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Review Article

From Control to Conversion: Optimizing Systemic Therapy for Curative-Intent Conversion Surgery in Metastatic Gastric Cancer

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ABSTRACT

Conversion therapy enables curative-intent resection in patients with initially unresectable or metastatic cancers after effective systemic therapy. Recently, advances in systemic therapy with molecular targeted agents and immune checkpoint inhibitors (ICIs) have renewed clinical and research interest in this approach, particularly for metastatic gastric cancer (GC). This review aimed to summarize the international guidelines and expert consensus informed by contemporary evidence on conversion therapy for metastatic GC, emphasizing the central role of systemic therapy, the emergence of biomarker-driven strategies, and the optimal timing for surgical intervention. Key consensus statements (Bertinoro, OMEC, and KINGCA WEEK 2024) and pivotal studies covering the cytotoxic, targeted, and immunotherapy eras were reviewed, focusing on regimen selection, treatment duration, and prognostic determinants associated with surgical outcomes. According to global guidelines, conversion surgery is not yet standard of care but may be considered for biologically and clinically selected patients demonstrating a major response to systemic therapy. Retrospective and prospective studies have reported a median overall survival of 24–36 months in the cytotoxic era and >48 months in the ICI/targeted era among patients who underwent R0 resection. Emerging evidence supports approximately 6 months of preoperative systemic therapy, followed by R0 resection, and up to one year of postoperative maintenance therapy. Therefore, conversion surgery should be viewed as the culmination of effective systemic therapy rather than as a substitute. A biology-driven, multidisciplinary strategy integrating treatment response assessment and prognostic factor evaluation represents the next frontier in potentially curative management of metastatic GC.

Keywords: Stomach neoplasms; Multimodal treatment; Drug therapy; Precision medicine

INTRODUCTION

Conversion therapy is a treatment approach that transitions from palliative systemic therapy, aimed at disease control, to curative-intent local therapy, including radical surgery for

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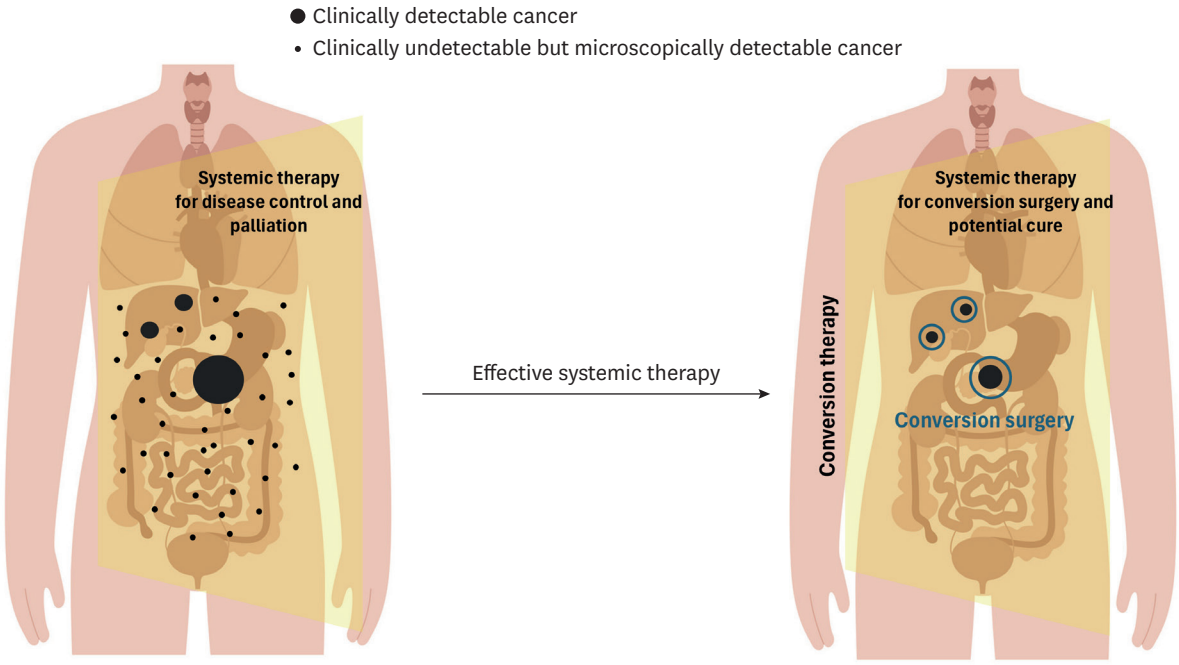

Fig. 1. Concept of conversion surgery for metastatic gastric cancer.

primary and/or metastatic tumors, with the goal of achieving complete (R0) resection. In this approach, effective systemic therapy not only induces sufficient tumor regression to enable resection of lesions initially considered technically and/or oncologically unresectable, but also aims to eradicate clinically undetectable micrometastatic disease that may contribute to relapse (**Fig. 1**).

Conversion surgery (CS) is an important treatment strategy for metastatic colorectal cancer, particularly for patients with initially unresectable liver or lung metastases [1]. In colorectal cancer, the concept of metastatic disease has been further refined: metastases confined to a single organ without peritoneal involvement are classified as M1a (stage IVA); metastases to 2 or more organs without peritoneal spread as M1b (stage IVB); and peritoneal metastasis as M1c (stage IVC) [1]. This stratification underscores the importance of disease burden and metastatic patterns in determining the surgical feasibility and long-term outcomes. Thus, conversion therapy represents a strategic bridge between palliative intent and potentially curative treatment. In metastatic colorectal cancer, multimodal approaches that integrate systemic therapy and surgical resection have achieved 5-year survival rates exceeding 30% in carefully selected patients [2,3]. This success inspired efforts to adapt the same concept to other cancers, including gastric cancer (GC). However, GC presents with greater biological heterogeneity, is more aggressive, and exhibits more diffuse metastatic dissemination, making conversion therapy considerably challenging.

Nevertheless, recent progress in systemic therapy has transformed the therapeutic landscape for metastatic GC toward a potential cure. The introduction of triplet cytotoxic regimens, human epidermal growth factor receptor 2 (HER2)- and claudin 18.2 (CLDN18.2)-targeted agents, and immune checkpoint inhibitors (ICIs) has enabled unprecedented tumor regression and durable disease control. Consequently, curative-intent resection, once considered unfeasible for metastatic GC, has become a therapeutic option for a subset of

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patients who achieve a major response to systemic therapy. This review aimed to summarize the international guidelines and expert consensus informed by contemporary evidence on conversion therapy for metastatic GC, emphasizing the central role of systemic therapy, the emergence of biomarker-driven strategies, and the optimal timing for surgical intervention.

GUIDELINE PERSPECTIVES

Major societies classify CS as an investigational approach rather than standard of care (**Table 1**) because the level of evidence is low. Western guidelines, including those from the National Comprehensive Cancer Network (2025) and European Society of Medical Oncology (v1.4, 2024), restrict their use to selected patients with oligometastatic disease who demonstrate a durable and confirmed response to systemic therapy and recommend that such procedures be performed only in clinical trials or at high-volume tertiary centers [4,5]. In contrast, Asian guidelines, namely the Japanese Gastric Cancer Association (2021), Chinese Society of Clinical Oncology (2023), and Korean Gastric Cancer Association (2024), provide conditional or weak recommendations for CS in patients with limited and technically resectable metastases, such as para-aortic lymph nodes (16a2/b1), solitary hepatic lesions, or ovarian metastases, provided that radiological regression and favorable biological responses are achieved after systemic therapy [6-8]. These guidelines uniformly emphasize 3 key determinants of successful conversion therapy: sustained tumor response to systemic therapy, feasibility of R0 resection, and multidisciplinary evaluation to ensure potential curative benefits. Therefore, CS is not routine clinical care but rather a highly selected intervention guided by a favorable response to systemic therapy.

INTERNATIONAL CONSENSUS

The conceptual framework of conversion therapy for metastatic GC has been shaped by international initiatives that have collectively refined the definition, scope, and practical applications of this strategy (**Table 2**). The Bertinoro Workshop and OMEC-4 Project, both

Table 1. International guidelines for conversion surgery in metastatic gastric cancer

Guidelines	Version/year	Level of evidence; grade of recommendation	Recommendation
Western guidelines			
NCCN [4]	2025	–	Conversion surgery or metastasectomy may be considered only in highly selected cases that show a major response to systemic therapy, after multidisciplinary evaluation.
ESMO [5]	v1.4 – September 2024	V; C	Radical resection may be considered in highly selected cases. Resection of metastases is generally not recommended but may be considered individually in cases with oligometastatic disease that show a response to chemotherapy. Surgery should not be performed outside clinical trials except in very selected patients after a sufficiently long period of systemic therapy and multidisciplinary review at a high-volume tertiary center.
Asian guidelines			
JGCA [6]	2021	Evidence level C; weak recommendation	Surgical resection after neoadjuvant chemotherapy is weakly recommended for a small number of para-aortic lymph node metastases confined to No. 16a2/b1. Surgical resection is also weakly recommended for a solitary liver metastasis without other incurable factors.
CSCO [7]	2023	Evidence 2; grade II	For non-peritoneal, single distant metastases, such as para-aortic LN metastasis (2B), a single liver metastasis (2A), or ovarian metastasis (2B), surgery combined with systemic chemotherapy can be considered for both the primary and metastatic tumors.
KGCA [8]	2024	Low; investigational	In stage IV gastric cancer patients with limited metastasis, conversion surgery may be considered as a treatment option for those who show a favorable response to systemic therapy.

NCCN = National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; JGCA = Japanese Gastric Cancer Association; CSCO = Chinese Society of Clinical Oncology; LN = lymph node; KGCA = Korean Gastric Cancer Association.

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Table 2. Comparison of international consensus statements on the conversion therapy for metastatic esophagogastric cancer

Feature	Bertinoro Workshop [9]	OMEC Project (OMEC-4) [10]	KINGCA WEEK 2024 Consensus [11]
Objective	Establish international principles and standards for conceptual feasibility for conversion surgery in metastatic gastric cancer.	Develop evidence-based European clinical practice guidelines for defining, diagnosing, and managing oligometastatic esophagogastric cancer.	Define practical selection criteria and surgical indications for conversion therapy following systemic therapy.
Expert composition	96 invited, 52 responded, and 78 participated; multidisciplinary team included surgeons, medical oncologists, radiologists, and pathologists.	69 experts from 16 European countries; multidisciplinary team included surgical, medical, and radiation oncologists, gastroenterologists, radiologists, and pathologists.	17 experts (4 from Europe, 1 from the USA, and 12 from Asia—Korea, Japan, and China); mainly surgical and medical oncologists with direct experience in conversion therapy.
Core concept	Recognizes OMD as a dynamic biological condition; R0 resection as the treatment goal; emphasizes multidisciplinary evaluation and the need for prospective randomized trials.	Defines OMD as a potentially curable, biologically distinct disease state; emphasizes patient selection based on systemic response and biological behavior; restaging required before local therapy.	Focuses on practical clinical decision-making—selecting patients who have achieved partial or complete response to systemic therapy and are suitable for R0 resection.
Organ-specific criteria	≤3 resectable lesions in a single organ (typically liver or lung); para-aortic nodes 16a2/16b1 may be considered; a low peritoneal burden (PCI ≤6) or cytology conversion ($CY^+ \rightarrow CY^-$) acceptable.	≤3 lesions in one organ or one extra-regional lymph node station (e.g., para-aortic 16a2/16b1); excludes peritoneal and pleural metastases.	Broader inclusion—unilobar (≤3) liver lesions, para-aortic 16a2/16b1 nodes, positive cytology only or limited P1–P2 peritoneal seeding, and unilateral ovarian metastasis; surgery performed only after a favorable systemic response.
Treatment strategy	Response-based timing; surgery considered only after systemic control and multidisciplinary review.	For synchronous or metachronous OMD (disease-free interval ≤2 years): systemic therapy → restaging → local treatment; for a DFI > 2 years: local therapy may be initiated upfront.	Systemic induction therapy followed by restaging; surgery performed only when curative (R0) resection is deemed feasible.
Evidence basis	Expert consensus supported by retrospective and phase II data.	Developed under AGREE II and GRADE frameworks; incorporates 5 clinical studies (1 RCT and 4 phase II); rated as moderate-quality evidence.	Expert consensus based on real-world experience; with no formal evidence grading.
Conceptual approach	"Discuss and define"—establish a multidisciplinary and international conceptual framework.	"Define first, treat later"—focus on conceptual standardization for future clinical trials.	"Treat when feasible"—emphasizes pragmatic surgical decision-making reflecting real-world practice.

OMEC = oligometastatic esophagogastric cancer; OMD = oligometastatic disease; PCI = peritoneal cancer index; DFI = disease-free interval; RCT = randomized controlled trial.

conducted in 2022, have established conceptual and methodological foundations [9,10]. The Bertinoro Workshop defines oligometastatic disease as a dynamic biological state in which R0 resection should only be considered after achieving systemic control, emphasizing multidisciplinary evaluation and the need for prospective validation [9]. The OMEC-4 Project employed the AGREE II and GRADE frameworks to formalize evidence-based standards, setting quantitative thresholds (≤3 lesions in a single organ or one extra-regional nodal station) and positioning systemic response as a key determinant for local therapy [10]. The KINGCA WEEK 2024 Expert Consensus extended these concepts to real-world clinical practice [11]. It focuses on pragmatic decision-making by selecting patients who respond to systemic therapy and are deemed suitable for R0 resection, including those with limited peritoneal (P1–P2) or ovarian metastases under conditions of favorable biological control.

These initiatives represent the progressive evolution summarized in our Conceptual Approach: "Discuss and define → Define first, treat later → Treat when biologically feasible." The collective trajectory from conceptual formulation and methodological standardization to clinical implementation illustrates a global convergence toward a response- and biology-driven paradigm in metastatic GC.

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EVIDENCE FROM CLINICAL STUDIES

Prospective clinical trials evaluating the efficacy of CS for metastatic GC are inherently challenging for several reasons. First, the disease is characterized by marked clinical heterogeneity, making it difficult to define a sufficiently homogeneous study population. Peritoneal metastasis is often difficult to detect accurately and classify consistently, complicating appropriate patient stratification and subgroup analyses. Similar challenges arise in the assessment of the treatment response to systemic therapy. As a result, the majority of available evidence has been derived from retrospective studies, which are inevitably subject to selection bias and therefore provide a relatively low level of evidence supporting CS or conversion therapy. Nevertheless, accumulating data increasingly suggest a potential role for CS in carefully selected patients. Accordingly, efforts to generate robust and methodologically sound evidence are gradually expanding.

Cytotoxic chemotherapy and trastuzumab era

During the cytotoxic and trastuzumab era, CS was considered in patients who achieved a favorable response to platinum- or fluoropyrimidine-based chemotherapy, with or without trastuzumab. Most of these were retrospective studies conducted in Asia. The International Retrospective Cohort Study of Conversion Therapy for Stage IV Gastric Cancer 1 (CONVO-GC-1) study (2001–2014; n=1,206) provided the largest international dataset to date, reporting a median overall survival (OS) of 36.7 months among surgical patients and identifying R0 resection as the principal prognostic factor [12]. In Western countries, the FLOT3 trial (2009–2010) prospectively demonstrated the feasibility of triplet chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) in patients with limited metastases, achieving a median OS of 31.3 months [13].

Beyond these landmark studies, most reports from this period were small-scale retrospective cohort studies characterized by heterogeneous selection criteria, treatment regimens, and surgical indications [14-22]. Nevertheless, several recent systematic reviews and meta-analyses synthesizing these data have shown that in patients with stage IV GC, survival is significantly improved with CS following systemic therapy compared with systemic therapy alone [23,24]. These pooled analyses confirmed that curative-intent resection after systemic therapy provides a distinct survival advantage, despite the inherent heterogeneity of the included studies.

These investigations established the foundation for CS in the cytotoxic chemotherapy and trastuzumab era, emphasizing that success depends primarily on achieving a major radiological response and performing R0 resection in technically feasible cases. Representative data from this era are summarized in **Table 3**.

Immunotherapy and targeted therapy era

The FLOT5-RENAISSANCE (AIO) trial (2015–2023) was the first phase III study to evaluate CS in patients with metastatic GC [25]. This randomized study evaluated multimodal therapy incorporating FLOT ± trastuzumab or nivolumab, followed by CS versus continued systemic therapy. The trial did not demonstrate an OS advantage for the CS arm, despite a high R0 resection rate. The lack of benefit was largely attributable to early postoperative mortality and treatment-related complications, which offset the advantages of local disease control. Moreover, the short duration of systemic therapy—4 preoperative and 4 postoperative cycles (approximately 4 months in total)—was likely insufficient to achieve durable systemic control. Subgroup

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Table 3. Clinical outcomes and prognostic factors of conversion surgery in the cytotoxic chemotherapy and trastuzumab era for gastric cancer

Studies	Design (study period)	No. of patients (CS group)	Median OS (mo)	Prognostic factors	Regimen of systemic therapy	Key implication
Western studies						
Al-Batran et al. (2017) [13]	Prospective, multicenter phase II trial (2009–2010)	252 (60)	31.3	Response to chemotherapy, R0 resection	FLOT	First prospective evidence suggesting survival benefit of CS after FLOT in limited metastases.
Palaj et al. (2025) [14]	Retrospective cohort study (2007–2020)	123 (31)	19.4	R0 resection	NR	Laboratory markers (CEA, NLR, PLR) were identified as predictors of successful CS.
Asian studies						
Yoshida et al. (2021) [12]	Retrospective, international, multicenter cohort study (2001–2014)	1,206	36.7	R0 resection	Cytotoxic agent(s) ± trastuzumab	Multicenter, real-world validation of CS feasibility and prognostic impact; favorable survival was observed in P1 patients.
Yamamoto et al. (2013) [15]	Retrospective/case series (2008–2011)	34 (20)	24.9	Chemotherapy response, R0 resection	Cytotoxic agent(s)	Short neoadjuvant therapy; this suggests early CS in responders.
Beom et al. (2018) [16]	Retrospective (2005–2012)	101	26.0	Chemotherapy response, R0 resection	Cytotoxic agent(s)	R0 resection and CEA response were significant prognostic factors.
Kano et al. (2022) [17]	Multicenter retrospective study (2008–2013)	79	NR	Initially resectable, R0 resection	Cytotoxic agent(s) ± trastuzumab, IP chemotherapy	-
Takeno et al. (2024) [18]	Retrospective cohort study (2007–2017)	210	32.0	R0 resection, pT4, pN+	Cytotoxic agent(s) ± trastuzumab, IP chemotherapy	There was no significant survival difference according to initial metastatic site.
Masuike et al. (2025) [19]	Retrospective cohort study with PSM analysis (2007–2021)	128	29.0	R0 resection	Platinum doublet ± trastuzumab	Postoperative monotherapy was found to yield outcomes comparable to combination therapy.
Kakinuma et al. (2025) [20]	Retrospective cohort study (NR)	647 (57)	28.0	R0 resection	Cytotoxic agent(s) ± trastuzumab	-
Dat et al. (2025) [21]	Retrospective cohort study (2018–2023)	52 (26)	23.4	Yoshida category 3	Platinum doublet	CS was particularly beneficial in patients classified as Yoshida category 3.
Tanprasert et al. (2025) [22]	Retrospective cohort study (2005–2019)	86 (26)	25.8	Chemotherapy response	Platinum doublet	All CS patients achieved R0; this supports CS in responders.

CS = conversion surgery; OS = overall survival; FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel; R0 = complete (microscopic margin-negative) resection; NR = not reported; CEA = carcinoembryonic antigen; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; IP = intraperitoneal; PSM = propensity score matching.

analyses revealed that the potential benefit was confined to patients with retroperitoneal lymph node metastases, while patients with peritoneal metastases showed no advantage. These findings highlight that the success of conversion therapy depends on sustained biological response and systemic disease control rather than early surgical intervention.

Since 2020, multiple retrospective and phase II studies have evaluated ICI- or targeted therapy–based regimens in conversion settings, mostly from Asia, leading to the era of biologically driven conversion therapy [26-33] (**Table 4**). Across these cohorts, anti-programmed death-1 (PD-1) plus chemotherapy achieved response rates exceeding 60%; among those proceeding to surgery, R0 resection was achieved in 70%–90% of patients, with a median OS frequently unreached at 3 years. Key prognostic factors included PD-L1 positivity, HER2 status, and blood-based inflammatory indices such as the neutrophil-to-lymphocyte ratio, albumin, and lactate dehydrogenase. In HER2-positive disease, the addition of ICIs to trastuzumab-based therapy extended the median OS to 50.9 months versus 31 months with trastuzumab plus chemotherapy alone [32].

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Table 4. Clinical outcomes and prognostic factors of conversion surgery in the era of immunotherapy and targeted therapy for gastric cancer

Studies	Design (study period)	No. of patients (CS group)	Median OS (mo)	Prognostic factors	Regimen of systemic therapy	Key implication
Western studies						
Al-Batran et al. (2024) [25]	Phase III RCT (2015–2023)	139 (67)	18.5	Retroperitoneal LN metastases only	FLOT ± trastuzumab or nivolumab, 4 cycles	No OS benefit overall; the benefit was confined to retroperitoneal LN metastases.
Asian studies						
Liang et al. (2023) [26]	Retrospective cohort study (2019–2022)	136 (42)	Not reached	PD-L1 CPS ≥5, non-SCC	ICIs + chemotherapy ± anti-HER2	ICIs plus chemotherapy demonstrated higher response and resectability rates than chemotherapy alone.
Shin et al. (2023) [27]	Retrospective cohort study (2016–2022)	118 (R0 resection)	79.9	BMI at the time of diagnosis, the use of targeted agents or ICIs	Platinum doublet (62%) HER2 inhibitors (15%) ICIs (15%) MET or VEGFR2 inhibitors (5%)	The use of targeted agents or ICIs according to biomarker status was a prognostic factor for successful CS.
Liu et al. (2025) [28]	Prospective phase II study (2019–2022)	47 (35)	Not reached	R0 resection	Sintilimab + S-1 + nab-paclitaxel + apatinib	The multimodal regimen, combining anti-PD-1, taxane, fluoropyrimidine, and anti-angiogenic agents, achieved high R0 resection and pCR rates.
Nakazawa et al. (2024) [29]	Multicenter retrospective cohort study (NR)	104 (12)	Not reached	Low-risk Gustave Roussy Immune Score	Nivolumab + oxaliplatin-based doublet	These blood-based biomarkers (NLR, albumin, LDH) may serve as prognostic indicators for CS.
Huang et al. (2025) [30]	Multicenter retrospective cohort study (2020–2022)	105 (48)	Not reached	Yoshida category 1, 2 (no peritoneal metastasis) PD-L1-positive	Anti-PD-1 + chemotherapy	Conversion surgery was feasible in PD-L1–positive, non-peritoneal metastatic GC responding to anti-PD-1-based therapy.
Hojo et al. (2025) [31]	Retrospective cohort study (2017–2023)	103 (14)	Not reached	Nivolumab treatment	Nivolumab + oxaliplatin-based doublet (28) vs. oxaliplatin-based doublet (75)	Treatment with anti-PD-1 plus chemotherapy yielded a higher conversion rate than chemotherapy alone.
Liang et al. (2025) [32]	Multicenter retrospective cohort study (2012–2024)	232 (50)	50.9	Peritoneal metastasis, ypN3	ICI + trastuzumab + chemotherapy (118) vs. trastuzumab + chemotherapy (114)	Addition of ICIs to trastuzumab-based therapy improved survival and downstaging compared with trastuzumab + chemotherapy alone.
Han et al. (2025) [33]	Retrospective cohort with PSM analysis (2015–2023)	254 (127)	54.4	Well/moderate differentiation, longer pre-/peri-therapy, ypStage I–II, R0 resection	Platinum doublet (58.3%) HER2 inhibitors (20.5%) ICIs (21.2%)	Optimal survival was achieved with ~6–8 months of preoperative therapy and R0 resection after a durable systemic response.

CS = conversion surgery; OS = overall survival; RCT = randomized controlled trial; LN = lymph node; FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel; PD-L1 = programmed death-ligand 1; CPS = combined positive score; SCC = squamous cell carcinoma; ICI = immune checkpoint inhibitor; HER2 = human epidermal growth factor receptor 2; BMI = body mass index; MET = Mesenchymal-Epithelial Transition; VEGFR2 = vascular endothelial growth factor receptor 2; R0 = complete (microscopic margin-negative) resection; pCR = pathologic complete response; NLR = neutrophil-to-lymphocyte ratio; LDH = lactate dehydrogenase; PD-1 = programmed death-1; GC = gastric cancer; PSM = propensity score matching.

Furthermore, perioperative maintenance of effective systemic agents for up to one year may enhance durability and reduce the risk of recurrence. Our own propensity score-matched retrospective cohort (2015–2023), comprising 2,563 patients with stage IV GC treated with first-line systemic therapy, provides complementary real-world evidence [33]. Among these patients, 127 underwent CS and were matched 1:1 with systemic therapy-only controls using ten clinical prognostic variables. CS resulted in a median OS of 54.4 months versus 25.1 months in the control group (P<0.0001). Time-dependent analysis suggested an optimal preoperative therapy duration of approximately 6 months, followed by maintenance therapy for approximately one year.

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These findings reinforce the theory that CS is most effective when integrated within a prolonged, biology-driven, multimodal strategy rather than as a premature surgical intervention. A detailed overview of representative studies from this era is presented in **Table 4**.

IMPROVING SYSTEMIC THERAPY FOR CONVERSION THERAPY

Palliative first-line trials

The integration of ICIs and molecular targeted agents has revolutionized systemic therapy for metastatic GC, providing a biological foundation for modern conversion strategies (**Table 5**, **Fig. 2A and B**) [34-41].

In HER2-negative GC, CheckMate-649 showed that nivolumab plus fluoropyrimidine–platinum doublets achieved an objective response rate (ORR) of 60%, including a complete response (CR) rate of 12%, with a median duration of response (DoR) of 9.6 months and a median OS of 13.7 months among patients with PD-L1 combined positive score (CPS) ≥5 [34,35]. Similarly, KEYNOTE-859 demonstrated comparable efficacy for pembrolizumab combined with fluoropyrimidine–platinum doublets in patients with PD-L1 CPS ≥1, yielding an ORR of 52%, a CR rate of 10%, DoR of 8.3 months, and OS of 13 months [36]. In RATIONALE-305, tislelizumab plus chemotherapy produced a response rate of approximately 50% and a median OS of 17 months among patients with PD-L1 tumor area positivity score ≥5% [37].

For HER2-negative and CLDN18.2-positive GC, zolbetuximab plus chemotherapy produced ORRs exceeding 50% and OS ranging from 14 to 18 months in the SPOTLIGHT and GLOW trials, establishing CLDN18.2 as a new actionable biomarker [38,39].

For HER2-positive disease, the ToGA trial first established trastuzumab-based chemotherapy as a biomarker-guided standard (ORR, 47%; OS, 13.8 months) [40]. Subsequently, KEYNOTE-811 demonstrated that the addition of pembrolizumab to trastuzumab plus fluoropyrimidine–platinum regimens markedly enhanced efficacy, with an ORR of 73%, a CR rate of 17%, DoR of 11.3 months, and OS of 20 months [41].

Table 5. Key efficacy outcomes of pivotal palliative first-line trials for the locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinomas

Trials	Population	Experimental regimen	ORR (%)	CR (%)	Median DoR (mo)	Median PFS (mo)	Median OS (mo)
HER2-negative							
CheckMate-649 [34,35]	PD-L1 CPS ≥5	Nivolumab + FOLFOX or CAPOX	60.0	12.0	9.6	7.7	13.7
KEYNOTE-859 [36]	PD-L1 CPS ≥1	Pembrolizumab + FP or CAPOX	52.0	10.0	8.3	6.9	13.0
RATIONALE-305 [37]	PD-L1 TAP ≥5%	Tislelizumab + CAPOX or FP	50.0	3.0	9.0	7.2	17.2
SPOTLIGHT [38]	CLDN18.2-positive	Zolbetuximab + FOLFOX	61.1	6.2	8.9	11.0	18.2
GLOW [39]	CLDN18.2-positive	Zolbetuximab + CAPOX	54.1	3.6	6.3	8.3	14.3
HER2-positive							
ToGA [40]		Trastuzumab + FP or XP	47.0	5.0	6.9	6.7	13.8
KEYNOTE-811 [41]	PD-L1 CPS ≥1	Pembrolizumab + Trastuzumab + FP or CAPOX	73.2	17.0	11.3	10.9	20.0

ORR = objective response rate; CR = complete response; DoR = duration of response; PFS = progression-free survival; OS = overall survival; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed death-ligand 1; CPS = combined positive score; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; CAPOX = capecitabine and oxaliplatin; FP = 5-fluorouracil and cisplatin; TAP = tumor area positivity; CLDN18.2 = claudin 18.2; XP = capecitabine and cisplatin.

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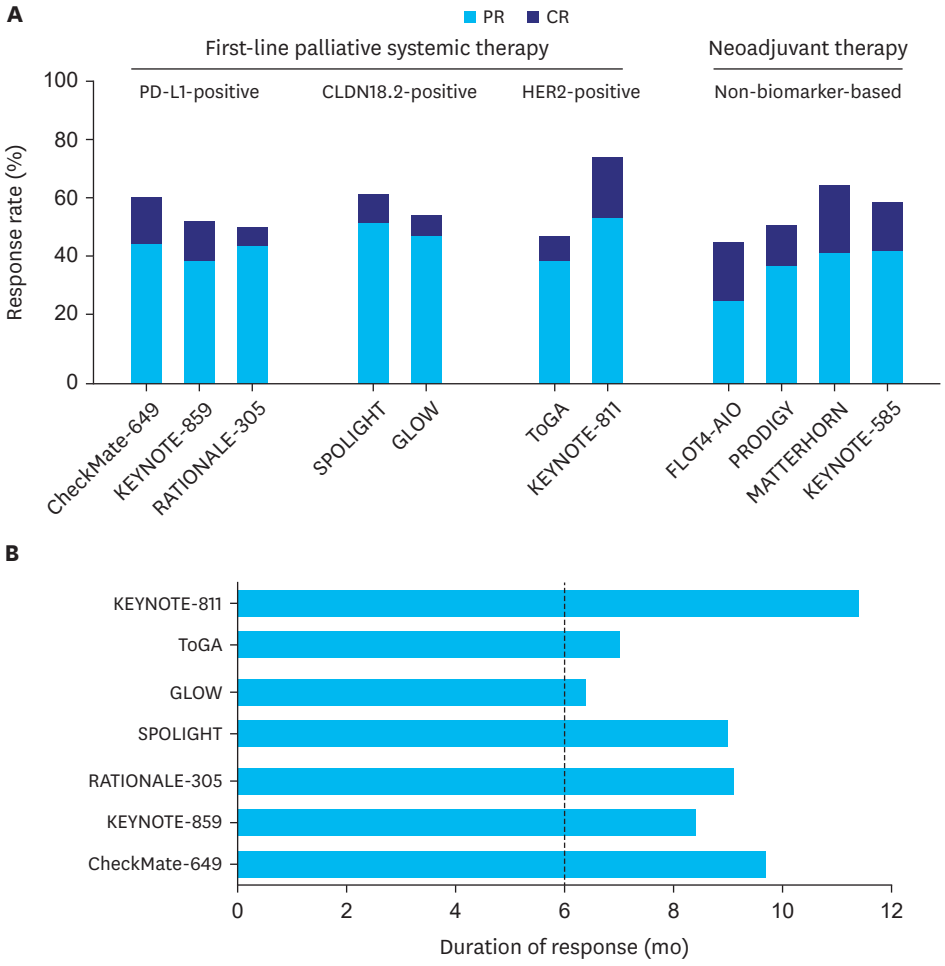

Fig. 2. Response depth and durability in pivotal trials of advanced gastric or gastroesophageal junction adenocarcinomas. (A) Objective response rate. (B) Median duration of response.
PD-L1 = programmed death-ligand 1; CLDN18.2 = claudin 18.2; HER2 = human epidermal growth factor receptor 2; PR = partial response; CR = complete response.

Across these studies, the median DoR was consistently greater than 6 months, with most trials reporting values ranging between 8 and 10 months, providing a biologically meaningful window for considering curative-intent surgery after achieving sustained systemic disease control (**Table 5**, **Fig. 2B**) [34-41]. Maintaining systemic therapy for approximately 6 months before surgery allows the confirmation of a sustained response and maximizes the probability of achieving R0 resection. These findings collectively establish that conversion feasibility is determined not by the specific regimen, but by the depth and durability of the systemic response (systemic control first, surgery second, and biology-driven approach) as determinants of curability.

Neoadjuvant and perioperative trials

Parallel progress in resectable and locally advanced disease has provided insights directly applicable to the conversion paradigm (**Table 6**, **Fig. 2A**) [42-46]. The FLOT4-AIO trial established perioperative FLOT (4 + 4 cycles) as the standard regimen, achieving an ORR of 45% and a pathologic CR (pCR) of 16%, significantly improving survival compared with ECF/ECX [42]. The Korean PRODIGY trial further validated docetaxel, oxaliplatin, and S-1 (DOS)

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Table 6. Key efficacy outcomes of pivotal perioperative trials for resectable or locally advanced gastric or gastroesophageal junction adenocarcinomas

Trials	Population	Neoadjuvant regimen	ORR (%)	pCR (%)	Adjuvant regimen
FLOT4-AIO [42]	cT2–T4 or N+, M0	FLOT, 4 cycles	45.0	16.0	FLOT, 4 cycles
PRODIGY [43,44]	cT2–T4 or N+, M0	DOS, 3 cycles	50.5	10.0	S-1, 8 cycles (1 year)
MATTERHORN [45]	Stage II–IVa	Durvalumab + FLOT, 4 cycles	64.0	19.2	Durvalumab + FLOT, 4 cycles → durvalumab monotherapy for 6 months (total duration up to 1 year)
KEYNOTE-585 [46]	cT3–T4 or N+, M0	Pembrolizumab + FLOT, 4 cycles	58.4	12.9	Pembrolizumab + FLOT, 4 cycles → pembrolizumab monotherapy, 11 cycles (total duration up to 1 year)

ORR = objective response rate; pCR = pathological complete response; FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel; DOS = docetaxel, oxaliplatin, and S-1.

as an effective neoadjuvant chemotherapy, reporting an ORR of 50.5% and a pCR of 10%, followed by adjuvant S-1 for 1 year [43,44].

Immunotherapy-enhanced perioperative regimens have yielded unprecedented responses. In MATTERHORN, durvalumab plus FLOT achieved an ORR of 64% and a pCR of 19.2%, followed by adjuvant durvalumab and 6 months of maintenance therapy (total ≈1 year) [45]. Similarly, the KEYNOTE-585 trial demonstrated that pembrolizumab combined with FLOT achieved an ORR of 58% and a pCR of 13%, with postoperative pembrolizumab continued for up to 11 cycles [46].

These findings confirm that intensified immunomodulatory systemic therapy markedly enhances tumor regression and increases the potential for curative (R0) resection. The observed pCR >10%–20% in these studies supports the principle that prolonged, effective systemic therapy, ideally 6 months or longer, can biologically downstage tumors even in a metastatic setting. For biomarker-negative diseases, triplet cytotoxic regimens, such as FLOT or DOS, remain rational cytoreductive options, whereas biomarker-positive patients benefit the most from targeted or ICI-based combinations. These results converge on the unified therapeutic logic of systemic disease control, surgery, and tumor biology as determinants of curability.

CLINICAL FRAMEWORK: FROM PALLIATION TO POTENTIAL CURE

Clinical management of metastatic GC is gradually improving, shifting from palliation to a potential cure. Historically, surgical decisions have been driven by anatomical resectability at the time of diagnosis; however, they also depend on biological behavior and systemic response.

Fig. 3 outlines the proposed clinical framework for conversion therapy in metastatic GC, which is summarized as follows: Conversion therapy should begin with the careful selection of patients within the oligometastatic spectrum who exhibit major radiologic and biological responses to first-line systemic therapy. Biomarker-based stratification using PD-L1, HER2, and CLDN18.2 further refines eligibility. Systemic therapy should generally be maintained for approximately 6 months, with close monitoring of disease progression to confirm durable disease control, as supported by real-world studies on CS and duration-of-response data from pivotal first-line trials. After sustained control, R0 resection may only be considered after a multidisciplinary evaluation to verify technical feasibility and biological suitability. Postoperatively, the continuation of effective agents such as fluoropyrimidines, ICIs, or molecularly targeted therapies for up to one year helps consolidate systemic control and reduce the risk of recurrence.

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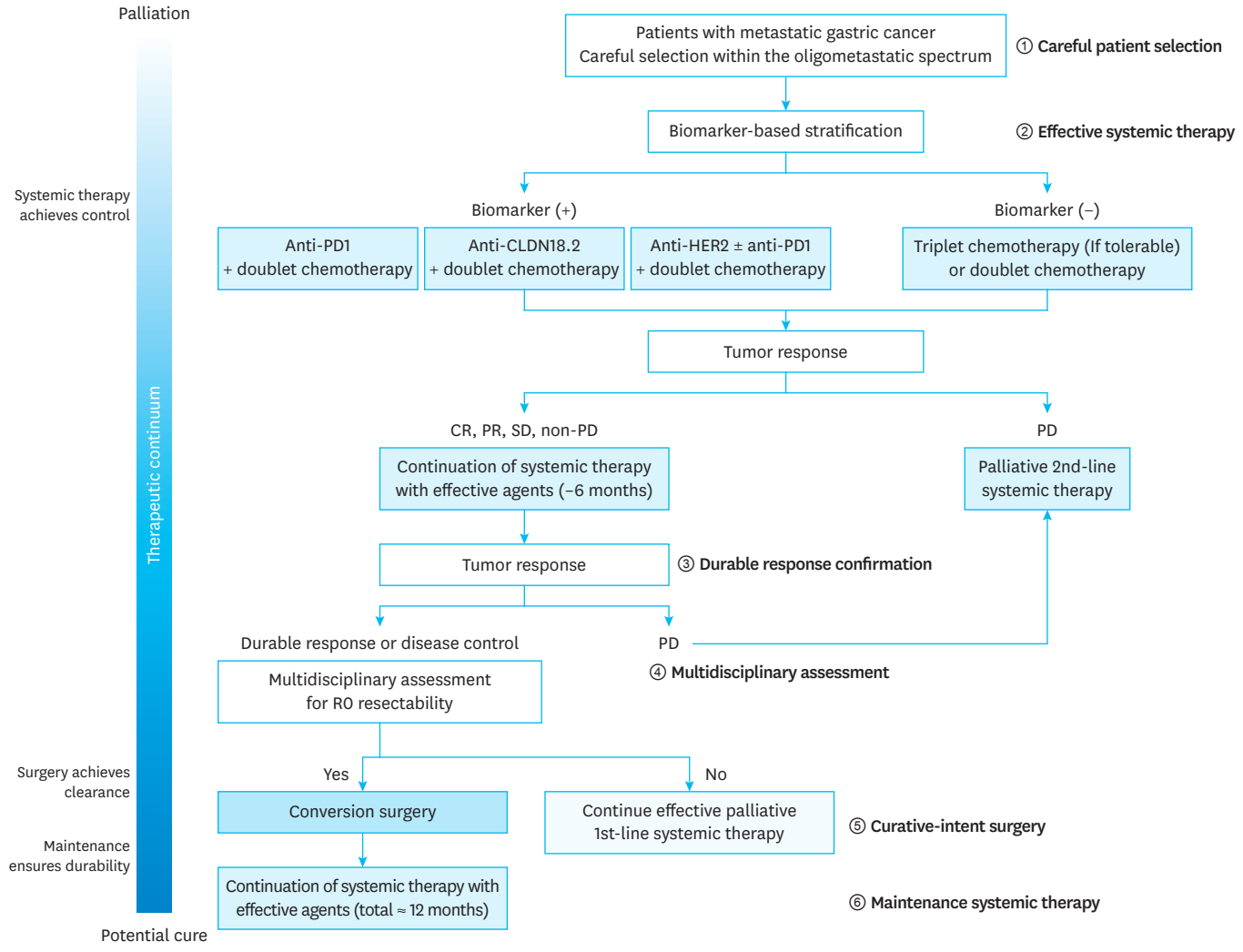

Fig. 3. Clinical framework of conversion therapy for metastatic gastric cancer.
PD-1 = programmed death-1; CLDN18.2 = claudin 18.2; HER2 = human epidermal growth factor receptor 2; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Ultimately, conversion therapy is not a discrete surgical action but a therapeutic continuum: systemic therapy achieves control, surgery and local therapy achieve clearance, and maintenance ensures durability. This integrated framework redefines metastatic GC care from disease management to potential cure (**Fig. 4**).

FUTURE DIRECTIONS

The next evolution of conversion therapy for metastatic GC will be defined by precision, molecular guidance, and the adaptive integration of multimodal treatment. Regarding patient selection refined by biomarker-driven stratification, therapies targeting PD-1, HER2, and CLDN18.2 have demonstrated that biologically defined subgroups can achieve profound and durable systemic control. Future multiomics profiling encompassing genomic, transcriptomic, and immunological data will help differentiate truly oligometastatic and immune-active diseases from transient responders with aggressive biology.

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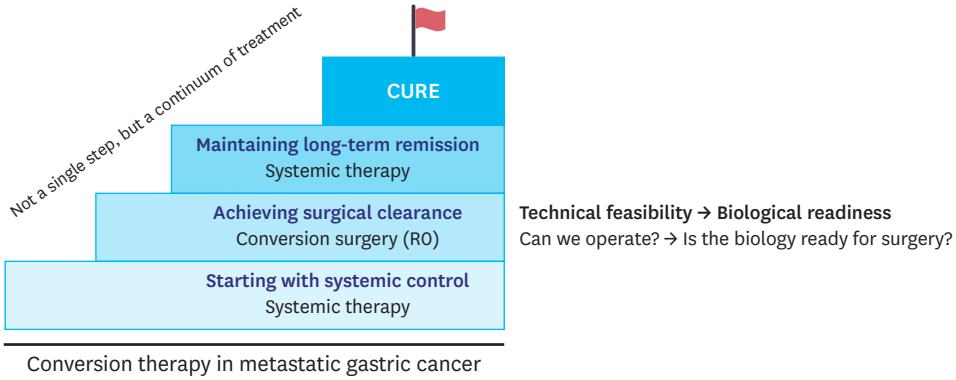

Fig. 4. Stepwise therapeutic continuum toward curative-intent conversion therapy in metastatic gastric cancer.

Circulating tumor DNA (ctDNA) and minimal residual disease (MRD) monitoring will also transform response assessments and surgical timing from current clinical evaluations to biological judgments. Serial ctDNA testing provides a dynamic and noninvasive measure of tumor burden and clonal evolution [47-50]. Persistent MRD positivity after systemic therapy may warrant extended or maintenance treatment, whereas ctDNA clearance may indicate a readiness for curative resection or treatment de-escalation. These emerging surveillance tools provide a novel framework for early detection of molecular relapses and individualized maintenance strategies.

Therefore, rigid treatment schedules should be replaced by adaptive systemic therapy. While current data support approximately 6 months of preoperative systemic therapy, future approaches will rely on molecular response kinetics rather than fixed time intervals, prioritizing biology-guided surgery over calendar-guided surgery.

Regarding perioperative immunotherapy and targeted maintenance reshaping treatment sequences, trials such as MATTERHORN and KEYNOTE-585 have demonstrated the feasibility of sustained perioperative ICI exposure [45,46], suggesting that immunological priming before surgery and extended maintenance thereafter may enhance immune surveillance and reduce the risk of recurrence. Therefore, prospective randomized trials and real-world validations are essential. Ongoing randomized trials (CONVO-GC-2, SURGIGAST, and JCOG2301) will define the true survival impact of CS [51-53], whereas registry-based analyses will provide real-world validation and support evidence harmonization across regions. In summary, the future of conversion therapy lies in precision-guided conversion, a biology-driven multimodal approach that aligns systemic efficacy with curative resection based on molecular monitoring and individualized treatment adaptation.

CONCLUSIONS

Conversion therapy for metastatic GC has evolved from surgical attempts to systemic-therapy–driven, precision-guided paradigms for a potential cure. The focus has shifted from technical feasibility to biological readiness—from “when can we operate?” to “when is the biology ready for local control?” Current evidence supports proper patient selection, with the maintenance of effective systemic therapy for at least 6 months before considering R0 resection, along with a validated response assessment within a multidisciplinary framework. Postoperative maintenance therapy further consolidates systemic control and reduces recurrence.

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Ultimately, CS should be regarded as the culmination, not a replacement, of systemic therapy, representing the biological endpoint of a successful systemic response. Through the continued integration of molecular profiling, dynamic response monitoring, and coordinated multidisciplinary care, conversion therapy holds promise for transforming metastatic GC from a uniformly palliative disease into a disease with genuine curative potential.

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