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CONSENSUS STATEMENT

Consensus guideline for the management of gastric cancer with synchronous peritoneal metastases

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Abstract

Background: Gastric cancer with synchronous peritoneal metastases is a debilitating disease with limited treatment options. This article describes an update of the 2018 Chicago Consensus guidelines addressing the management of gastric cancer with synchronous peritoneal metastases in line with the most recent evidence.

Methods: A clinical management pathway was updated through two rounds of a Delphi consensus to assess agreement levels with pathway blocks. Supporting evidence underwent evaluation using a rapid literature review. Meta-analyses were performed as appropriate.

The collaborators for the Peritoneal Surface Malignancies Consortium Group for this article are listed in the Supporting Materials. These expert leaders had critical input into this article and approve its publication.

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Results: Overall, the level of evidence in this disease subset was low to moderate. Of 124 participants in the first round, 109 (88%) responded in the second round. Strong consensus (>90%) was achieved in six of eight blocks (75%) in rounds 1 and 2. A multidisciplinary preoperative assessment and diagnostic laparoscopy should be offered to all patients, whereas patients with a high burden of disease or progression should undergo nonsurgical management. Patients with stable/responsive disease and a low peritoneal carcinomatosis index should subsequently be offered treatment with regional therapeutic interventions and cytoreductive surgery. In patients who are cytology-positive, systemic therapy can be used to convert them to cytology-negative, with subsequent surgery offered according to the patient's goals of care. Meta-analysis of observational and randomized control trials revealed a survival benefit with the addition of intraperitoneal chemotherapy to cytoreductive surgery (hazard ratio, 0.52).

Conclusions: The consensus-driven clinical pathway for gastric cancer with synchronous peritoneal metastases offers vital clinical guidance for practitioners. There is a growing body of high-quality evidence to support management strategies, and future clinical trials are eagerly awaited.

KEYWORDS
cytoreductive surgical procedures, gastric cancer, guidelines, peritoneal surface malignancies, peritoneal surface neoplasms

INTRODUCTION

Gastric cancer is the fifth leading cause of cancer mortality worldwide and was responsible for just under 1 million new cases in 2022, ranking fifth for incidence.[1] In the United States, up to 65% of patients present with stage III or IV disease; and, in those with metastatic disease, the peritoneum is a common site of metastatic spread.[2,3] Traditionally, stage IV gastric cancer is not a surgical disease. Although advancements in systemic and regional therapeutic interventions hold promise, there are several matters of equipoise and variations between institutional practices regarding gastric cancer with peritoneal metastases (GCPM).[4]

Considering this lack of standardization, consensus guidelines on the management of GCPM were created in 2018 as part of the Chicago Consensus Working Group.[5] Since the inception of these guidelines, there have been major advancements in systemic and regional interventions for GCPM and cytology-positive gastric cancer. Herein, we present updated recommendations, including a revised clinical management pathway, supported by evidence from rapid systematic reviews.

MATERIALS AND METHODS

This initiative was part of a national multidisciplinary consortium group process aimed at streamlining guidelines for the care of patients with peritoneal surface malignancies (PSMs). The consensus and rapid review methodology has been described in detail in a separate article and can be found in the Supporting Information (Supporting Methods).[6] Major components are summarized below.

Consensus group structure

In brief, seven experts were appointed to lead the section (the Gastric Cancer Working Group), and each pathway iteration was reviewed by the Steering Committee. Two core group members (S.D.B. and V.V.B.) coordinated the effort. A team of nine surgical residents and surgical oncology fellows conducted the rapid reviews.

Modified Delphi process

The original Chicago Consensus guidelines were first reviewed and revised by the Gastric Cancer Working Group and the consortium leadership to align with evidence published since the last consensus. Recommendations were revised using a Delphi method across the entire PSM Consortium group by soliciting degrees of agreement with each recommendation on a five-point Likert scale using a Qualtrics survey. A threshold of 75% was set to retain a given guideline subject, and 90% was required to finalize a guideline.

Two Delphi rounds were conducted; at the conclusion of each, the results of the previous round were collected and analyzed, and revisions were proposed by the Disease Site Working Groups. Voting

eligibility was first screened by participation in both Delphi rounds; only those who voted in Delphi round 1 qualified to vote in Delphi round 2. Levels of evidence were assigned to pathway blocks. Simultaneously, a summary table outlining first-line systemic therapies for GCPM was generated in conjunction with medical oncologists in the Working Group.

Rapid review of literature

A MEDLINE search using PubMed between January 2000 and August 2023 addressed the following key questions:

1. Key question 1: What is the optimal management strategy for peritoneal cytology positive gastric cancer without clinically evident peritoneal carcinomatosis?[7]
2. Key question 2: What regional (intraperitoneal) therapeutic interventions are effective in the management of GCPM?[8]

Search strategies (see Table S11) were peer-reviewed by a medical librarian specialist, and the reviews were registered with PROSPERO before data extraction (PROSPERO registration numbers CRD42023466035 and CRD42023466032). The Covidence platform facilitated title and abstract screening, full-text review, data extraction, and quality assessment using the Cochrane Risk of Bias 2.0 tool for randomized controlled trials (RCTs; see Figure S1) and the Newcastle–Ottawa Scale for nonrandomized studies, respectively (see Tables S9 and S10).[9–12] References from relevant articles were searched and reviewed manually by two reviewers. The review was conducted in alignment with recommendations from the Cochrane Rapid Review Methods Groups and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[13]

External perspectives

Patient advocates within the Hope for Stomach Cancer (STOCAN) organization reviewed the treatment pathway and offered insights regarding clinical trial enrollment, research outcomes, and available resources for patients with GCPM. In addition, members of the Peritoneal Surface Oncology Group International (PSOGI) Executive Council were invited to appraise the second version of the pathway. Their comments were consolidated to evaluate alignment with global practices regarding the management of GCPM.

Systemic therapy recommendations

A section on systemic therapies for GCPM was included under block 8 and summarized as a table. This was drafted collaboratively with the working group with particular assistance from the medical oncologists in the group.

RESULTS

Pathways

Two pathways were initially proposed, one for synchronous GCPM, and the other for metachronous GCPM. However, the latter was not established because of a lack of evidence. In total, 124 experts and thought leaders voted on the clinical pathway for synchronous GCPM, of which 109 (88%) responded in the second Delphi round. The group included 93 (75%) surgical oncologists, 16 (13%) medical oncologists, 11 (9%) pathologists, and four (3%) experts from other specialties. Given the low-to-moderate quality of existing evidence, many recommendations were based on expert opinion. This pathway was divided into eight main blocks (Figure 1). The results of two rounds of modified Delphi processes are summarized in Tables 1 and 2. Overall, strong consensus (>90%) was achieved in six of eight blocks (75%) in rounds 1 and 2.

Rapid review

The first key question regarding cytology-positive gastric cancer revealed 799 abstracts for screening. Of these, we considered 81 for full-text review and 21 for data extraction. For the second key question about GCPM, we screened 2637 abstracts, of which we considered 380 for full-text review and 27 for data extraction. Relevant exclusion criteria are detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 2). Meta-analysis was performed wherever feasible.

Summary of major changes

The current guidelines, building upon the 2018 Chicago Consensus, feature a more rigorous methodology involving a wider range of experts and patient advocates. They emphasize a thorough preoperative assessment encompassing genetic profiling, psychosocial support, nutrition, fertility considerations, and collaboration with patient advocacy groups. In contrast to the previous guidelines, which recommended direct initiation of standard chemotherapy for 6 months before restaging, the current pathway advocates for a diagnostic laparoscopy to evaluate the peritoneal carcinomatosis index (PCI). For patients with a PCI >7, systemic therapy, clinical trials, or supportive care are recommended; whereas those with low a PCI or positive cytology are advised to undergo systemic therapy with an intent for restaging. After restaging, the pathways converge, with patients who progress receiving additional systemic therapy or supportive care based on functional status and goals; of note, a second laparoscopy may be used for re-staging after

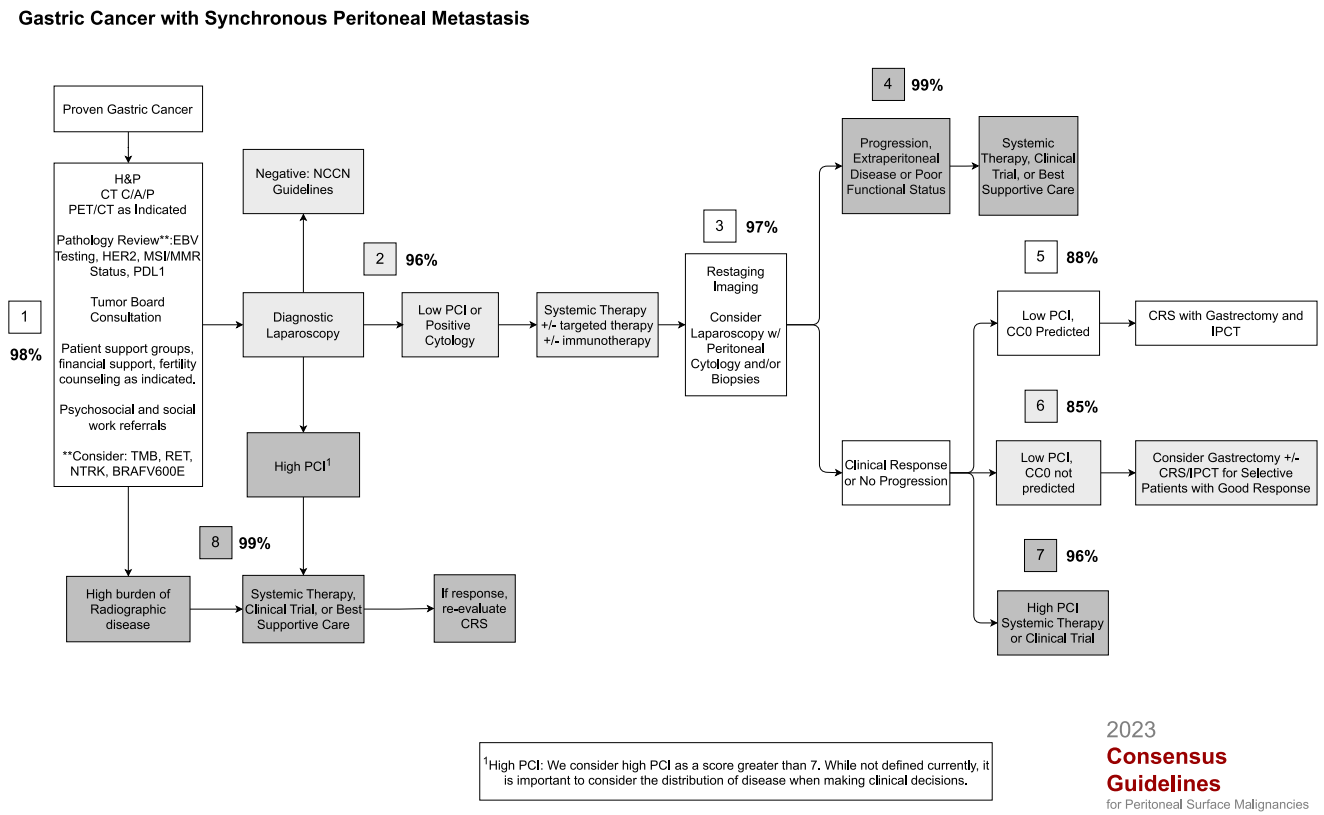

FIGURE 1 Gastric cancer with synchronous peritoneal metastasis—clinical pathway. Pathway components are designated by blocks, indicating critical areas of clinical decision making. Percentages adjacent to block numbers indicate agreement levels from the second Delphi round. ± indicates with or without; CC0, complete cytoreduction; CT, computed tomography; CT C/A/P, computed tomography of chest/abdomen/pelvis; CRS, cytoreductive surgery; EBV, Epstein–Barr virus; H&P, history and physical examination; IPCT, intraperitoneal chemotherapy; MMR, mismatch repair; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NIPS, neoadjuvant intraperitoneal and systemic therapy; PCI, peritoneal carcinomatosis index; PET, positron emission tomography; TMB, tumor mutational burden.

TABLE 1 Delphi round 1 agreement table.

	No. of participants						
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Total	Percentage
Block 1	90	32	1	1	0	124	98%
Block 2	86	34	3	1	0	124	97%
Block 3	84	36	4	0	0	124	97%
Block 4	89	30	4	1	0	124	96%
Block 5	64	46	9	4	1	124	89%
Block 6	59	44	14	6	1	124	83%
Block 7	79	34	7	3	1	124	91%
Block 8	78	36	7	3	0	124	92%

treatment for scenarios in which the response to treatment is unclear, but we have not made this requisite. Regional interventions are recommended for patients with stable/responsive disease, including intraperitoneal port-based therapies and cytoreductive surgery (CRS) in cases where complete cytoreduction (CC0) is anticipated. The latter is elaborated upon further with a meta-analysis comparing CRS plus intraperitoneal chemotherapy (IPC) versus CRS alone.

Block 1 (agreement: Round 1, 98%; round 2, 98%)

Preoperative evaluation entails a thorough history and physical examination, including an exploration of the patient's social history, financial environment, and support networks. After upper endoscopy and subsequent staging, a computed tomography scan of the abdomen and pelvis with intravenous contrast should be performed

TABLE 2 Delphi round 2 agreement table.

	No. of participants						
	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Total	Percentage
Block 1	99	8	0	2	0	109	98%
Block 2	96	9	3	1	0	109	96%
Block 3	99	7	3	0	0	109	97%
Block 4	103	5	1	0	0	109	99%
Block 5	89	7	9	2	2	109	88%
Block 6	76	17	12	2	2	109	85%
Block 7	94	11	2	2	0	109	96%
Block 8	101	7	1	0	0	109	99%

to identify the extent of peritoneal disease and tumor burden[14]; 18-fluorodeoxyglucose-positron emission tomography is reserved for patients with equivocal findings on computed tomography imaging or patients with clinical indications of metastatic disease and otherwise negative imaging.

High-risk features in advanced gastric cancer, such as tumor size, depth of serosal invasion, perforation, involvement of multiple anatomic regions, and lymph node positivity, warrant close attention because occult peritoneal metastases may be present in over one third of patients.[15] In addition, poor prognostic indicators identified on imaging, such as extensive lymph node metastases and obstructive lesions in the biliary, urinary, or gastrointestinal tracts, may necessitate alternative management strategies, as outlined in block 8.[16]

Any pathology specimens obtained should be tested for Epstein–Barr virus, *HER2*, microsatellite instability/mismatch-repair status, and *PD-L1*.[17–20] Although tumor markers are not involved directly in the decision for surgical treatment, they inform the overall management strategy and expected response rates for surgical interventions. Markers such as *HER2*, *PD-L1*, *CLDN18.2*, and microsatellite instability/mismatch-repair status help define underlying tumor biology and systemic therapy strategy, but their role in guiding surgical management is evolving. For example, in patients who are *HER2*-positive, surgeons may elect to operate less often because some patients have durable responses to targeted therapies. In contrast, blood-based tumor markers like carcinoembryonic antigen and cancer antigen 19-9 are often used to measure the burden of disease, but their use in GCPM is heterogeneous. Some surgeons might interpret a rapid increase in these markers to indicate more severe systemic disease and caution definitive surgical treatment. With the increasing adoption of circulating tumor DNA as a measure of disease burden, these tumor markers will possibly become less favorable in the coming years.

Establishing a comprehensive patient support network is also highly encouraged and includes patient support, counseling, social work referrals, and early palliative care, as indicated. Formal evaluation by a multidisciplinary team or tumor board is critical to guide appropriate steps in management.

Block 2 (agreement: Round 1, 97%; round 2, 96%)

A diagnostic laparoscopy is recommended to determine the PCI if preliminary workup reveals low radiographic burden of disease.[21] Washings should be considered in all patients with suspected peritoneal metastases on cross sectional imaging or biopsy confirmed from an outside hospital who are undergoing a staging laparoscopy for peritoneal biopsies. There is heterogeneity in how washings are conducted, but most groups are split into high-volume or low-volume washings. Low-volume washings are performed by instilling 200 milliliters of crystalloid solutions in several locations of the abdomen (right upper quadrant, left upper quadrant, and the pelvis), followed by suctioning of 50 milliliters in each location. High-volume washings involve the instillation of 1liter of crystalloid solution, followed by agitation and then removal of approximately 750 milliliters for examination.

Cytologic examination of peritoneal lavage fluid is a key prognostic factor in the classification of gastric carcinoma. Positive cytology is a poor prognostic factor.[22] In patients with any M1 disease or positive cytology, National Comprehensive Cancer Network guidelines recommend palliative management. However, our consensus and pathway recommend proceeding to systemic therapy.

Cytology-positive patients

In patients who are cytology-positive with low PCI (≤7), management remains controversial because positive cytology remains a poor prognostic indicator. Several groups have demonstrated that surgery plus IPC has therapeutic benefit for cytology-positive patients compared with standard therapy or surgery alone (see Tables S3 and S4).[23–36] In addition, converting patients from positive to negative cytology greatly improves their survival. Given this evidence, initiation of systemic therapy with the intent of restaging is recommended as the first step for patients who have positive peritoneal cytology and/or low PCI.

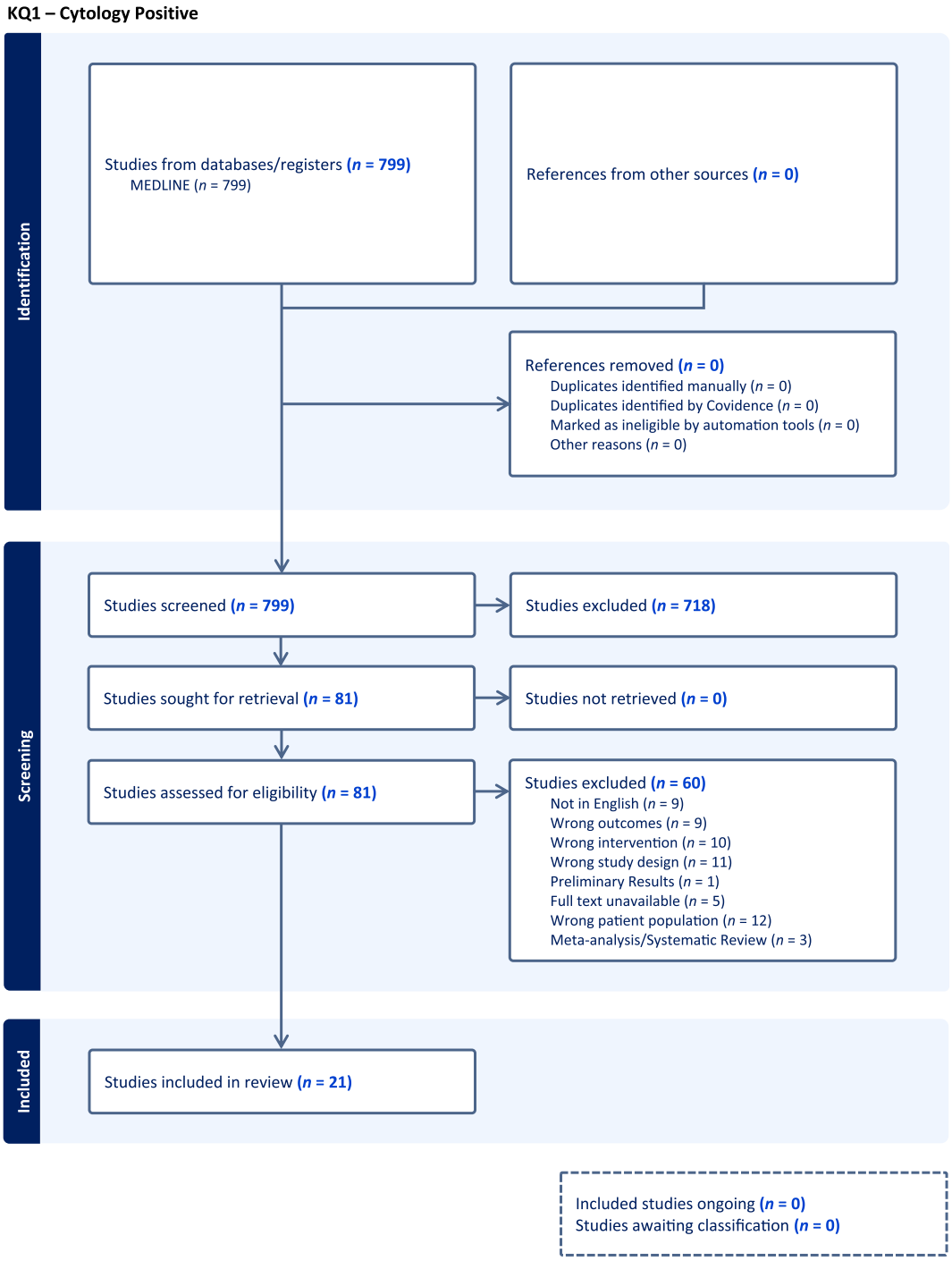

FIGURE 2 PRISMA flow diagrams for two key questions regarding GCPM. GCPM indicates gastric cancer with synchronous peritoneal metastases; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Peritoneal carcinomatosis index cutoff

Further disagreement exists about the optimal cutoff for low versus high PCI, which are often institution-dependent. A systematic review and meta-analysis published in 2015 reported that the median survival changes significantly above a PCI of 12.[37] The strongest trial representing these results is by Glehen et al., who demonstrated that the best results in terms of survival are in patients with a PCI ≤6.[38]

More recently, the CYTO-CHIP study (ClinicalTrials.gov identifier NCT03253939) further demonstrated that completeness of CRS was closely linked to tumor burden (PCI).[39] That trial indicated that long-term survival was rare in patients with a PCI >13. The mean PCI was 7.2 in the CRS–hyperthermic intraperitoneal

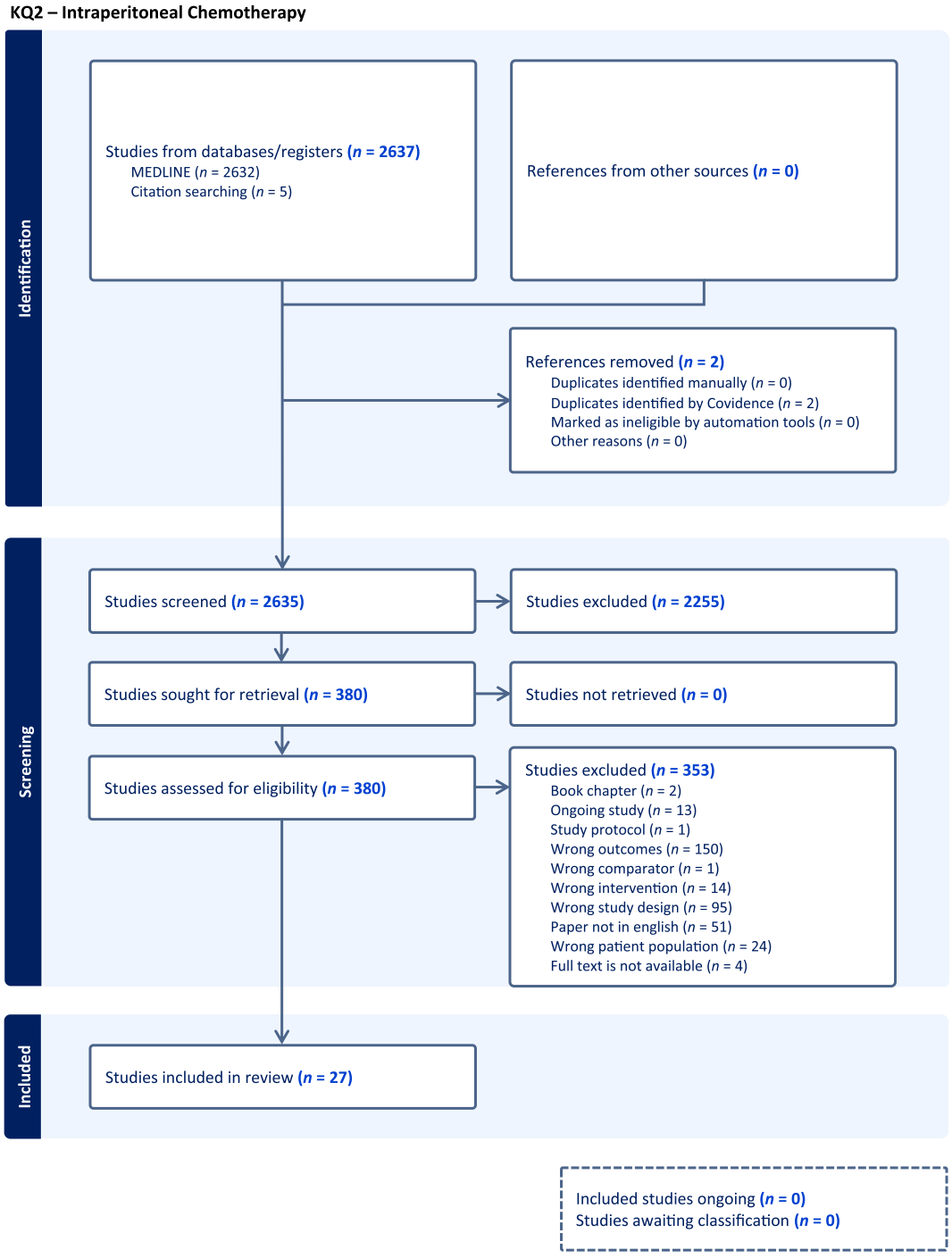

FIGURE 2 (Continued)

chemotherapy (HIPEC) group and 2.11 in the CRS-alone group. Ultimately, a PCI >7 was recommended for differentiating low versus high PCI to determine subsequent selection for regional therapeutic interventions. However, the anatomic distribution of peritoneal metastasis and histology should be incorporated into the decision-making process.[40] For example, a patient with PCI of 10 and signet ring cell gastric cancer should be advised against CRS given the poor prognosis associated with this histologic subtype.[41] In addition, a PCI cutoff of 10 might be used in patients with targetable biomarkers actionable by US Food and Drug Administration-approved drugs, such as HER2, MSI high, PD-L1–positive, and CLDN18.2.

Block 3 (agreement: Round 1, 97%; round 2, 97%)

Once systemic therapy has concluded, restaging should be performed using computed tomography and diagnostic laparoscopy with peritoneal washings and/or biopsies. Laparoscopy is the gold standard for determining disease response to therapy and may be used for restaging after treatment in scenarios in which the response to treatment is unclear, but we have not made this requisite.

Block 4 (agreement: Round 1, 96%; round 2, 99%)

In the presence of disease progression or poor functional status, regional therapeutic interventions are not recommended. Instead, further lines of systemic therapy, enrollment in a clinical trial, or supportive care should be initiated. Supportive care can include feeding access or relief of obstruction through surgical or endoscopic interventions; control of bleeding; antinausea medications; pain relief; initiation of palliative care if not already engaged; and hospice resources.

Block 5 (agreement: Round 1, 89%; round 2, 88%)

Recommendation

In patients with a PCI $\leq$7 and disease that is stable/responsive to chemotherapy, regional therapeutic interventions are recommended. These may include CRS with gastrectomy and D2 lymph node dissection, port-based IPC combined with systemic chemotherapy, and laparoscopic or open IPC.

Principles of surgery

The principles of surgery for patients with GCPM have largely been unchanged since the 2018 guidelines were published. CC0 cytoreduction remains the gold standard and is an independent predictor for overall survival (OS) in patients undergoing CRS for GCPM.[37] The extent of gastrectomy depends on tumor location and distribution; it has not been identified as an independent predictor of survival.[42,43] In patients who have locally advanced gastric cancer without peritoneal metastasis, a curative gastrectomy with D2 lymphadenectomy is the standard of care.[44]

CRS has emerged as an important treatment modality for patients with GCPM patients, as systemic therapies have limited effects on peritoneal carcinomatosis likely because of the blood–peritoneal barrier. The theory behind the efficacy of CRS is that debulking allows tumor cells to re-enter the proliferative phase of the cell cycle, potentially becoming more sensitive to antineoplastic agents. The goal of CRS is to remove all macroscopic disease, with the understanding that there is residual microscopic disease. This is referred to as a complete cytoreduction. A CC0 score indicates that no visible peritoneal seeding remains after cytoreduction. Frozen sections are typically not performed during CRS or for staging because a frozen section is often inaccurate in these settings. Patient selection remains crucial for CRS because the extent of disease as measured by the PCI can negate the benefit of surgery and IPC. A PCI cutoff for surgery of 7 should be used, as mentioned in block 2.

CRS plus chemotherapy versus chemotherapy alone

Several groups have evaluated whether CRS is superior to chemotherapy alone, but only two RCTs exist. The REGATTA trial (University Hospital Medical Information Network [UMIN] Clinical Trials Registry identifier UMIN000001012) examined whether CRS in combination with chemotherapy was superior to chemotherapy alone.[45] Conducted across three countries, the results failed to demonstrate an OS benefit for the surgical arm. This suggests that incomplete cytoreduction with residual metastatic disease does not confer a survival advantage. Some limitations include a failure to accrue patients and an unbalanced primary tumor location between groups. Because the trial included patients with extraperitoneal metastasis, it was not included in our rapid review.

The next trial was the GYMSSA trial (ClinicalTrials.gov identifier NTC00941655).[46] Conducted in the United States, patients were randomized to systemic chemotherapy or gastrectomy, CRS, HIPEC and systemic chemotherapy (the GYMS arm). The trial demonstrated an improved median OS with complete CRS-HIPEC compared with systemic chemotherapy alone (11.3 vs. 4.3 months). However, this trial failed to accrue the targeted sample size of 136 patients, precluding robust conclusions.

Five observational studies were included in the rapid review (see Table S6).[47–51] In 2016, Boerner et al. evaluated 38 consecutive patients with GCPM who received gastrectomy, CRS, and HIPEC and compared them with 27 patients who received chemotherapy with gastrectomy (PC-standard).[48] The authors observed that the CRS-HIPEC group had better overall, 1-year, 3-year and 5-year survival compared with the PC-standard group. In 2021, Canbay et al. evaluated 53 patients with cytology-positive or peritoneal metastases.[47] All patients underwent laparoscopic HIPEC followed by neoadjuvant intraperitoneal and systemic therapy. Of these, 34 patients went on to receive CRS and HIPEC, whereas 19 only underwent induction chemotherapy. The group that underwent CRS-HIPEC had improved OS compared with the chemotherapy-alone group (21.2 vs. 15.9 months). Most recently, Esen et al. demonstrated that patients undergoing CRS-HIPEC after neoadjuvant chemotherapy had improved OS compared with those who received chemotherapy only (19.7 vs. 6.8 months).[51]

CRS plus IPC versus CRS alone

In addition to evaluating whether the addition of CRS to chemotherapy improves outcomes in patients with GCPM, other groups

have examined the effect of intraperitoneal chemotherapy alongside CRS. Two RCTs exist in this space.

The first RCT was published in 2011 by Yang et al.[43] In their study, 68 patients with GCPM were randomized to either CRS alone ($n = 34$) or CRS-HIPEC ($n = 34$). Median survival was improved in the CRS-HIPEC group (11.0 vs. 6.5 months), with a nearly 70% extension of OS. It is worth noting that the median PCI for both groups was 15, which is above our recommended cutoff of 7–10. In addition, this study included patients with metachronous GCPM.

Although Yang et al. demonstrated improved survival with CRS-HIPEC, the GASTRIPEC-I trial (ClinicalTrials.gov identifier NCT02158988) demonstrated no difference in OS between CRS-HIPEC and CRS alone; there was also no difference in survival when comparing patients who had a PCI ≤6 with those who had a PCI of either 7–13 or ≥14.[52] In this study, patients were randomized to perioperative chemotherapy and CRS alone or CRS-HIPEC. Median survival was the same for both groups (14.9 months). Progression-free and metastasis-free survival were significantly better in the CRS-HIPEC group, however. This study ended prematurely because of slow recruitment; and, in 55 patients, treatment was stopped before CRS mainly because of disease progression and/or death. Importantly, 44% of patients in this study had a PCI ≥7, and 40% had ascites, both of which are known factors for a poor prognosis after CRS.

Aside from these two RCTs, there have been four observational studies evaluating CRS-HIPEC versus CRS alone (see Table S5). The CYTO-CHIP study was a propensity score analysis of patients with GCPM who underwent CRS-HIPEC or CRS-alone. The results indicated that patients who underwent CRS-HIPEC had improved OS (18.8 vs. 12.1 months) and recurrence-free survival (5.87% vs. 3.76%) compared with those who underwent CRS alone.[39] Rosa et al. reported that CRS-HIPEC performed as a cure or prophylaxis produced better 5-year disease-free survival compared with CRS alone.[53] In 2013, Wu et al. observed that CRS-HIPEC produced improved OS compared with CRS alone (15.5 vs. 10.4 months)[54]; of note, those authors specifically considered patients who had GCPM with ovarian metastasis. In 2022, Morgagni et al. observed that, in patients who received neoadjuvant chemotherapy, those who received CRS-HIPEC had improved OS compared with those who underwent CRS alone (46.7 vs. 14.4 months).[55]

Meta-analysis

We performed a meta-analysis comparing CRS-HIPEC versus CRS alone. Figure 3 illustrates the results of our meta-analysis evaluating hazard ratios (HRs), and Figure 4 illustrates median OS.[39,43,52–55] A benefit with the addition of HIPEC was observed in two observational studies (pooled HR, 0.52; 95% confidence interval [CI], 0.31–0.85) and in two RCTs (pooled HR, 0.52; 95% CI, 0.28–0.96) that reported HRs. With regard to median OS, neither the randomized trials nor the observational studies demonstrated a statistically significant improvement, although some individual trials studies did.

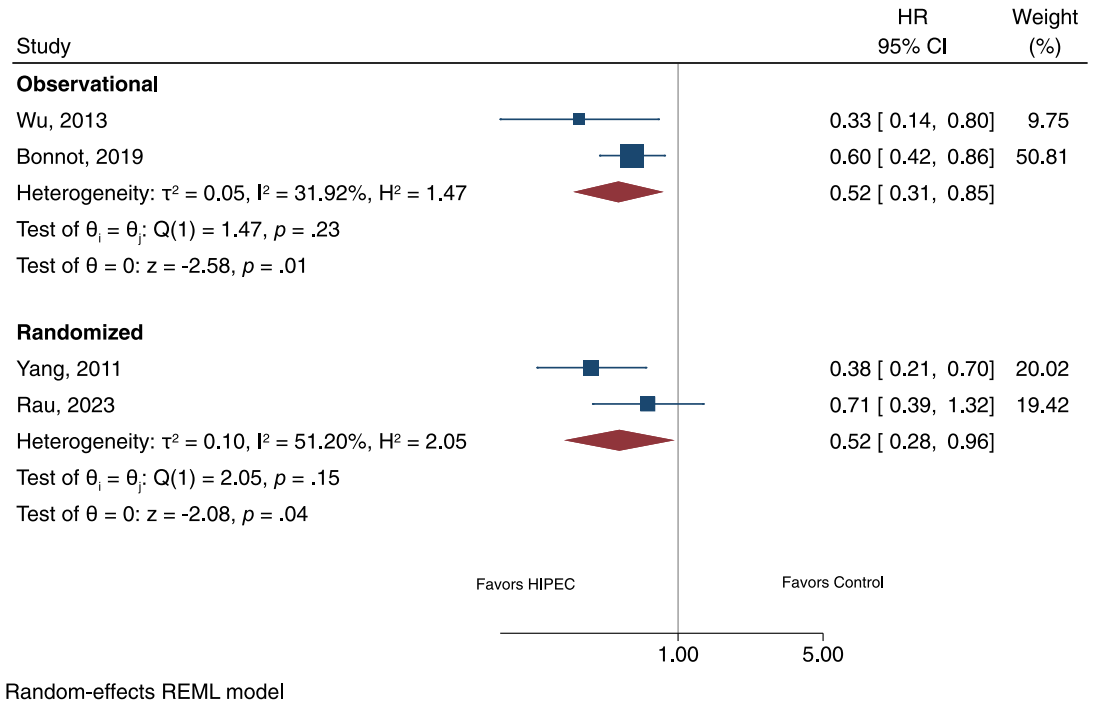

FIGURE 3 Meta-analysis for hazard ratios comparing CRS-HIPEC versus CRS alone. CI indicates confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; REML, restricted maximum likelihood.[39,43,52,54]

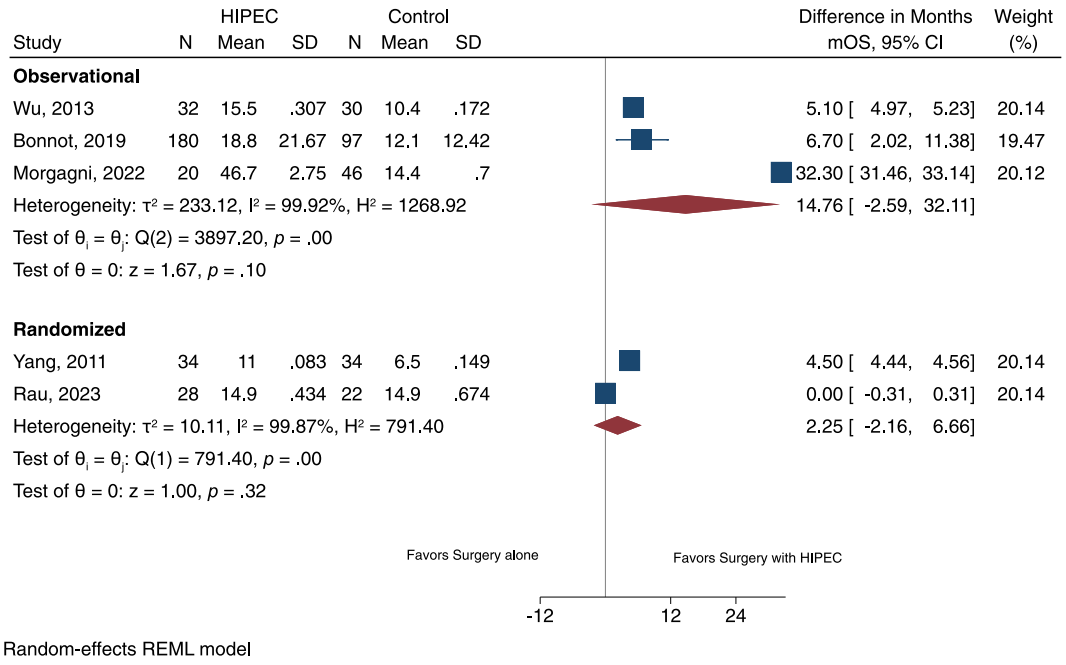

FIGURE 4 Meta-analysis for median overall survival comparing CRS-HIPEC versus CRS alone. CI indicates confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; mOS, median overall survival; REML, restricted maximum likelihood; SD, standard deviation.[39,43,52–55]

Block 6 (agreement: Round 1, 83%; round 2, 85%)

Recommendation

In patients with a PCI ≤ 7 but in whom complete cytoreduction is not predicted or whose functional status would not permit an extensive surgery (Eastern Cooperative Oncology Group performance status ≤2), intraperitoneal chemotherapy with or without additional systemic therapy may be considered.

Port-based approaches

The implantation of a peritoneal port is considerably less invasive than HIPEC, allows for repeated intraperitoneal administration of chemotherapy, and leads to high concentrations of chemotherapeutic drugs in the peritoneal cavity, allowing prolonged, direct exposure of free cancer cells or peritoneal deposits. The only RCT that examined the role of IPC is the PHOENIX-GC trial (Clinical Trials Registry identifier UMIN000005930), which demonstrated that there was no difference in survival between IPC plus systemic therapy versus systemic therapy alone.[56] However, subsequent analyses that adjusted for baseline ascites indicated potential benefits of the intraperitoneal regimen. In addition, there was a crucial imbalance in the amount of ascites that favored the systemic therapy-alone group.

Other observational studies have combined intraperitoneal and intravenous chemotherapy with cytoreduction and HIPEC. This is referred to as neoadjuvant intraperitoneal-systemic chemotherapy (NIPS) or bidirectional therapy (BIPSC). Table S8 provides the results of our rapid review for single-arm studies evaluating BIPSC. Notably, several groups have demonstrated that BIPSC prolonged survival in patients with GCPM.[57,58]

Several groups have compared BIPSC versus chemotherapy alone (see Table S7). Kim et al. observed that patients who underwent minimally invasive surgery after NIPS had a higher 2-year progression-free survival rate than those who only underwent NIPS (36.4% vs. 10.5%); of note, this was a propensity weighted study.[59] Lei et al. reported that patients who underwent BIPSC had better OS (15.9 vs. 10.8 months) and 3-year OS rates (18.4% vs. 10.1%) compared with those who received o chemotherapy alone.[60] In 2016, Yuan et al. demonstrated that patients who underwent BIPSC had better median OS (494 vs. 223 days) and progression-free survival (164 vs. 129 days) compared with those who received chemotherapy alone.[61] Lee et al. reported that patients who underwent laparoscopic HIPEC (L-HIPEC) plus NIPS followed by CRS-HIPEC had a better mean OS compared with those who only received CRS-HIPEC, chemotherapy, or palliative care.[62]

Laparoscopic HIPEC

Given the high morbidity associated with combining HIPEC and CRS, there has been an effort to administer HIPEC in a minimally invasive fashion to decrease the associated morbidity. First published by Yonemura and colleagues in 2016, other groups have demonstrated that L-HIPEC was well tolerated and could reduce PCI score.[63,64] Survival outcomes were examined by the Blumenthaler group of patients treated with L-HIPEC and reported in 2020.[65] Those authors reported that the median OS was 24.7 months in the L-HIPEC group

and 21.3 months in the standard care group. Of note, almost all studies evaluating the efficacy of L-HIPEC exclude patients with high-volume peritoneal disease. Although a survival benefit of L-HIPEC has yet to be demonstrated in small studies, larger, more strongly powered RCTs are necessary.

Pressurized intraperitoneal aerosol chemotherapy

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique for delivering drugs into the abdominal cavity as an aerosol under pressure. The theory behind PIPAC is that, by creating an artificial pressure gradient within the intraperitoneal cavity, there will be enhanced tissue uptake and distribution of the aerosolized drug within the abdominal cavity. In 2016, Nadiradze and colleagues performed a retrospective analysis of 60 PIPAC procedures applied in 24 consecutive patients with GCPM (average PCI, 16).[66] They observed that the median survival was 15.4 months, and nine patients had severe adverse events. Several other groups have discovered similar safety profiles of PIPAC (see Table S1). PIPAC has also been incorporated into BIPSC. Most recently, Casella et al. demonstrated that PIPAC used in a bidirectional approach is safe and feasible.[67] A phase 3 trial labeled PIPAC VEROne by the same group will evaluate secondary resectability rate and survival statistics (ClinicalTrials.gov identifier NCT05303714).

Block 7 (% agreement: Round 1, 91%; round 2, 96%)

CRS with IPC is not recommended for patients with PCI >7 despite stable/responsive disease. The survival benefit is reduced in these patients, and a risk of substantial morbidity exists with surgery and chemotherapy. Instead, these patients should be referred for further lines of systemic therapy, a clinical trial, or supportive care.

Block 8 (agreement: Round 1, 92%; round 2, 99%)

Recommendation

Armed with the last 15 years of research, we worked with medical oncologists in the Gastric Cancer Working Group to create first-line systemic therapy recommendations (Table 3). For more detailed therapies, National Comprehensive Cancer Network guidelines should be referenced. If, after diagnosis, patients are determined to have a high burden of disease on cross-sectional imaging and/or laparoscopy, they should be referred for further lines of systemic therapy, a clinical trial, or supportive care. If they respond to further lines of systemic therapy, candidacy for regional therapeutic interventions may be re-assessed based on discussions with a multidisciplinary team.

Systemic therapy

There are several challenges with systemic therapies for the treatment of GCPM. The presence of the plasma–peritoneal barrier and the poor blood supply of peritoneal metastases limit the therapeutic effect of systemic agents. In addition, patients with GCPM often develop complications, such as poor nutrition and decreased performance status, that hinder their ability to receive systemic therapy. The goals of palliative-intent systemic therapy include delaying disease progression and increasing OS, controlling cancer-related symptoms, and maintaining or improving quality of life. Several factors need to be considered when deciding on choices of systemic therapy, including treatment goals, burden of disease, molecular

TABLE 3 Systemic therapies for gastric cancer with peritoneal metastases.

Performance status	Therapy	Regimen
Karnofsky performance score ≥60% or ECOG ≤2	Systemic therapy[a]	*HER2 positive:* Fluoropyrimidine, oxaliplatin, and trastuzumab ± pembrolizumab *HER2 negative:* Fluoropyrimidine, oxaliplatin, ± nivolumab/pembrolizumab (PD-L1 CPS ≥5) *MSI-H/dMMR (independent of PD-L1 status):* Fluoropyrimidine, oxaliplatin, nivolumab/pembrolizumab *Claudin positive:* Fluoropyrimidine, oxaliplatin, and Zolbetuximab (pending FDA approval)
	Best supportive care[b]	Intended for patients who choose not to receive chemotherapy or for whom the risks of chemotherapy outweigh the benefits
Karnofsky performance score <60% or ECOG ≥3	Best supportive care	

Abbreviations: ±, with or without; CPS, cytoreductive surgery; dMMR, mismatch-repair deficiency; ECOG, Eastern Cooperative Oncology Group; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MSI-H, high microsatellite instability; PD-L1, programmed death ligand 1.

[a]Universal testing for microsatellite instability by polymerase chain reaction analysis/next-generation sequencing or mismatch repair by immunohistochemistry, along with HER2 and PD-L1 testing, should be complete if metastatic disease is documented/suspected.

[b]Measures should be taken to support the best possible quality of life for patients and their families. These measures include control of bleeding through interventional radiology, endoscopic treatment, external-beam radiation therapy, and gastrectomy in select patients and alleviation or bypass of obstructions; pain control; nausea and vomiting control.

characteristics, patients' performance status, organ function, and general tolerability to systemic therapy along with availability of treatment options. In general, patients with GCPM are included in most systemic therapy trials for metastatic or stage IV gastric cancer. However, outcomes of GCPMs compared with other sites of distant metastases, such as the liver or para-aortic lymph nodes, are not reported consistently in subgroup analyses. This has led to difficulty in discerning the benefit of these therapies specifically in the context of GCPM. Most of the trials that report GCPM subgroups indicate a similar or lower benefit for the intervention arm compared with non-GCPM subgroups, reinforcing the principle of resistance of peritoneal metastases to systemic therapy. Nevertheless, several therapies have been well studied and approved for the treatment of GCPM.

First-line treatment: Platinum-based and fluoropyrimidine-based chemotherapy doublet

Chemotherapy has been shown to prolong survival and improve symptom control.[68] The combination of fluoropyrimidine and platinum has been established as standard of care chemotherapy backbone for patients fit for doublet treatment.[69] The REAL-2 study ISRCTN [International Standard Randomized Controlled Trial Number] 51678883) demonstrated interchangeability and noninferiority between cisplatin and oxaliplatin as well as between capecitabine and infusional 5-fluorouracil. In general, oxaliplatin is preferred because of better tolerance and side-effect profile.[70]

Immune checkpoint Inhibitors

CHECKMATE 649 and KEYNOTE-859 (ClinicalTrials.gov identifiers NCT02872116 and NCT03675737, respectively) are randomized phase 3 trials that have demonstrated the benefit of the addition of nivolumab and pembrolizumab to chemotherapy in the first-line treatment of metastatic gastric cancer.[71,72] Neither trial has reported GCPM-specific outcomes. There remains much controversy about the role of *PD-L1* as a biomarker for selecting for patients who may derive the maximum benefit from treatment with anti–PD-1 immune checkpoint inhibition, and this is beyond the scope of the current article.[73] The ATTRACTION-2 study (ClinicalTrials.gov identifier NCT02267343) demonstrated an OS benefit of nivolumab compared with placebo for patients with metastatic gastric cancer who had progressed on at least two prior lines of therapy (i.e., third line and beyond). The GCPM subgroup had a lower benefit from nivolumab treatment (HR, 0.74; 95% CI, 0.48–1.15) compared with the non-GCPM subgroup (HR, 0.64; 95% CI, 0.50–0.82).

Targeted therapy

Several targeted therapies have now been approved for the treatment of metastatic gastric cancer. Ramucirumab, an anti-angiogenic agent, has been approved in the second line, either as a single agent or in combination with paclitaxel chemotherapy, based on the REGARD and RAINBOW trials (ClinicalTrials.gov identifiers NCT00917384 and NCT01170663, respectively).[74,75] In both trials, the GCPM subgroups appeared to benefit from ramucirumab treatment but to a lesser extent compared with the non-GCPM subgroup.

The addition of trastuzumab to platinum-fluoropyrimidine doublet chemotherapy for *HER2*-positive gastric cancer was established as a standard-of-care based on the TOGA trial (ClinicalTrials.gov identifier NCT01041404).[76] More recently, the addition of pembrolizumab to the combination of trastuzumab and chemotherapy was shown to improve survival in the KEYNOTE-811 trial (ClinicalTrials.gov identifier NCT03615326), particularly in the *PD-L1*–positive subgroup, and has attained regulatory approval.[77] However, neither of those trials reported GCPM subgroup outcomes.

More recently, the addition of zolbetuximab to chemotherapy in *CLDN18.2*-positive metastatic gastric cancer has demonstrated a survival benefit and is pending regulatory approval.[78,79] GCPM subgroup data have not been reported to date.

DISCUSSION

Herein, we summarize the updated consensus guidelines on the management of gastric cancer with PMs. Our current consensus group expanded to include surgical oncologists, medical oncologists, radiologists, pathologists, and patient advocates. Consensus was achieved in all eight question blocks after two rounds of review. Despite the low-to-moderate level of evidence, substantial work had been produced in the field of GCPMs to require major adoptions and revisions.

There were two areas of contention within the care pathway, namely, blocks 5 and 6. The REGATTA trial provided negative results on the value of incomplete surgical resection compared with chemotherapy alone, whereas the GYMSSA trial supported the use of CRS-HIPEC over chemotherapy. However, given the numerous observational studies that have demonstrated the benefit of CRS-HIPEC over chemotherapy, the Disease Site Working Group strongly indicated that it should be recommended for patients in whom a CC0 resection is predicted.

In addition, the two RCTs comparing CRS-IPC versus CRS alone also contradicted each other. Yang et al. reported that median OS was improved with the addition of IPC to CRS, whereas GASTRIPEC-1 did not demonstrate any difference between the two groups. Again, four observational studies have demonstrated that the addition of CRS to IPC does improve survival. With this information, the Disease Site Working Group strongly indicated that the addition of IPC has value for patients who have GCPM when combined with CRS.

For block 6, the PHOENIX-GC trial remains the only RCT examining the utility of BIPSC alone compared with systemic therapy, and it failed to demonstrate a survival benefit for patients who have GCPM. Several observational studies subsequently have indicated that BIPSC in addition to CRS-HIPEC does provide a survival

benefit. Furthermore, L-HIPEC and PIPAC remain safe and feasible options for patients who have GCPM, especially in converting patients with a high burden of disease to a level acceptable for a CC0 resection. Therefore, we recommend using these treatment modalities in conjunction with CRS and IPC in patients with a low PCI and a level of disease that may preclude them from moving directly to CRS.

Major limitations of this expert consensus merit discussion. First, the expert panel consisted primarily of surgical oncologists. Having expected this bias from the inception phases, thought leaders in medical oncology and other disciplines were involved early on for reviewing feedback from the first Delphi round and outlining principles of systemic therapy. Second, the Delphi consensus entailed voting on blocks rather than individual itemized recommendations, aligning with the original Chicago Consensus framework. Although this approach helped mitigate survey fatigue, it may have may compromised the granularity of feedback received. Finally, one or two members were engaged at each level of the rapid review process, but many more were involved for only one or two stages. This could have led to different interpretations of the criteria used to screen literature and extract data. The two-person verification system should have mitigated this effect, however.

International perspective

There are several notable international guidelines for the management of gastric cancer, ranging from individual countries to large, multinational organizations.[80–84] All of these guidelines recommend palliation in the form of supportive care and systemic chemotherapy for GCPM. However, it is worth examining these guidelines' recommendations for staging laparoscopy and surgery in the management of GCPM.

With regard to staging laparoscopy, the 2018 Korean national guidelines recommend peritoneal washing cytology for all patients because cytology-positive patients are associated with cancer recurrence and poor prognosis. The 2016 PSOGI guidelines also recommend staging laparoscopy in all patients with gastric cancer. In 2020, the French Association of Surgery disagreed with this consensus, recommending exploratory laparoscopy only for patients with clinical T3/T4 tumors and/or lymph node-positive disease. The European Society for Medical Oncology (ESMO) and pan-Asian–adapted ESMO guidelines agreed with this narrowing of criteria, recommending diagnostic laparoscopy and peritoneal washings for cytology only in selected patients with resectable gastric cancer.

In addition, surgery for GCPM has been controversial. Both the ESMO guidelines and the pan-Asian guidelines reference the phase 3 REGATTA trial to recommend against gastrectomy in these patients. The caveat to this is that they recommend the resection of metastases on an individual basis, especially for those who respond to chemotherapy. This contrasts the 2016 PSOGI guidelines, which suggest that CRS combined with perioperative intraperitoneal/systemic chemotherapy is the only strategy to improve the long-term survival of patients who have GCPM. Those investigators do note, however, that CRS should be offered to patients with a low PCI level and negative cytology. The French guidelines echo this sentiment, adding a PCI cutoff of 7 and implementing HIPEC alongside CRS. Chinese guidelines only recommend *reductive surgery* for patients who have GCPM and urgent symptoms, such as bleeding or obstruction. Finally, Korean guidelines suggest that CRS can be considered for locally advanced, unresectable or clinical M1 gastric cancer not detected in preoperative evaluation but incidentally identified during surgery and if R0 resection is possible.

In patients with a high PCI, conversion therapy and subsequent surgery is also highly debated (see Table S2). PSOGI recommends reducing PCI with neoadjuvant L-HIPEC and/or bidirectional therapy. However, PSOGI does not comment on subsequent surgery. In China and Korea, if systemic chemotherapy leads to complete resolution of peritoneal metastases, conversion gastrectomy is recommended. For French centers, patients who have GCPM with a high PCI should undergo intravenous chemotherapy or PIPAC alternating with intravenous chemotherapy. Those centers do note that this is an expert opinion not based on strong evidence. The ESMO and pan-Asian–adapted ESMO guidelines do not make recommendations for patients who are successfully converted to negative cytology and/or lower PCIs.

Patient/caregiver perspective

Understanding the impact of GCPM on patients and their caregivers is crucial to their holistic treatment. Organizations like STOCAN offer invaluable resources, fostering early detection, clinical trial access, and a supportive community for patients. Through STOCAN, we were able to connect with patients about their experiences with clinical trials and research in the GCPM space. For many patients, enrollment in trials instills hope, offering not only potential survival benefits but also a sense of purpose through contributing to research. Although clinical trial availability may be ample, navigating enrollment often requires tenacity and robust support networks. Patients prioritized OS as a primary outcome measure for research while also valuing progression-free survival and recurrence rates. They emphasized the importance of incorporating quality-of-life metrics into outcome measures. In addition, patients highlighted the necessity of diverse support networks, blending online and offline resources, including friends, family, peers, and medical professionals. The medical team's guidance is vital, directing patients to specialized centers when necessary. Overall, patient perspectives underscore the significance of holistic care and collaborative support networks in navigating the challenges of GCPM management.

CONCLUSION

In summary, we report an updated Delphi consensus on the management of GCPM that included a multidisciplinary team of experts. Preoperative evaluation should be comprehensive and should include

genetic testing and a diagnostic laparoscopy to assess peritoneal disease burden. In patients with a high PCI (>7), supportive care should be offered; whereas patients with a low PCI should be enrolled in systemic therapy based on their genetic status. In those who respond to systemic therapy, we recommend CRS-HIPEC for patients with predicted CC0 or BIPSC before CRS-HIPEC. Finally, in those who continue to have a high PCI after therapy, systemic therapy and/or a clinical trial is recommended.

AUTHOR CONTRIBUTIONS

Samuel D. Butensky: Conceptualization; investigation; data curation; formal analysis; project administration; visualization; writing—original draft; writing—review and editing. **Varun V. Bansal**: Conceptualization; investigation; formal analysis; writing—original draft; methodology; project administration. **David G. Su**: Conceptualization; methodology; writing—original draft. **Muhammad Talha Waheed**: Formal analysis. **Andrei Nikiforchin**: Formal analysis. **Jorge L. Gomez-Mayorga**: Formal analysis. **Elizabeth Olecki**: Formal analysis. **Shannon N. Radomski**: Formal analysis. **Beatrice Sun**: Formal analysis. **Kiran K. Turaga**: Project administration; visualization; supervision; methodology; conceptualization; writing—review and editing. **Craig G. Gunderson**: Formal analysis; methodology; project administration; supervision; visualization. **Jill Lacy**: Writing—original draft; writing—review and editing; supervision. **Brian D. Badgwell**: Supervision; writing—original draft; writing—review and editing. **Haejin In**: Writing—original draft; writing—review and editing. **Timothy Kennedy**: Supervision; writing—original draft; writing—review and editing. **Harry H. Yoon**: Supervision; writing—original draft; writing—review and editing. **Jonathan B. Greer**: Supervision; writing—original draft; writing—review and editing. **Raghav Sundar**: Supervision; writing—original draft; writing—review and editing. **Yanghee Woo**: Supervision; writing—original draft; writing—review and editing.

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DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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