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Letter to the Editor

Reply: Comment on The Necessity of Guidance: Optimizing Adjuvant Therapy for Stage II/III MSI-H Gastric Cancer Through the Interplay of Evidence, Clinical Judgment, and Patient Preferences

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▸ See the letter "The Necessity of Guidance: Optimizing Adjuvant Therapy for Stage II/III MSI-H Gastric Cancer Through the Interplay of Evidence, Clinical Judgment, and Patient Preferences" in volume 24 on page 243.

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Dear Prof. Geum Jong Song and Prof. Yoon Young Choi,

We sincerely appreciate the thoughtful and detailed letter from Song and Choi [1] emphasizing the need for guidance in the management of stage II/III gastric cancer (GC) with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) tumors. Your insights into the evolving recommendations for (neo)adjuvant therapy, particularly the updates from the European Society of Medical Oncology (ESMO) and the Chinese Society of Clinical Oncology (CSCO), are invaluable as we continue to refine the Korean Practice Guidelines for Gastric Cancer [2].

As mentioned in your letter to the editor, several guidelines provide recommendations on (neo)adjuvant therapy before and/or after surgical resection for resectable dMMR/MSI-H GC [3-5], which has a favorable prognosis compared to mismatch repair proficient/microsatellite stable disease [6]. The National Comprehensive Cancer Network (NCCN) guidelines (Version 4.2024) recommend that perioperative immune checkpoint inhibitors (ICIs) or surgery alone should be considered in consultation with a multidisciplinary team for patients with dMMR/MSI-H tumors (category 2A) [3]. The ESMO guidelines (v1.3 June 2024) state that adjuvant chemotherapy should not be recommended to patients with MSI-H GC who have undergone curative surgery (level of evidence IV, grade of recommendation D) [4]. The CSCO guidelines do not grade the recommendations for resectable dMMR/MSI-H GC patients; however, based on previous meta-analyses and retrospective studies, the guidelines suggest that (neo) adjuvant treatments such as immunotherapy in clinical trial settings may be considered after a detailed discussion with the patient, while options for postoperative observation

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or chemotherapy are simultaneously considered [5]. These recommendations are based on meta-analyses and retrospective studies on (neo)adjuvant chemotherapy in the dMMR/MSI-H subgroup [7-9]. In a large retrospective study involving patients with pathologic stage II/III GC (n=1,990; 8.5% MSI-H), adjuvant 5-fluorouracil (5-FU)-based chemotherapy failed to improve disease-free survival (DFS) in patients with MMR/MSI-H tumors [7]. In another retrospective study involving pathologic stage II/III GC patients (n=1,276; 8.2% MSI-H), the authors found that patients with dMMR/MSI-H tumors who did not receive adjuvant chemotherapy exhibited superior overall survival (OS) [8]. Pietrantonio et al. [9] conducted a multinational, individual patient data meta-analysis of the MAGIC, CLASSIC, ARTIST, and ITACA-S studies. Among the included patients, those with MSI-H GC (n=1,556; 7.8% MSI-H) did not benefit from (neo)adjuvant chemotherapy plus surgery compared to surgery alone (5-year DFS: 70% vs. 77%; 5-year OS: 75% vs. 83%). In the most recent large-scale meta-analysis including 23 studies (n=22,011; 9.8% MSI-H), (neo)adjuvant chemotherapy did not significantly reduce the risk of death or relapse in patients with MSI-H GC [10]. Conversely, another recent meta-analysis and retrospective study focusing solely on adjuvant chemotherapy for locally advanced dMMR/MSI-H GC suggested that adjuvant chemotherapy is beneficial in terms of OS [11,12]. Therefore, as you mentioned, multidisciplinary discussions among experts and evidence-based comments on the value of chemotherapy in adjuvant and/or neoadjuvant settings are necessary in routine clinical practice for patients diagnosed with locally advanced dMMR/MSI-H GC. Moreover, the efficacy of (neo)adjuvant chemotherapy in stage II/III GC patients with dMMR/MSI-H tumors may be an important clinical issue, considering that dMMR/MSI-H is more prevalent in older patients and those with an early-stage disease [9,12], which raises concerns about the use of cytotoxic chemotherapy in real clinical practice.

As you have noted, previous meta-analyses that informed current guidelines were based on data extracted from a small subset of patients with MSI-H GC in several pivotal adjuvant and/or neoadjuvant chemotherapy trials. These studies also featured significant heterogeneity in terms of surgical approaches (D1 vs. D2), treatment strategies (neoadjuvant vs. adjuvant chemotherapy), and regional differences (European vs. Asian populations). Furthermore, more recent evidence supports the use of (neo)adjuvant ICIs, including in patients with dMMR/MSI-H GC [13-17], although data on dMMR/MSI-H subgroups in randomized phase 3 trials have not been reported [14-17]. Therefore, we believe that a better designed meta-analysis of cytotoxic 5-FU-based chemotherapy and results from latest clinical trials on immunotherapy are required to provide clearer guidelines for (neo)adjuvant therapy in patients with MSI-H GC.

For the updated 2024 Korean Practice Guidelines for Gastric Cancer, we shall consider expert consensus and provide recommendations based on previously reported study results. Moving forward, we are committed to plan for a well-structured key question, conduct a meta-analysis, and survey patient preferences for the 2026 Korean Practice Guidelines for Gastric Cancer. This will enable the development of evidence-based recommendations specifically for resectable advanced GC with MSI-H in Asian patients, tailored to the unique characteristics of our population.

We appreciate your dedication to advancing the field and look forward to incorporating these insights into future guideline updates to better support clinicians and patients in making informed treatment decisions.

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