

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

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Conversion Therapy

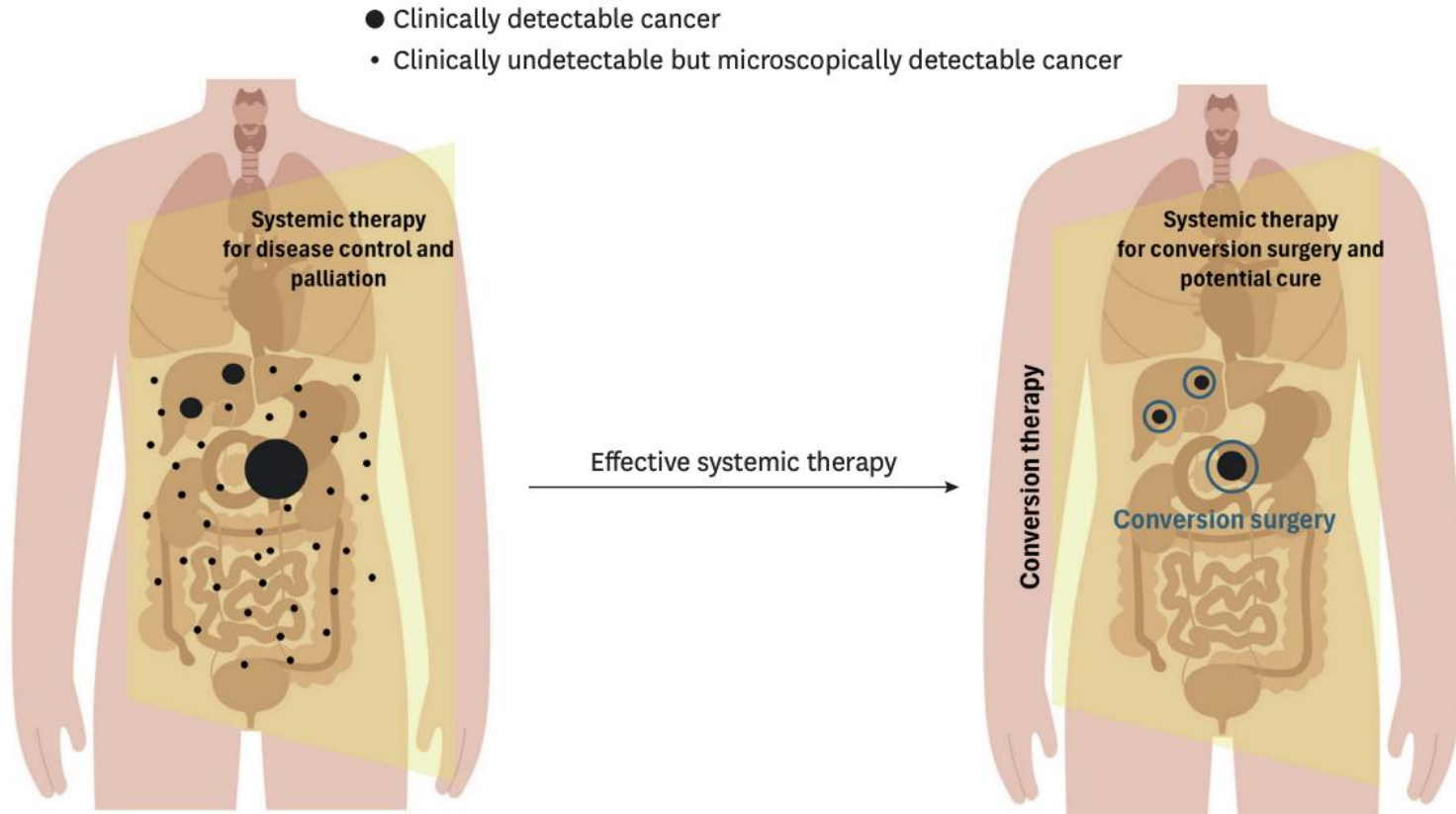


Fig. 1. Concept of conversion surgery for metastatic gastric cancer.

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Guideline Perspectives

- An investigational approach rather than standard of care
- Western guidelines (NCCN 2025, ESMO 2024)
 - Restrict it to selected patients
 - Oligometastatic disease
 - A durable and confirmed response to systemic therapy
 - Only in clinical trials or at high-volume tertiary centers
- Asian guidelines (JGCA 2021, CSCO 2023, KGCA 2024)
 - Conditional or weak recommendations
 - Limited and technically resectable metastases
 - Radiological regression and favorable biological responses
- 3 key determinants
 - Sustained tumor response to systemic therapy
 - Feasibility of R0 resection
 - Multidisciplinary evaluation

International Consensus

- Bertinoro Workshop (2022)
 - Establish a multidisciplinary and international conceptual framework
- OMEC-4 (2024)
 - Focus on conceptual standardization for future clinical trials
- KINGCA WEEK 2024 Consensus
 - Emphasizes pragmatic surgical decision-making reflecting real-world practice

Evidence From Clinical Trials

- **Cytotoxic CTx & Trastuzumab era**
 - CONVO-GC-1 study (2001-2014)
 - Retrospective cohort study
 - mOS 36.7mo among surgical pts (56.6mo, if R0)
 - R0 resection : the principal prognostic factor
 - FLOT3 trial (2009-2010)
 - Prospective phase 2 study (non-randomized)
 - Among pts with limited metastasis (n=60), 60% got surgery
 - mOS 31.3mo among surgical pts (vs. 15.9mo among non-op)
 - Several systematic reviews and meta-analysis
 - Survival : Conversion surgery > systemic Tx alone

Evidence From Clinical Trials

- **Immunotherapy and targeted therapy era**
 - FLOT5-RENAISSANCE (AIO) trial (2015-2023)
 - The first phase III study to evaluate CS in pts with metastatic GC
 - FLOT ± trastuzumab or nivolumab x 4 -> n = 176
 - > Randomization : CS vs. Continued systemic Tx
 - > CTx x 4
 - No OS advantage
 - Early postop mortality, tx-related cx
 - The short duration of systemic tx (4 preop & 4 postop)
- ➔ The success of CS depends on sustained biological response rather than early surgical intervention

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.

Improving Systemic Therapy for CS

- Palliative first-line trials

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 $\geq 5\%$	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.

Improving Systemic Therapy for CS

- Neoadjuvant and perioperative trials

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+, MO	FLOT, 4 cycles	45.0	16.0	FLOT, 4 cycles
PRODIGY [43,44]	cT2-T4 or N+, MO	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+, MO	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.

Clinical Framework : From Palliation To Potential Cure

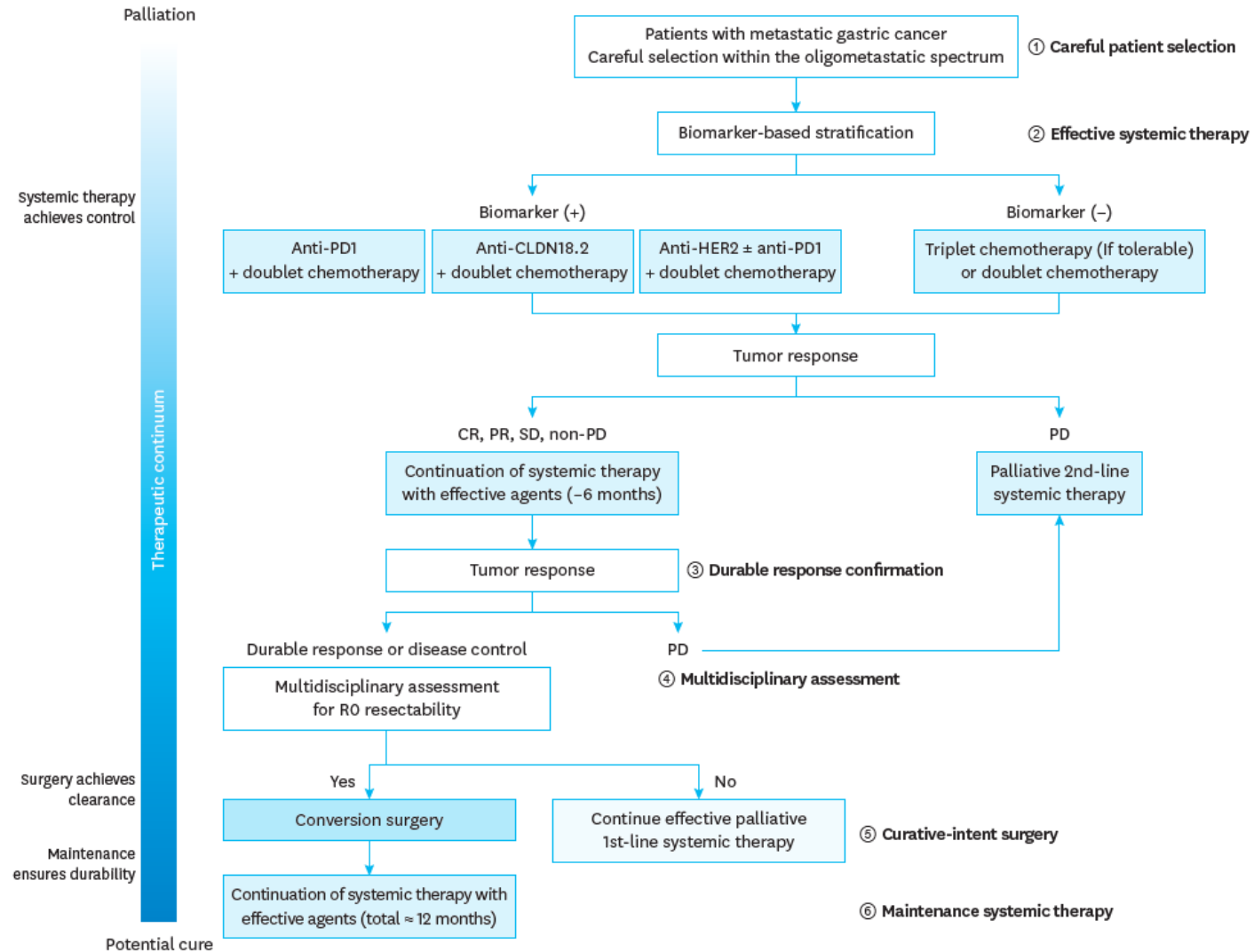


Fig. 3. Clinical framework of conversion therapy for metastatic gastric cancer.

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.

Future Directions

- Multiomics profiling -> truly oligometastatic & immune-active disease vs. transient responders
- ctDNA & MRD monitoring -> response assessment & surgical timing
- Further prospective randomized trials & real-world validations

Conclusions

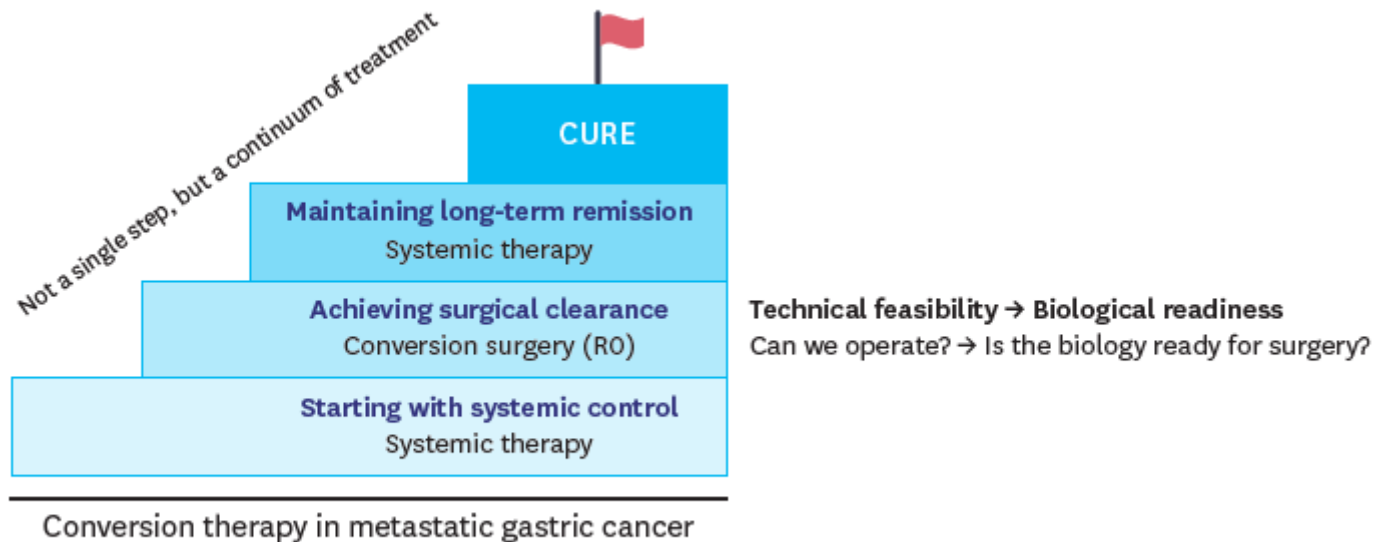


Fig. 4. Stepwise therapeutic continuum toward curative-intent conversion therapy in metastatic gastric cancer.

- **CS** should be regarded as **the culmination, not a replacement, of systemic therapy**, representing the biological endpoint of a successful systemic response.

Thank you for listening