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Review Article

The Current Evidence and Future Direction of Adjuvant Treatment for Gastric Cancer in the Era of Precision Medicine

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Although gastric cancer remains a significant global health burden, its treatment strategies vary across different geographical regions, leading to distinct guidelines. In Asia, particularly in Korea, D2 gastrectomy followed by adjuvant chemotherapy has been established as the standard treatment for stage II/III gastric cancer based on landmark clinical trials. However, this "one-size-fits-all" approach requires refinement as emerging evidence suggests heterogeneous outcomes even within the same stage. This review discusses the evolving landscape of adjuvant treatment in gastric cancer, emphasizing the transition towards precision medicine. Recent molecular characterization of gastric cancer has revealed distinct subtypes with varying prognoses and chemotherapy responses, exemplified by the favorable outcomes of microsatellite instability–high tumors without adjuvant chemotherapy. Additionally, clinical factors including sub-stages within stage II/III, patient performance status, comorbidities, and personal preferences should be considered in treatment decisions. The integration of these molecular and clinical factors, along with shared decision-making between physicians and patients, represents a crucial step toward personalized treatment approaches. Looking ahead, the field is poised for further evolution with the emergence of immune checkpoint inhibitors, growing evidence for neoadjuvant chemotherapy in selected cases, and the potential of circulating tumor DNA as a biomarker for minimal residual disease. This comprehensive approach to treatment decision-making, considering both tumor biology and patient factors, will be essential for realizing precision medicine in gastric cancer care.

Key words Stomach neoplasms, Precision medicine, Adjuvant chemotherapy, Microsatellite instability, Single-patient classifier, Circulating tumor DNA, Biomarkers

Introduction

Gastric cancer (GC) remains a significant global health burden, ranked fifth in incidence and fourth in cancer-related mortality worldwide [1]. Each year, nearly one million new cases are diagnosed, with more than 800,000 deaths reported. The disease is particularly prevalent in East Asia, including Korea, Japan, and China, where the burden is the highest [2]. Despite advancements in diagnostic methods and therapeutic strategies, the prognosis for patients with advanced-stage GC remains poor [1,3]. The 5-year survival rate for stage II GC is approximately 70%-88%, while stage III GC sees a much lower survival rate, ranging from 45%-71% [4,5]. These figures highlight the urgent need for more effective treatment approaches, especially in managing advanced diseases.

This review focuses on the evolving landscape of adjuvant treatment in GC, particularly emphasizing the transition from a "one-size-fits-all" approach to precision medicine. While adjuvant chemotherapy following D2 gastrectomy has been established as the standard of care for stage II/III GC [2,3] accumulating evidence suggests that not all patients derive equal benefit from this approach. We discuss how molecular characterization, refined staging systems, and individual patient factors can guide more precise treatment decisions. Additionally, we explore the current evidence supporting biomarker-guided treatment strategies and discuss future directions, including the potential role of circulating tumor DNA (ctDNA) and pre-emptive immunotherapy in the adjuvant setting. By integrating these various elements, we aim to provide a comprehensive framework for implementing precision medicine in adjuvant treatment of advanced GC.

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Regional Variations in Treatment Strategies for GC: Evolution of Evidence-Based Guidelines

The management of GC has evolved distinctly across different geographical regions, reflecting various factors including epidemiology, ethnic characteristics, and surgical expertise [6,7]. These regional differences have led to the development of independent treatment guidelines tailored to specific populations and healthcare environments [8,9].

Surgical resection with D2 lymphadenectomy represents the cornerstone of treatment for locally advanced GC, serving as the most critical therapeutic strategy [3,10]. A crucial aspect of this surgical approach is the extent of lymph node dissection. D2 lymphadenectomy, which involves complete removal of regional lymph nodes where cancer cells may have spread, represents a technically demanding procedure. Initially, Western countries were reluctant to adopt D2 dissection due to higher reported morbidity and mortality rates in early randomized trials [11,12]. Consequently, D1 lymphadenectomy became the standard surgical approach in Western practice, necessitating the addition of chemoradiotherapy to address potential residual disease. Currently, Western guidelines acknowledge the importance of D2 lymphadenectomy; however, due to persistent concerns about surgical complications, they recommend that this procedure should be performed only at high-volume centers by experienced surgeons [13,14]. In the United States, based on the pivotal Intergroup 0116 trial [15], postoperative chemoradiotherapy became the standard of care [13]. European countries, guided by the MAGIC trial and subsequently the FLOT4 study [16,17], adopted perioperative chemotherapy as their primary treatment approach [14].

In contrast, Asian countries, particularly Korea and Japan, have traditionally performed D2 lymphadenectomy with excellent outcomes, attributed to higher case volumes and surgical expertise. This surgical proficiency, combined with the positive results from the ACTS-GC (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer) and CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) trials, established radical gastrectomy followed by postoperative adjuvant chemotherapy as the standard treatment for stage II/III GC in Asia [18,19].

These regional differences are reflected in current major guidelines. The National Comprehensive Cancer Network (NCCN) guidelines in the United States and the European Society for Medical Oncology (ESMO) guidelines maintain their distinct approaches [13,14]. In Asia, the Japanese Gastric Cancer Association (JGCA) guidelines have historically served as a reference [10]. More recently, the Korean Gastric Cancer Association (KGCA) published its first evidence-based guidelines, with updates planned for the coming year [3,20]. Similarly, the Chinese Society of Clinical Oncology (CSCO) has developed its own guidelines, further contributing to the region-specific approach to GC management (Table 1) [21]. This regional variation in treatment strategies underscores the importance of considering local geographical factors, including healthcare systems, surgical expertise, and patient characteristics, in developing optimal treatment approaches.

The Concept and Impact of Adjuvant Treatment in GC

In most cancers, including GC, early-stage disease, stage I, typically does not require adjuvant therapy after surgical resection. This approach is based on the understanding that early tumors, when completely resected, have minimal risk of harboring microscopic residual disseminated disease, cancer cells in the surgical bed as well as disseminated cells present before or potentially spread during surgery. The excellent prognosis observed in stage I GC patients treated with surgery alone (with 5-year survival rates exceeding 90%) supports this treatment strategy [22,23]. The decision to omit adjuvant therapy in stage I disease reflects both the high likelihood of surgical cure and the unfavorable risk-benefit ratio of additional systemic therapy in this setting, where potential toxicities would outweigh the minimal potential benefit [24-27]. This treatment paradigm stands in contrast to locally advanced disease (stages II and III), where the risk of microscopic residual disseminated disease is substantially higher, justifying the use of adjuvant therapy despite its associated toxicities.

Radical surgery (D2 surgery) for GC aims to achieve complete removal of all visible and possible tumor burden. However, the potential presence of microscopic residual disseminated disease necessitates additional therapeutic interventions in the form of adjuvant chemotherapy or chemoradiation therapy to control disseminated and residual cancer cells in the surgical bed or distant organs that are undetectable with current medical imaging techniques (e.g., computed tomography and positron emission tomography–computed tomography). Through numerous clinical trials, the benefit of adjuvant treatment for stage II/III GC has been unequivocally established [15-19]. However, a critical analysis of adjuvant treatment efficacy reveals an intriguing pattern. Evidence suggests that only approximately 10% of the total patient population derives meaningful benefit from adjuvant therapy [18,19]. This observation warrants careful interpretation within the context of overall treatment outcomes.

Data from landmark trials such as ACTS-GC and CLAS-

Table 1. Guidelines for stage II/III gastric cancer

Perioperative treatment	KGCA (2022)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
Lymph node dissection					
D2					
Recommendation	Strong for		Grade I	Category 2A	Grade B
Indication	T2-T4, T1N+	T2-T4, T1N+	T2-T4, T1N+	Should be done by experienced surgeon	Only by experienced surgeon
D2+					
Recommendation			Grade II, III		
Indication	Not mentioned	Metastasis to No. 10, 14v, 13, 16 LNs	Metastasis to No. 10, 14v (grade II), 13 (grade III) LNs	Not mentioned	Not mentioned
Neoadjuvant chemotherapy					
Recommendation	Conditional for	No clear recommendation	Grade I (cT3-4aN+M0)	Category 1 (cT2 or higher, any N)	Grade A (cT2 or higher, any N)
Regimen	DOS, SOX		SOX	FLOT, fluoropyrimidine +oxaliplatin Consider neoadjuvant or perioperative ICI if tumor is MSI-H/dMMR[a)]	FLOT, DOS
Neoadjuvant chemoradiotherapy					
Recommendation	Investigational	Not mentioned	Grade I (gastric cancer invading the EGJ: cT3-4aN+M0)	Category 2B	Not mentioned
Adjuvant chemotherapy					
Recommendation	Strong for (stage II or III)	Recommended (stage II or III)	Grade I (stage II or III)	Category 1 (primary D2 LND)	Grade A (primary surgery with ≥ stage II)
Regimen	S-1, XELOX	S-1 (stage II, conditionally recommended for stage III), XELOX, S-1+docetaxel (stage III)	S-1, XELOX (stage II) XELOX, SOX (stage III) For dMMR/MSI-H: postoperative observation can be considered[b)]	XELOX, 5-FU+oxaliplatin	S-1 (stage II), XELOX, SOX, S-1+docetaxel For MSI-H, adjuvant ChT should be carefully considered[c)] (grade C)

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Table 1. Continued

Perioperative treatment	KGCA (2022)	JGCA (2021)	CSCO (2023)	NCCN (2024)	ESMO (2024)
Adjuvant chemoradiotherapy					
Recommendation	Conditional against	Not mentioned	Grade I (< D2 LND and/or R1 or R2 resection)	Category 2A (< D2 LND)	Grade C (< D2 LND and/or R1)

This table only includes the CSCO "Grade I recommendations," NCCN "Preferred Regimens." Recommendations backed by robust evidence and characterized by high accessibility are categorized as Grade I in CSCO 2023. Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. In ESMO guideline, grade A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended; grade B: Strong or moderate evidence for efficacy but with limited clinical benefit, is generally recommended; grade C: Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional. ChT, chemotherapy; CSCO, Chinese Society of Clinical Oncology; dMMR, DNA mismatch repair; DOS, docetaxel, oxaliplatin, and S-1; EGJ, esophagogastric junction; ESMO, European Society for Medical Oncology; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; ICI, immune checkpoint inhibitor; JGCA, Japanese Gastric Cancer Association; KGCA, Korean Gastric Cancer Association; LN, lymph node; LND, lymph node dissection; MSI-H, microsatellite instability–high; NCCN, National Comprehensive Cancer Network; SOX, S-1 and oxaliplatin; XELOX, capecitabine and oxaliplatin; 5-FU, 5-fluorouracil. [a]In patients with a MSI-H/dMMR tumor, perioperative immunotherapy or surgery alone should be considered in consultation with a multidisciplinary team. The role of surgery after biopsy proven and radiologic/metabolic complete response on neoadjuvant immunotherapy is unclear. The role for surgery in the setting of favorable neoadjuvant response should be carefully discussed, [b]Taking adverse reactions related to chemotherapy and patients' financial implications into account, it is suggested that for dMMR/MSI-H patients, (neo)adjuvant treatments such as immunotherapy in clinical trial settings could be first considered, unless unwillingness from the patient's side, after detailed discussion with the patient and families about the risk and benefits of different treatment strategies, postoperative observation or chemotherapy can be considered, [c]For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT should be carefully considered.

Table 2. Key characteristics of four molecular classifications of gastric cancer

Molecular classification			
Intrinsic subtypes			
-	-	G-INT - Lauren intestinal type - High expression of carbohydrate and protein metabolism - High expression of cell adhesion - Sensitive to 5-FU chemotherapy	G-DIF - Lauren diffuse type - High expression of cell proliferation - High expression of fatty acid metabolism - Resistance to 5-FU chemotherapy
TCGA			
MSI - DNA hypermethylation (*MLH1*) - Elevated mutation rate - Alteration of MHC class I related genes (B2M, HLA-B) - Older age - Female	EBV[a)] - DNA hypermethylation (*CDKN2A*) - *PIK3CA* mutation - *PD-L1/2* amplification - Elevated immune cell signaling pathway - Male - Gastric fundus and body	CIN - Lauren intestinal type - Activation of RTK/RAS pathways - RTK amplification - *TP53* mutation - Gastroesophageal junction and cardia	GS - Lauren diffuse type - *CDH1* and *RHOA* mutation - *CLDN18/ARHGAP* gene fusion - Cell adhesion and angiogenesis pathway activation - Younger age
ACRG			
MSI - Lauren intestinal type - Gastric antrum - Hypermutation - Good prognosis - Hepatic recurrence - Earlier stage	MSS/TP53-activated - Frequent EBV-positive - *APC*, *ARID1A*, *KRAS*, *PIK3CA*, and *SMAD4* mutation - Intermediate prognosis	MSS/TP53-inactivated - *TP53* mutation - Focal amplification RTK - Intermediate prognosis	MSS/EMT - Lauren diffuse type - Signet ring cell carcinoma - *CDH1* loss of expression - Less mutation - Bad prognosis - Peritoneal recurrence - Later stage - Younger age

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Table 2. Continued

Molecular classification			
Single Patient Classifier (SPC)			
IM type	-	EP type	ST type
- *GZMB*/*WARS*		- *CDX1*	- *SRFP4*
- Immune/inflammatory gene signature		- Proliferative gene signature	- Stem-ness/stromal gene signature
- EBV GC predominant		- Biomarker for intestinal metaplasia	- EMT-related classifier gene
- Lauren intestinal type		- EBV negative GC	- TCGA GS predominant
- Older age		- MSS/MSI-L	- Lauren diffuse type
- Favorable prognosis		- Younger age	- Younger age
- Unresponsive to chemotherapy		- Responsive to chemotherapy	- Unfavorable prognosis

ACRG, Asian Cancer Research Group; *ARHGAP*, Rho GTPase activating protein 25; *ARID1A*, AT-rich interaction domain 1A; B2M, beta-2-microglobulin; *CDH1*, cadherin 1; *CDX1*, caudal-type homeobox 1; CIN, chromosomal instability; *CLDN18*, claudin 18; EBV, Epstein-Barr virus; EMT, epithelial-mesenchymal transition; EP, epithelial; GC, gastric cancer; G-DIF, genomic-diffuse; G-INT, genomic-intestinal; GS, genomically stable; *GZMB*, granzyme B; IM, immune; MHC, major histocompatibility complex; MSI, microsatellite instability; MSI-L, MSI-low; MSS, microsatellite stable; PD-L1, programmed death-ligand 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *RHOA*, Ras homolog family member A; RTK, receptor tyrosine kinase; *SFRP4*, secreted frizzled-related protein 4; ST, stem-like; TCGA, The Cancer Genome Atlas; TP53, tumor suppressor p53; *WARS*, tryptophanyl-tRNA synthetase; 5-FU, 5-fluorouracil. [a]The representation of EBV-positive cases is limited within molecular subtypes, necessitating cautious interpretation.

SIC demonstrate that surgery alone achieves cure (defined as 5-year disease-free survival) in more than 50% of patients, suggesting complete eradication of disease through surgery only in these cases [18,19]. The mathematical implications of these statistics are enlightening: (1) Approximately 50% of patients achieve cure through surgery alone, thus no additional benefit from systemic treatment. (2) The remaining 50% have potential microscopic residual disease, therefore this group, only about 20% (translating to 10% of the total population) demonstrate meaningful response to adjuvant therapy. This mathematical framework raises important questions about treatment optimization: (1) How can we identify patients who truly need and do not need adjuvant therapy? (2) What characterizes the subset of patients who respond to adjuvant treatment? (3) Can we develop more precise strategies to target the specific patient population that will benefit from adjuvant therapy?

These patterns of heterogeneous clinical outcomes, despite similar clinical stages, reflect the underlying molecular heterogeneity of GC. In the era of precision medicine, understanding the molecular characteristics of GC is crucial for optimizing adjuvant treatment strategies.

Current Understanding of Molecular Subtypes and Characteristics in GC

Several landmark studies have established distinct molecular classifications of GC, each contributing unique insights into disease biology and clinical implications. The key findings are summarized in Table 2.

1. Intrinsic molecular subtypes

The first classification of GC based on gene expression patterns was published by a Singapore group [28]. They initially analyzed gene expression patterns in 37 GC cell lines and subsequently validated their findings in independent patient tumor samples. Their analysis identified two distinct groups: genomic-intestinal (G-INT) and genomic-diffuse (G-DIF). G-INT tumors demonstrated better survival and showed sensitivity to 5-fluorouracil (5-FU) and oxaliplatin while exhibiting resistance to cisplatin. Conversely, G-DIF tumors were associated with poor prognosis but demonstrated sensitivity to cisplatin.

Building on these findings, they conducted a proof-of-concept phase II '3G' trial, where G-INT and G-DIF were classified as 'G1' and 'G2', respectively, with an indeterminate group designated as 'G3' [29]. The trial demonstrated that gene profiling could be completed within a clinically practical timeframe, suggesting its potential for clinical implementation. This pioneering work established the feasibility

of bench-to-bedside translation and laid the foundation for molecular-based treatment stratification.

2. The Cancer Genome Atlas classification

The most widely appreciated and representative study for the molecular characteristics of GC was reported by The Cancer Genome Atlas (TCGA) group [30]. Through comprehensive bulk-sequencing–based multi-omic analysis, TCGA established four distinct molecular subtypes of GC, microsatellite instability (MSI), Epstein-Barr virus (EBV) associated, chromosomal instability (CIN), and genomically stable (GS) types. MSI type is associated with CpG island methylator phenotype and *MLH1* silencing, one of the major gene of mismatch repair (MMR) system, causing hypermutation of tumor. EBV type is associated frequent *PIK3CA* mutations and up-regulated immune cell signaling including programmed death-ligand 1/2 (PD-L1/2) overexpression. Therefore, both MSI and EBV-positive GCs are recently considered as promising candidates for immune checkpoint inhibitor (ICI) therapy [31-33]. The remaining tumors are classified based on their copy number burden: those harboring extensive somatic copy number alterations are designated as CIN subtype, while the rest are categorized as GS subtype. The CIN subtype is strongly associated with intestinal-type histology and frequently harbors *TP53* mutations and receptor tyrosine kinase activation. The GS subtype is characterized by diffuse-type histology and features *CDH1*/*RHOA* mutations and *CLDN18-ARHGAP* fusion. While the TCGA classification effectively captured the molecular heterogeneity of GC, initial prognostic correlations were limited, potentially due to the heterogeneous treatment protocols across contributing institutions.

3. Asian Cancer Research Group classification

Asian Cancer Research Group reported the results from microarray data (mRNA expression) of 300 GC tumors and they classified GC into four distinctive subtypes: MSI, microsatellite stable (MSS) with epithelial-mesenchymal transition (EMT), and MSS with and without TP53 activation [34]. The characteristics of MSI type is like the result of TCGA and showing better prognosis compared to other subtypes. EMT subtype is predominantly diffuse-type histology with worst prognosis, resembling GS type of TCGA. MSS/TP53-activated subtype encompasses most EBV-positive tumors; however, EBV-positive cases represent only a small proportion of the overall MSS/TP53-activated subtype, and MSS/TP53-inactivated is associated with *TP53* mutation and is comparable to CIN type of TCGA. The prognosis of MSS/TP53-activated and -inactivated subtypes shows intermediate prognosis compared to MSI and EMT subtype. This classification demonstrated significant prognostic stratification, providing additional clinical utility.

4. Single patient classifier (nProfiler I)

An effort to translate molecular characteristics into adjuvant treatment strategies for GC was conducted by the Yonsei group [35]. Through comprehensive analysis of gene expression profiles from more than 1,000 tumor specimens, they classified GC into three distinct phenotypes: immune (IM), epithelial (EP), and stem-like (ST) types. The IM type was characterized by high *GZMB*/*WARS* expression, demonstrating favorable prognosis but limited benefit from adjuvant chemotherapy. The EP type, marked by high *CDX1* expression, showed good response to adjuvant chemotherapy, while the ST type, characterized by high *SFRP4* expression, was associated with poor prognosis and limited chemotherapy response.

Based on these findings, they developed a single patient classifier (SPC) that could predict both prognosis and potential benefit from adjuvant chemotherapy at patient-level. The clinical utility of this classifier was validated in a subset of the CLASSIC trial cohort, a randomized controlled study comparing surgery alone versus surgery with adjuvant chemotherapy, providing robust clinical evidence for its application [35]. The unique property of SPC is that, unlike other molecular subtyping schemes which are population-level classifications, it provides pivotal information on prognosis and responsiveness to adjuvant chemotherapy for individual patients.

The SPC was subsequently commercialized as the nProfiler I Stomach Cancer Assay and was designated as the first innovative medical technology in Korea (2019-243). Several consecutive studies have evaluated its clinical performance, including feasibility studies [23,36-38]. Currently, additional retrospective and prospective multicenter validation studies have completed enrollment and are undergoing analysis (SPRINT trial, NCT04600518; PREDICT trial, NCT04487717).

5. Convergent findings across molecular classifications of GC

The above-mentioned molecular classification systems for GC have revealed several consistent patterns in terms of prognosis and treatment response (Table 2). From a prognostic perspective, microsatellite instability–high (MSI-H) tumors, EBV-positive cases, and the IM type identified by SPC consistently demonstrate favorable outcomes compared to other subtypes within the same stage. The favorable prognosis of MSI-H tumors can be attributed to their hypermutation status resulting from MMR deficiency, which generates numerous neoantigens recognizable by tumor-infiltrating T cells. This enhanced host immune response enables effective tumor control, often resulting in presentation at ear-

lier stages with better outcomes [39]. Similarly, EBV-positive tumors and IM types are characterized by enriched immune cell infiltration and elevated expression of immune-related genes, reflecting effective host immune surveillance system. This pattern mirrors observations in other solid tumors, where high tumor-infiltrating lymphocyte density correlates with improved outcomes [40-43].

Conversely, subtypes associated with diffuse histology, including GS, EMT, and ST types, consistently demonstrate poor prognosis. These subtypes show elevated EMT-related signaling and significant influence of cancer-associated fibroblasts (CAFs) in their tumor microenvironment [44].

Regarding chemotherapy response, tumors exhibiting intestinal-like characteristics, including the G-INT and EP type (*CDX1*-positive group in SPC), generally demonstrate good response to conventional chemotherapy. This pattern parallels observations in colorectal cancer (CRC), where *CDX2*-positive tumors show better chemotherapy response [45].

Two distinct patterns of poor chemotherapy response have emerged. First, EMT-like subtypes, characterized by elevated EMT signaling (including Wnt and transforming growth factor β pathways) and well-developed CAF infrastructure, typically show poor response. These tumors, often manifesting as diffuse type of histology or Borrmann type IV, exhibit extensive desmoplasia, which may impair drug penetration and delivery [46,47]. Second, despite their favorable prognosis, immune-enriched subtypes often show limited benefit from chemotherapy. This paradox might be explained by the low probability of microscopic residual disease due to effective immune control, and the potential negative impact of chemotherapy on tumor-controlling immune cells, possibly neutralizing their prognostic advantage [48].

This understanding of molecular subtypes and their relationship to the prognosis and treatment response provides crucial insights for treatment stratification and the development of personalized therapeutic approaches in GC management. The consistent patterns observed across different classification systems strengthen the validity of these findings and their potential clinical applications.

Evidence for Clinical Implementation of Personalized Adjuvant Therapy: Key Considerations in Treatment Decision-Making

1. Clinical implementation of molecular characteristics in GC treatment

The rationale for omitting adjuvant chemotherapy in stage I GC provides valuable insights for treatment optimization in more advanced stages. This approach in stage I is based on excellent prognosis with surgery alone and minimal potential benefit from chemotherapy, coupled with the risk of treatment-related toxicities.

Extending this concept to stage II/III GC raises an important question: Should all patients with stage II/III disease receive adjuvant chemotherapy after D2 gastrectomy? Historical clinical trials such as CLASSIC and ACTS-GC, adopted a "one-size-fits-all" approach, conducted before our current understanding of molecular heterogeneity in GC. These trials demonstrated an overall survival benefit from adjuvant chemotherapy, but the benefit was limited to a subset of patients. Notably, approximately 50% of patients could be cured by surgery alone [18,19], suggesting that these patients may not require additional adjuvant chemotherapy. This highlights the critical need for better patient selection strategies, as many patients may be unnecessarily exposed to chemotherapy toxicity without deriving actual benefit.

2. Microsatellite instability–high

MSI-H phenotype, associated with Lynch syndrome, has been extensively studied in CRC. Multiple retrospective studies demonstrated that MSI-H CRC shows favorable prognosis and lacks benefit from 5-FU–based chemotherapy [49]. These findings were validated through retrospective analyses of samples from various randomized controlled trials (RCTs) comparing surgery alone versus surgery plus chemotherapy, and subsequent meta-analyses pooling these results [50]. Consequently, NCCN guidelines have recommended considering MSI status when making decisions about adjuvant chemotherapy in CRC [51].

In GCs, although initial retrospective studies showed conflicting results, a meta-analysis [52] pooling these studies revealed that MSI-H GC similarly demonstrates better prognosis within the same stage and limited benefit from adjuvant chemotherapy. These findings were validated in subset analyses of major RCTs including MAGIC and CLASSIC trials [53,54], comparing surgery alone versus surgery plus chemotherapy. Furthermore, an individual patient data meta-analysis of four RCT cohorts provided further confirmation of these results [55].

Given the nature of biomarker research, conducting additional RCTs specifically examining surgery alone versus surgery plus chemotherapy in MSI-H patients would be challenging. However, despite the retrospective approach, the level of evidence is considerable, as the hypothesis was validated using RCT samples [56]. Moreover, considering the well-established biology of MSI-H in solid tumors, these findings appear to have accumulated sufficient evidence for clinical implementation in GC, as is the case in CRC.

Based on these results, the recent ESMO guideline recommends that "*Adjuvant (postoperative) chemotherapy should be*

avoided in resected MSI-H GC" [57]. Additionally, the updated CSCO guideline suggests that "*Taking adverse reactions related to chemotherapy and patients' financial implications into account, it is suggested that for dMMR/MSI-H patients, (neo)adjuvant treatments such as immunotherapy in clinical trial settings could be first considered, unless unwillingness from the patient's side, after detailed discussion with the patient and families about the risk and benefits of different treatment strategies, postoperative observation or chemotherapy can be considered*" [21]. The KGCA guidelines are expected to reflect similar considerations in their upcoming update [20,58,59]. While challenging within Korea's healthcare environment, there is a growing need to provide patients with comprehensive information and involve them in treatment decisions [60].

3. SPC and EBV subtype

The IM type of SPC and EBV-positive GC share similar biological characteristics, particularly in terms of activated immune-related signaling pathway genes. Both subtypes demonstrate better prognosis compared to the same-stage tumors and limited benefit from chemotherapy. The performance of SPC has been validated in RCT samples (CLASSIC trial) [35], and it is currently being utilized in Korean clinical practice as a non-reimbursed test. Based on additional large-scale retrospective cohort results [23,36,37], SPC is now applicable to stage II/III GC according to TNM 8th edition criteria (It should be noted that the CLASSIC trial was conducted based on TNM 6th edition, and thus SPC was previously limited to stage II/III GC as defined by the 6th edition.). If the ongoing multicenter prospective validation study (PREDICT trial, NCT04487717) confirms these findings, SPC, like MSI status, is expected to become an additional biomarker that should be considered in guideline recommendations for determining the need for adjuvant chemotherapy after surgery.

Regarding EBV-positive GC, while its characteristics were initially confirmed in CLASSIC trial samples [38], subsequent studies have shown conflicting results [61,62]. Although the biological characteristics suggest similar outcomes, additional research and evidence will be necessary before implementing EBV status as a determinant for adjuvant chemotherapy decisions in clinical practice.

4. Clinicians' point of views: dilemma to treat or not to treat

From a clinician's perspective, the decision to omit adjuvant chemotherapy presents significant challenges. In the current practice environment where adjuvant chemotherapy has become standard for all stage II/III GC patients, the decision to withhold chemotherapy creates understandable anxiety about potentially exposing patients to increased risk of recurrence. Even with evidence suggesting that certain subtypes (e.g., MSI-H) show excellent prognosis without adjuvant therapy, translating population-based evidence to individual patient care creates considerable psychological burden. Clinicians may experience guilt if their patient, despite having favorable molecular features, experiences recurrence after omitting adjuvant therapy.

From the patient's perspective, receiving ineffective chemotherapy represents a significant burden. Patients endure treatment-related toxicities without therapeutic benefit, and in cases where the disease recurs despite chemotherapy, they suffer both the adverse effects and disease progression. Additionally, this approach has broader socioeconomic implications, creating unnecessary healthcare costs and insurance burden.

However, clinical practice already presents situations where universal application of adjuvant chemotherapy is challenging, such as in cases of advanced age (e.g., over 85 years), significant comorbidities, or when patients or families express preference against chemotherapy. The varying risk levels even within the same stage (II or III) further complicate treatment decisions.

Current guidelines provide uniform recommendations across stages II and III, primarily due to the design of previous landmark clinical trials [18,19]. However, emerging evidence shows that certain molecular subtypes, such as MSI-H or immune-enriched tumors, demonstrate excellent prognosis (> 90% 5-year survival) in stage II disease, comparable to stage I outcomes [37,38,54]. These findings suggest the potential for a more refined approach that integrates both anatomical staging and molecular features, potentially leading to more personalized treatment strategies.

Taken together, the evolution toward personalized treatment approaches requires several key elements: (1) enhanced risk stratification tools incorporating both clinical and molecular features, (2) comprehensive patient communication strategies, (3) implementation of shared decision-making processes, (4) institutional support systems for personalized treatment protocols. Despite the challenges of implementing personalized treatment approaches within the situation of the Healthcare system in Korea, we must move forward with careful consideration. The key is striking a delicate balance between de-escalation of therapy based on molecular evidence and ensuring appropriate patient selection with rigorous monitoring protocols. This paradigm shift demands careful consideration of both physician concerns regarding treatment optimization and patient perspectives regarding treatment decisions, while acknowledging the practical constraints of the healthcare environment.

Future Consideration

1. Neoadjuvant chemotherapy

In Asia, where radical gastrectomy with D2 lymphadenectomy has been well-established, adjuvant chemotherapy following surgery has been the standard treatment approach. However, there has been a growing interest in neoadjuvant chemotherapy for locally advanced GC. The recently updated PRODIGY trial demonstrated improved survival outcomes, including both disease-free and overall survival, compared with postoperative adjuvant chemotherapy [63,64]. Given the well-documented advantage of neoadjuvant chemotherapy in increasing R0 resection rates, this approach is likely to become a standard treatment option for clinically diagnosed lymph node or serosa positive disease.

However, this evolution in treatment strategy raises important considerations regarding molecular subtypes. Since the chemotherapeutic agents used in neoadjuvant and adjuvant settings are largely similar, there is concern that tumor subtypes known to be unresponsive to adjuvant chemotherapy might be disadvantaged by neoadjuvant treatment. In these cases, neoadjuvant chemotherapy could potentially worsen outcomes by delaying definitive surgery [53].

The case of MSI-H tumors warrants thoughtful consideration. While subgroup analysis from the PRODIGY trial showed comparable outcomes between adjuvant and neoadjuvant approaches, not surgery alone for MSI-H tumors [65], these findings need to be interpreted within the broader context of MSI-H tumor biology. Previous studies have shown that MSI-H tumors often demonstrate favorable outcomes with surgery alone [53-55], and their response to conventional chemotherapy may be limited [66,67]. These observations suggest that careful consideration may be needed when planning neoadjuvant chemotherapy for MSI-H tumors, and further investigation could help clarify optimal treatment strategies for this specific molecular subtype [68].

However, the situation is nuanced by the fact that MSI-H tumors are prime candidates for immunotherapy. While moderate-to-far advanced MSI-H GCs might theoretically benefit from neoadjuvant chemotherapy, such cases are relatively rare given that MSI-H tumors typically present at earlier stages. This scenario underscores the need for additional clinical trials specifically addressing the role of neoadjuvant therapy in molecularly defined subtypes.

These considerations highlight the growing complexity of treatment decision-making in the era of precision medicine and emphasize the need for molecular subtype-guided treatment strategies in both the adjuvant and neoadjuvant settings. Future clinical trials should incorporate molecular stratification to better define optimal treatment approaches for specific tumor subtypes.

2. Immune checkpoint inhibitors

The advent of ICIs targeting programmed death-1/PD-L1 has revolutionized cancer treatment, demonstrating remarkable long-term survival benefits in recurrent and metastatic solid tumors [69,70]. In GC, ICIs have already been established as first-line treatment for PD-L1–positive cases [71-73]. This success prompted investigation into their potential role as adjuvant therapy, expanding their therapeutic applications.

However, contrary to expectations, ICIs as adjuvant therapy in an unselected "one-size-fits-all" approach failed to demonstrate superiority of neoadjuvant and adjuvant chemotherapy pembrolizumab over conventional chemotherapy in GC [74]. This unexpected outcome may be attributed to several factors. Notably, tumors likely to respond to ICI, such as MSI-H or immune-enriched types (e.g., EBV or IM type of SPC), might have been adversely affected by conventional chemotherapy. In these cases, standard chemotherapy may have not only shown limited anti-tumor efficacy but potentially suppressed beneficial host immune responses [48].

In alignment with the principles of precision medicine, there is a clear need for additional clinical trials specifically targeting: PD-L1 positive tumors, MSI-H cases, and immune-enriched subtypes. Such molecularly guided trials would better evaluate the true potential of ICIs in the adjuvant setting for specific patient populations. This approach represents a more nuanced strategy that acknowledges the molecular heterogeneity of GC and the importance of patient selection in ICI response. Future studies should focus on identifying and validating predictive biomarkers to optimize patient selection for adjuvant ICI in GC.

3. ctDNA and minimally residual disease

The fundamental rationale for adjuvant chemotherapy lies in addressing potential minimally residual disease (MRD) following curative resection. A reliable method for detecting MRD would enable precise identification of patients who truly require adjuvant therapy, revolutionizing treatment decision-making.

This concept was elegantly demonstrated in CRC, where a landmark study showed that ctDNA status effectively stratified patients' need for adjuvant therapy [75,76]. In stage II/III CRC, patients with negative ctDNA showed identical outcomes regardless of adjuvant chemotherapy administration, while the benefit of adjuvant therapy was confined to ctDNA-positive patients. This represents a paradigm shift in selecting patients for adjuvant therapy based on molecular evidence of residual disease.

Similar study designs could be applied to GC, and results from such investigations are anticipated in near future [77-79]. However, several technical challenges need to be

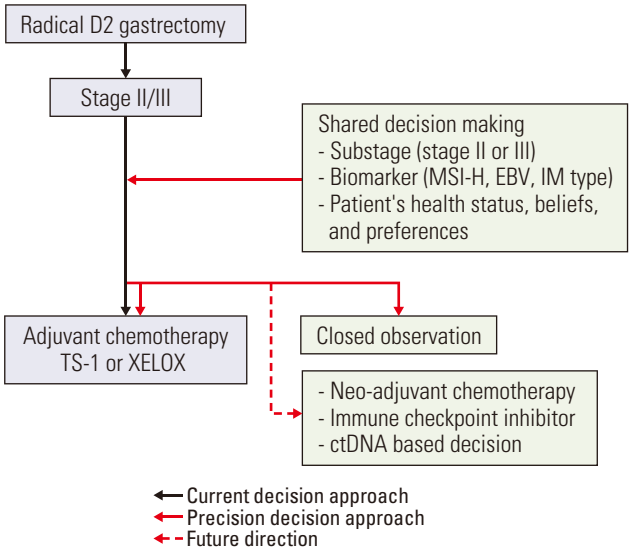

Fig. 1. Evolving decision-making in stage II/III gastric cancer: current practices and future direction. ctDNA, circulating tumor DNA; EBV, Epstein-Barr virus; IM, immune; MSI-H, microsatellite instability–high; XELOX, capecitabine plus oxaliplatin.

addressed: while the potential application of MRD detection in GC holds great promise, several significant challenges must be addressed [80]. The technical limitations of ctDNA analysis in GC present a primary concern, particularly the consistently low yield of ctDNA obtained from patients. Unlike some other cancer types, GC lacks widely prevalent molecular alterations that could serve as universal targets for detection. Moreover, GC typically demonstrates lower tumor purity compared to other cancer types, particularly in diffuse-type tumors where cancer cell cellularity is notably low [81]. This inherent characteristic could result in lower ctDNA yields, further complicating detection. This molecular heterogeneity, combined with the challenges of low tumor purity, poses substantial challenges for developing standardized MRD detection methods. Overcoming these challenges may be possible through personalized approaches to MRD detection in GC. Rather than relying on universal mutation panels, analyzing individual tumor-specific somatic alterations and developing customized libraries for each patient could prove more successful for ctDNA detection. This patient-specific approach, while more resource-intensive, may better capture the molecular heterogeneity of GC. The successful implementation of such personalized ctDNA analysis could transform the current paradigm of adjuvant therapy in GC, moving from a stage-based approach to a more precise, molecularly guided treatment strategy. While this represents a significant step forward in the personalization of GC treatment, careful validation through well-designed clinical studies is still needed.

As medicine has evolved, evidence-based practice has become a fundamental and prerequisite condition of modern healthcare. Driven by advances in genomic analysis technologies, we are now moving toward personalized treatment based on individual tumor characteristics, and further advancing toward comprehensive care that considers each patient's unique characteristics and environmental factors (Fig. 1).

The field of genomic analysis has progressed so rapidly that next-generation sequencing is no longer "next generation." We have advanced from bulk to single-cell sequencing, and now to spatial genomics and 3D spatial imaging, which capture the precise location of individual cancer cells and their interaction with neighboring cells and extracellular matrix [82]. These technological advances will deepen our understanding of cancer biology and its complexity.

GC remains a global health burden beyond Asian and Korean disease. This presents both a responsibility and an opportunity—this is our mission, and no one else will undertake it on our behalf. As Sir Isaac Newton once said, "*If I have seen further, it is by standing on the shoulders of giants*." Our continued efforts will contribute to building these giants' shoulders even higher, and in the near future, our successors will stand upon them to see even further, ultimately realizing precision cancer medicine beyond adjuvant therapy for GC. The journey toward precision medicine in GC is not just about adopting new technologies or implementing existing knowledge; it represents our commitment to advancing medical science to cure disease that significantly impacts our society.

Author Contributions

Conceived and designed the analysis: Yun JH, Choi YY, Cheong JH.
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Contributed data or analysis tools: Yun JH, Choi YY, Cheong JH.
Performed the analysis: Yun JH, Choi YY, Cheong JH.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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