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Letter to the Editor

Refining Patient Selection for CRS and HIPEC in Gastric Cancer: Reflections on the GASTRIPEC-I Trial

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To the Editor,

We read with great interest the recently published GASTRIPEC-I trial – the first randomized study specifically evaluating cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer patients with synchronous peritoneal metastases (1). This trial's rigorous design, including mandatory preoperative chemotherapy and quantitative peritoneal cancer index (PCI) assessment, set a high standard for investigating locoregional therapy in a setting historically marked by dismal outcomes. Patients with gastric cancer and peritoneal metastasis face a median overall survival (OS) of only ~4–10 months even with modern systemic therapy (2,3). Such poor prognoses have spurred exploration of intraperitoneal chemotherapy strategies. For example, the phase III PHOENIX-GC trial in Japan tested intraperitoneal paclitaxel combined with systemic chemotherapy and, while it did not achieve a significant OS benefit, it hinted at improved outcomes in patients without ascites (4). Against this backdrop, the GASTRIPEC-I trial provides crucial prospective data on the added value of HIPEC after maximal surgical cytoreduction.

In GASTRIPEC-I, the authors reported no significant difference in OS between the two arms (median ~14.9 months in both) (1). However, notably, progression-free survival (PFS) was significantly prolonged in the HIPEC arm (median 7.1 vs 3.5 months, P = .047) (1). We consider this secondary endpoint to be of particular clinical relevance. Slowing peritoneal disease progression not only preserves quality of life but also provides a window for additional systemic therapies. The lack of observed OS improvement despite a PFS benefit may reflect the natural history of peritoneal metastases – once systemic or distant progression occurs, the initial locoregional control advantage of HIPEC might be overcome. A parallel can be drawn to the REGATTA trial, which found no survival benefit to palliative gastrectomy in metastatic gastric cancer (peritoneal disease left in situ) (5). That trial underscored that debulking the primary tumor alone is insufficient when diffuse metastases remain; similarly, GASTRIPEC-I suggests that even with aggressive peritoneal-directed therapy, long-term OS improvements are elusive unless systemic disease control is achieved. Importantly, HIPEC in GASTRIPEC-I did not increase perioperative morbidity or mortality, confirming its safety in this high-risk cohort (1). Prior concerns about added toxicity with HIPEC – for instance, meta-analyses suggested higher complication risk when HIPEC was added (3) – were not borne out in this randomized setting, as Grade ≥3 adverse event rates were statistically similar between arms. This safety profile is encouraging and aligns with other recent data showing HIPEC can be delivered without excessive toxicity in experienced centers (6).

Several factors likely contributed to the absence of an OS benefit. Nearly half the patients had PCI ≥7 and ~40% presented with malignant ascites – both well-established adverse prognostic indicators (2,7). In fact,

extensive disease burden at presentation greatly limits the efficacy of any locoregional approach. For instance, a German multicenter registry study of CRS±HIPEC reported median OS of 18 months for patients with PCI 0–6, versus only 5 months when PCI ≥16 (10). Similarly, in a Spanish series, patients with PCI <7 achieved a 5-year survival of ~47%, whereas those with higher PCI had 0% five-year survival (6). Ascites is an indicator of diffuse peritoneal spread and portends a very poor outcome – often a surrogate for PCI at the upper extreme. The PHOENIX-GC trial findings underscore this point: in that study, patients receiving intraperitoneal chemotherapy trended toward longer OS overall (17.7 vs 15.2 months), but a significant survival benefit emerged only after adjusting for ascites presence (4). Taken together, these observations suggest that including many patients with bulky peritoneal disease or ascites in GASTRIPEC-I likely diluted the potential survival impact of HIPEC. Indeed, more than half of the enrolled patients never even underwent the intended CRS/HIPEC surgery (progressing or being deemed inoperable after neoadjuvant therapy), which further confounded the intent-to-treat survival analysis (1). We applaud the investigators' transparency in reporting these challenges, as they highlight the importance of meticulous patient selection.

Notably, updated guidelines now reflect a more conservative approach to patient selection. The National Comprehensive Cancer Network (NCCN) 2025 guidelines recommend considering CRS ± HIPEC for gastric cancer with peritoneal metastases only if the disease burden is limited (PCI ≤10) and responsive or stable after systemic therapy (8). This threshold is slightly higher than the PCI ~6–7 cut-offs suggested by registry analyses, but it underscores the same principle – volume of disease matters. We suspect that the lack of OS benefit in GASTRIPEC-I is partly due to inclusion of patients above this optimal threshold. Had the study been restricted to PCI ≤10 (and no significant ascites), a trend toward improved OS might have emerged. Indeed, a large French propensity-score analysis (CYTO-CHIP study) demonstrated an OS benefit with CRS+HIPEC, but that too was driven by patients with lower tumor burden and complete cytoreduction (6). In light of this, future trials would ideally stratify or limit enrollment by PCI group. We are encouraged that ongoing studies are moving in this direction. For example, the PERISCOPE II phase III trial in Europe is enrolling only patients with limited peritoneal dissemination to test CRS+HIPEC vs chemotherapy alone (7). Likewise, in East Asia, strategies like conversion therapy with iterative intraperitoneal chemotherapy (NIPS) or pressurized intraperitoneal aerosol chemotherapy (PIPAC) are being explored to downstage peritoneal disease before surgery (6).

Beyond tumor burden, emerging evidence suggests that host factors and nutritional status significantly influence outcomes after aggressive surgery. For instance, Gül et al. recently showed that a low preoperative Cachexia Index independently predicts severe postoperative morbidity in gastric cancer patients undergoing

gastrectomy (9). Frailty, systemic inflammation, and nutritional deficits likely become even more consequential when adding a demanding procedure like CRS+HIPEC. Therefore, an optimal candidate is not only one with limited tumor burden but also one with sufficient physiological reserve. Integrating such host-related parameters (e.g. sarcopenia indices, performance status, inflammatory markers) into selection criteria could further improve outcomes by avoiding non-beneficial extreme interventions in frail patients.

In conclusion, the GASTRIPEC-I trial is a landmark study that underscores the crucial importance of proper patient selection in applying CRS and HIPEC for gastric cancer with peritoneal metastases. While HIPEC did not extend overall survival in an unselected cohort, it significantly delayed disease progression without adding undue toxicity – an achievement that should not be overlooked. We believe that patients with truly limited peritoneal disease (PCI ≤10, ideally ≤6) and absence of malignant ascites are the most promising subset in whom CRS+HIPEC may confer meaningful oncologic benefit. Selecting such patients (likely after a favorable response to induction chemotherapy) is now supported by both clinical data and consensus guidelines. Moving forward, trials focusing on this refined population – potentially combined with novel systemic agents – are warranted to clarify the ultimate impact on survival. We commend Rau et al. for their meticulous work and contribution. The GASTRIPEC-I trial provides a valuable foundation of evidence and, importantly, a cautionary lesson that “more” treatment is not always better unless given to the right patient.

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