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Special Article

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Conversion Therapy for Stage IV Gastric Cancer: Report From the Expert Consensus Meeting at KINGCA WEEK 2024

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ABSTRACT

Conversion therapy is a treatment strategy that shifts from palliative systemic therapy to curative surgical treatment for primary and/or metastatic stage IV gastric cancer (GC). To address its clinical statements, the Korean Gastric Cancer Association aims to present a consensus on conversion therapy among experts attending KINGCA WEEK 2024. The KINGCA Scientific Committee and Development Working Group for Korean Practice Guidelines prepared preformulated topics and 9 clinical statements for conversion therapy. The Delphi method was applied to a panel of 17 experts for consensus and opinions. The final comments were announced after the statement presentation and discussed during the consensus meeting session of KINGCA WEEK 2024. Most experts agreed that conversion

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therapy provides a survival benefit for selected patients who respond to systemic therapy and undergo R0 resection (88.3%). Patients with limited metastases were considered good candidates (94.2%). The optimal timing was based on the response to systemic therapy (70.6%). The regimen was recommended to be individualized (100%) and the duration to be at least 6 months (88.3%). A minimally invasive approach (82.3%) and D2 lymph node dissection (82.4%) were considered for surgery. However, resection for metastases with a complete clinical response after systemic therapy was not advocated (41.2%). All experts agreed on the need for large-scale randomized-controlled trials for further evidence (100%). Recent advancements in treatment may facilitate radical surgery for patients with stage IV GC. Further evidence is warranted to establish the safety and efficacy of conversion therapy.

Keywords: Surgery; Gastric cancer; Metastasis; Chemotherapy

INTRODUCTION

The standard treatment for metastatic gastric cancer (GC) is palliative systemic therapy. Patients with metastatic GC are typically not considered candidates for surgery unless they are required for palliative reasons such as obstruction or bleeding [1-5].

Conversion therapy is a therapeutic concept in which the treatment strategy is converted from palliative systemic therapy to curative surgical treatment of primary and/or metastatic tumors, with the aim of complete resection (R0 resection) of tumors that were originally considered unresectable or marginally resectable for technical and/or oncological reasons. Conversion surgery refers specifically to curative intent, distinct from palliative surgery or other terms related to surgical resection for advanced incurable tumors such as “salvage,” “adjuvant,” or “secondary” surgery. After systemic therapy for metastatic GC, primary and metastatic lesions can be well controlled, presenting an opportunity for radical surgery that could prolong the survival of these patients. With progress in preoperative imaging diagnosis, anesthesia, surgical techniques, and nutritional support, the surgery-related mortality rate has markedly decreased from more than 20% 2 decades ago to 4% [6-8]. Furthermore, the increasing awareness of clinical decision-making by multidisciplinary teams has led to the reconsideration of surgery as part of the treatment of metastatic GC [1]. Consequently, in recent years, conversion therapy has been increasingly adopted for the treatment of metastatic GC [7,9].

However, despite its potential benefits, our meta-analysis of the previous Korean Practice Guidelines for conversion surgery revealed limitations due to inherent biases in the included studies and a lack of strong supporting evidence (levels of evidence: low; grades of recommendation: investigational) [1].

To elucidate conversion therapy in clinical practice, the Korean Gastric Cancer Association (KGCA) aims to reach a consensus among experts attending KINGACA WEEK 2024.

MATERIALS AND METHODS

Under the KGCA, a consensus committee was formed with members selected from the Scientific Committee of KINGCA WEEK 2024 and the Development Working Group for

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the Korean Practice Guidelines for Gastric Cancer 2024 Task Force Team. The definition and scope of the consensus topics were determined through committee meetings after the publication reviews. There were nine statements on the following topics: overall effect, optimal candidates, optimal timing, systemic therapy regimen, extent of lymph node (LN) dissection, extent of surgery, minimally invasive surgery, duration of systemic therapy, and future perspectives. The consensus panel consisted of 11 invited experts and 6 committee members, including 7 medical oncologists and 10 surgeons, selected based on expertise and research achievements.

The Delphi method was applied for the consensus methodology [10]. The survey was sent by e-mail to panels in June 2024, and responses were collected anonymously through an online survey system. Each expert commented on and suggested modifications to the draft.

Survey responses were collected on a 5-point scale (1. strongly disagree, 2. disagree, 3. neutral, 4. agree, 5. strongly agree). Each figure represents the strength of agreement, and the mean value was calculated to reflect the strength of the general opinion of the panel. The coefficient of variation (CV), defined as the standard deviation divided by the mean, was calculated to assess the degree of dispersion. The CV offers a proportional measure of variation, providing an interpretable metric for comparing variability across entities. Consistent with prior Delphi studies, CV values were used to evaluate response density: no further discussion (CV ≤0.5), additional discussion required (0.5< CV <0.8), or major modification required (CV ≥0.8). The definition and scope for this discussion are presented in **Table 1**.

In the KINGCA WEEK 2024 consensus session, previously identified topics were discussed, and the invited expert panels were asked to comment on their expert opinions on the matter with suggestions. Definitive finalization and confirmation of the statements were conducted onsite. Commentaries and opinions from the participating panelists have been added below each statement. This report presents the agreement results, discussions of each statement, and expert opinions.

RESULTS

All panel responses were collected by July 17, 2024. The CV values for all nine surveys were below 0.5, and no further surveys were conducted. Detailed responses are provided in the **Supplementary Data 1**, and a summary of the results is presented in **Table 2** and **Fig. 1**. Commentaries and discussions from the conference are described for each topic.

Table 1. Expert consensus discussion points on conversion therapy

Definition of conversion therapy		
Conversion therapy is defined as the treatment strategy in which therapy is converted from systemic medical treatment with a palliative intent to curative surgical treatment of primary and/or metastatic tumors, with the aim of complete resection (R0 resection) of tumors that were originally considered unresectable or marginally resectable for technical and/or oncological reasons.		
Discussion points		
Points	Inclusion	Exclusion
Disease	· Distant metastasis (M1) considered unresectable or marginally resectable	· Locally advanced unresectable (M0)
Treatment before conversion surgery	· Systemic therapy only	· Treatments other than systemic therapy (e.g., radiotherapy and intraperitoneal chemotherapy)
Conversion surgery	· Primary and/or metastatic tumors where R0 resection is expected to be achieved	· Primary and/or metastatic tumors where R0 resection is not expected to be achieved

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Table 2. Summary of the survey responses

No.	Statements	Agreement (%)	Mean	CV
1	Conversion therapy provides a survival benefit for select patients with metastatic GC who respond favorably to systemic therapy and achieve an R0 resection.	88.3	4.29	0.16
2	Conversion therapy could be considered for patients with metastatic GC who have limited metastases at the time of the initial diagnosis of metastatic GC.	94.2	4.17	0.19
3	The optimal timing for conversion surgery should generally be based on the tumor response to systemic therapy, regardless of the duration of systemic therapy, typically when primary and metastatic tumors demonstrate the most favorable response, maximizing the possibility of R0 resection.	70.6	4.12	0.24
4	The systemic therapeutic regimen used in conversion therapy should be individualized for each patient to achieve 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	5.0	0.0
5	Given the curative intent of conversion surgery, D2 is recommended as the extent of lymph node dissection to reduce locoregional recurrence, regardless of clinical or surgical staging after systemic therapy.	82.4	4.23	0.21
6	After systemic therapy, when metastatic lesions in the liver and para-aortic lymph nodes show a clinically complete response and disappear on imaging studies, surgical resection of these metastatic lesions should be performed because of the possibility of a residual tumor.	41.2	3.06	0.39
7	A minimally invasive approach for conversion surgery can be considered in patients with metastatic gastric cancer. Selection should be made by highly experienced surgeons, considering the extent of surgery and patient safety.	82.3	4.11	0.17
8	For patients with metastatic GC undergoing conversion surgery with R0 resection, the total duration of systemic therapy is estimated to be at least 6 months with a preoperative effective regimen. The total duration and selection of maintenance anticancer drug(s) should be individualized based on the patient's performance status, toxicities of systemic therapy, tumor burden, and postoperative pathological status.	88.3	4.29	0.20
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.	100	4.7	0.10

CV = coefficient of variation; GC = gastric cancer.

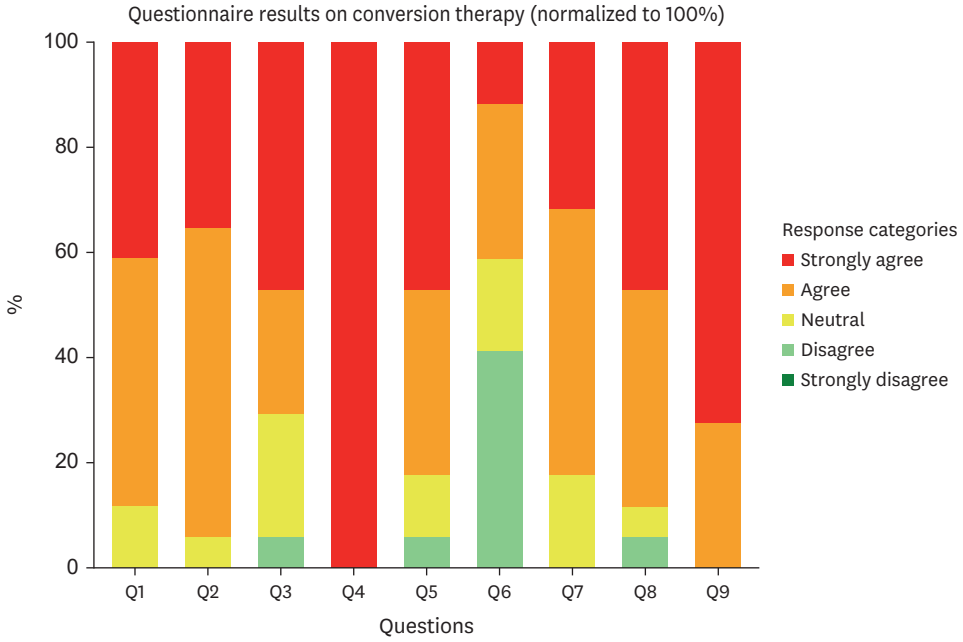

Fig. 1. Results of panel response for the questionnaire.

Overall effect

Improved survival outcomes in patients with stage IV GC may be attributable to the selection of patients with favorable prognostic factors and/or a favorable response to chemotherapy. This suggests that conversion surgery is a promising option for improving the survival outcomes of patients with stage IV GC.

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Previous reports have shown that patients who achieved R0 resection (defined as en bloc resection without microscopic or macroscopic residual disease at primary and metastatic sites) after conversion surgery had significantly better overall survival (OS) rates than those who did not, and that R0 resection was an independent favorable prognostic factor for OS [6,7,9,11,12].

In the CONVO-GC-1 study, a retrospective, international, multicenter cohort study, the median OS of all resected patients was 36.7 months, with OS for R0, R1, and R2 resections being 56.6, 25.8, and 21.7 months, respectively [6].

The phase II AIO-FLOT3 trial evaluated the efficacy and safety of surgical resection combined with perioperative chemotherapy using 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for resectable or limited metastatic GC [13]. Among 60 patients with limited metastasis, 36 (60%) underwent surgery following preoperative chemotherapy, resulting in a longer median OS than for those who did not undergo surgery (31.3 months [95% confidence interval {CI}, 18.9 months–not achieved] vs. 15.9 months [95% CI, 7.1–22.9 months]).

Based on these findings, the panel was asked, "Does conversion therapy provide a survival benefit for selected patients with metastatic GC who respond favorably to systemic therapy and achieve an R0 resection?"

> Statement 1. Conversion therapy provides a survival benefit for selected patients with metastatic GC who respond favorably to systemic therapy and achieve an R0 resection.
>
> Agreement (88.3%), mean (4.29), CV (0.16).

Commentary and opinions from panelists

- Conversion therapy may provide a survival benefit for select patients with limited metastatic GC who respond favorably to systemic therapy, with R0 resection being crucial for improved survival outcomes.
- Immuno-oncology (IO) therapy may induce a higher probability of R0 resection and better survival.
- Randomized data are needed to confirm the survival impact of conversion therapy.

Optimal candidates

Patients with a favorable response to systemic therapy should be selected as optimal candidates for conversion therapy. Recent developments in molecular targeted therapies and immunotherapy have resulted in remarkable tumor shrinkage and even the disappearance of metastatic lesions. A recent retrospective cohort study conducted by Liang et al. [14] included 136 patients with stage IV GC who responded well to first-line IO therapy and/or anti-human epidermal growth factor receptor 2 (HER2)-targeted therapy. Another retrospective cohort study by Shin et al. [8] found that body mass index at the time of diagnosis, HER2-positive status, high microsatellite instability or deficient DNA mismatch repair, and the use of targeted agents were significant prognostic factors.

In the current era of targeted therapies and/or immunotherapies with increasing response rates, patients who respond to systemic therapy and undergo R0 resection as conversion surgery may expect promising survival outcomes regardless of the site of metastasis, even when metastases are identified in multiple organs or locations.

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However, it is natural to consider only patients with a limited degree of metastasis. As shown in the AIO-FLOT3 trial, the subset of patients with limited number of distant metastases so-called "oligometastatic disease" displayed the most favorable outcome [13]. Limited metastasis or oligometastasis is addressed in the Japanese Gastric Cancer Treatment Guidelines, Chinese Society of Clinical Oncology clinical guidelines, European Society for Medical Oncology guidelines, and Korean Practice Guidelines for Gastric Cancer, with local treatment mentioned as the pivotal option for cancer treatment [1-3,5]. The OligoMetastatic Esophagogastric Cancer (OMEC) consensus determined that oligometastatic disease is considered in patients with one affected organ with ≤3 metastases or one involved extra-regional LN station [15]. In one Western meeting, consensus on oligometastsis in terms of various distant metastasis was displayed, including liver (≤3 unilobar lesions), para-aortic LNs (PAN) (16a1, 16a2, 16b1, 16b2), cytology (conversion to negative after systemic therapy), etc. [16].

This topic involved 2 surveys. First, we investigated whether patients with limited metastasis at the time of initial diagnosis should be considered as optimal candidates for conversion therapy. Second, a survey was conducted to determine to what extent metastasis to each organ in various situations should be considered as limited metastasis (questionnaire details provided in **Supplementary Data 1**).

> Statement 2. Conversion therapy could be considered for patients with metastatic GC who have limited metastases at the time of the initial diagnosis of metastatic GC.
>
> Agreement (94.2%), mean (4.17), CV (0.19).

The panels reached over 80% consensus for limited metastasis definitions, including solitary (liver), 16a2/16b1 (PANs), positive cytology only (peritoneal), and category 1 (Yoshida classification). Consensus ranged from 80 to 60% for unilobar ≤3 (liver), P1 or P2 (peritoneal), and unilateral (ovary); 60%–40% for bilobar ≤3 (liver), 16a1/16b2 (PAN), bilateral (ovary), unilateral (adrenal gland), and category 2 (Yoshida classification); and 40 to 20% for unilobar ≤5 (liver), bilateral (adrenal gland), and category 3 (Yoshida classification). The consensus was 20%–10% for bilobar >5 (liver) and less than 10% for bilobar>5 (liver), extra-abdominal LN, P3 (peritoneal), metastases regardless of site and number, and category 4 (Yoshida classification) (**Table 3**).

Commentary and opinions from panelists

- The recently reported results of the RENAISSANCE (FLOT-5) trial, a prospective randomized controlled trial (RCT), showed no significant difference in OS between the surgical resection after systemic therapy group and the systemic therapy-only group,

Table 3. The optimal extent of limited metastases at the time of initial diagnosis to consider conversion surgery

Site of metastasis	Strength of agreement					
	100%–80%	80%–60%	60%–40%	40%–20%	20%–10%	<10%
Liver	Solitary	Unilobar ≤3	Bilobar ≤3	Unilobar ≤5	Bilobar ≤5	Bilobar >5
Distant lymph nodes	16a2 16b1		16a1 16b2			Extra-abdominal
Peritoneal	Only positive cytology	Limited (P1 or P2 score)				Diffuse (P3 score or clinically detectable diffuse affection of peritoneum)
Ovary		Unilateral	Bilateral			Regardless of sites and number of metastases
Adrenal gland			Unilateral	Bilateral		
Yoshida's classification	Category 1		Category 2	Category 3		Category 4

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thus not meeting the primary end point [17]. Only patients with distant abdominal LN metastases showed a trend toward survival benefits from conversion surgery. However, an extensive definition of oligometastatic disease, as well as high mortality in the surgical arm, limits the outcome of the trial.

- Recently, IO therapy combination treatment has shown remarkable progress in chemotherapy. The addition of targeted therapy or IO to previous standard fluoropyrimidine and platinum combination therapy increased the tumor response by 10–15% compared to conventional therapy, leading to more profound and durable tumor responses [18-20]. Surgical techniques have improved, and many experienced surgeons have reported that conversion surgery can be safely performed in most patients.
- Considering these circumstances, although the RENAISSANCE trial showed negative results, conversion surgery should be considered for selected patients. Careful selection is necessary to identify those who are most likely to benefit. Furthermore, surgical intervention should be minimally invasive and should be performed at expert centers.
- Although there is no clear evidence regarding the limits of liver metastasis, metastasis of fewer than 3 lesions is generally considered manageable. For distant LN metastasis, the Japanese guidelines specify that only 16a2 and 16b1 have curative effects. For peritoneal metastases, there is little hope of a treatment effect for macroscopic peritoneal disease; therefore, it may be safe to target CY0.

Optimal timing

The optimal timing for conversion surgery is generally when the tumor shows the best response to systemic therapy over a significant period and not when the tumor is increasing in size or has acquired the ability to regrow. Previous studies for conversion therapy in patients with metastatic GC have reported that conversion surgery was considered when a partial or complete response to systemic therapy was attained after a regimen of 4–6 courses in a 3–5-week cycle [7,9,11,12]. One multicenter retrospective study indicated that the administration of 5 or more cycles of preoperative chemotherapy did not extend survival compared with that of 3 or 4 cycles, suggesting that the 4 cycles of chemotherapy in the AIO-FLOT3 trial would be sufficient for conversion to surgery [7,13].

However, the ideal duration of systemic therapy before conversion surgery and optimal timing of conversion surgery in patients with stage IV GC remain controversial. This topic explores the optimal timing for conversion therapy.

> Statement 3. The optimal timing for conversion surgery should generally be based on the tumor response to systemic therapy, regardless of the duration of systemic therapy, typically when primary and metastatic tumors demonstrate the most favorable response, maximizing the possibility of R0 resection.
>
> Agreement (70.6%), mean (4.12), CV (0.24).

Commentary and opinions from panelists

- The strategy for conversion therapy should vary depending on the severity of metastasis in each patient.
- For patients with oligometastatic disease, where R0 resection could be achieved in the initial disease volume and given the absence of a consensus on the treatment scheme or schedule, systemic therapy might be better considered as a neoadjuvant approach. In this scenario, surgery should consider the initial volume of the disease.

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- However, in cases of poly- or heavily metastatic disease, radical resection is not feasible at the time of diagnosis. Therefore, it is necessary to await an optimal response to systemic therapy before proceeding with surgery or other ablative treatments aimed at achieving R0 resection for residual disease, as it is initially unresectable at the time of diagnosis.
- Careful patient selection and tailored treatment should be considered, and differentiation between oligometastatic and true conversion strategies is important.
- Systemic therapy involves 2 steps: elimination of metastatic tumors and eradication of micrometastatic cells. However, prolonged treatment increases the risk of tolerance to systemic therapies. The unnecessary extension of systemic therapy may compromise conversion therapy.
- However, some experts have suggested that even if the tumor is significantly reduced after palliative chemotherapy and surgery seems possible immediately, there are quite a few cases in which the tumor shows a transient response and then grows again shortly thereafter. In such cases, the tumor relapses immediately even after the conversion surgery. Therefore, they suggest that surgery should be carefully decided at least 5 to 6 months after starting chemotherapy.

Regimen

To date, the primary regimens used in conversion therapy are doublet or triplet chemotherapies including 5-fluorouracil, platinum compounds, and/or taxanes. Notably, the FLOT regimen was used for patients with limited metastatic GC in the AIO-FLOT3 trial [6,7,9,12,13].

In the era of molecular targeted therapies and IO therapy, newer agents have been developed for palliative systemic therapy. For HER2-negative diseases, chemotherapy combined with nivolumab or pembrolizumab is recommended based on PD-L1 expression levels [1-3,5,13]. Recent phase III trials have demonstrated the efficacy of zolbetuximab, a claudin 18.2 (CLDN18.2)-targeting antibody, in combination with oxaliplatin-based chemotherapy for CLDN18.2-positive, HER2-negative diseases [21,22]. For HER2-positive disease, the recommended treatment is chemotherapy combined with trastuzumab or with trastuzumab and pembrolizumab [1-3,5].

The systemic therapeutic regimen used in conversion therapy should be selected because of its potential to provide the best tumor response and enable R0 resection. However, many previous studies have exhibited significant limitations, including selection bias, heterogeneous study populations, small sample sizes, and often unclear treatment regimens. Contemporary research has emphasized that the most effective regimen for conversion therapy continues to be the subject of considerable discussion. Although evidence is emerging, it is not sufficiently robust to make recommendations. Therefore, expert opinions and consensus were obtained to address this issue.

> Statement 4. The systemic therapeutic regimen used in conversion therapy should be individualized for each patient to achieve 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.
>
> Agreement (100%), mean (5.0), CV (0.0).

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Commentary and opinions from panelists

- The objective of systemic conversion therapy is to achieve maximum reduction in the size of existing lesions and effectively manage micrometastatic disease.
- Cytotoxic chemotherapy, particularly regimens such as docetaxel, cisplatin, and 5-fluorouracil, has been the standard treatment for 30 years. It showed improved survival and response rates, but challenges in tolerability. While triplet regimens offer higher efficacy, doublet regimens provide better tolerability and are commonly used sequentially to maintain quality of life [23].
- New agents and combinations, including IO therapies, improve response rates and increase the potential for conversion surgery. For HER-2 positive patients, targeted therapies combined with chemotherapy have shown higher response rates, with a 73% objective response rate observed in the KEYNOTE-811 study [18].
- In HER2-negative patients, 8 phase III trials comparing doublet vs. IO+doublet regimens showed an approximately 10% increase in survival outcomes with a trend toward higher complete response rates, which may facilitate better outcomes for conversion therapy [19,20,24-29].
- Zolbetuximab, an anti-CLDN18.2-targeting monoclonal antibody, provided survival benefits when combined with cytotoxic chemotherapy but did not significantly shrink tumors. Therefore, further research is needed on its role when considering conversion surgery [21,22].
- A significant challenge remains the lack of chemotherapeutic regimens tailored to the specific status of metastasis, which creates a gap in current treatment strategies.

The extent of LN dissection

D2 LN dissection has been associated with lower locoregional recurrence and improved survival outcomes compared to D1 dissection, and is currently recommended as the standard surgical approach for resectable GC [1,2,30].

Most retrospective studies reported survival benefits in patients who underwent D2 LN dissection [9,31-33]. In the CONVO-GC-1 study, which represented the largest cohort of stage IV GC patients treated with surgical resection following chemotherapy, 19.3% of patients underwent D0 or D1 LN dissection, 65.5% underwent D2 dissection, and 13.8% underwent D3 dissection [6]. Additionally, the AIO-FLOT3 study recommended total or subtotal distal gastrectomy with D2 LN dissection [13].

However, no previous studies have directly compared the extent of LN dissection with gastrectomy in conversion therapy for patients with metastatic GC. Therefore, the evidence supporting the universal recommendation of D2 dissection as the standard extent of LN dissection in conversion surgery remains limited.

> Statement 5. Given the curative intent of conversion surgery, D2 is recommended as the extent of lymph node dissection to reduce locoregional recurrence, regardless of clinical or surgical staging after systemic therapy.
>
> Agreement (82.4%), mean (4.23), CV (0.21).

Commentary and opinions from panelists

(Pros)

- D2 LN dissection has been shown to be as safe as D1 and safer than D3 dissection,

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establishing it as the standard treatment for locally advanced GC [34,35].
- Limited studies on conversion therapy for stage IV GC suggest survival benefits when combined with D2 dissection [6,13]. The AIO-FLOT3 trial reported an 80.5% rate of D2 dissection, and the CONVO-GC study reported a rate of 65% [6,13].

(Cons)
- The primary goal of systemic therapy is to eliminate metastatic sites, followed by eradication of micrometastatic disease. To achieve this, patients should receive systemic adjuvant therapy after conversion surgery.
- Surgical risk must be minimized, as procedures such as D2 dissection, especially total gastrectomy involving the greater curvature, carry higher morbidity. Careful attention is required during nodal dissection of the splenic hilar and suprapancreatic nodes along the splenic artery because of the increased risk of pancreatic leakage.
- Although adjuvant systemic therapy is crucial post-operatively, surgical morbidity can prevent its administration. In such cases, D1+ dissection may be a safer option to minimize risks while maintaining treatment efficacy.

Extent of surgery

When systemic therapy leads to tumor shrinkage and conversion surgery is considered, restaging using thorough imaging is essential. Although metastatic GC lesions may disappear on imaging and show a complete clinical response, the possibility of residual pathological tumors remains.

A retrospective analysis revealed that patients with distant metastases, such as peritoneal, extensive LN, or liver metastases that had disappeared on imaging, gained a significant survival advantage from gastrectomy with D1 LN dissection compared with continued chemotherapy alone, even without metastasectomy [9].

On the other hand, in patients with extensive LN metastasis including PAN, several prospective studies in Japan (JCOG001, JCOG0405, JCOG1002) have reported long-term survival outcomes following preoperative chemotherapy and gastrectomy with D2 plus PAN dissection [36-40].

Because the evidence for this matter is limited and confounding, a survey was conducted to assess the role of surgical resection in confirming the absence of pathological residual tumors for technically resectable organ metastases in the liver and PAN when imaging studies indicated a complete response.

> Statement 6. After systemic therapy, when metastatic lesions in the liver and PAN show a clinically complete response and disappear on imaging studies, surgical resection of these metastatic lesions should be performed because of the possibility of a residual tumor.
>
> Agreement (41.2%), mean (3.06), CV (0.39).

Commentary and opinions from panelists

(Pros)
- Surgical resection remains the only definitive treatment to achieve a cure in GC patients. The assessments on complete response based on imaging and endoscopic biopsy are not always reliable. However, these findings do not consistently predict true pathological

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responses. Some studies have indicated that long-term survival can be achieved after resection of metastatic disease in cases with a complete clinical response.

- It is important to note that surgery should only be considered when performed at an acceptable risk level. Surgical outcomes are also highly dependent on the site of metastasis, which contributes to the observed variability in patient outcomes. Historical data, including a selective study conducted over a 15-year period, suggests that targeting metastatic sites could offer the potential for long-term survival in certain cases [41].
- Patients with cytology-positive findings who subsequently convert to a negative status may represent a distinct subgroup with different prognostic implications.
- Some studies have compared the outcomes of metastectomy and non-metastectomy approaches, although randomized data are limited. The RENAISSANCE trial showed significant limitations; notably, only 53% of patients in the surgical arm underwent complete resection of both the primary and metastatic sites, leaving questions regarding the efficacy of comprehensive surgical intervention [17].
- Retroperitoneal LN metastases yield the most favorable outcomes and may represent lower-risk surgical targets. However, interruption of systemic therapy during surgical intervention poses a significant challenge. To address these questions effectively, it is imperative that tumor resection be complete, as partial resection has not demonstrated a substantial benefit.
- Additionally, the REGATTA trial provided insights into the limited value of isolated gastric resection, emphasizing that resecting the stomach alone does not significantly improve outcomes in patients with metastatic disease [42].
- Further research is needed to clarify these complex scenarios and provide optimal treatment strategies for patients with metastatic GC.

(Cons)

- The primary question is not whether to resect lesions demonstrating a complete response, because resection in this setting is often palliative. Even in patients with a good response to systemic therapy, the risks of morbidity and mortality associated with surgery must be carefully considered. These patients often demonstrate favorable tumor biology with significant responses to chemotherapy with or without immune checkpoint inhibitors.
- In the context of limited metastatic disease, it is acknowledged that patients with better tumor biology, as shown in the RENAISSANCE trial, exhibit improved OS compared to data from global phase III trials where diffuse metastatic disease predominates [17]. The treatment of limited metastatic GC spans a broad spectrum, and the decision to pursue local therapies, such as metastasectomy, depends on the specific tumor location, biology, and patient profile.
- Surgical resection of distant LN metastases has been associated with improved outcomes because of the feasibility of this surgical approach and favorable tumor biology.
- Data on patients achieving complete remission are limited in terms of surgical treatment for oligometastatic disease. Meta-analyses evaluating the effect of surgical resection on hepatic metastases indicated no significant benefit, although these analyses were limited by patient heterogeneity [43].
- The AIO-FLOT3 trial, while often cited, was not a randomized trial and included a highly heterogeneous patient cohort. Although this trial suggested potential benefits for surgical resection in patients with limited metastatic disease, it must be noted that the outcomes varied widely owing to the non-randomized design and differing tumor biology. Patients with diffuse metastases generally showed worse prognoses regardless of surgical

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intervention, which was attributed to their more aggressive tumor behavior [13].
- Local procedures for stage IV disease remain experimental with limited data available. The RENAISSANCE trial included a small number of patients with peritoneal metastasis (20–23 per arm), reflecting the selective nature of the current evidence. Larger and more comprehensive trials are required to clarify the role of local interventions [17].
- Vanishing metastases, whether retroperitoneal or in organs, should not prompt local treatment if there is no active disease. However, careful positron emission tomography-computed tomography follow-up is recommended to monitor for recurrence. Further treatment can be considered when locoregional recurrence is detected.

Minimal invasive surgery (MIS)

For resectable advanced GC, 4 RCTs (KLASS-02, CLASS-01, JLSSG0901, LOGICA trial) demonstrated that laparoscopic distal gastrectomy resulted in similar postoperative complications without compromising oncologic outcomes compared to open gastrectomy [44-47]. According to the Korean Practice Guidelines for Gastric Cancer 2022, both laparoscopic and open distal gastrectomy are recommended for locally advanced GC [1]. A recent randomized phase II trial of patients receiving neoadjuvant chemotherapy reported that laparoscopic surgery could offer better postoperative morbidity and adjuvant chemotherapy completion rates than open surgery [40]. Additionally, a recent retrospective study of highly advanced GC after preoperative chemotherapy reported that MIS, including the robotic approach, was feasible [48]. Both studies focused on patients with highly advanced GC who underwent R0 resection after preoperative chemotherapy. However, because patients who might require metastasectomy were not included, the potential benefits of the MIS approach for conversion surgery in cases where metastasectomy is required remain uncertain.

> Statement 7. A minimally invasive approach for conversion surgery can be considered in patients with metastatic GC. Selection should be made by highly experienced surgeons, considering the extent of surgery and patient safety.
>
> Agreement (82.3%), mean (4.11), CV (0.17).

Commentary and opinions from panelists

- MIS should be considered if it is feasible and safe to achieve R0 resection.
- The benefits of metastasectomy in MIS have not yet been established. Therefore, careful patient selection is required for combined resection.
- There is no need to choose open surgery alone as a conversion surgery. Experienced surgeons can opt for an MIS approach based on their expertise and the difficulty of the operation.

Duration of systemic therapy

Previous retrospective cohort studies on conversion therapy have described the median duration of systemic therapy administered before surgery, but information on systemic therapy following conversion surgery remains limited [6,9,11,12]. In the AIO-FLOT3 trial, perioperative FLOT therapy consisting of 8 cycles was employed [13]. For patients with metastatic colorectal cancer who achieved complete resection, the preferred duration of systemic chemotherapy (preoperative and/or postoperative) was approximately 6 months [49].

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In this era, various factors must be considered in conversion therapy. When metastatic GC responds to primary systemic therapy and becomes eligible for R0 resection, the treatment duration is typically estimated to be at least 6 months, which is supported by studies indicating that the median progression-free survival for stage IV GC with different regimens is approximately 6 months. However, progression-free survival can extend to 8–10 months with chemotherapy combined with molecular targeted therapies or immunotherapies [19-22,50].

Additionally, due to the more aggressive clinical course of GC compared to that of colorectal cancer, careful assessment of the tumor burden is crucial when determining the overall duration of systemic therapy. For patients with metastatic GC who undergo conversion surgery aimed at R0 resection, but end up with R1 or R2 resection, early postoperative systemic therapy with palliative intent is recommended.

> Statement 8. For patients with metastatic GC undergoing conversion surgery with R0 resection, the total duration of systemic therapy is estimated to be at least 6 months with a preoperative effective regimen. The total duration and selection of maintenance anticancer drug(s) should be individualized based on the patient's performance status, toxicities of systemic therapy, tumor burden, and postoperative pathological status.
>
> Agreement (88.3%), mean (4.29), CV (0.20).

Commentary and opinions from panelists

- The current statement is that the total duration of systemic therapy is estimated to be at least 6 months for patients undergoing conversion surgery to achieve complete resection. In general, it does not extend significantly beyond this timeframe. It is essential to ensure that patients remain in good condition during this period. Subsequently, patients are sent to the operating room with the expectation of a potential cure.
- The course of metastatic GC is completely different from that of metastatic colorectal cancer, therefore, some oncologists prefer to maintain the postoperative chemotherapy period for more than 6 months after conversion surgery. Preoperative chemotherapy mostly includes platinum, but fluoropyrimidine monotherapy is frequently used after surgery, and in this case the adverse effects are mostly mild; therefore, there is no problem with long-term use.
- We must await prospective studies such as the European OMEC5 trial, which aims to answer questions regarding the appropriate length and type of chemotherapy in the adjuvant setting. This study includes both consolidated chemotherapy and immunotherapy of varying durations, and incorporates biomarkers such as circulating tumor DNA (ctDNA). Over time, perhaps within 5–10 years, we will obtain these crucial data for GC.

Future perspectives

Currently, there is no evidence from prospective randomized controlled studies demonstrating the superiority of conversion surgery combined with systemic therapy over palliative systemic therapy alone in terms of survival outcomes in patients with stage IV GC.

However, further prospective studies are needed on conversion surgery, particularly in Asian populations, and other detailed treatment strategies for conversion therapy, including indications for conversion therapy, timing of conversion surgery, extent of surgical resection, regimen, and total duration of systemic therapy.

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Statement 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.

Agreement (100%), mean (4.7), CV (0.10).

Commentary and opinions from panelists

- The current data demonstrate the critical need for additional RCTs. A review of ongoing trials reveal several active studies investigating the impact of local treatment versus no local treatment, including surgery and radiotherapy.
- The ESO-Shanghai trial focused on patients with controlled primary tumors and limited metastatic lesions (fewer than 4, across up to 3 organs, with lesions <5 cm) who were candidates for local therapy. It compared radiotherapy combined with systemic therapy to systemic therapy alone. The findings showed that the addition of local therapy improved both disease-free survival and OS [51].
- The RENAISSANCE trial faced challenges owing to premature termination, low patient numbers, and inclusion criteria. High postoperative morbidity and mortality rates affect the survival outcomes. Although liver metastases showed no significant difference, conversion surgery may be helpful for retroperitoneal metastases [17].
- Establishing a consistent definition of oligometastatic disease is essential, along with ensuring that surgical interventions do not adversely affect outcomes owing to the associated mortality and morbidity. The OMEC project defines it as 3 or fewer metastases confined to one organ or an extra-regional LN station. Therefore, clear definitions are vital for future RCTs [52].
- MIS should be prioritized in local treatments to optimize safety and effectiveness.
- The OMEC 4 and OMEC 5 projects aim to address these gaps with prospective RCTs to evaluate the duration of chemotherapy and provide clarity on treatment strategies.

DISCUSSION

This is a report of an international multidisciplinary consensus meeting for conversion therapy in stage IV GC, developed using the Delphi method. This study aimed to provide a clinical rationale through insights from a panel of experts who could offer guidance based on their experience. Conversion therapy for stage IV GC involves a wide range of clinical settings and treatments. Evidence from various patient populations and treatment approaches is required to establish a comprehensive treatment strategy applicable to diverse scenarios. Consequently, there are limited comprehensive evidence-based treatment guidelines.

The Delphi method is a structured approach that facilitates effective group communication, allowing a panel of experts to collectively address complex issues [10]. The primary objective of the Delphi technique is to establish reliable consensus among experts through an iterative questionnaire process combined with controlled feedback. However, unlike other quantitative and qualitative clinical research methodologies, the Delphi method lacks standardized reporting forms and validated quality metrics for healthcare research applications [53]. The consensus meeting led to fair agreement among experts on topics related to the overall effect, optimal candidates, optimal timing, regimen, extent of LN dissection, minimally invasive surgery, duration of systemic therapy, future perspectives, and details of limited metastasis. However, no definitive consensus has been reached regarding the extent of surgery.

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The panel reached a 94.2% agreement that conversion therapy should be considered for patients with limited metastases at the time of initial diagnosis. A key point of discussion is that patient settings should be categorized into limited and extensive distant metastases, which may align with the proposal of Yoshida et al. [54]. This distinction has 2 implications. First, complete resection, including local treatment, may be technically achievable for some stage IV patients. Second, this subset may be an earlier state of tumor spread or less diffuse in tumor biological characteristics. The consensus is that stage IV disease with limited metastasis is the most suitable for conversion therapy.

The second question clarifies the definition of limited metastasis. Strong agreement (>80%) was reached for solitary liver metastasis, 16a2 and 16b1 LNs, isolated positive peritoneal cytology (CY+), and category 1 (Yoshida). Moderate agreement (60%–80%) was achieved for unilobar ≤3 metastases in the liver, limited peritoneal metastasis (P1 or P2), and unilateral ovary metastasis. These results were more conservative compared to the OMEC criteria (≤2 bilobar or ≤3 unilobar liver metastases, unilateral adrenal involvement, or a single metastasis in either soft tissue or bone [52]) or other international consensus (3 technically resectable liver metastases regardless of location; posterior LNs of 12p, 13, 16a1, 16a2, 16b1; and 16b2, and isolated CY+ after systemic therapy), limited peritoneal carcinomatosis index (<6) [16]. This difference may be attributed to concerns about maintaining postoperative integrity, emphasizing the need for surgical procedures that support early recovery without adversely affecting postoperative systemic therapy.

The experts discussed the optimal timing for conversion surgery, with 70.6% agreeing that the timing should be based on tumor response rather than a fixed systemic therapy schedule. On the other hand, even if the tumor has shrunk significantly after palliative chemotherapy and surgery seems possible immediately, some experts preferred to carefully decide on surgery at least 5–6 months after starting chemotherapy, as there are some cases where the tumor relapses immediately after conversion surgery, even in cases with very good response to chemotherapy. Experts agreed that in cases of heavy metastasis, following a fixed systemic therapy schedule may not significantly affect the tumor response; therefore, it is necessary to await the optimal response to systemic therapy. Assessment after systemic therapy should be performed using imaging studies and also laparoscopic exploration [1]. Biomarkers or indicators, if available, can provide valuable guidance for this process. For example, a Japanese *GALAXY* study demonstrated that ctDNA, a novel biomarker, is useful in colorectal cancer. In patients with stage IV cancer, ctDNA positivity after surgery was linked to poor outcomes and reduced disease-free survival [55]. However, whether these findings apply to GC remains unclear.

There is unanimous consensus (100% agreement) on the principle that treatment regimens should be determined by considering both patient and tumor factors, including relevant predictive biomarkers. However, owing to the diversity in healthcare environments, racial backgrounds, and preferred therapies across countries, specific regimens were not suggested in this meeting. Heavy distant metastasis, in contrast to limited metastasis, generally refers to a condition with widespread metastatic lesions. However, it remains unclear whether this reflects advanced disease progression or a biological propensity for certain aggressive tumor types. Given the challenges in achieving complete resection of metastatic lesions, even after systemic therapy, systemic therapy response was emphasized as the most important factor. During this meeting, opinions favored decisions regarding conversion therapy based on the systemic therapy response rather than on the standard duration or timing of preoperative

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therapy. This approach is expected to become increasingly relevant with the advances in new GC-targeting agents. For example, 2 randomized phase III trials (SPOTLIGHT and GLOW) demonstrated the efficacy of zolbetuximab, a CLDN18.2-targeting antibody, in combination with chemotherapy for CLDN18.2-positive, HER2-negative diseases [21,22]. While both studies reported improved survival outcomes, controversies remain regarding its preferential use in conversion surgery due to its limited tumor shrinkage potential.

In the 6th statement, we aimed to clarify the possible extent of surgery after systemic therapy for technically resectable organ metastases with the potential for pathological residual tumors when imaging studies indicated a complete response. Only 41% of the panelists agreed with the statement, and it was decided that it should remain inconclusive owing to limited evidence. Although surgical resection is the only definitive treatment for achieving a cure in GC patients, there may be a need to surgically resect the site of initial metastasis. In this context, the RENAISSANCE phase III trial was extensively discussed [17]. This study compared 2 approaches: 2 months of preoperative FLOT-based systemic therapy followed by surgery and adjuvant systemic therapy versus FLOT-based or IO systemic therapy alone. The surgical procedures included curative gastrectomy or esophagectomy with resection of metastatic lesions or local ablation procedures. Although the trial showed no significant difference in OS between the 2 groups, poor surgical outcomes in the surgery group, with morbidity of up to 60%, 20% reoperation rate within 90 days, and postoperative mortality of approximately 8%, impacted survival and prevented many patients from completing the postoperative systemic therapy. Furthermore, a survival benefit was mainly observed in patients with retroperitoneal LN metastasis, suggesting some potential advantage, whereas no significant benefit was observed in patients with liver or peritoneal metastasis. The subgroup analyses indicated that retroperitoneal LN involvement may be a viable target for surgical intervention. During the discussion, the panelists emphasized that to achieve optimal overall treatment outcomes, surgery should only be considered when it can be performed with an acceptable level of risk. Given the experimental nature of local procedures in stage IV GC, comprehensive trials are needed to better define the role of surgery in cases of limited metastatic disease and optimize treatment protocols for high-risk patients.

Regarding the extent of LN dissections (the 5th statement), 82.4% of the panel agreed that D2 dissection should be recommended for conversion surgery. D2 dissection provides better survival outcomes than D1 dissection in patients with LN metastasis, and a higher number of retrieved LNs enables more accurate staging with improved survival chances, making D2 dissection widely recommended [30,56]. D2 dissection was the primary treatment approach in 2 studies that demonstrated positive outcomes with conversion therapy [6,13]. In the CONVO-GC-1 study, an Eastern retrospective multicenter study, 65% of the patients underwent D2 dissection and 14% underwent D3 dissection [6]. In the AIO-FLOT-03 trial, a Western multicenter prospective study, the D2 dissection rate was 80.5% [13]. However, concerns remained regarding the potential increase in surgical morbidity associated with D2 dissection, which may impact subsequent systemic therapy; thus, D1+ dissection was considered as an alternative.

Regarding MIS for conversion therapy (the 7th statement), 82.3% of the panel agreed. In a previous report from a cohort of advanced GC patients who underwent MIS followed by systemic therapy performed by highly experienced surgeons, the morbidity (Clavien Dindo Classification [CDC], grade ≥3a) rate was 12% and the local complication rate was 10.7% [48]. These results were comparable to the morbidity of 8.9% (CDC, grade ≥3a) and local

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complication rate of 12.3% observed in the KLASS-02 study, an RCT comparing laparoscopic distal gastrectomy versus open surgery in locally advanced GC [57]. The panel opinion warranted that conversion surgery itself should not be a limitation of MIS, as it offers many advantages, including early postoperative recovery. However, the safety of extended surgical resections, including PAN or liver resections, has not been proven in large-scale studies; therefore, caution should be exercised in their application.

This consensus meeting emphasized the need for further research to optimize conversion therapy strategies. The panel members agreed that patient selection based on consistent criteria is crucial for successful trials and that global collaboration is essential for progression. However, the scope of conversion therapy is expanding owing to advancements in surgery, systemic therapy, and new treatments for managing metastases. However, the report acknowledges limitations, including reliance on partial clinical research and expert opinions, and challenges in achieving diverse panel representations across expertise and regions, despite efforts to balance Western and Eastern specialists.

CONCLUSIONS

This work represents a collaborative effort by the international participants of KINGCA WEEK 2024, aiming to clarify and gather expert opinions on clinical topics related to conversion therapy in metastatic GC. Through the Delphi process, an expert panel developed a set of statements to guide decision-making in the treatment of stage IV GC. Recent advancements in anticancer treatments have improved response rates, potentially enabling radical surgery for patients with stage IV GC. However, further evidence is required to validate the safety and efficacy of conversion therapy in prolonging the survival of these patients. It is essential to emphasize that even when treating the most advanced stages of GC, prioritizing patient safety and proceeding with caution must remain the foremost considerations.

SUPPLEMENTARY MATERIAL

Supplementary Data 1

The questionnaire for consensus on conversion therapy

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