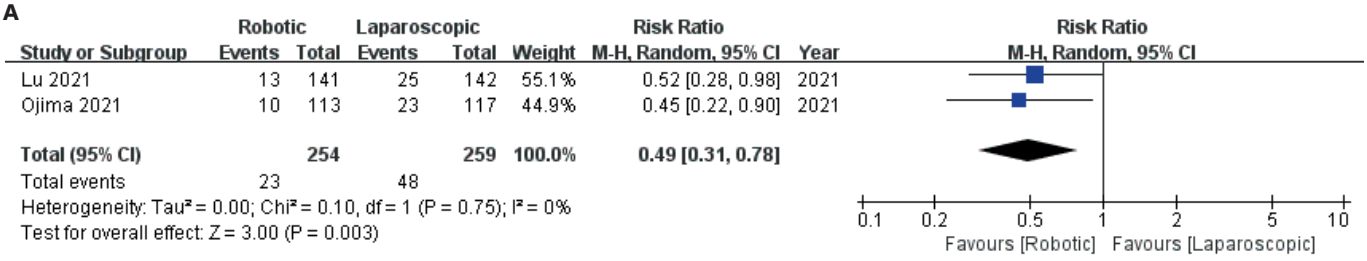

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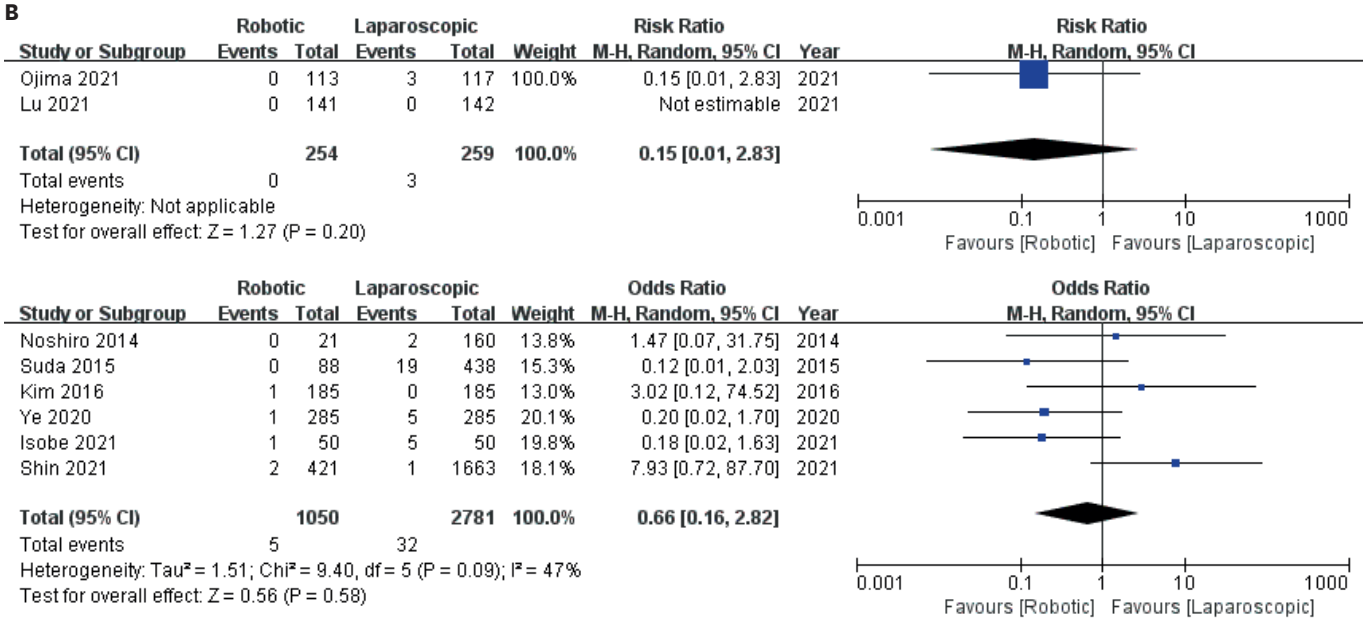

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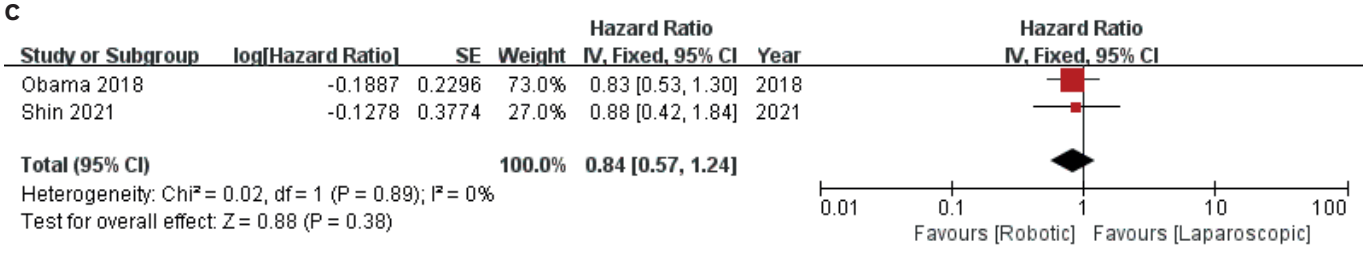

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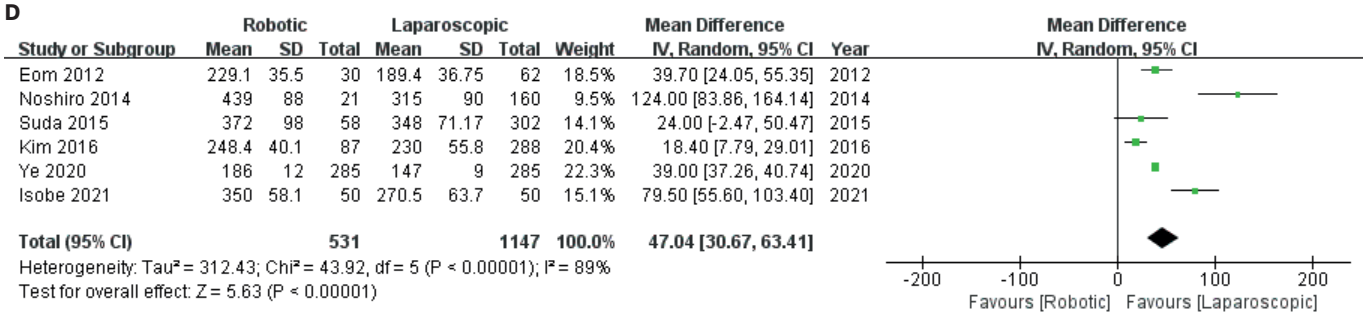

Fig. 12. Forest plots for comparisons between daVinci™ robot gastrectomy (Robotic) vs. laparoscopic gastrectomy (Laparoscopic). (A) Complications (RCTs). (B) Pancreatic fistula (RCTs and observational studies). (C) Overall survival (observational studies). (D) Operation time (observational studies).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

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widely adopted as a safe procedure for EGC based on excellent survival outcomes observed in RCTs where PO was predominantly performed. Therefore, our meta-analysis focused on the applicability of PO for AGC [148,303].

Our meta-analysis included 5 retrospective studies comparing PO and TO [337-341]. Among these, 5 studies with propensity-matched survival data were selected to minimize selection bias. PO was found to be noninferior to TO in progression-free survival (PFS) (HR, 0.89; CI, 0.74 to 1.07; P=0.20) and OS (HR, 0.82; CI, 0.67 to 1.00; P=0.06). Seven studies were combined for complication meta-analysis, which showed no differences in overall complications (P=0.10) or serious complications (P=0.92) between PO and TO (**Fig. 13**) [337-343].

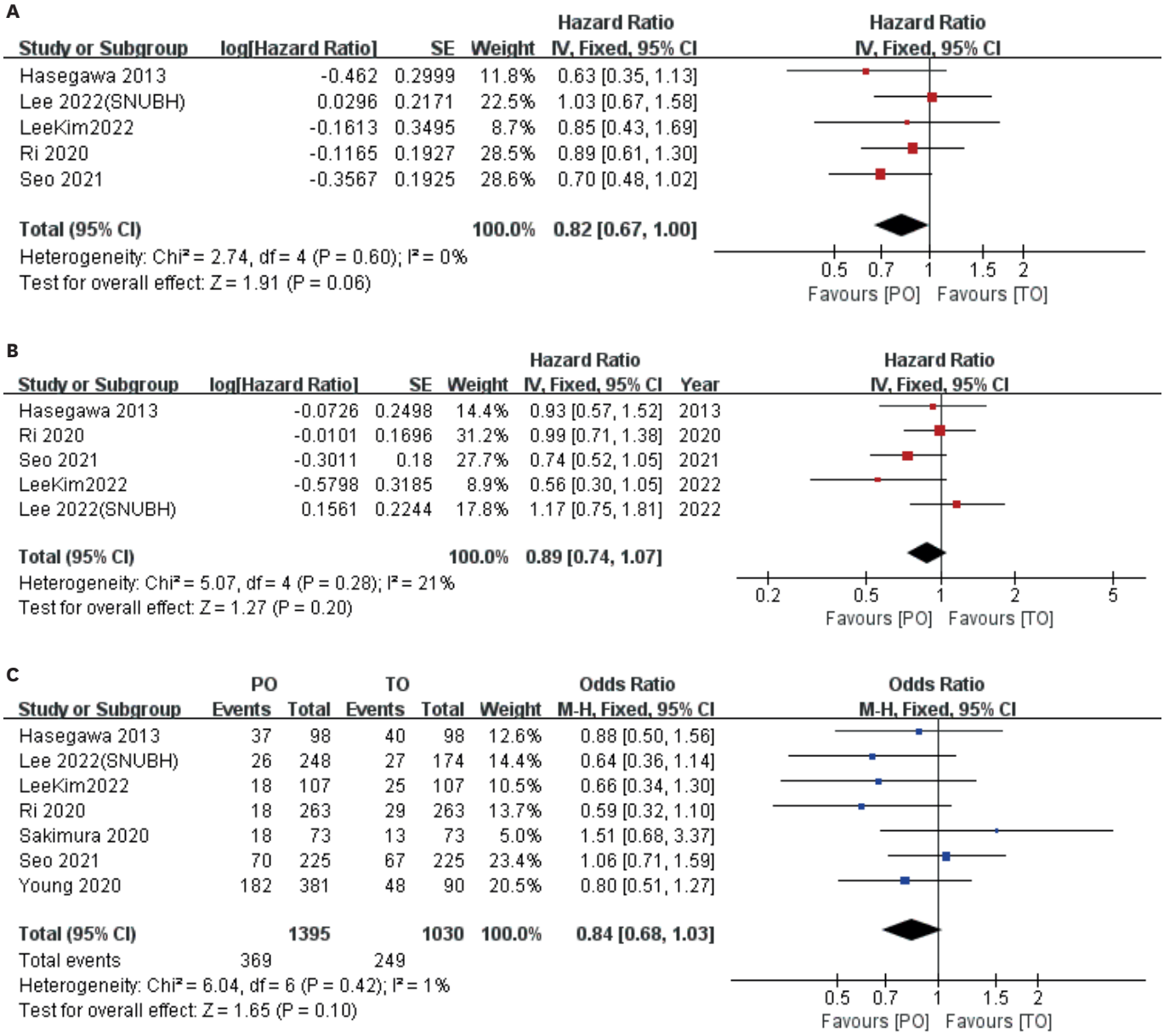

Fig. 13. Forest plots for comparisons between PO vs. TO in advanced gastric cancer in observational studies. (A) Overall survival (propensity score matched). (B) Relapse-free survival (propensity score matched). (C) Complications.
PO = partial omentectomy; TO = total omentectomy; SE = standard error;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

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Seven previous meta-analyses evaluated the oncologic feasibility of PO [344-350]. All showed that PO was not inferior to TO regarding OS and relapse-free survival. Additionally, PO required less operation time and resulted in lower blood loss.

Although these studies included a significant proportion of patients with serosal invasion (T4a), the development working group of guidelines expressed concern about the possibly insufficient extent of resection in locally far advanced cancer, including cT4a cases. They recommended careful consideration of PO 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 [208]. Denervation of the vagus nerve, obesity, rapid weight loss, and TG increase both the incidence and severity of gallstone formation [207,351,352]. Given the positive effects of prophylactic UDCA on reducing gallstones after bariatric surgery, UDCA can be as effective for patients undergoing gastrectomy for gastric cancer.

One RCT studied the use of prophylactic UDCA after gastrectomy in patients with gastric cancer [353]. Patients were randomized into 3 groups: placebo, 300 mg UDCA, or 600 mg UDCA, administered for one year. Compared to placebo, both 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) of UDCA showed decreased gallstone formation. A daily dose of 300 mg seems to be sufficient as the protective effect did not differ between 300 mg and 600 mg doses.

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 are needed to determine which patients may particularly benefit from UDCA prophylaxis and to assess the long-term effect over one year postoperatively.

SYSTEMIC TREATMENT

Systemic therapy plays a critical role in the management of AGC. In resectable patients, upfront surgery followed by adjuvant chemotherapy has been the standard of care in Korea. However, recent clinical trials have demonstrated that the addition of neoadjuvant chemotherapy (NCT) can improve survival outcomes, offering an alternative approach for selected patients. In locally advanced unresectable or metastatic gastric cancer, systemic therapy is essential for prolonging survival and alleviating symptoms. Several cytotoxic agents, such as fluoropyrimidines, platinum-based agents (cisplatin, oxaliplatin), taxanes (docetaxel, paclitaxel), and irinotecan, have played a significant role in treatment and are used in various combinations depending on patient performance status and treatment goals. Recently, the treatment landscape of gastric cancer has evolved with the advent of targeted agents and ICIs.

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These novel agents, when integrated with traditional cytotoxic chemotherapy, have introduced new strategies for personalized treatment and contributed to improved survival outcomes in advanced disease. Furthermore, the integration of biomarkers has further refined therapeutic decisions, enabling clinicians to tailor regimens based on individual tumor biology, which enhances the potential for treatment response and long-term benefits.

Adjuvant chemotherapy

S23. Adjuvant chemotherapy following curative gastrectomy

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 capecitabine and oxaliplatin [CAPOX]) 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 for AGC remains poor [354,355]. Two phase III RCTs conducted in Asia showed significant survival benefits for adjuvant chemotherapy over observation after curative gastrectomy with D2 LN dissection in patients with gastric cancer [356,357]. 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 [357,358]. 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 trial of 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 [359]) who underwent D2 gastrectomy received either CAPOX for 6 months or were observed [356]. 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 studies confirmed these findings [360,361]. Our meta-analysis further showed that 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 CAPOX) are currently accepted as standard treatments in patients with pathological stage II or III gastric cancer after curative gastrectomy. It should be noted, however, that there is currently no evidence to support 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) [362].

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 [15,363]. 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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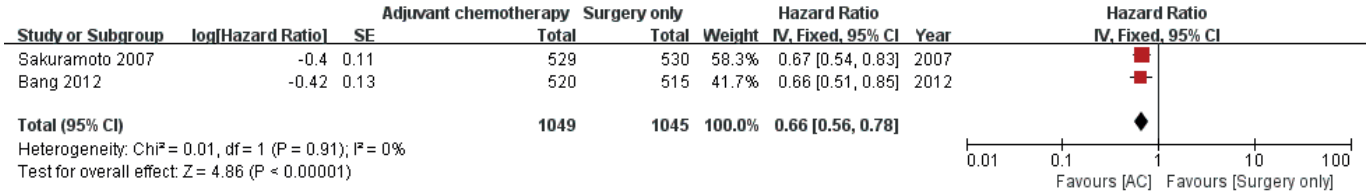

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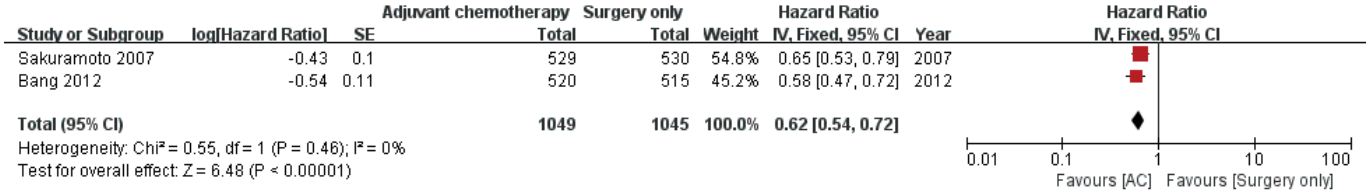

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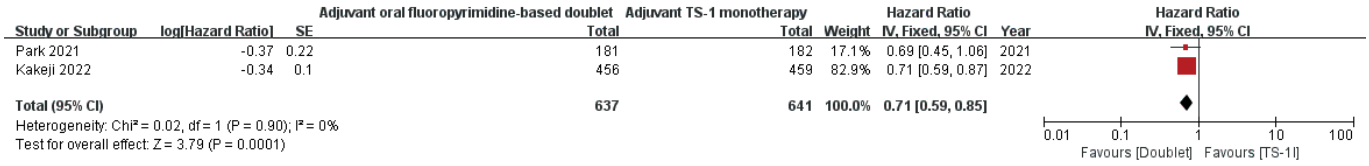

Fig. 14. Forest plots for comparisons between AC vs. surgery only and doublet vs. S1 monotherapy. (A) Overall survival for AC vs. surgery only (Surgery only). (B) DFS for AC vs. surgery only (Surgery only). (C) DFS for oral fluoropyrimidine-based doublet (Doublet) vs. S1 monotherapy (TS-1).
SE = standard error; IV = interval variable; CI = confidence interval; AC = adjuvant chemotherapy; DFS = disease-free survival.

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 one year remains the standard adjuvant treatment for pathological stage II gastric cancer.

Despite the benefit of adjuvant S-1 for gastric cancer in the ACTS-GC trial, there was a question about a lack of efficacy in more advanced stages [357,361]. In the JACCRO GC-07 trial, adjuvant chemotherapy of the S-1 plus docetaxel showed a survival benefits compared to the S-1 monotherapy in patients with stage III gastric cancer (by Japanese Classification, 3rd English edition) who underwent D2 gastrectomy [15,364]. 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). Similarly, the ARTIST-2 trial for stage II or III gastric cancer with positive LNs (by AJCC 7th edition [365]) 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) [366]. Our meta-analysis, including data from JACCRO GC-07 and ARTIST-2 (**Fig. 14**), showed that 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 [356] revealed that the efficacy of CAPOX was maintained even in a more advanced stage, which was not observed in the ACTS-GC trial. These findings suggest that oral pyrimidine-based doublet regimens, such as CAPOX, can be a more favorable treatment option than S-1 monotherapy for pathological stage II with positive LN or stage III gastric cancer.

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Recent advances have demonstrated the clinical benefits of combining immunotherapy with chemotherapy as a standard treatment option for unresectable or metastatic gastric cancer. Building on this progress, the ATTRACTION-5 study explored the addition of nivolumab, an anti-PD-1 monoclonal antibody, to adjuvant chemotherapy for resected stage III (by AICC 7th edition [365]) gastric or GEJ cancer [367]. This study showed that the addition of nivolumab to adjuvant chemotherapy did not significantly improve the primary end point of RFS compared to chemotherapy alone, with 3-year RFS rates of 68.4% in the nivolumab plus chemotherapy group and 65.3% in the chemotherapy group (HR, 0.90; 95% CI, 0.69 to 1.18; P=0.44). Similarly, there was no significant improvement in OS, with an HR of 0.88 (95% CI, 0.66 to 1.17). These results suggest that the addition of immunotherapy has not been established as an adjuvant treatment strategy in gastric cancer.

MSI-H was associated with a better prognosis in resected gastric cancer, but has not shown a survival benefit from adjuvant chemotherapy in the post hoc analysis of the CLASSIC trial [368] and a multinational meta-analysis [369] of individual patient data from the MAGIC [370], CLASSIC [356], ARTIST [371], and ITACA-S [372] trials. Meanwhile, previous retrospective study reported the conflicting result of adjuvant chemotherapy in resectable MSI-H/dMMR gastric cancer [373]. Currently, the benefit of adjuvant chemotherapy in resectable MSI-H/dMMR gastric cancer remains unclear due to conflicting data and the small proportion of this population included in these studies. Therefore, further investigation is warranted to clarify the role of adjuvant chemotherapy in resected MSI-H gastric cancer.

NCT

S24. NCT for resectable gastric cancer

KQ 24: Could NCT as part of perioperative chemotherapy improve survival in patients with resectable locally AGC compared to upfront surgery followed by adjuvant chemotherapy?

Statement 24: NCT as part of perioperative chemotherapy can be considered for patients with resectable locally AGC (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 remain suboptimal, particularly for patients with stage III disease. Additionally, adjuvant chemotherapy is often delayed following surgical resection due to surgical morbidities, and administrating chemotherapy after gastrectomy is associated with more frequent adverse events. In this context, NCT can be considered to intensify chemotherapy and initiate chemotherapy earlier when patients are more medically fit.

Three prospective RCTs in Asia have evaluated the clinical benefit of NCT as part of perioperative chemotherapy for locally AGC. The PRODIGY study in Korea investigated whether NCT with docetaxel, oxaliplatin, and S-1 (DOS) followed by surgery and adjuvant S-1 could improve outcomes compared to upfront surgery followed by adjuvant S-1 in patients with locally AGC with clinical T2/3N+ or cT4Nany disease. Neoadjuvant DOS achieved a higher rate of complete (R0) resection compared to upfront surgery (95% vs. 84%, P<0.001). It also 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) [374]. In the long-term

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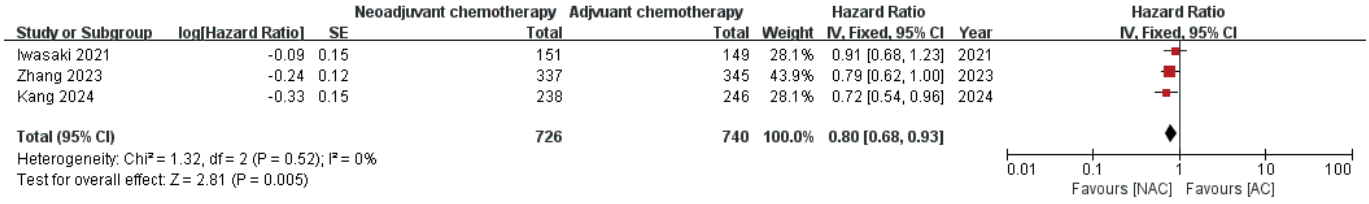

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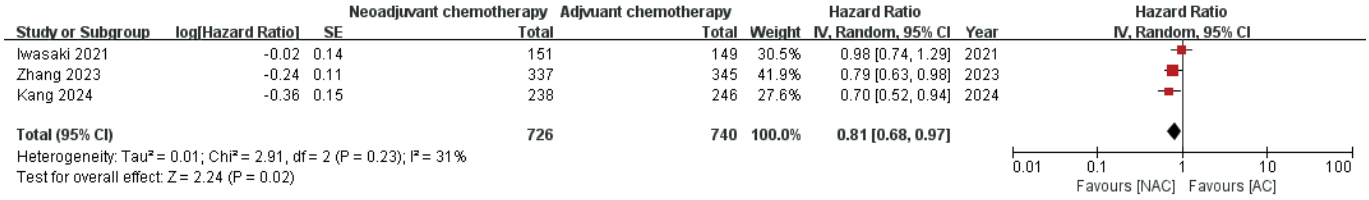

Fig. 15. Forest plot for a comparison between NAC as part of perioperative chemotherapy vs. AC). (A) Overall survival. (B) Progression free survival.
SE = standard error; IV = interval variable; CI = confidence interval; NAC = neoadjuvant chemotherapy; AC = adjuvant chemotherapy.

follow-up, neoadjuvant DOS significantly prolonged OS (adjusted HR, 0.72; 95% CI, 0.54 to 0.96; stratified log-rank P=0.027) [375]. The RESOLVE study compared perioperative SOX vs. upfront surgery followed by adjuvant CAPOX in patients with cT4aN+ or cT4bNany disease. Perioperative SOX significantly improved DFS compared with adjuvant CAPOX (HR, 0.77; 95% CI 0.61 to 0.97, P=0.027) [376]. Long-term follow-up confirmed a significant OS benefit with perioperative SOX (HR, 0.79; 95% CI, 0.62 to 1.00; P=0.049) [377]. 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 [378]. However, NCT with S-1 plus cisplatin did not demonstrate a survival benefit. Our meta-analysis of these Asian trials showed that NCT provided a clinical benefit compared to upfront surgery with improved DFS (HR, 0.81; 95% CI, 0.68 to 0.97; P=0.02) (**Fig. 15**).

On the other hand, it should be noted that the standard perioperative treatment for locally AGC varices by region [379]. Indeed, the efficacy and safety of perioperative chemotherapy regimens commonly used in Western countries such as fluorouracil (5-FU) plus leucovorin, oxaliplatin, and docetaxel (FLOT), have not been investigated in Asian populations. Therefore, FLOT should not be adopted in Asia without further evidence.

Given its OS benefit, NCT as part of perioperative chemotherapy can be considered a viable therapeutic option for patients with resectable, locally AGC in Korea. Clinical decision to proceed with NCT should be made based on a careful discussion considering various factors including clinical stage as well as its potential advantages and limitations over upfront surgery (either followed by adjuvant chemotherapy or not according to the pathological stage). A multidisciplinary team approach is recommended to guide these treatment decisions.

Recently, several studies have investigated the addition of ICIs to NCT. In the phase III KEYNOTE-585 study, pembrolizumab, an anti-PD-1 monoclonal antibody, combined with chemotherapy didn't showed event-free survival benefit, although this study showed an

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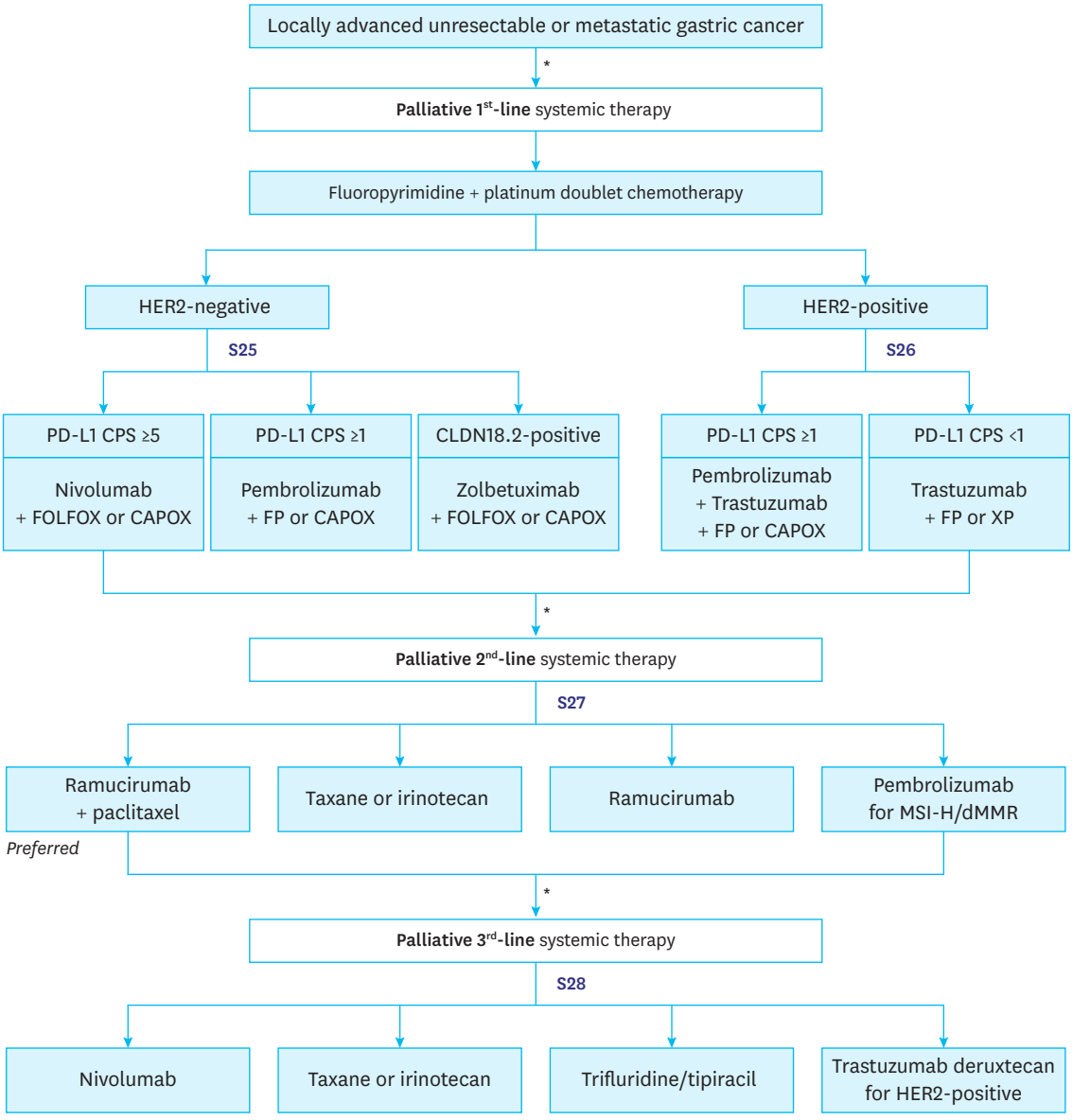
improvement in pathologic complete response (pCR) rate [380]. In a pre-planned analysis of the phase III MATTERHORN study, the combination of durvalumab, an anti-PD-L1 monoclonal antibody, with FLOT significantly increased pCR rate from 7% to 19% [381]. While the survival results of the MATTERHORN study are still pending, there is currently no established clinical benefit to adding ICIs to perioperative treatment regimens.

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; CAPOX = capecitabine and oxaliplatin; CLDN18.2 = Claudin 18.2; FP = 5-fluorouracil and cisplatin; XP = capecitabine plus cisplatin; MSI-H = microsatellite instability-high; dMMR = mismatch repair deficient.
*Evaluation of performance status, comorbidities, and organ function → Best supportive care if unfit for systemic therapy.

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S25. Palliative first-line systemic therapy for HER2-negative disease

KQ 25: Could palliative first-line systemic therapy improve survival in patients with HER2-negative, locally advanced, unresectable or metastatic gastric cancer?

Statement 25-1: Palliative first-line systemic therapy with anti-PD-1 antibody combined with fluoropyrimidine/platinum-based chemotherapy is recommended in patients with HER2-negative and PD-L1-positive locally advanced unresectable or metastatic gastric cancer. Nivolumab combined with chemotherapy is recommended for tumors with PD-L1 CPS ≥5, and pembrolizumab combined with chemotherapy is recommended for tumors with PD-L1 CPS ≥1 (evidence: high, recommendation: strong for).

Nivolumab is the first successful ICI used in combination with chemotherapy as palliative first-line systemic therapy for HER2-negative locally advanced, unresectable or metastatic gastric cancer. The global phase III CheckMate-649 trial demonstrated a significant improvement in OS with the addition of nivolumab to capecitabine or 5-FU/oxaliplatin compared to chemotherapy alone across all randomized patients (median OS, 13.8 vs. 11.6 months; HR, 0.80; 99.3% CI, 0.68 to 0.94; P=0.0002), with even greater benefit observed in patients with PD-L1 CPS ≥5 (median OS, 14.4 vs. 11.1 months; HR, 0.71; 98.4% CI, 0.59 to 0.86; P<0.01) [123,382]. PD-L1 IHC in this study was performed using the Dako PD-L1 IHC 28-8 pharmDx assay (Dako, Santa Clara, CA, USA). The ATTRACTION-4 phase III trial, conducted in Japan, Korea, and Taiwan, also evaluated palliative first-line nivolumab combined with chemotherapy in HER2-negative gastric cancer. Nivolumab plus capecitabine or S-1/oxaliplatin significantly improved PFS (median PFS, 10.5 vs. 8.3 months; HR, 0.68; 95% CI, 0.51 to 0.90; P<0.01), though no OS benefit was observed [383].

Pembrolizumab has also been investigated as a first-line palliative systemic therapy in 2 phase III trials. In the KEYNOTE-062 phase III trial, pembrolizumab plus chemotherapy (5-FU or capecitabine and cisplatin) did not demonstrate superiority over chemotherapy for OS in patients with HER2-negative and PD-L1 CPS ≥1 gastric cancer (median OS, 12.5 vs. 11.1 months; HR, 0.85; 95% CI, 0.70 to 1.03; P=0.05) [384]. PD-L1 IHC for KEYNOTE-062 trial was performed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). However, the phase III KEYNOTE-859 trial demonstrated a significant improvement in OS with pembrolizumab combined with 5-FU/cisplatin (FP) or CAPOX as palliative first-line systemic therapy. In the intention-to-treat population, which included patients regardless of their PD-L1 status, the median OS was 12.9 months for pembrolizumab plus chemotherapy compared to 11.5 months for chemotherapy alone (HR, 0.78; 95% CI, 0.70 to 0.87; P<0.01). The benefit of adding pembrolizumab was more pronounced in patients with PD-L1 CPS ≥1 (median OS, 13.0 vs. 11.4 months; HR, 0.74; 95% CI, 0.65 to 0.84; P<0.01), and CPS ≥10 (median OS, 15.7 vs. 11.8 months; HR, 0.65; 95% CI, 0.53 to 0.79; P<0.01) [385]. PD-L1 IHC was also performed using the 22C3 pharmDx assay in KEYNOTE-859.

In our meta-analysis, the combination of anti-PD-1 antibody with chemotherapy showed superior outcomes in OS (HR, 0.81; 95% CI, 0.76 to 0.86), PFS (HR, 0.78; 95% CI, 0.73 to 0.83; P<0.001), objective response rate (ORR), and disease control rate (DCR) compared to chemotherapy alone (**Fig. 16**). Based on the CheckMate-649 and KEYNOTE-859 trials, nivolumab combined with chemotherapy (CAPOX or 5-FU, leucovorin, and 5-FU [FOLFOX]) and pembrolizumab combined with chemotherapy (FP or CAPOX) are currently approved

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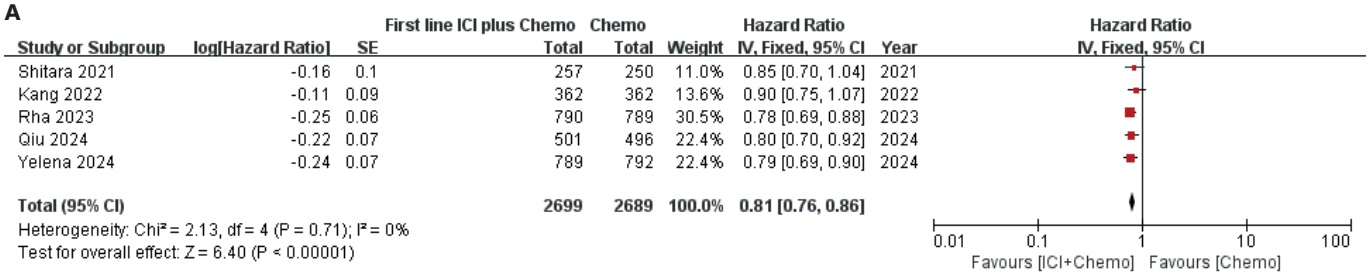

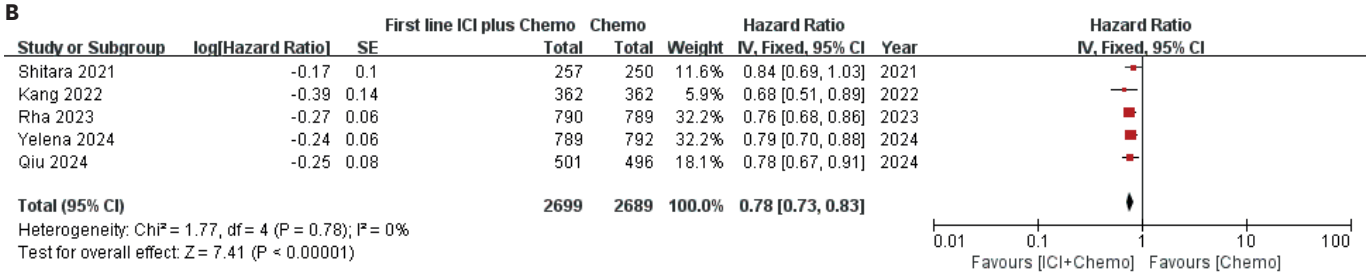

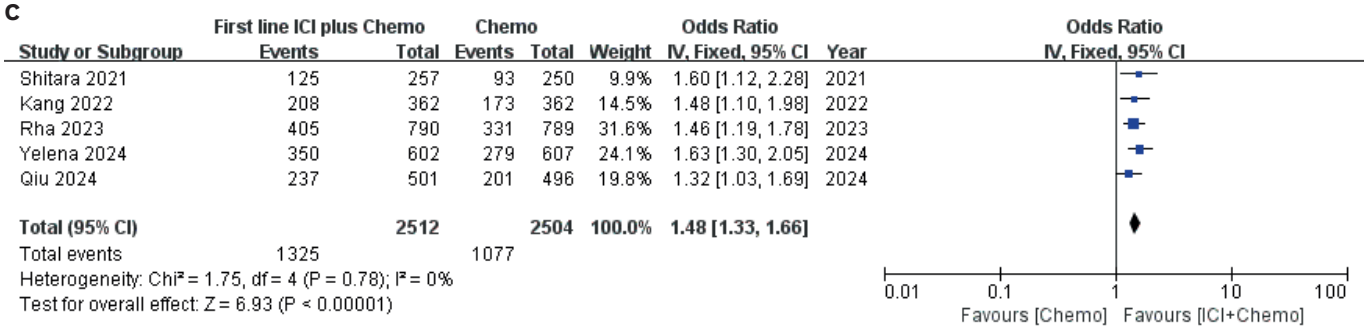

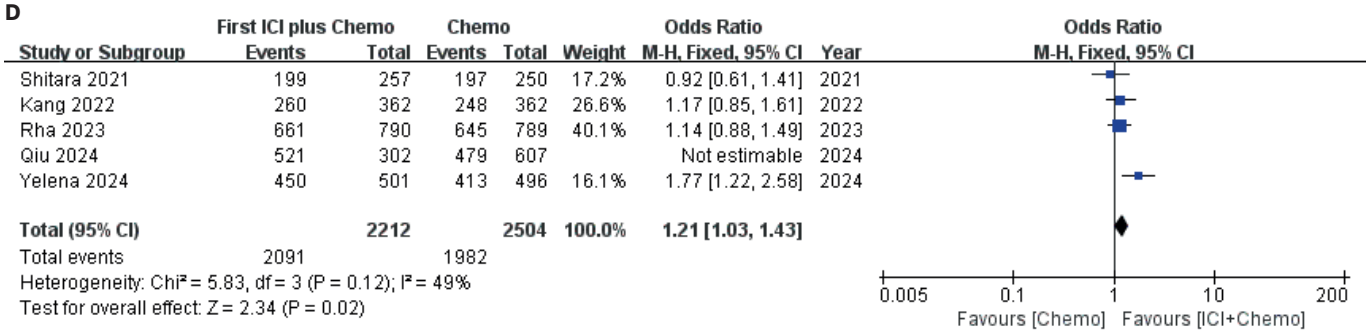

Fig. 16. Forest plots for comparisons between palliative first-line ICI+Chemo vs. Chemo in human epidermal growth factor receptor 2 negative patients. (A) Overall survival. (B) Progression-free survival. (C) Objective response rates (D) Disease control rates.
Chemo = chemotherapy; SE = standard error; IV = interval variable; M-H = Mantel-Haenszel; CI = confidence interval; ICI = immune checkpoint inhibitor.

as palliative first-line systemic therapy in Korea, regardless of PD-L1 status. Our meta-analysis also revealed that the benefit of anti-PD-1 antibody plus chemotherapy was more pronounced in the PD-L1-positive group (**Fig. 17**). Therefore, nivolumab with chemotherapy is recommended for patients with a PD-L1 CPS ≥5, and pembrolizumab with chemotherapy is recommended for those with a PD-L1 CPS ≥1.

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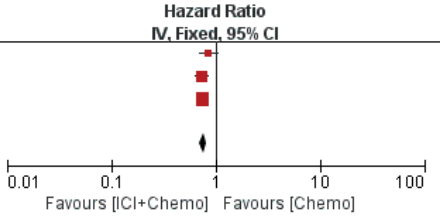
A

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Shitara 2021	-0.16	0.1	257	250	17.2%	0.85 [0.70, 1.04]	2021
Rha 2023	-0.3	0.07	618	617	35.1%	0.74 [0.65, 0.85]	2023
Yelena 2024	-0.29	0.06	641	655	47.7%	0.75 [0.67, 0.84]	2024
Total (95% CI)			**1516**	**1522**	**100.0%**	**0.76 [0.70, 0.83]**	

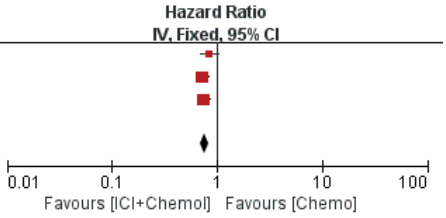
Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 6.54 (P < 0.00001)



B

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Shitara 2021	-0.17	0.1	257	250	19.7%	0.84 [0.69, 1.03]	2021
Rha 2023	-0.33	0.07	362	362	40.2%	0.72 [0.63, 0.82]	2023
Yelena 2024	-0.3	0.07	641	655	40.2%	0.74 [0.65, 0.85]	2024
Total (95% CI)			**1260**	**1267**	**100.0%**	**0.75 [0.69, 0.82]**	

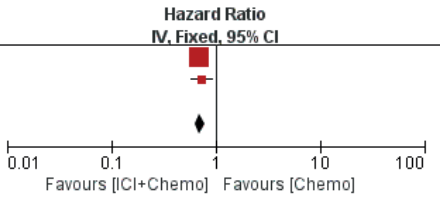
Heterogeneity: Chi² = 1.78, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 6.46 (P < 0.00001)



C

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Qiu 2024	-0.36	0.07	473	482	74.6%	0.70 [0.61, 0.80]	2024
Yelena 2024	-0.3	0.12	274	272	25.4%	0.74 [0.59, 0.94]	2024
Total (95% CI)			**747**	**754**	**100.0%**	**0.71 [0.63, 0.80]**	

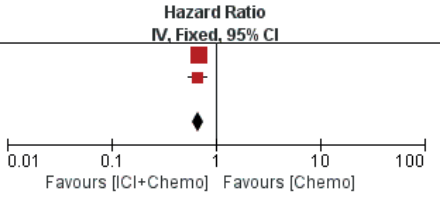
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 5.70 (P < 0.00001)



D

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Qiu 2024	-0.36	0.08	473	482	61.0%	0.70 [0.60, 0.82]	2024
Yelena 2024	-0.4	0.1	274	272	39.0%	0.67 [0.55, 0.82]	2024
Total (95% CI)			**747**	**754**	**100.0%**	**0.69 [0.61, 0.78]**	

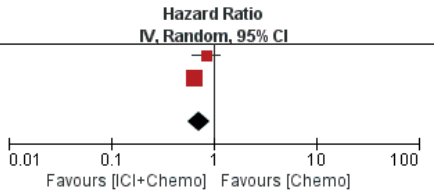
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 6.01 (P < 0.00001)



E

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Shitara 2021	-0.16	0.16	99	90	38.0%	0.85 [0.62, 1.17]	2021
Rha 2023	-0.43	0.09	279	272	62.0%	0.65 [0.55, 0.78]	2023
Total (95% CI)			**378**	**362**	**100.0%**	**0.72 [0.56, 0.93]**	

Heterogeneity: Tau² = 0.02; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 2.50 (P = 0.01)



F

Study or Subgroup	log[Hazard Ratio]	SE	First line ICI plus Chemo Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Shitara 2021	-0.31	0.16	99	90	28.1%	0.73 [0.54, 1.00]	2021
Rha 2023	-0.48	0.1	279	272	71.9%	0.62 [0.51, 0.75]	2023
Total (95% CI)			**378**	**362**	**100.0%**	**0.65 [0.55, 0.77]**	

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 5.10 (P < 0.00001)

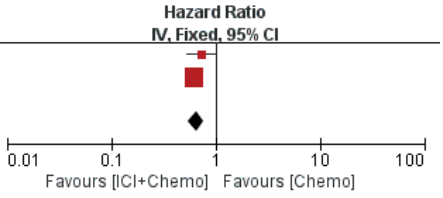


Fig. 17. Forest plots for comparisons between palliative first-line ICI+Chemo vs. Chemo in human epidermal growth factor receptor 2 negative patients according to PD-L1 expression level. (A) Overall survival in patients with PD-L1 CPS ≥1 (B) Progression-free survival in patients with PD-L1 CPS ≥1 (C) Overall survival in patients with PD-L1 CPS ≥5. (D) Progression-free survival in patients with PD-L1 CPS ≥5. (E) Overall survival in patients with PD-L1 CPS ≥10. (F) Progression-free survival in patients with PD-L1 CPS ≥10.
Chemo = chemotherapy; ICI = immune checkpoint inhibitor; SE = standard error; IV = interval variable; CI = confidence interval; PD-L1 = programmed cell death ligand-1; CPS = combined positive score.

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In metastatic gastric cancer, MSI-H/dMMR tumors are rare, occurring in less than 5% of cases, making it challenging to conduct RCTs specifically for this subgroup. Nevertheless, anti-PD1 antibodies have demonstrated remarkable clinical benefits, especially in patients with MSI-H/dMMR tumors. Subgroup analyses from the CheckMate-649, KEYNOTE-062, and KEYNOTE-859 trials have consistently showed significant advantages when anti-PD-1 antibodies were combined with chemotherapy as first-line palliative systemic therapy for MSI-H/dMMR gastric cancer [382,384-386]. This consistent and significant survival benefit underscores the robust efficacy of anti-PD-1 antibodies for MSI-H/dMMR tumors in gastric cancer, positioning them as a highly effective treatment approach for this unique subset.

Tislelizumab, an anti-PD-1 monoclonal antibody, has also shown clinical benefit when combined with chemotherapy as a first line palliative systemic therapy. The global phase III RATIONALE-305 trial compared tislelizumab plus chemotherapy vs. chemotherapy alone. This study met its primary endpoints, showing significant improvements in OS across all randomized patients (median OS, 15.0 vs. 12.9 months; HR, 0.80; 95% CI, 0.70 to 0.92; P=0.001), and in patients with PD-L1 tumor area positivity score ≥5 (median OS, 17.2 vs. 12.6 months; HR, 0.74; 95% CI, 0.59 to 0.94) [387]. PD-L1 IHC was performed using the Ventana PDL1 (SP263) assay. Currently, tislelizumab has not yet been approved for the treatment of gastric cancer in Korea.

> Statement 25-2: Palliative first-line systemic therapy with zolbetuximab combined with capecitabine or fluorouracil plus oxaliplatin (CAPOX or FOLFOX) is recommended in patients with HER2-negative and CLDN18.2-positive locally advanced unresectable or metastatic gastric cancer (evidence: high, recommendation: strong for).

Zolbetuximab is a first-in-class immunoglobulin G1 monoclonal antibody targeting CLDN18.2, a tight junction protein exclusively expressed in normal gastric mucosal cells and retained in most gastric adenocarcinomas. The phase III SPOTLIGHT and GLOW trials demonstrated the efficacy of zolbetuximab plus modified FOLFOX6 (mFOLFOX6) or CAPOX as first-line treatment in patients with HER2-negative and CLDN18.2-positive AGC [125,126]. CLDN18.2-positive was defined as ≥75% of tumor cells showing moderate-to-strong membranous CLDN18 staining, as determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay (Roche Diagnostic Solutions, Tucson, AZ, USA) [125,126].

The SPOTLIGHT phase III trial showed that the addition of zolbetuximab to mFOLFOX6 significantly improved PFS (median, 11.0 vs. 8.9 months; HR, 0.73; 95% CI, 0.59 to 0.91; P<0.01) and OS (median, 18.2 vs. 15.6 months; HR, 0.78; 95% CI, 0.64 to 0.95; P<0.01), Recent longer-term follow-up data confirm the persistence of these clinical benefits [125,388]. The GLOW phase III trial showed that the addition of zolbetuximab to CAPOX significantly improved PFS (median, 8.3 vs. 6.8 months; HR, 0.68; 95% CI, 0.55 to 0.85; P<0.01) and OS (median, 14.3 vs. 12.2 months; HR, 0.77; 95% CI, 0.62 to 0.95; P<0.01), with persistent results upon longer follow-up [126,389]. The most common treatment-emergent adverse events (TEAEs) with zolbetuximab plus mFOLFOX6 or CAPOX were nausea, vomiting, and decreased appetite, and incidence of serious TEAEs was similar between treatment arms in both trials [388,389]. In our meta-analysis, zolbetuximab combined with chemotherapy showed the clinical benefit of OS and PFS (HR, 0.85; 95% CI, 0.75 to 0.97; P=0.01) in patients with CLDN18.2-positive AGC (**Fig. 18**).

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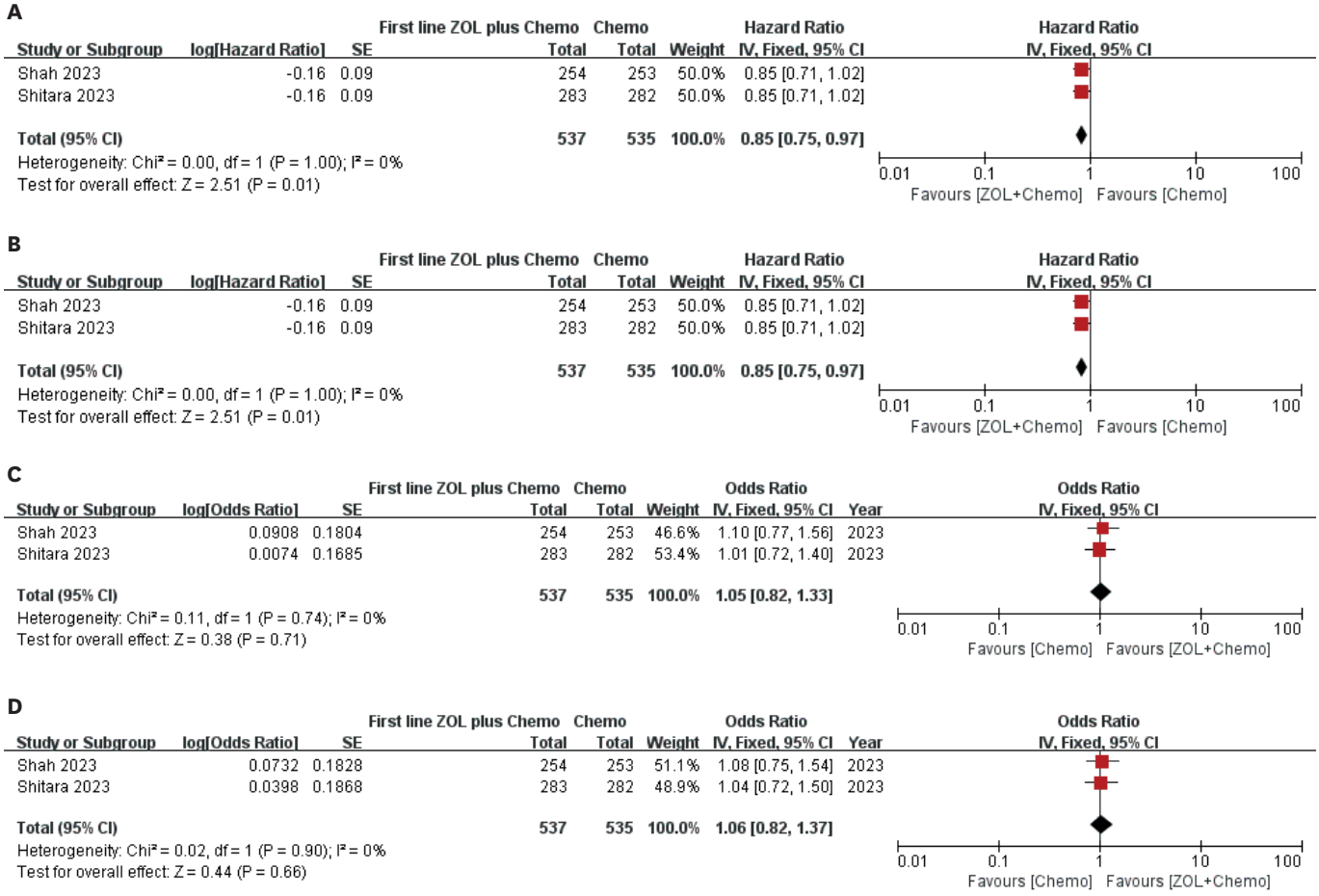

Fig. 18. Forest plots for comparisons between palliative first-line ZOL+Chemo vs. Chemo in human epidermal growth factor receptor 2 negative patients. (A) Overall survival. (B) Progression-free survival. (C) Objective response rates. (D) Disease control rates.
ZOL = zolbetuximab; Chemo = chemotherapy; SE = standard error; IV = interval variable; CI = confidence interval.

Therefore, zolbetuximab combined with mFOLFOX6 or CAPOX is recommended as first-line treatment in patients with HER2-negative and CLDN18.2-positive locally advanced unresectable or metastatic gastric cancer.

S26. Palliative first-line systemic therapy for HER2-positive disease

KQ 26: Could palliative first-line systemic therapy including trastuzumab improve survival in patients with HER2-positive, locally advanced unresectable, or metastatic gastric cancer?

Statement 26: Palliative first-line systemic therapy with trastuzumab combined with fluoropyrimidine/platinum-based chemotherapy is recommended in patients with HER2-positive locally advanced unresectable or metastatic gastric cancer. Pembrolizumab and trastuzumab combined with chemotherapy is recommended for patients with HER2-positive and PD-L1 CPS ≥1 (evidence: high, recommendation: strong for).

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The Trastuzumab for Gastric Cancer (ToGA) phase III trial demonstrated the efficacy of trastuzumab, a monoclonal antibody targeting HER2, plus fluoropyrimidine/cisplatin as a first-line treatment in patients with HER2-positive gastric cancer [110]. The addition of trastuzumab to capecitabine or FP improved OS (median, 13.8 vs. 11.1 months; HR, 0.74; 95% CI, 0.60 to 0.91; P=0.0046). The survival benefit was more pronounced in patients with IHC 3+ or IHC 2+ and fluorescence ISH + (median OS, 16.0 vs. 11.8 months; HR, 0.65; 95% CI, 0.51 to 0.83; P<0.01). PFS was also significantly extended in the trastuzumab plus chemotherapy group (median, 6.7 vs. 5.5 months; HR, 0.71; 95% CI, 0.59 to 0.85; P=0.036). The ORR was higher with trastuzumab plus chemotherapy compared to chemotherapy alone (ORR, 47% vs. 35%; OR, 1.70; 95% CI, 1.22 to 2.38; P=0.002). Similarly, the DCR was superior in the trastuzumab plus chemotherapy group (DCR, 75% vs. 70%; OR, 1.66; 95% CI, 1.14 to 2.41; P=0.008) (**Fig. 19**).

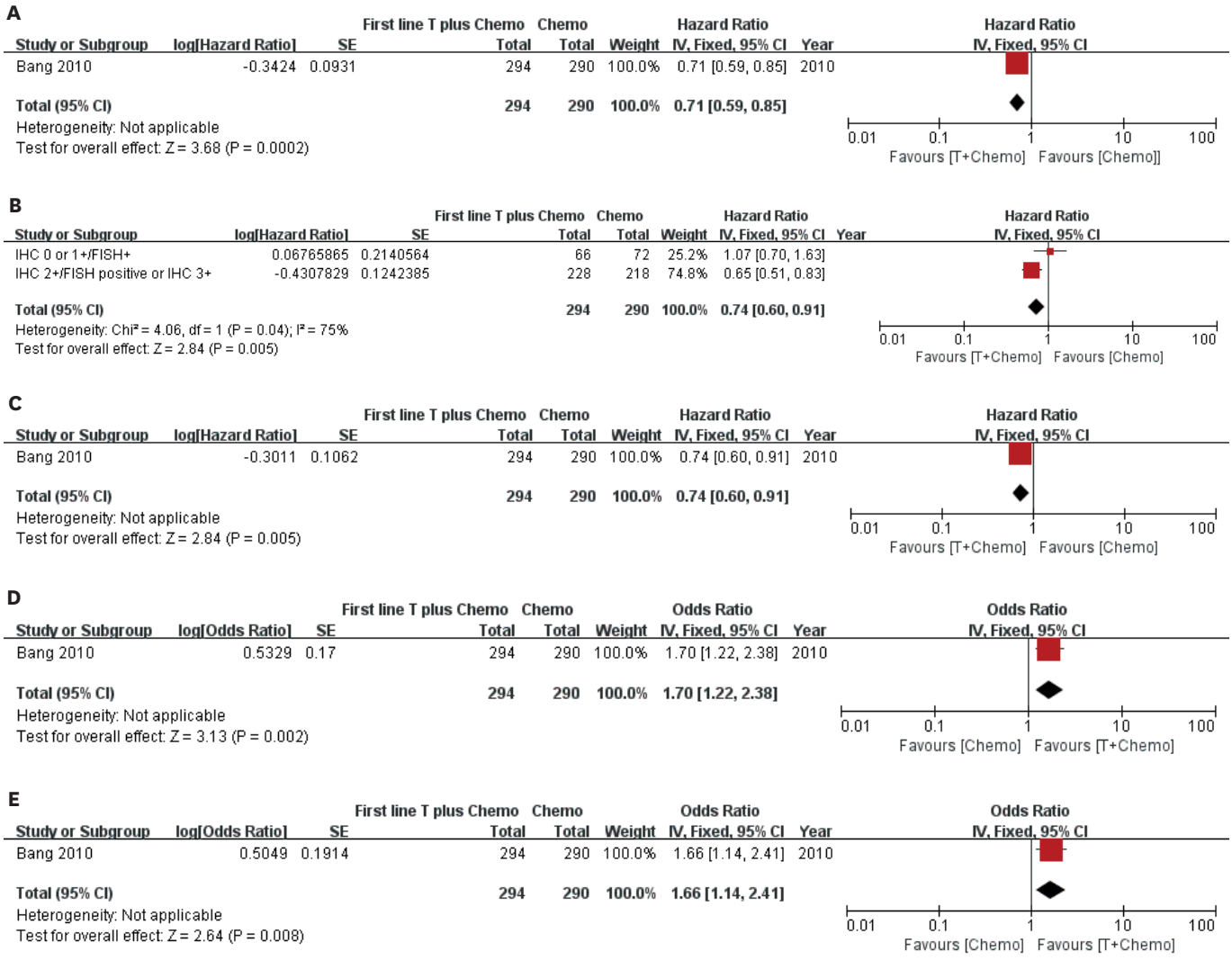

Fig. 19. Forest plots for comparisons between palliative first-line T+Chemo vs. Chemo in ToGA trial. (A) Overall survival in all patients. (B) Overall survival in in patients with HER2 2+/FISH+ or IHC 3+ and IHC 0 or 1+/FISH+. (C) Progression-free survival in all patients. (D) Objective response rates in all patients (E) Disease control rates in all patients.
T = trastuzumab; Chemo = chemotherapy; SE = standard error; IV = interval variable; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; FISH = fluorescence in situ hybridization.

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For dual blockade of HER2, the JACOB phase III trial evaluated the efficacy of pertuzumab, a monoclonal antibody that interferes with HER2 heterodimerization with other EGFR family members, combined with trastuzumab and chemotherapy as a first-line therapy, compared to trastuzumab and chemotherapy [390]. Although PFS was improved 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 gastric cancer (median, 17.5 vs. 14.2 months; HR, 0.84; 95% CI, 0.71 to 1.00, P=0.057). Lapatinib, a small-molecule tyrosine kinase inhibitor of EGFR and HER2, was evaluated in the LOGiC phase III trial, where lapatinib and CAPOX 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 CAPOX in HER2-amplified gastric cancer. Therefore, trastuzumab plus capecitabine or FP is recommended in patients with HER2-positive locally advanced unresectable or metastatic gastric cancer [391].

Integrating ICI into the standard chemotherapy regimen for first-line treatment of HER2-negative gastric cancer has improved survival outcomes, and these results have been extended to HER2-positive gastric cancer as well. The randomized, phase III KEYNOTE-811 trial showed the efficacy of combined pembrolizumab and trastuzumab with standard chemotherapy (fluoropyrimidine/platinum-based therapy) vs. trastuzumab with standard chemotherapy in first-line treatment in patients with HER2-postivie gastric cancer [392]. At the third interim analysis, PFS was improved in the pembrolizumab group compared to the placebo group in the intention-to-treat population (median 10.0 vs. 8.1 months; HR, 0.73; 95% CI, 0.61 to 0.87, P=0.0005), and OS was also significantly improved in pembrolizumab group (median, 20.0 vs. 16.8 months; HR, 0.84; 95% CI, 0.70 to 1.01; P=0.06). In patients with PD-L1 CPS ≥1, the pembrolizumab group showed a more pronounced improvement in PFS (median, 10.9 vs. 7.3 months; HR, 0.72; 95% CI, 0.60 to 0.87; P<0.01), and OS (median, 20.1 vs. 15.7 months; HR, 0.79; 95% CI, 0.66 to 0.95; P=0.006). The ORR was also higher in the pembrolizumab group (ORR, 72.6% vs. 60.1%; OR, 1.76; 95% CI, 1.28 to 2.42; P<0.001), with a better DCR (91.7% vs. 87.4%; OR, 1.60; 95% CI, 0.98 to 2.63; P=0.06) (**Fig. 20**). Based on these results, the addition of pembrolizumab to trastuzumab and chemotherapy is recommended for patients with HER2-positive and PD-L1 CPS ≥1.

S27. Palliative second-line systemic therapy

KQ 27: 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 27: Palliative second-line systemic therapy with ramucirumab combined with paclitaxel is recommended in patients with locally advanced unresectable or metastatic gastric cancer; however, other agents may 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 [393-396]. 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. 21**). Weekly paclitaxel

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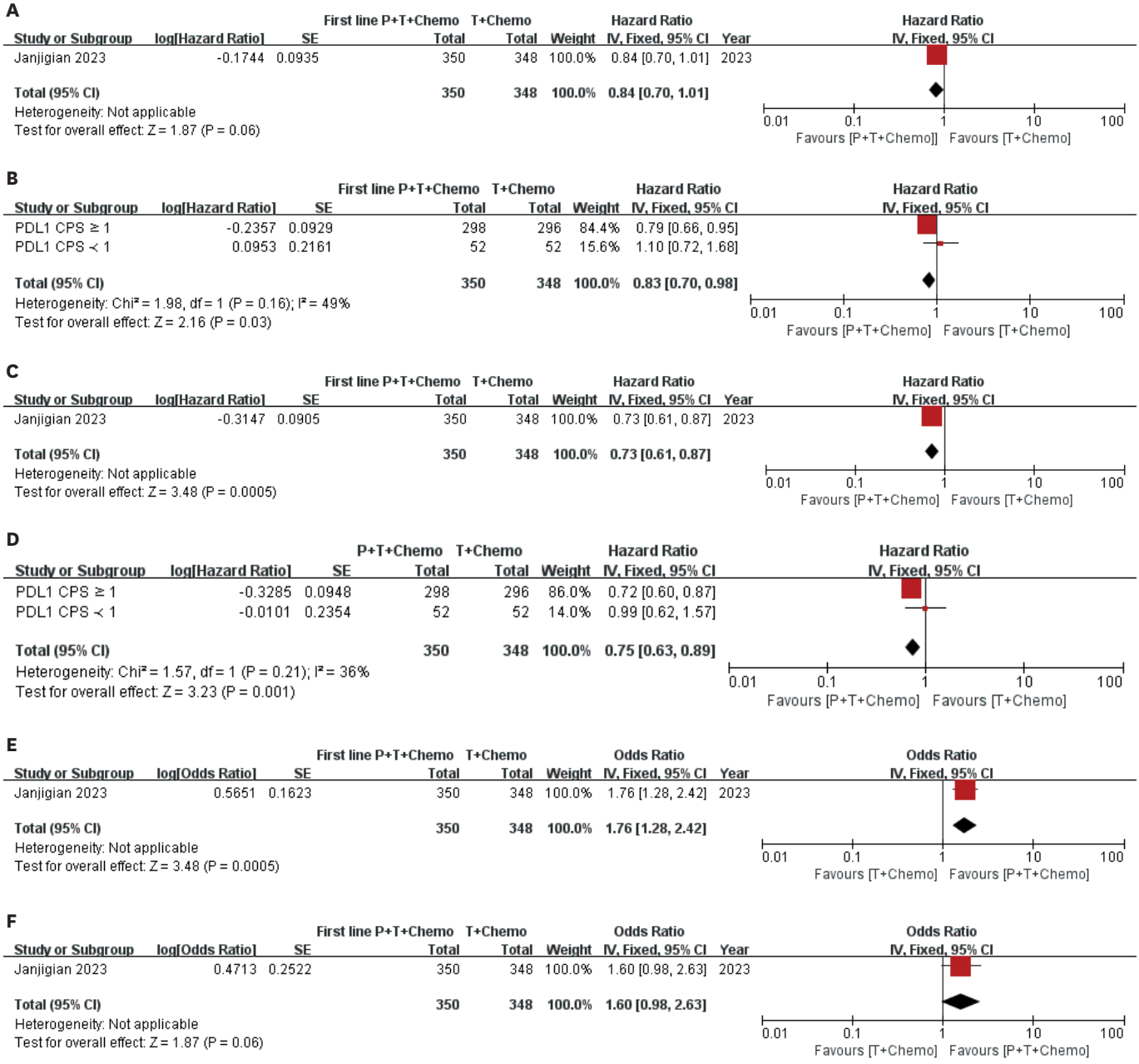

Fig. 20. Forest plots for comparisons between palliative first-line P+T+Chemo vs. T+Chemo in human epidermal growth factor receptor 2 positive patients. (A) Overall survival in all patients. (B) Overall survival in patients with PD-L1 CPS ≥1 and <1. (C) Progression-free survival in all patients. (D) Progression-free survival in patients with PD-L1 CPS ≥1 and <1. (E) Objective response rates in all patients. (F) Disease control rates in all patients.
P = pembrolizumab; T = trastuzumab; Chemo = chemotherapy; SE = standard error; IV = interval variable; CI = confidence interval; PD-L1 = programmed cell death ligand-1; CPS = combined positive score.

was associated with similar survival outcomes to biweekly irinotecan in previous phase III trials [397,398]. Meanwhile, ramucirumab monotherapy, a monoclonal antibody targeting vascular endothelial growth factor receptor-2, significantly improved OS and PFS compared to placebo in the REGARD trial [399]. Furthermore, the addition of ramucirumab to weekly paclitaxel significantly prolonged OS (median, 9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.68 to 0.97; P=0.017) and PFS (median, 4.4 vs. 2.9 months; HR, 0.635; 95% CI, 0.53 to 0.76; P<0.0001) compared to paclitaxel plus placebo in the RAINBOW trial (**Fig. 22**) [400].

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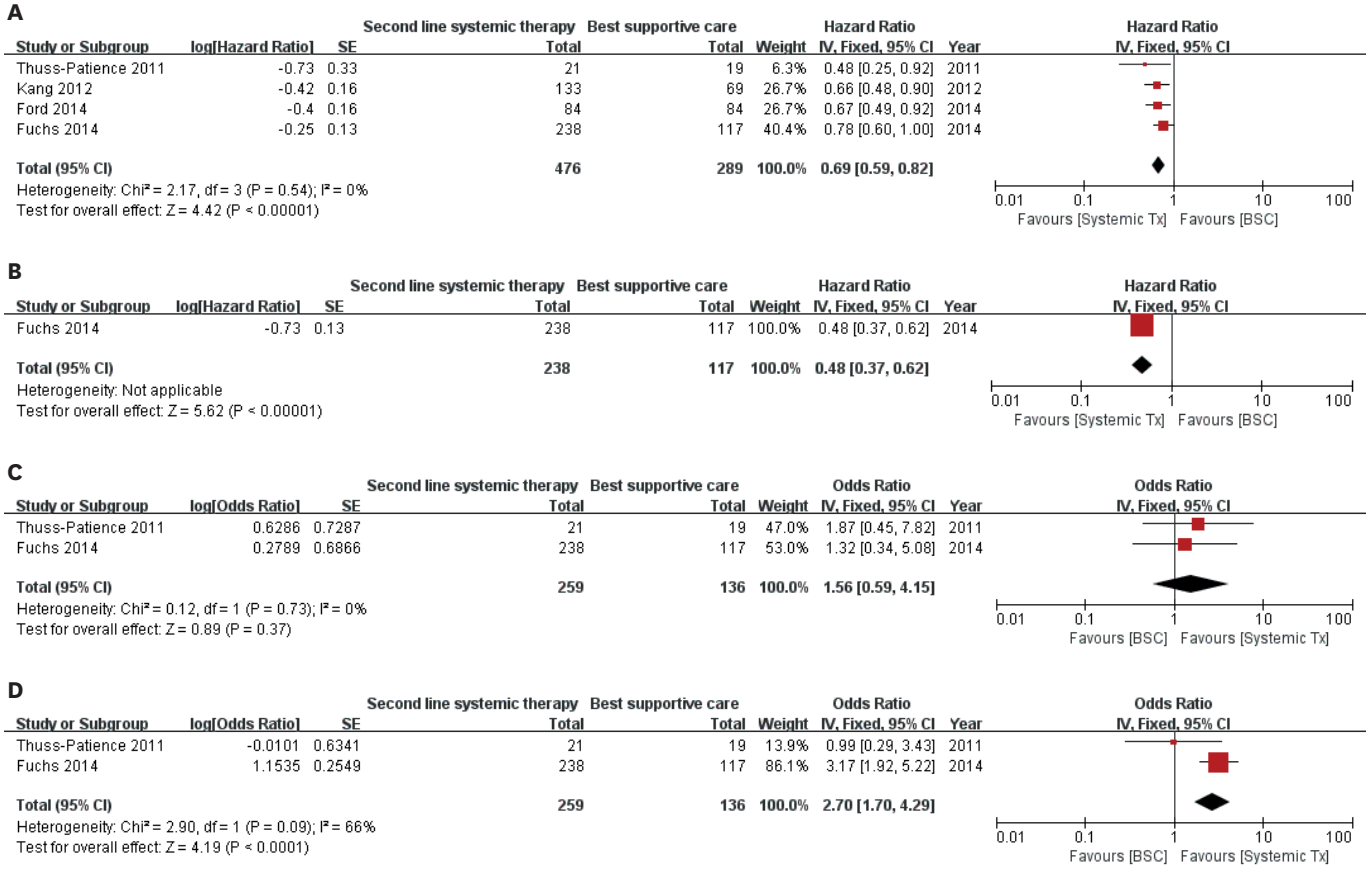

Fig. 21. Forest plots for comparisons between palliative second-line systemic Tx vs. BSC or placebo. (A) Overall survival. (B) Progression-free survival. (C) Objective response rates. (D) Disease control rates.
Tx = therapy; BSC = best supportive care; SE = standard error; IV = interval variable; CI = confidence interval.

Based on previous trials, ramucirumab in combination with paclitaxel is recommended as the preferred second-line treatment. Other agents, including irinotecan, docetaxel, paclitaxel can also be considered second-line options if not previously administered in the first-line treatment. In addition, various investigational agents are currently being tested in combination with paclitaxel or paclitaxel plus ramucirumab as second-line treatment [401-403].

Pembrolizumab failed to provide a significant survival benefit compared to paclitaxel [404-406], however, it was effective in patients with solid tumors characterized as MSI-H, dMMR, or TMB-high (≥10 mutations/megabase) [407,408]. 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 approved by the Food and Drug Administration for the treatment of patients with HER2-positive gastric cancer who have received a prior trastuzumab-based regimen. The phase II trial of trastuzumab deruxtecan as second-line treatment provided clinical evidence in the Western population only [409]. Currently, a global phase III trial (DESTINY-Gastric04), which includes Asian patients, is ongoing to compare the survival outcomes of trastuzumab

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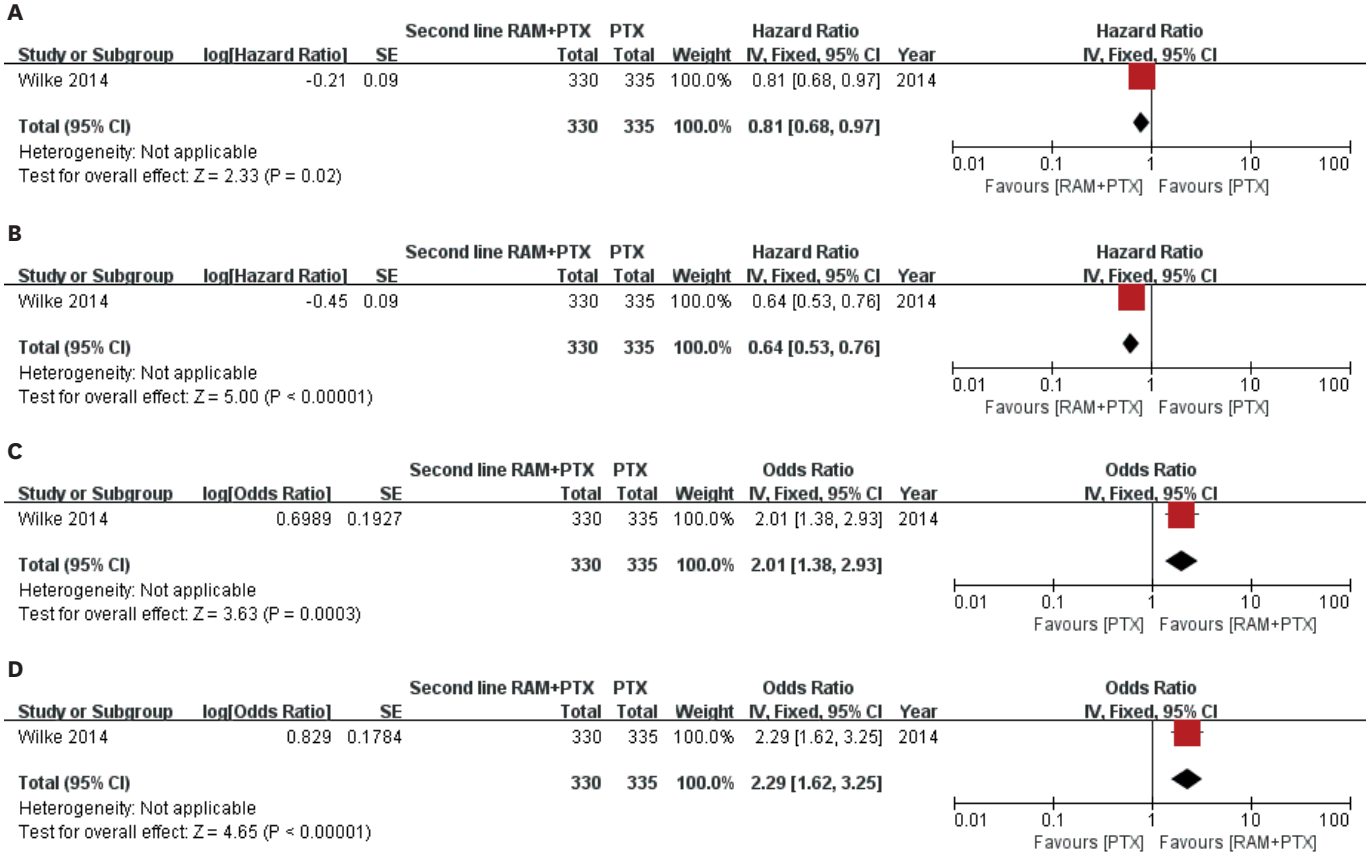

Fig. 22. Forest plots for comparisons between palliative second-line Ram+PTX vs. PTX. (A) Overall survival. (B) Progression-free survival. (C) Objective response rates. (D) Disease control rates.
Ram = ramucirumab; PTX = paclitaxel; SE = standard error; IV = interval variable; CI = confidence interval.

deruxtecan to ramucirumab plus paclitaxel, the current standard second-line treatment, in patients with HER2-positive gastric cancer.

S28. Palliative third-line systemic therapy

KQ 28: 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 28: Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer. Trastuzumab-deruxtecan is preferentially recommended in patients with HER2-positive 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, 0.61 to 0.76, P<0.001) (**Fig. 23**).

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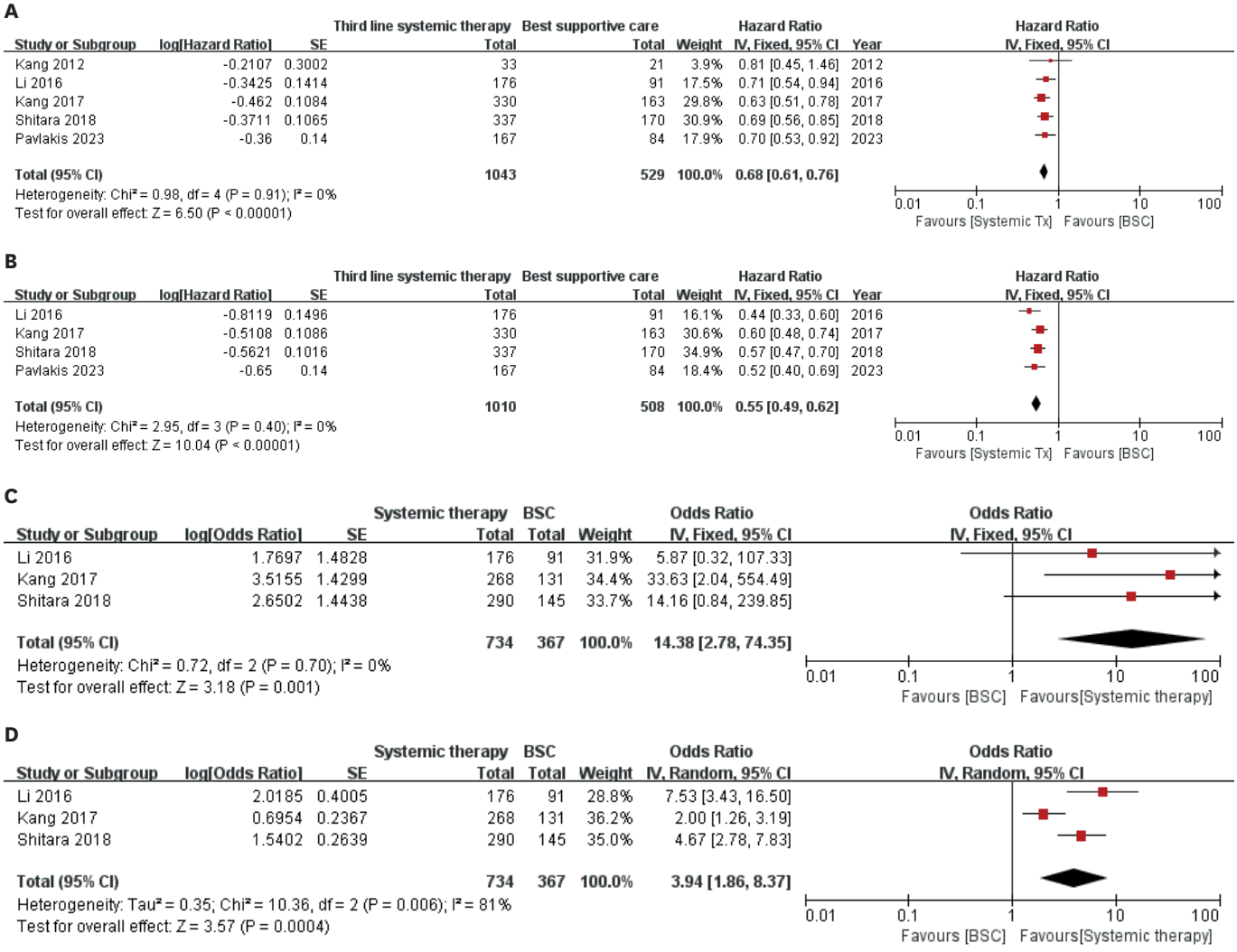

Fig. 23. Forest plots for comparisons between palliative third-line systemic Tx vs. BSC or placebo. (A) Overall survival. (B) Progression-free survival. (C) Objective response rate. (D) Disease control rate.
Tx = therapy; BSC = best supportive care; SE = standard error; IV = interval variable; CI = confidence interval.

Cytotoxic agents, such as docetaxel or irinotecan, can be recommended as palliative third-line therapy. A randomized phase III trial showed a survival benefit with docetaxel or irinotecan (median OS, 5.3 vs. 3.8 months; HR, 0.66; 95% CI, 0.49 to 0.89; P=0.007) [393]. Several phase II and retrospective studies investigating taxane- or irinotecan-based chemotherapy as third-line treatments also have shown consistent results [410-412]. A randomized phase III trial of trifluridine/tipiracil significantly improved OS compared to placebo (median OS, 5.7 vs. 3.6 months; HR, 0.69; 95% CI, 0.56 to 0.85; P=0.00058) in gastric cancer patients who had received at least 2 previous systemic treatments [413].

Nivolumab also showed a survival benefit over placebo in heavily pre-treated patients who had received 2 or more previous systemic therapies in the randomized phase III ATTRACTION-2 trial (median OS, 5.3 vs. 4.1 months; HR, 0.63; 95% CI, 0.51 to 0.78; P<0.0001) [414]. Two-year updated data from ATTRACTION-2 confirmed the long-term survival benefit of nivolumab regardless of PD-L1 expression status [415]. Based on these results, nivolumab is recommended as a palliative third-line therapy for gastric cancer patients who are naïve to ICI therapy.

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In the phase II 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 had received at least 2 prior palliative systemic treatments including trastuzumab [416]. In this trial, trastuzumab deruxtecan was associated with significant improvements in the ORR (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 the approval of trastuzumab deruxtecan in patients with HER2-positive gastric cancer who have received a prior trastuzumab-based regimen as a second-line or later treatment in the US and a third-line or later treatment in Korea.

In the double-blinded, placebo-controlled phase III trial (INTEGRATE IIa), regorafenib plus best supportive care was compared to a placebo plus best supportive care in a 2:1 randomization among patients who had failed or were intolerant to at least 2 or more prior lines of therapy including a platinum agent plus fluoropyrimidine [417]. In this trial, regorafenib was associated with significant improvements in the OS (median, 4.5 vs. 4.0 months; HR, 0.70; 95% CI, 0.53 to 0.92; P=0.011) and PFS (median, 1.8 vs. 1.6 months; HR, 0.52; 95% CI, 0.40 to 0.69; P<0.0001) compared to the placebo. The ongoing international randomized phase III INTEGRATE IIb trial is evaluating regorafenib combined with nivolumab compared to standard chemotherapy in pre-treated patients with AGC (NCT0487936).

RADIATION THERAPY

Adjuvant radiation therapy

S29. Adjuvant chemoradiation

KQ 29: Could adjuvant concurrent chemoradiation improve treatment outcomes compared to adjuvant chemotherapy alone in patients with pathological stage II or III gastric cancer who have undergone curative gastrectomy?

Statement 29: Adjuvant chemoradiation is not 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 [366,371,418-421]. 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 chemoradiation therapy (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=0.25) and OS (HR, 1.03; 95% CI, 0.87 to 1.23; P=0.70) (**Fig. 24**).

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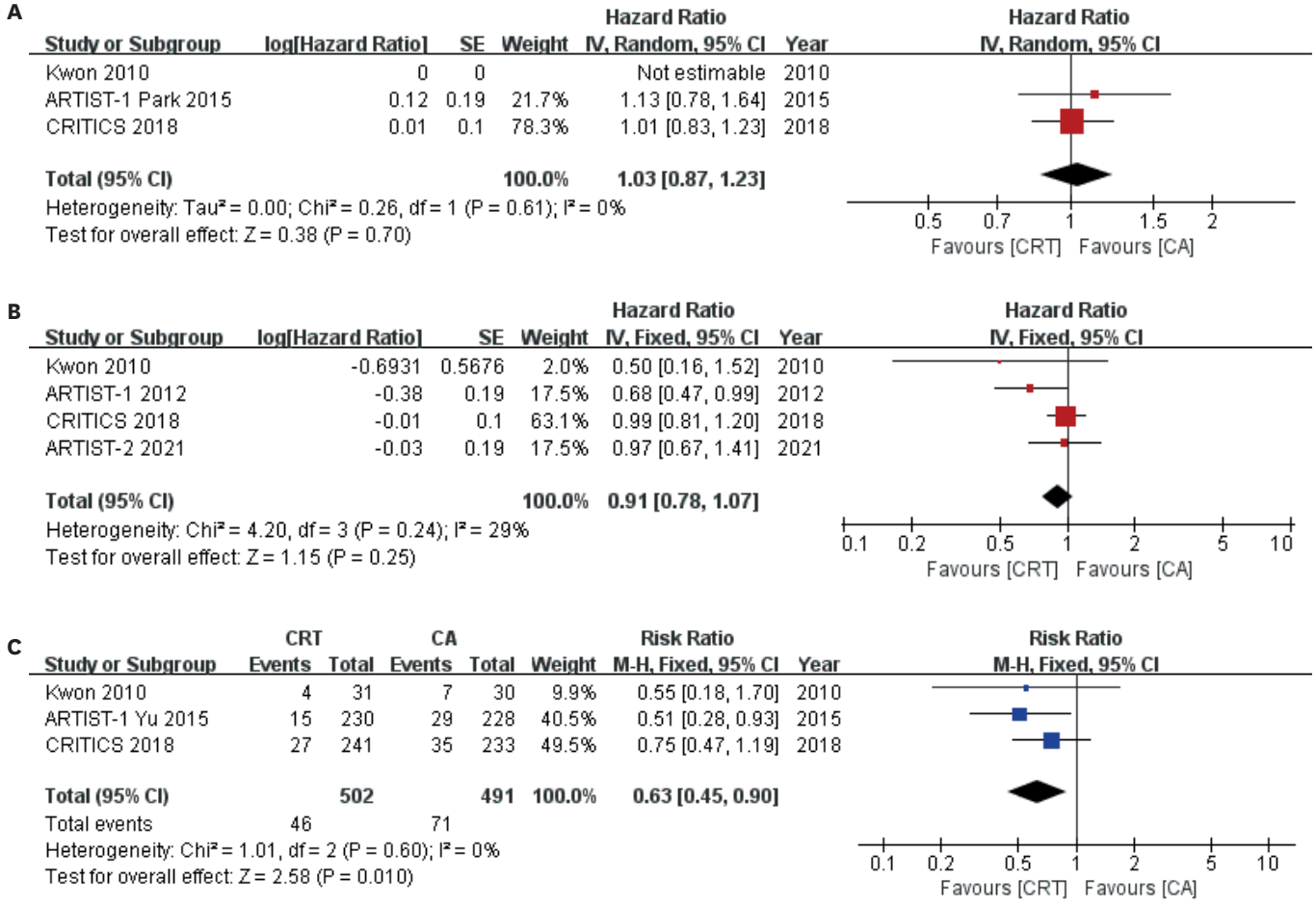

Fig. 24. Forest plots for comparison between adjuvant concurrent CRT vs. adjuvant platinum-based combination CA. (A) Overall survival. (B) Disease-free survival. (C) Locoregional recurrence.
CRT = chemoradiation therapy; CA = chemotherapy alone; SE = standard error; IV = interval variable; CI = confidence interval; M-H = Mantel-Haenszel.

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

Neoadjuvant radiation therapy

S30. Neoadjuvant chemoradiation (NCRT)

KQ 30: Could neoadjuvant concurrent chemoradiation improve treatment outcomes compared to NCT alone in patients with locally AGC?

Statement 30: The evidence for adding radiation to NCT is not conclusive in patients with locally AGC (evidence: moderate, recommendation: investigational).

NCRT is mainly studied for cancer of the esophagus, GEJ, and/or gastric cardia, where achieving a complete R0 resection is challenging and the locoregional relapse is high. The MAGIC trial showed that perioperative chemotherapy significantly improved OS over surgery alone for distal esophageal and gastric cardia adenocarcinoma [370]. Studies have

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focused on assessing whether adding radiation therapy to NCT would provide benefits in gastric cancer. Two RCTs have been conducted, and one RCT is ongoing to compare the outcomes of NCRT vs. NCT alone in resectable cancer of the GEJ or stomach [422-426].

Final treatment outcomes were reported in the POET and NeoRes trials [421,424]. In our meta-analysis (**Fig. 25**), the pCR 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 higher in the NCRT group. Local PFS was reported only in the POET trial, showing a significant improvement with NCRT in long-term follow-up (HR, 0.37; 95% CI, 0.16 to 0.85). However, these improved pathologic

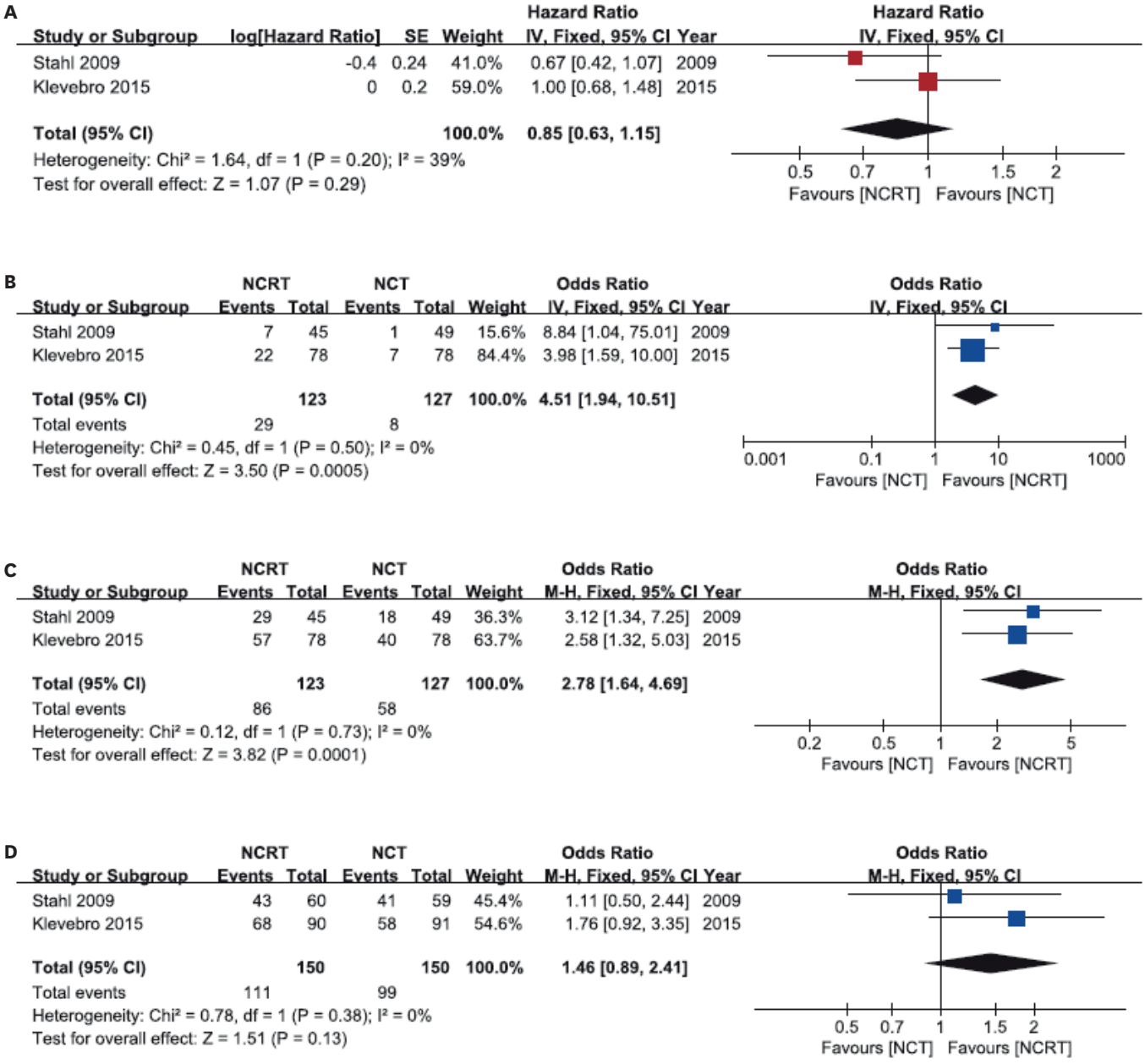

Fig. 25. Forest plots for comparisons between NCRT compared to NCT. (A) Overall survival. (B) Pathologic complete response. (C) Pathologic complete nodal regression. (D) R0 resection.
NCRT = neoadjuvant chemoradiation; NCT = neoadjuvant chemotherapy; SE = standard error; IV = interval variable; CI = confidence interval; M-H = Mantel-Haenszel.

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responses did not lead to a significant OS benefit (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, with 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 [423]. 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).

It is noteworthy that these studies were conducted mainly in patients with esophageal and/or GEJ cancer, which is more common in Western countries. Most studies evaluating the efficacy of NCRT for gastric cancer (mainly GEJ cancer) have also been conducted in Western populations. In addition, in the NeoRes trial, some patients with esophageal squamous cell carcinoma were included. Evidence remains limited, and further prospective studies including Asian populations and nonjunction cancers are needed to establish more robust evidence.

TREATMENT FOR FAR AGC

S31. Endoscopic stenting (ES) vs. surgical gastrojejunostomy (GJ) for malignant gastric outlet obstruction (GOO)

KQ 31: Can endoscopic stent insertion as a palliative therapy improve oral intake with comparable complication rate for malignant GOO compared to surgical bypass?

Statement 31: 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 the patients' performance status, projected clinical course, and individual preferences (evidence: low, recommendation: conditional for).

In patients with advanced or metastatic gastric cancer, GOO often manifests with symptoms such as nausea, vomiting, dehydration, and malnutrition, significantly deteriorating patients' QOL. Given that radical surgery is not indicated in patients with incurable gastric cancer, palliative treatments are required to relieve symptoms of GOO and restore the ability to consume an oral diet.

Surgical GJ and ES are palliative treatments for GOO caused by unresectable gastric cancer. GJ has been the standard for effective symptom relief in GOO; however, it carries a risk of substantial early major complications and procedure-related mortality [427,428]. ES, with its shorter procedure time, quicker resumption of oral intake, and shorter duration of hospital stay than GJ, offers a less invasive alternative [427,428]. However, ES is associated with higher rate of complications, reinterventions, and recurrent obstructions compared to GJ [427,428].

In this clinical guideline, we compared the outcomes of ES with GJ through a meta-analysis of 1,637 articles [187,429-441], ultimately including 15 studies (12 observational and 3 RCTs), with 5 studies conducted in Korea [187,434,437-439]. Of the 1,286 patients, 818 patients received ES, and 468 patients underwent GJ. The overall certainty for outcomes from RCTs was rated as low, and very low for observational studies due to a limited number of events and bias from confounding and selection of participants. Regarding procedure outcomes, there

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was no significant difference between the ES and GJ groups in terms of 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) (**Fig. 26A and B**). There was no significant difference in procedure-related mortality

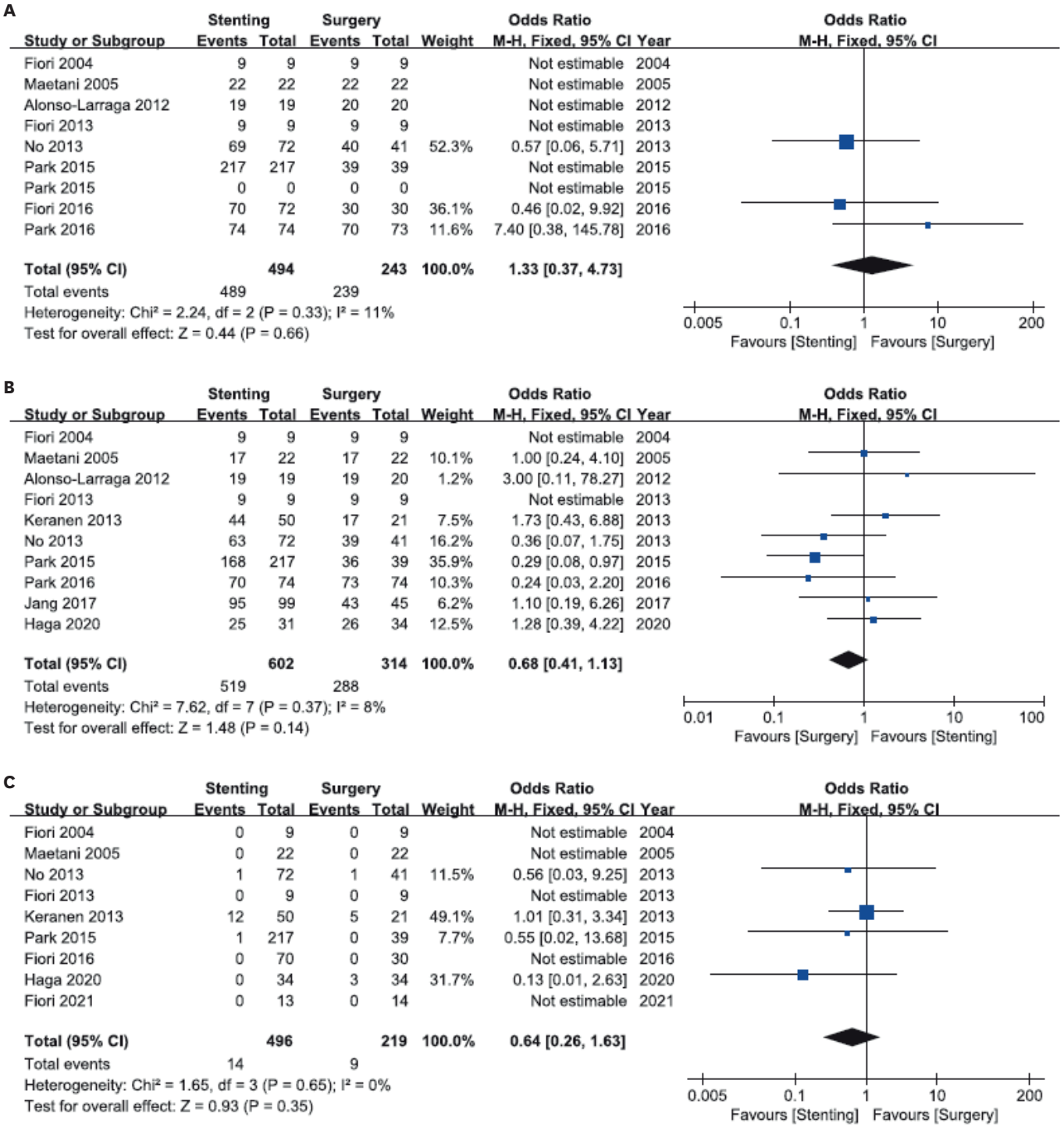

Fig. 26. Forest plots of procedure outcomes between stent insertion (Stenting) and surgery (Surgery). (A) Technical success. (B) Clinical success. (C) Procedure related mortality.
CI = confidence interval; M-H = Mantel-Haenszel.

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(OR, 0.64; 95% CI, 0.26 to 1.63; P=0.35) (**Fig. 26C**). For postoperative outcomes, patients in the ES group had a faster resumption of oral intake (mean duration, −3.94 days; 95% CI, −4.01 to −3.88 days; P<0.001) and a shorter duration of hospital stay (mean duration, −6.56 days; 95% CI, −7.20 to −5.92 days; P<0.001) (**Fig. 27A 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. 27C**). However, major complications (OR, 1.81; 95% CI, 1.10 to 2.96; P=0.02) and reintervention rates (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. 27D and E**). Additionally, ES was significantly associated with a shorter patency duration (mean duration, −4.97 months; 95% CI, −6.42 to −3.51 months; P<0.001) (**Fig. 27F**). However, OS was not significantly different between the ES and GJ groups (mean duration, 0.12 months; 95% CI, −0.48 to 0.72 months, P=0.69) (**Fig. 27G**).

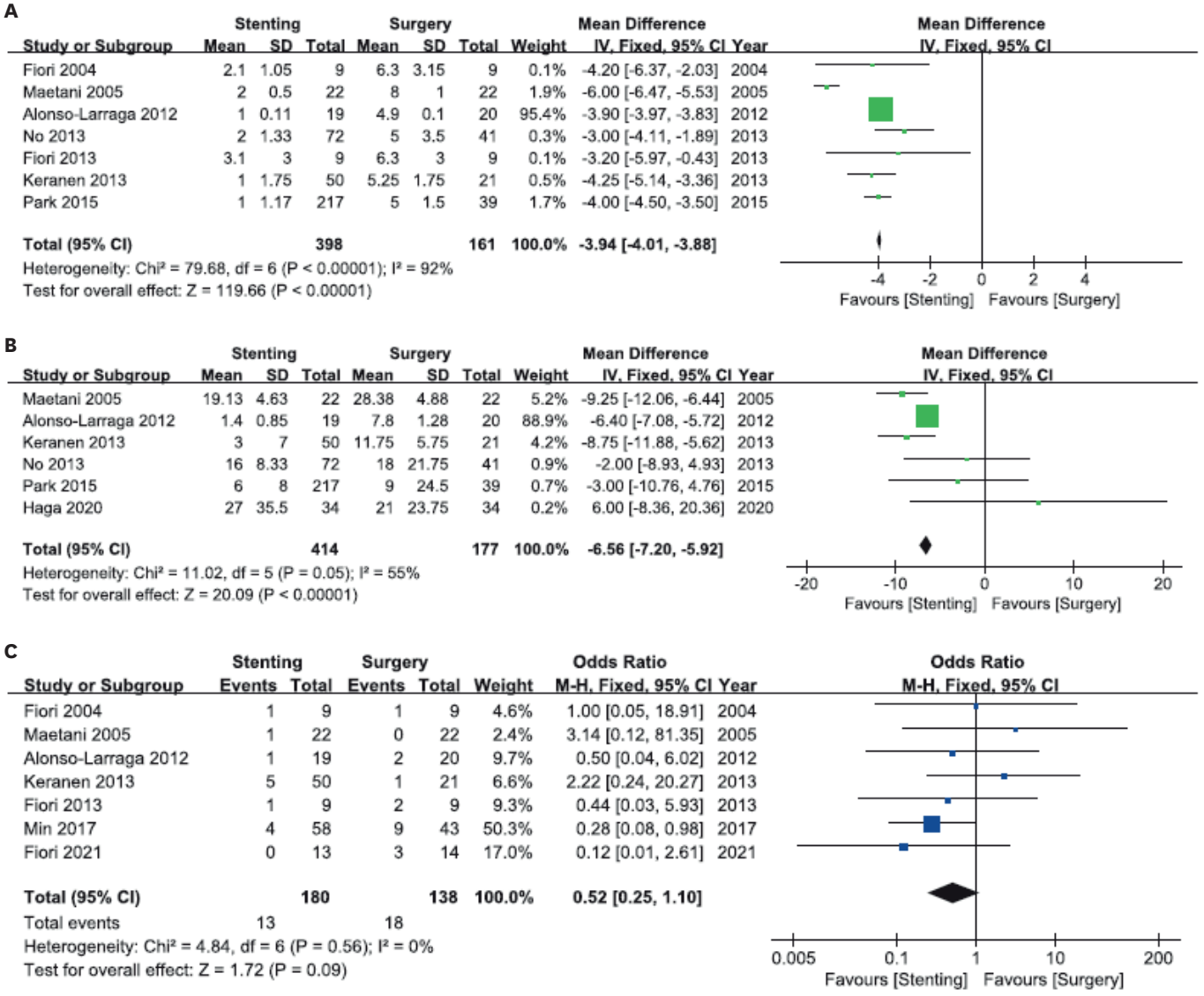

Fig. 27. Forest plots of post procedure or operative outcomes between stent insertion (Stenting) and surgery (Surgery). (A) Resumption of oral intake. (B) Duration of hospital stay. (C) Minor complications. (D) Major complications. (E) Re-intervention. (F) Patency duration. (G) Overall survival.
SD = standard deviation; IV = interval variable; CI = confidence interval; M-H = Mantel-Haenszel.

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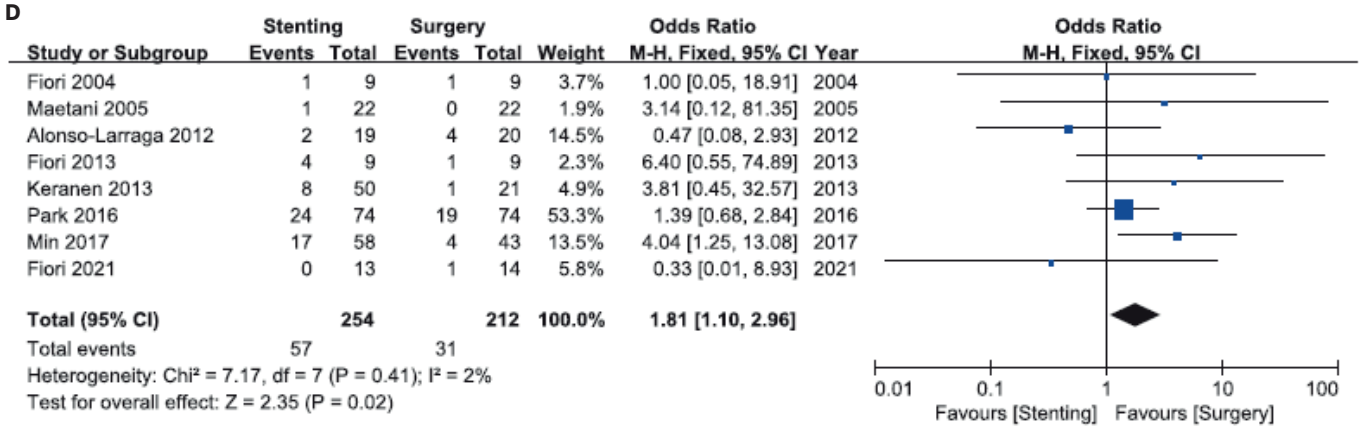

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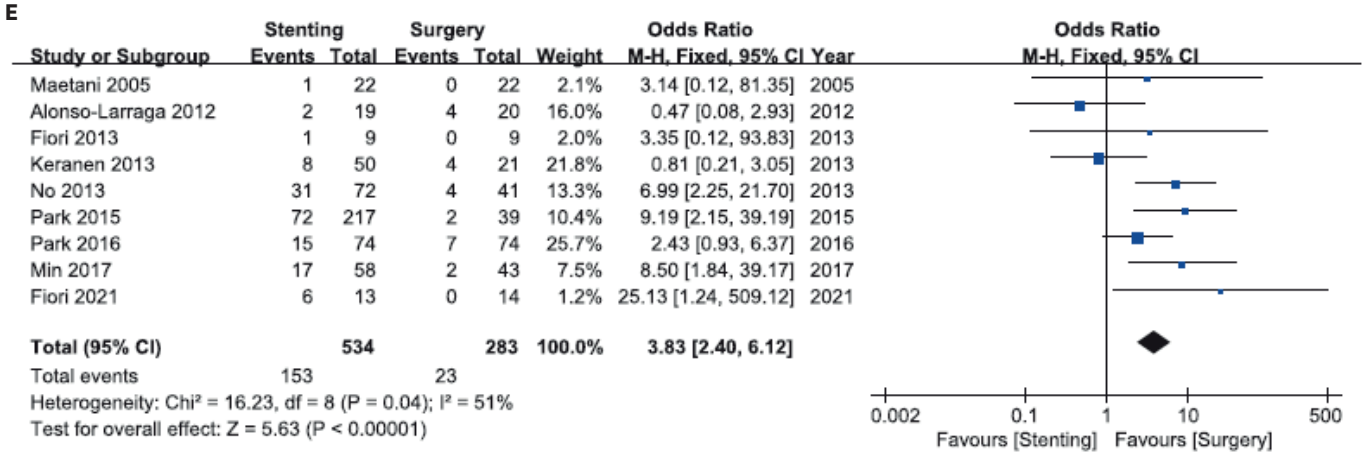

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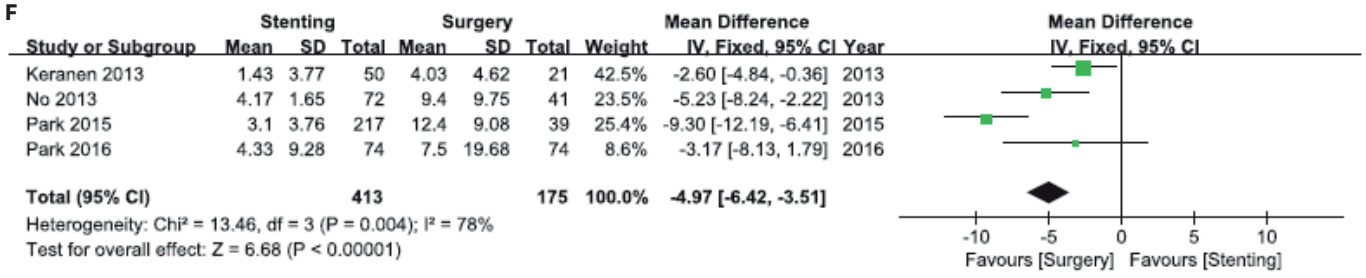

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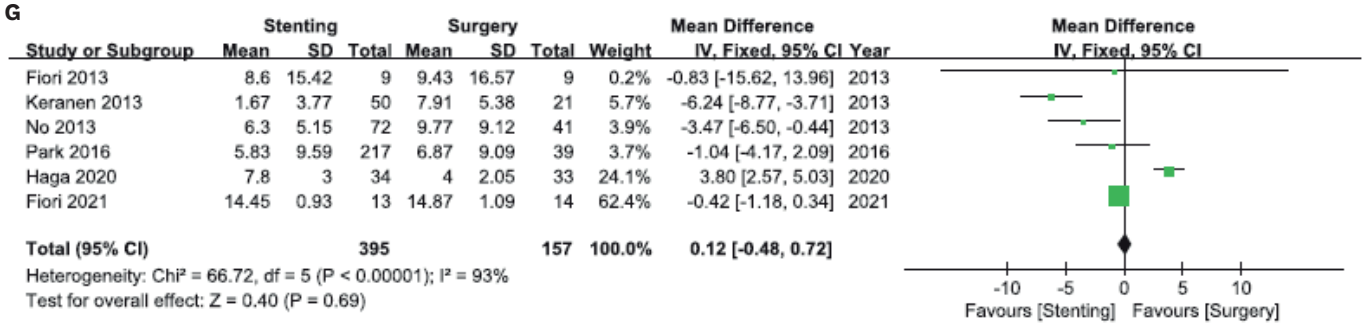

Fig. 27. (Continued) Forest plots of post procedure or operative outcomes between stent insertion (Stenting) and surgery (Surgery). (A) Resumption of oral intake. (B) Duration of hospital stay. (C) Minor complications. (D) Major complications. (E) Re-intervention. (F) Patency duration. (G) Overall survival.
SD = standard deviation; IV = interval variable; CI = confidence interval; M-H = Mantel-Haenszel.

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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 for patients who are poor surgical candidates with relatively short life expectancy and who prioritize resuming an oral diet and early discharge, while GJ is preferable in patients with a longer prognosis and good performance status. Stent insertion by radiologic intervention showed similar efficacy to endoscopic stent insertion in a single-center study [439], and radiologic stent insertion can also be considered for GOO when available.

S32. Surgical resection for metastatic gastric cancer

KQ 32: Can surgery plus systemic therapy improve survival outcomes for stage IV gastric cancer patients compared to chemotherapy only?

Statement 32-1: Reduction gastrectomy (or upfront debulking gastrectomy without systemic LN dissection) should not be considered as an initial treatment option for stage IV gastric cancer patients who are susceptible to systemic therapy (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 [439]. Gastric cancer patients with a single non-curable factor were enrolled. Reduction surgery showed no survival benefit compared to chemotherapy alone, and the trial was terminated after the first interim analysis due to the lack of benefit in the surgery group (HR, 1.08; 95% CI, 0.74 to 1.58; P=0.66). Based on these findings, it was concluded that reductive gastrectomy is not justified in patients with metastatic gastric cancer.

Statement 32-2: 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 systemic therapy (evidence: low, recommendation: investigational).

Our meta-analysis included 3 retrospective studies and one prospective study. The data on OS showed better survival outcomes in stage IV gastric cancer patients who underwent systemic chemotherapy followed by radical surgery compared to those who received chemotherapy alone (HR, 0.58; 95% CI, 0.42 to 0.80; P<0.001) (**Fig. 28**).

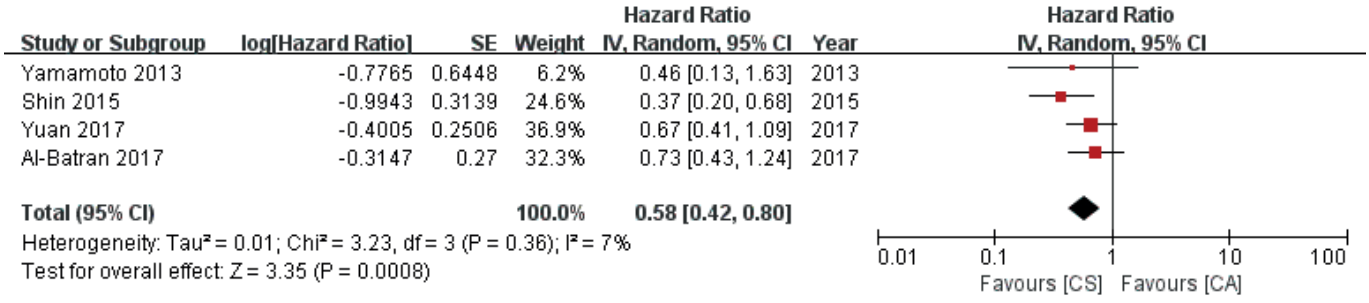

Fig. 28. Forest plot for overall survival between CS vs. CA in metastatic gastric cancer.
CS = conversion surgery after chemotherapy; CA = chemotherapy alone; SE = standard error; IV = interval variable; CI = confidence interval.

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A large retrospective review showed that stage IV cancer patients who were responsive to chemotherapy and underwent R0 resection following chemotherapy had better survival than those in the R1 and R2 resection groups [442]. In a prospective nonrandomized trial, surgery after chemotherapy, particularly in R0 resection, was associated with a survival benefit for gastric cancer patients with limited distant metastasis [443]. However, as most studies included are retrospective and potentially subject to selection bias, the evidence is limited for making stronger recommendations.

While the meta-analysis suggests possible benefits, the role of conversion surgery and detailed indications are inconclusive due to inherent selection biases in observational studies comparing surgery and systemic therapy for stage IV gastric cancer. Additionally, it remains uncertain whether advancements in systemic therapies will enhance or reduce the relevance of conversion surgery.

The recently reported results of the RENAISSANCE prospective RCT (AIO-FLOT5) [444] showed no significant difference in OS between the surgical resection after systemic therapy group and the systemic therapy-only group (median OS, 18.5 vs. 23.6 months; HR, 1.037; 95% CI, 0.691 to 1.556; P=0.861), thus not meeting the primary endpoint. The limitation of the study was considered due to non-favorable surgical outcomes; morbidity up to 60%, 20% reoperation rate within 90 days, and postoperative mortality of approximately 8% in the surgery group. This high morbidity rate not only impacted survival but also prevented many patients from completing postoperative systemic therapy, unlike those who remained on continuous FLOT. Subgroup analysis indicated a need for strategies to address early mortality in the surgery group, with a significant survival benefit observed in the retroperitoneal LN group but significantly worse survival in the peritoneal disease subgroup. The implementation of safe local treatment was important in the continuation of systemic therapy.

At the KINGCA 2024 conference, an expert consensus meeting on conversion surgery was held. A panel of 17 experts, consisting of 10 surgeons and 7 medical oncologists from both domestic and international institutions, participated in discussions focused on 9 key topics. The results of this consensus meeting are described in **Table 5** and the details will be reported in a separate report [445].

S33. Surgical resection plus systemic therapy for gastric cancer patients with single-organ oligometastasis

KQ 33: Can radical gastrectomy with local treatment plus systemic therapy improve survival outcomes compared to systemic therapy alone for gastric cancer patients with single organ oligometastasis?

Statement 33-1: Radical gastrectomy, metastatectomy and systemic therapy 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 [446]. However, the definition remains unclear, and oligometastasis generally defined as fewer than 3 or 5 metastatic lesions involving one or 2 organs [447,448].

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Table 5. Consensus rate from the expert consensus meeting on conversion therapy at KINGCA 2024

No.	Statement	Strongly agree (%)	Agree (%)	Neutral (%)	Disagree (%)	Strongly disagree (%)
1	Conversion therapy may provide a survival benefit for selected patients with metastatic GC who respond favorably to systemic therapy and achieve an R0 resection.	41.2	47.1	11.8	0	0
2	Conversion therapy could be considered for patients with metastatic GC who have limited metastases at the time of initial diagnosis of metastatic GC.	35.2	58.9	5.8	0	0
3	The optimal timing for conversion surgery generally coincides with the tumor demonstrating the most favorable response to systemic therapy, ensuring the possibility of achieving an R0 resection.	47.1	23.5	23.5	5.8	0
4	The regimen for systemic therapy used in conversion therapy should be individualized for each patient to enable the best tumor response for R0 resection, considering patient-related factors such as performance status, comorbidities, and organ function, as well as tumor-related factors, including relevant predictive biomarkers.	100	0	0	0	0
5	Given the curative intent of conversion surgery, D2 lymph nodes dissection is recommended as the extent of lymphadenectomy.	47.1	35.3	11.8	5.8	0
6	After systemic therapy, even if metastatic lesions in the liver and para-aortic lymph nodes show a clinically complete response and have disappeared on imaging studies, surgical resection should still be considered owing to the possibility of residual tumor.	11.8	29.4	17.6	41.2	11.8
7	The surgical approach, whether open or laparoscopic, depends on the individual surgeon's decision. The laparoscopic approach may be considered for selected patients with a low tumor burden by highly experienced surgeons.	29.4	52.9	17.6	0	0
8	For patients undergoing conversion surgery to achieve complete resection (R0 resection) of metastatic GC, the total duration of systemic therapy is estimated to be at least 6 months, depending on the regimen used.	47.1	41.2	5.8	5.8	0
9	Large-scale, multicenter randomized controlled trials are required to determine the role of conversion therapy and investigate the optimal treatment strategy for conversion therapy in metastatic GC.	72.2	27.8	0	0	0

GC = gastric cancer.

For hepatic oligometastasis in gastric cancer, 2 retrospective studies were included in our meta-analysis (**Fig. 29**) [449,450]. The meta-analysis showed that radical gastrectomy with hepatectomy plus chemotherapy provided a survival benefit compared to chemotherapy alone (HR, 0.27; 95% CI, 0.12 to 0.62; P=0.002). Local treatments, such as transarterial chemoembolization (TACE), radiofrequency ablation, and hepatic arterial infusion, have also been reported to provide potential survival benefits [451-454]. However, most of the related studies were single-arm or compared outcomes with hepatectomy, so they could not be

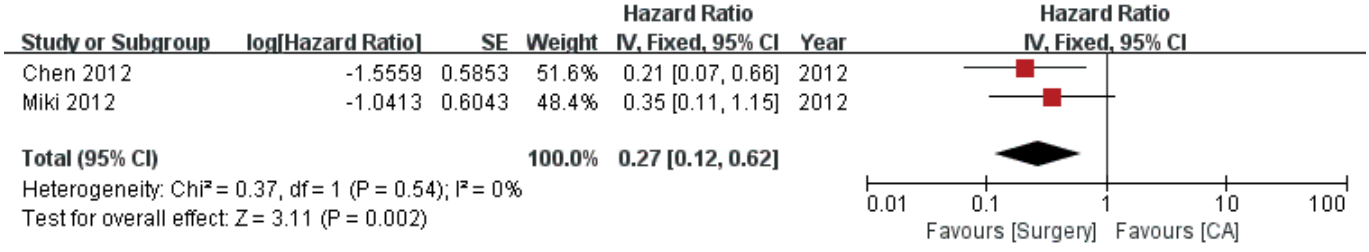

Fig. 29. Forest plot for comparison of overall survival between surgery, mastectomy and gastrectomy with chemotherapy (Surgery) vs. CA in gastric cancer with oligometastasis confined to liver from observational studies.
CA = chemotherapy alone; SE = standard error; IV = interval variable; CI = confidence interval.

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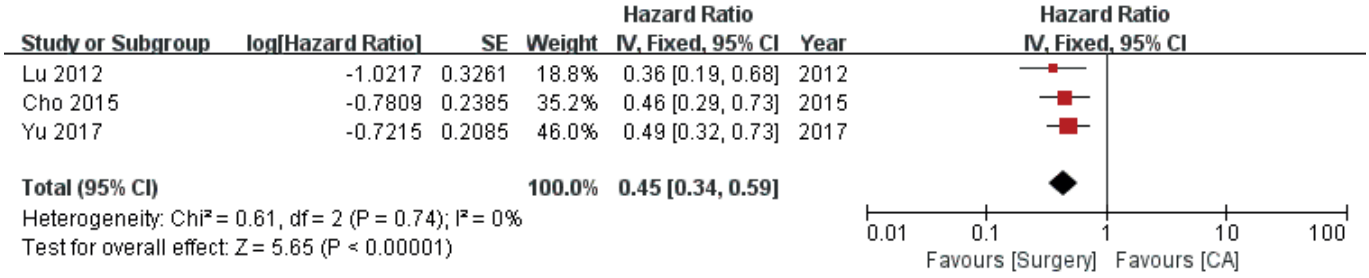

Fig. 30. Forest plot for comparison of overall survival between surgery, oophorectomy with chemotherapy (Surgery) vs. CA in gastric cancer with oligometastasis confined to liver from observational studies.
CA = chemotherapy alone; SE = standard error; IV = interval variable; CI = confidence interval.

included in the meta-analysis. Liu et al. [454] retrospectively compared radical gastrectomy with TACE plus chemotherapy with chemotherapy alone, including all types of liver metastasis (H1, H2, H3) in the study. The median OS was 14 months in the surgery group and 8 months in the chemotherapy groups (P<0.001) [453].

There is some promising evidence that resection of liver oligometastasis may provide a survival benefit. However, due to the small sample sizes and retrospective nature of the studies, the evidence is weak, so candidates for liver resection should be selected cautiously. Further evidence is needed for generalization.

Statement 33-2: Radical gastrectomy, oophorectomy, and systemic therapy 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 included in the meta-analysis, showing better survival in the metastasectomy group (HR, 0.45; 95% CI, 0.34 to 0.59, P<0.001) [455-457] (**Fig. 30**). Cheong et al. [458] reported that Krukenberg tumors were often accompanied by peritoneal dissemination, which was associated with a significantly worse prognosis (HR, 1.74; 95% CI, 1.28 to 2.36; P<0.001), and only when curative resection was achieved was the median OS time longer in the resection group than in the non-resection group (17 vs. 3 months, P<0.001).

For para-aortic LNs, only 3 prospective nonrandomized studies evaluated the response rate of preoperative chemotherapy and the efficacy of subsequent D2 LN dissection plus para-aortic LN dissection; they did not show favorable survival outcomes [459-461].

S34. Intraperitoneal (IP) chemotherapy for patients with peritoneal carcinomatosis

KQ 34: Can additional IP chemotherapy improve survival outcome for gastric cancer patients with peritoneal carcinomatosis compared to chemotherapy alone?

Statement 34: For gastric cancer patients with peritoneal carcinomatosis, additional IP chemotherapy should be applied for investigational purposes (evidence: low, recommendation: investigational).

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Peritoneal metastasis is known to be less responsive to systemic therapy and is associated with a worse prognosis than hematogenous or lymphatic metastasis [462,463]. One reason is the limited delivery of anticancer drugs to the peritoneum due to the peritoneum-plasma barrier. To directly target cancer cells on the peritoneum, IP infusion using anticancer drugs with lower systemic absorption and 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 [464-470].

In gastric cancer patients with peritoneal metastasis, phase I and II studies showed improved survival for patients in the IP (paclitaxel + docetaxel) plus systemic chemotherapy group compared the systemic chemotherapy alone group, with median OS of 24.6 vs. 15.1 months and 1-year survival rates of 78% vs. 70.4% [463].

However, in a phase III trial conducted by Ishigami et al. [471], IP plus systemic chemotherapy did not show a significant improvement in survival outcome compared to systemic chemotherapy alone (HR, 0.72; 95% CI, 0.49 to 1.04; stratified log-rank P=0.080). The authors suggested that patient withdrawal and protocol violations may have led to an underestimation of the true effect of IP therapy.

Currently, phase I, II, and III studies are ongoing in Korea. Further investigation is required for recommendation, and until trial outcome data become available, IP chemotherapy should be applied only 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 the early detection of recurrence or secondary cancer, allowing for 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 examinations should be performed or how frequently. Although the NCCN, Japanese, and Chinese guidelines for gastric cancer recommend some follow-up schedules, these recommendations were based on expert opinions [87,90,109]. Due to this lack of evidence, we conducted a nationwide survey targeting all tertiary or general hospitals. The purpose of this survey was only to provide baseline information regarding current practices, without intending to recommend, impose, or restrict 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 6** shows the main intervals (months) for the physical examination, blood tests, tumor markers, abdomen pelvis CT, chest X-ray, and endoscopy. For patients with pathological stage I tumors, physical examination, and blood tests, including tumor markers, were mainly conducted every 6 months for the first 3 years and then every 6–12 months until 5 years postoperatively. Abdomen pelvis CT and chest X-ray were mainly performed every 6 months for the first 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 the first postoperative year and then every 6 months until 5 years postoperatively. Abdomen pelvis CT

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Table 6. 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	6	6	6 or 12	None or 12
	Abdomen CT, chest X-ray	6	6	6 or 12	12	None or 12
	Endoscopy	6 or 12	12	12	12	12
Stage II/III	Physical examination, blood test, tumor makers	3	6	6	6	None or 12
	Abdomen CT, chest X-ray	3 or 6	6	6	6 or 12	None or 12
	Endoscopy	6 or 12	12	12	12	12

Korea numbers in the parenthesis are proportions of the response from the participants (interval, months).
CT = computed tomography.

and chest X-ray were mainly performed every 3 or 6 months in the first year, 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 the first year, then annually until 5 years postoperatively regardless of stage. After 5 years, the 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 (**Table 6**).

Nutritional follow-up

Patients who undergo gastrectomy for gastric cancer may experience both short- and long-term nutritional deterioration. Therefore, monitoring nutritional status after surgery and providing appropriate nutritional supplements are essential. **Table 7** shows the main interval (in months) for monitoring body weight, nutritional parameters, anemia, and bone health according to the nationwide survey.

Significant weight loss is common after gastric cancer surgery, with lower preoperative body mass index (BMI), female sex, and TG or PG identified as significant risk factors for malnutrition (BMI, < 18.5 kg/m^2) 6 months after surgery [472]. Postoperative sarcopenia could serve as a prognostic factor for survival in gastric cancer patients [472]. Although some studies have suggested that postoperative oral nutritional supplementation could improve nutritional outcomes in high-risk patients, strong evidence is still lacking [473,474].

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 post-surgery was reported at 64.8% and 90.5% after DG and TG, respectively, and overt anemia was observed in 31.9% of patients after gastric cancer surgery [475]. Female sex and TG have been consistently identified as independent risk factors for iron deficiency in the literature [475-477]. Oral iron supplementation should be given in patients with iron deficiency to correct anemia and replenish iron reserves, Intravenous iron can be used when oral preparations are not tolerated or are ineffective. Ferric carboxymaltose as intravenous iron 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 [478]. Transfusions are reserved for patients with an urgent need or those at risk of cardiovascular decompensation [479].

Vitamin B12 deficiency is another common issue due to reduced 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

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Table 7. 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 (40)	12 (5)	12 (20)	12 (60)	12 (50)
		3 (50)	6 (80)	6 (80)	6 (38)	None (50)
		1–2 (10)	3 (15)		3 (2)	
	Nutritional parameters (total protein, albumin, total cholesterol)	6 (40)	6 (80)	12 (15)	12 (40)	12 mo (50)
		3 (60)	3 (20)	6 (80)	6 (60)	None (50)
				3 (5)		
	Anemia study (hemoglobin, iron, ferritin, vitamin B12, folate)	6 (50)	6 (70)	12 (50)	12 (60)	12 (50)
		3 (50)	3 (25)	6 (50)	6 (40)	6 (10)
						None (40)
	Bone related	6 (40)	6 (60)	12 (20)	12 (40)	12 (40)
		3 (40)	3 (20)	6 (60)	6 (40)	6 (10)
		None (20)	None (20)	None (20)	None (20)	None (50)
Partial gastrectomy	Body weight	6 (40)	12 (5)	12 (20)	12 (60)	12 (50)
		3 (60)	6 (80)	6 (80)	6 (38)	None (50)
			3 (15)		3 (2)	
	Nutritional parameters (total protein, albumin, total cholesterol)	6 (40)	6 (80)	12 (15)	12 (40)	12 (50)
		3 (60)	3 (20)	6 (80)	6 (60)	None (50)
				3 (5)		
	Anemia study (hemoglobin, iron, ferritin, vitamin B12, folate)	6 (40)	6 (80)	12 (40)	12 (40)	24 (5)
		3 (50)	3 (20)	6 (30)	6 (30)	12 (35)
		1–2 (10)		None (30)	None (30)	None (60)
	Bone related	6 (40)	6 (60)	12 (20)	12 (40)	12 (40)
		3 (40)	3 (20)	6 (60)	6 (40)	6 (10)
		None (20)	None (20)	None (20)	None (20)	None (50)

Values are presented as number of months (%). Numbers in the parenthesis are proportions of the response from the participants.

15.7% was seen after DG [475]. 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 [480,481]. 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. Daily oral vitamin B12 supplementation at a high dosage (1,500 μg once daily) can be an alternative option with similar efficacy [482-484].

Metabolic bone disorders, including significantly reduced bone mineral density, may also occur after gastrectomy [485-487]. Common mechanisms include reduced oral calcium intake and generalized malabsorption induced by rapid gut transit in the early postoperative period, as well as vitamin D deficiency and secondary hyperparathyroidism in the longer term [486,488]. A nationwide Korean cohort study found that gastric cancer survivors had a high risk of osteoporotic fractures (HR, 1.61; 95% CI, 1.53 to 1.70) [489]. Older age,

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female sex, and marked weight loss (≥20%) were independent risk factors for osteoporosis [490]. Although there is currently little evidence of 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. Currently, no universal guidelines are available for the prevention or management of metabolic bone disorders related to gastrectomy. Oral calcium and vitamin D supplements are generally recommended in populations at higher risk of osteoporosis. A few recent RCTs demonstrated that alendronate therapy effectively reduced bone loss and bone resorption in gastrectomy patients [491].

According to a nationwide survey in 2022, the postoperative nutritional monitoring schedule was not significantly different between TG and PG. During the first year after surgery, most respondents monitored patients every 3 months (50%–51%) or every 6 months (41.7%–43.7%). In the second and third years, the interval increased to every 6 months (73.6%–80.0%), and up to the 5th years, patients were monitored either every 6 months (43.7%–48.6%) or 12 months (41.7%–49.3%). After 5 years, about half of the respondents continued annual nutritional monitoring, while the other half discontinued it. Most centers evaluated body weight, hemoglobin, total protein, albumin, and total cholesterol at every visit. Other commonly monitored nutritional indices included 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 fewer 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 (**Table 7**).

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 approach may include improved diagnostic accuracy, better treatment plans, shorter decision-making times, and survival benefits [492-495]. For these reasons, health services in several countries have implemented MDT as the preferred system in cancer treatment [109,492,493,496]. 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 specialists, social workers, nurses, and palliative care specialists [497-500].

Several studies have shown the advantages of MDT in managing gastrointestinal malignancies. After MDT meeting, changes in diagnosis were observed in 18.4%–26.9% of evaluated patients [501,502], and treatment plans were changed in 23.0%–76.81% of cancer patients [502-504].

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 [505]. MDT meetings offer a good opportunity to record specialists' opinions on complex cases and improve diagnostic accuracy, treatment quality, and accurate communication [505,506].

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However, despite 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, questions arise on how to select patients for MDT discussion and organize these meetings can be one of the issues because many patients without substantial comorbidities can follow routine decision-making processes without MDT team discussion [507]. Nevertheless, 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 those with comorbidities. Allum et al. [508] recommended that MDT team activities should also involve patients in discussing treatment decisions. However, there is no evidence to suggest that direct patient involvement in MDT discussions leads to better outcomes than the traditional 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 patients [508-514]. Further research is needed to determine which MDT discussion type offers the best treatment outcome and cost-effectiveness.

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