review articles

Integration of Genomic Biology Into Therapeutic Strategies of Gastric Cancer Peritoneal Metastasis

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abstract

The peritoneum is a common site of metastasis in advanced gastric cancer (GC). Diagnostic laparoscopy is now routinely performed as part of disease staging, leading to an earlier diagnosis of synchronous peritoneal metastasis (PM). The biology of GCPM is unique and aggressive, leading to a dismal prognosis. These tumors tend to be resistant to traditional systemic therapy, and yet, this remains the current standard-of-care recommended by most international clinical guidelines. As this is an area of unmet clinical need, several translational studies and clinical trials have focused on addressing this specific disease state. Advances in genomic sequencing and molecular profiling have revealed several promising therapeutic targets and elucidated novel biology, particularly on the role of the surrounding tumor microenvironment in GCPM. Peritoneal-specific clinical trials are being designed with a combination of locoregional therapeutic strategies with systemic therapy. In this review, we summarize the new knowledge of cancer biology, advances in surgical techniques, and emergence of novel therapies as an integrated strategy emerges to address GCPM as a distinct clinical entity.

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KEY POINTS

- Gastric cancer peritoneal metastasis (GCPM) is a distinct clinical entity that is common in advanced gastric cancer with dismal prognosis.
- We describe 11 biologic hallmarks of GCPM across four categories: tumor-related factors, the peritoneal microenvironment, paracrine factors, and biomechanical forces.
- Although systemic therapies may benefit patients with GCPM, the magnitude of benefit is lower.
- Therefore, a combination of peritoneal-directed treatment strategies and systemic therapy may be required for the treatment of GCPM.
- Unraveling the genomic biology of GCPM offers the opportunity to integrate these treatment strategies, which may lead to improved outcomes.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Gastric cancer (GC) is an important cause of cancer mortality and morbidity, being the fifth most frequently diagnosed cancer and the fourth leading cause of cancer death globally.[1] The peritoneum is a common site of metastasis for GC, occurring in nearly a third of patients at diagnosis.[2] The prognosis of patients with GC peritoneal metastases (PM) remains dismal, with a median survival of less than 1 year.[3] Several clinical challenges in the management of GCPM contribute to the poor prognosis. GCPM is difficult to accurately detect and measure using conventional imaging modalities, leading to an increasing use of peritoneal staging modalities such as diagnostic laparoscopy and cytology washings, which have led to earlier diagnosis of PMs.[4]

To date, treatment algorithms and clinical practice guidelines for patients with GCPM are included under the broader umbrella of metastatic (or stage IV) GC, with recommendations largely focused only on systemic therapy. Yet, because of the difficulty in measuring GCPM on conventional imaging modalities, patients with PM-only metastatic disease do not have measurable disease, as per RECIST, a common inclusion criterion for most clinical trials.[5] This has led to an underrepresentation of this subgroup of patients in major trials.

CONTEXT

Key Objective

Peritoneal metastasis (PM) is common in advanced gastric cancer (GC) and confers a dismal prognosis. Advances in genomic sequencing have provided deeper insights into the biology of GCPM. Concurrently, several clinical studies are evaluating peritoneal-directed strategies to treat GCPM. This review aims to integrate these new data to provide an update on this difficult-to-treat disease.

Knowledge Generated

We review and synthesize recent major genomic studies of GCPM into 11 biologic hallmarks across four categories, including tumor-related factors, the peritoneal microenvironment, paracrine factors, and biomechanical forces. Next, we summarize various peritoneal-directed treatment strategies that are being used to target therapeutic vulnerabilities aimed to prevent the occurrence of GCPM or its treatment.

Relevance

Integration of recent novel genomic biology unraveled in GCPM with peritoneal-specific therapeutic strategies may lead to improved outcomes of this distinct clinical entity.

Because of the presence of the peritoneal-plasma barrier and poor cancer tissue vascularity, PMs respond poorly to systemic antineoplastic therapy.[6] This has led to the need to develop locoregional (intraperitoneal) treatment strategies such as catheter-based intraperitoneal chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC), and pressurized intraperitoneal aerosol chemotherapy (PIPAC). Unless patients with GCPM are enrolled in peritoneal-directed clinical trials, there are limited opportunities for direct access to the PM for tissue sampling, leading to a poor understanding of the biologic components of GCPM, such as the tumor microenvironment (TME). However, recent advances in molecular characterization and genomic sequencing have enabled analysis of various aspects of GCPM, starting with analysis of cells derived from malignant ascites and inferring the role of the TME. This has led to advances in precision oncology in this area, through subclassification of GCPM patients on the basis of gene expression profiles, and identification of novel therapeutic targets.[7]

These emerging data of the molecular and biologic characteristics of GCPM suggest consideration of targeted (*or peritoneal-directed*) treatment, distinct from GC with metastases to distant organs. Here, we discuss GCPM as a unique clinical entity, explain the biology of the disease, summarize its natural history, and cover emerging biomarkers and, importantly, the potential application of genomic biology as an integrated strategy to improve existing and future potential therapeutic approaches to GCPM.

DIAGNOSIS AND EPIDEMIOLOGY OF GCPM

The diagnosis of PM made simultaneously with the primary GC is referred to as synchronous GCPM, whereas metachronous GCPM refers to the emergence of PM (usually at least 6 months) after the primary GC diagnosis.

Synchronous GCPM

Patients with synchronous GCPM may present with symptomatic ascites, with confirmation of PM through abdominal paracentesis and cytologic examination of ascitic fluid.[8] In asymptomatic patients, synchronous GCPM is often diagnosed via (1) imaging as part of routine staging, (2) staging laparoscopy with or without peritoneal washing cytology, or (3) as an incidental intraoperative finding in patients planned for curative gastrectomy (Fig 1).

The imaging modality of choice to evaluate for distant metastases in the staging of GC is a computed tomography (CT) scan of the chest, abdomen, and pelvis.[9-11] Although the specificity of CT for the detection of PM is high (97%-99%), the sensitivity is low (28%-51%).[12,13] Recently, whole-body diffusion-weighted magnetic resonance imaging has emerged as an alternative imaging modality for the diagnosis of PM.[14] Because of the difficulty in diagnosing PM through radiology, methods to standardize reporting have been created.[15] A radiomic signature on the basis of CT phenotypes of primary tumors and adjacent peritoneum in patients with GC was developed to improve the predictive capability of CT imaging for occult GCPM.[16] Positron emission tomography-CT is not routinely recommended for staging,[9-11] in particular, for diffuse-type GC (mucinous and signet ring cell [SRC] histology) that tends to have lower uptake of ^{18}F-fluoro-2-deoxy-D-glucose.[17] Fluoro-2-deoxy-D-glucose positron emission tomography-CT scans were found to detect only 3% of occult PM, compared with 19% by diagnostic laparoscopy.[18]

Diagnostic laparoscopy with or without peritoneal washing cytology is recommended for routine staging of most stage II and III tumors by various international guidelines although slight variations exist in recommendations (Fig 1).[9,10,19,20] Staging laparoscopy as a preoperative staging tool has a high sensitivity (85%) and specificity (100%) in the detection of PM not found on imaging.[21]

Several studies have shown that the rate of synchronous PM at the time of diagnosis of GC ranges between 12.9% and 26.5% (Appendix Table A1, online only).[2,22-25] Incorporation of diagnostic laparoscopy in routine staging of

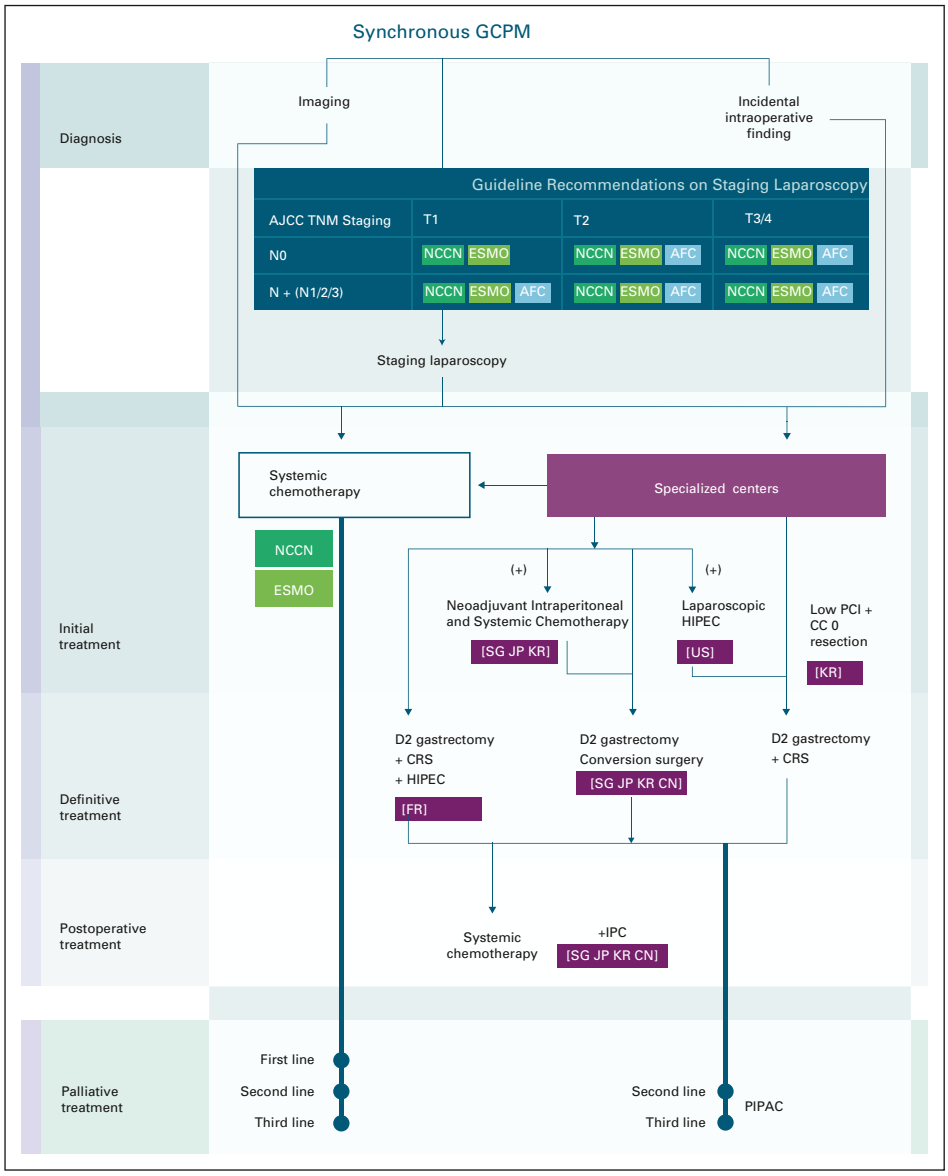

FIG 1. Diagnosis and treatment strategies of GCPM. Various groups across the world use different strategies in the management of GCPM. This figure aims to highlight the most commonly used approaches. Major guidelines (NCCN and ESMO) recommend treatment of GCPM with systemic therapy alone, similar to patients with advanced or inoperable metastatic GC. However, academic and high-volume subspecialized tertiary centers (in SG, JP, KR, CN, FR and the US, within purple boxes) tend to deploy more aggressive and experimental approaches with peritoneal-directed therapies, which are not recommended by either NCCN or ESMO. Guidelines on staging laparoscopy not represented in the figure include those from the JGCA and the SSO. JGCA recommends weakly for staging laparoscopy to decide on the treatment plan for patients with relatively high risk of peritoneal dissemination, referring also to the results of peritoneal lavage cytology using samples that are collected at staging laparoscopy, and for patients with advanced GC (TNM not otherwise specified) who can be indicated for neoadjuvant chemotherapy. SSO guidelines recommend strong consideration for diagnostic laparoscopy before the initiation of systemic chemotherapy in all patients with proven GC. AFC, French Association for Surgery; AJCC, American Joint Committee on Cancer; CN, China; CRS, cytoreductive surgery; ESMO, European Society for Medical Oncology; FR, France; GCPM, gastric cancer peritoneal metastasis; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; JGCA, Japanese Gastric Cancer Association; JP, Japan; KR, Korea; NCCN, National Comprehensive Cancer Network; PCI, Peritoneal Cancer Index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; SG, Singapore; SSO, Society of Surgical Oncology Chicago Consensus 2020.

newly diagnosed GC has led to an increase in the diagnosis of synchronous GCPM. A Dutch nationwide cohort study found that the proportion of patients with GC diagnosed with synchronous PM had increased from 18% to 26.5% over a 10-year period from 2008 to 2017.[2]

Metachronous GCPM

Metachronous GCPM is often diagnosed late when patients present with symptomatic ascites or mass effects, or can be detected on routine surveillance scans in asymptomatic patients. There are currently little data to guide surveillance strategies in patients who have undergone surgical resection of primary tumors for early-stage GC (with or without adjuvant/perioperative chemotherapy). Some clinical guidelines recommend routine annual surveillance CT scan,[9] whereas others recommend scans only if patients present with symptoms or elevated serum tumor markers.[11] The incidence of metachronous GCPM after curative gastrectomy ranges between 7% and 32%, within a median of 8.5-26 months after surgery in various studies (Appendix Table A1).[25-33] Metachronous PM accounts for between one fifth and three fifths of all patients who have metastatic disease recurrence after gastrectomy.[25,26,28-33]

BIOLOGIC HALLMARKS OF GCPM

The peritoneum is the largest of three serous cavities (along with the pleura and pericardium), which are known to be immunologic niches, controlled by a diverse range of signaling networks. The peritoneum consists of a basement membrane, mesothelial cells, and connective tissue including hyaluron, collagen, proteoglycans, and interstitial cells (endothelial, fibroblasts, and pericytes).[34] In addition to GC, several other tumor types display a propensity to metastasize to the peritoneum, such as colorectal and ovarian tumors. Lobular breast cancer is a unique disease entity with metastatic spread to the peritoneum reported similar to GC.[35] This affinity is likely due to specific molecular characteristics of the primary tumor and the interaction with peritoneum during transcoelomic metastases. Malignant ascites often contain various growth factors, cytokines and chemokines, and other soluble factors. The interaction of the niche peritoneal microenvironment and malignant ascites with tumor cells is an area of great interest from a cancer biology point of view, as perturbation of these interactions may form potential therapeutic targets (Figs 2 and 3).

Tumor-Related Factors

The dissociation of tumor cells from the primary tumor is a multistep process, which involves several pathways and networks being co-opted to enable metastasis to the peritoneal lining.

Epithelial mesenchymal transition. Epithelial mesenchymal transition (EMT) is a process through which epithelial cells undergo a transformation into a mesenchymal phenotype, with increased migratory and invasive capability, resistance to anoikis, and production of extracellular matrix (ECM) components.[36] Primary GC tumors of the EMT subtype, identified using the Asian Cancer Research Group classification, were found to develop PM more frequently and had the worst prognosis, compared with all other non-EMT subtypes.[37] A large multiomic profiling study of malignant ascites collected from patients with GCPM was recently reported.[38] The study was predominantly in diffuse subtype (Lauren classification) tumors, with integrated profiling being performed including bulk whole-genome, whole-transcriptome, and epigenetic profiling (ChIP-Seq and methylation). A key finding in this study was that unsupervised hierarchical clustering of GCPM revealed two distinct molecular subtypes: EMT and non-EMT, with the EMT group associated with diffuse GC and having poorer prognosis. Several studies are pursuing diffuse-type GC-specific treatment strategies.[39,40]

Downregulation of expression and function of intercellular adhesion molecules, particularly classical cadherins such as E-cadherin, has been associated with EMT and peritoneal carcinomatosis.[41] High expression of discoidin domain receptor 2 (*DDR2*) in primary GC tumors, a type I collagen receptor tyrosine kinase, was found to be significantly associated with EMT and peritoneal dissemination and could potentially be inhibited using dasatinib, a clinically available drug used in leukemia therapy.[42]

Genomic drivers. Whole-genome/whole-exome sequencing and whole-transcriptome sequencing (RNA-seq) on tumor cells purified from malignant ascites of patients have started to provide some insight into the genomic determinants of GCPM.[7,38] Although *TP53* mutations in PM occurred at a rate similar to primary tumors, *CDH1* mutations tended to occur more frequently, particularly in the diffuse subtype (Lauren classification) tumors. Novel drivers such as *PIGR* and *SOX9* have also been identified in the tumor cells derived from malignant ascites.[38] *PIGR* encodes the polyimmunoglobulin receptor, which transports polymeric immunoglobulins produced by plasma cells in the lamina propria across the epithelial barrier to be secreted into the luminal space.[43] *SOX9* is involved in embryonic developmental pathways.[44] Clonality analyses suggest that tumor cells in malignant ascites are derived from only a single clone per patient or just a few subclones.[38] Somatic copy number analysis has identified amplifications in several potential therapeutic targets such as *KRAS*, *FGFR2*, *MET*, *ERBB2*, *EGFR*, and *MYC* (several of which were found to be actionable in animal models).[38] This finding is of clinical importance, as The Cancer Genome Atlas and Asian Cancer Research Group analysis of *primary* GC tumors report scarce aberrations of the mitogen-activated protein kinase/oncogenic pathways in diffuse GC.[37,45] This suggests the importance of profiling the PM to identify potential therapeutic options for patients with refractory disease, which may be missed by profiling the primary tumor alone.

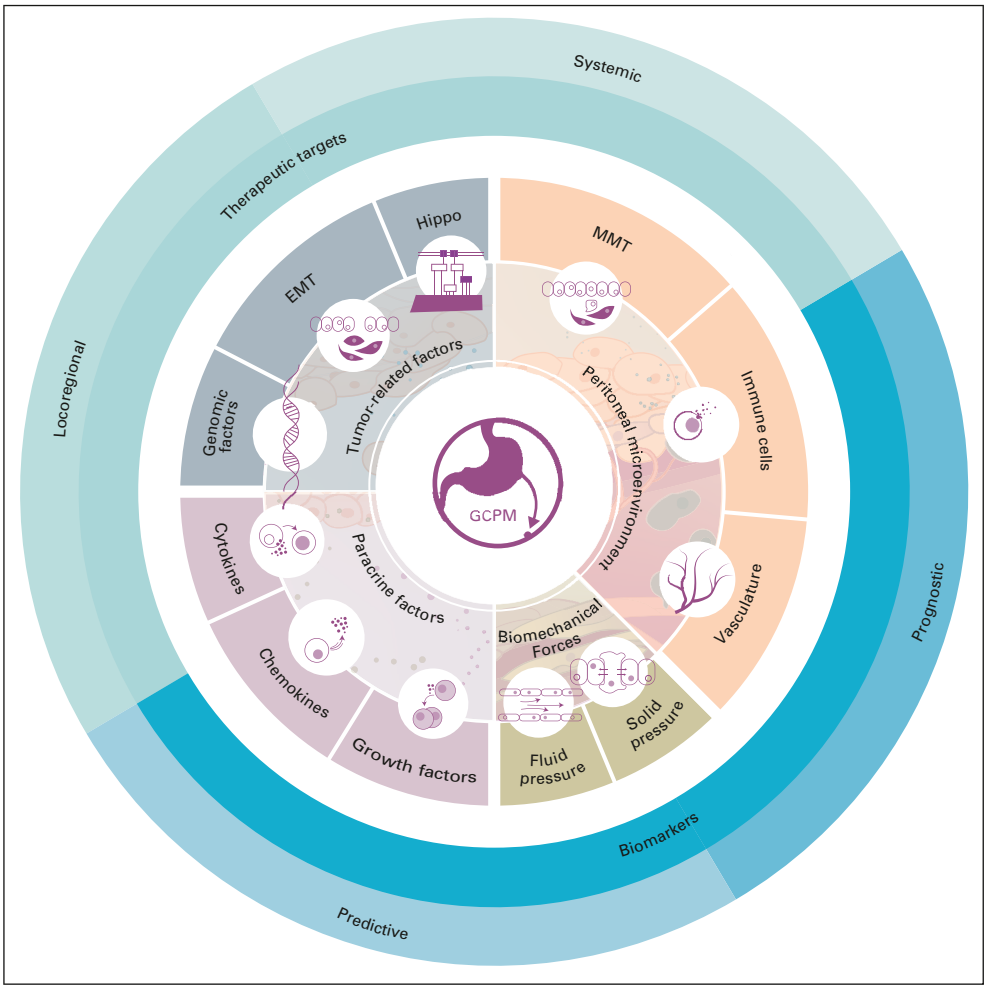

FIG 2. Biologic hallmarks of GCPM. The 11 biologic hallmarks of GCPM derived from four broad factors, including tumor-related factors, peritoneal microenvironment, paracrine factors, and biomechanical forces. Deeper understanding of these hallmarks has led to the development of novel therapeutic strategies and biomarkers. EMT, epithelial-mesenchymal transition; GCPM, gastric cancer peritoneal metastasis; MMT, mesothelial mesenchymal transition.

Single-cell RNA sequencing (scRNA-seq) has been recently used to characterize gene expression across thousands of cells simultaneously and provide a more granular understanding of the different cell states. In an scRNA-seq analysis of malignant ascites from 15 patients, tumor cells from different patients broadly clustered separately, reflective of the single clonality analysis described earlier.[46] Approximately two thirds of tumor cells mapped to cells of GC origin, such as pit, mucosal, and chief cells. The remaining third mapped to other gastrointestinal organs such as the duodenum and colon. Samples could be classified into two main subtypes, on the basis of tumor cell lineage compositions—gastric-dominant (mainly gastric cell lineages) and GI-mixed (with mixed gastric and colorectal-like cells), although no significant difference was observed in the histopathologic features between these two subtypes. This classification was found to have a strong correlation with patient survival.

Evolutionary Hippo pathway dysregulation. The Hippo signaling pathway is involved in tissue homeostasis.[47] Expression of genes involved in the Hippo pathway, including *TEAD1*, *TEAD2*, *TEAD4*, and *WWTR1*, was significantly elevated in EMT-associated malignant ascites.[38] The role of *TEAD* inhibition was explored through the administration of K-975, a TEAD inhibitor, resulting in significant PM tumor suppression and improved survival in a mouse model.[38]

The transforming growth factor-β (TGF-β) superfamily consists of various cytokines and proteins including activins and inhibins, as well as bone morphogenetic proteins, and is downstream of the Hippo pathway.[48] The TGF-β pathway is involved in several cellular processes, including EMT, cellular migration and invasion, and ECM remodeling. Excessive production of TGF-β leads to oncogenesis through dysregulation of these cellular processes. Integrative classification of malignant ascites, incorporating

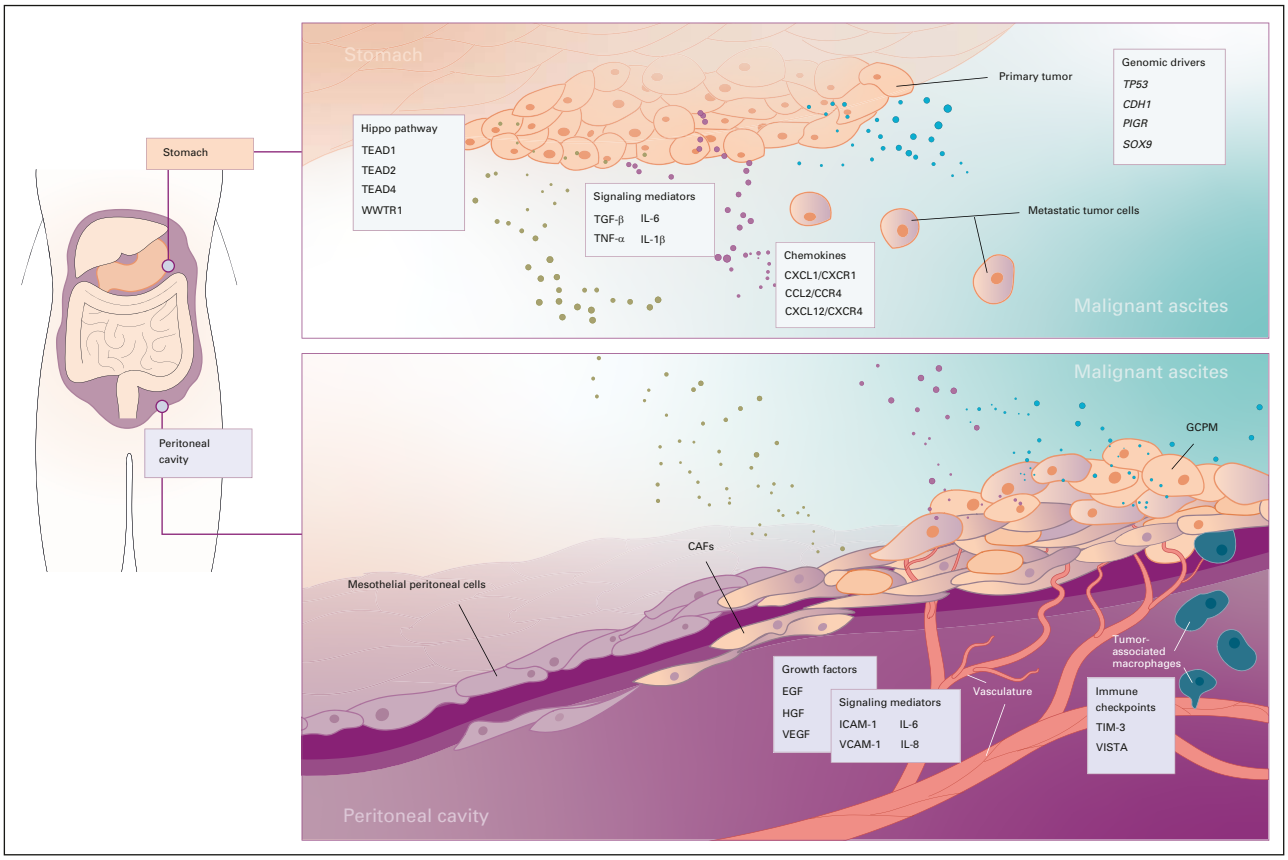

FIG 3. Regulators of metastasis to the peritoneum in GC. Metastasis of the GC primary tumor to the peritoneum is a multistep process involving several pathways and networks. In this figure, we highlight some of the key regulators of this process, with factors that determine the metastatic cascade being present in the primary tumor, malignant ascites, and the peritoneal cavity. CAF, cancer-associated fibroblast; EGF, endothelial growth factor; GCPM, gastric cancer peritoneal metastasis; HGF, hepatocyte growth factor; ICAM-1, intercellular adhesion molecule-1; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM-1, vascular adhesion molecule-1; VEGF, vascular endothelial growth factor.

DNA, RNA, and clinicopathologic characteristics, has identified a mesenchymal and an epithelial subtype of GCPM.[7] The mesenchymal subtype was found to have higher expression of TGF-β pathway genes, less frequent mutations of *TP53* and *CDH1*, a lower level of chromosomal instability, and decreased response to chemotherapy.

Paracrine Factors

Malignant ascites, with its admixture of cytokines, chemokines, and growth factors, has been shown to provide a tumorigenic environment for PM. Ascites also contains multiple ligands, which are upstream regulators of signaling, leading to phenotypic changes to the cell, enhanced tumor cell proliferation and migration, and attenuated drug-induced malignant cell apoptosis.

The TGF-β pathway has been shown to be upregulated within the tumor cells, and elevated levels of the TGF-β1 cytokine have been detected in the peritoneal washings of patients with GCPM.[49] Through the Smad pathways, TGF-β upregulates collagen and fibronectin deposition, leading to peritoneal fibrosis and increased GC tumor cell adhesion. TGF-β also increases crosstalk between cancer-associated fibroblasts (CAFs) and endothelial and other stromal cells, sustained through cytokines such as *CXCL*s, interleukins (ILs), and vascular endothelial growth factors (VEGFs).

Inflammatory cytokines such as tumor necrosis factor-α, interferon-γ, and the IL-6 and IL-1β, found in malignant ascites, increase the expression of adhesion molecules such as intercellular adhesion molecule-1 and vascular adhesion molecule-1 on mesothelial cells.[50] GCPM also secretes IL-6 and IL-8, which increase cell growth, invasiveness, motility, and chemoresistance.[51]

Several chemokines and their axes detected in malignant ascites, including CXCL1/CXCR1, CCL2/CCR4, and CXCL12/CXCR4, have been shown to play an important role in migration, chemotaxis, proliferation, and adhesion of tumor cells.[52-54] Growth factors regulating various pathways instrumental to tumor cell metastasis and propagation have been found in malignant ascites of GCPM. These, which include endothelial growth factor, hepatocyte growth factor, and VEGF, induce mesothelial cell contraction, leading to exposure of the peritoneal basement membrane.[55] VEGF, an angiogenic growth factor, promotes vascular

permeability of the peritoneal microenvironment. Crosstalk between heparin-binding-endothelial growth factor–like growth factor, CXCR4, CXCL12, and tumor necrosis factor-α converting enzyme was shown to stimulate GCPM through an autocrine/paracrine mechanism.[56]

Notably, some of the paracrine factors described are not unique to GCPM. In ovarian cancer, several studies have demonstrated the possibility of using peritoneal-directed treatment to target specific paracrine factors, such as anti-IL6R (tocilizumab)[57] and anti-VEGF (bevacizumab)[58] therapies, to control malignant ascites, suggesting a similar potential to target these factors in GCPM.

Peritoneal Microenvironment

The localization of free-floating tumor cells (either transcoelomic or translymphatic) to the peritoneal mesothelial lining is regulated by adhesion molecules such as CD44 and integrin and selectin superfamilies.[59] Cancer-associated stem cells have been isolated with a propensity for peritoneal homing and EMT.[60] Several cell types within the peritoneal microenvironment then determine the fate and progression of these tumor cells. However, because of lack of tissue availability, detailed analyses of the TME of GCPM are yet to be performed.

Mesothelial mesenchymal transition. Tumor cells adhere to the mesothelial peritoneal cells and submesothelial connective tissue through interaction of integrins.[61] Mesothelial cells secrete adhesion molecules for a variety of basement membrane proteins, including collagen, laminin, and fibronectin. Mesothelial mesenchymal transition, a process well described in the field of peritoneal dialysis for renal failure, has also been reported in PM. Mesothelial cells have been demonstrated to progressively acquire features of CAFs.[62]

CAFs driven through TGF-β signaling pathways sustain and stimulate tumor proliferation. *RHBDF2* expressed by CAFs is induced by inflammatory cytokines present in the malignant ascites and secreted by tumor cells.[63] Through TGF-β, RHBDF2 promotes motility of CAFs inducing invasion of the ECM and lymphatic vessels. CAFs have also been associated with secretion of ILs and growth factors.[49,54]

Immune cell–mediated immunosuppressive niche. Few studies have been performed directly on the immune cells within the TME of the PM, and this remains an area of intense research. In one study, the TME of GCPM was inferred through bulk RNA-Seq deconvolution to deduce immune cell types and proportions and two major subgroups were identified: T-cell–exclusive and T-cell–exhausted. Immune checkpoint *TIM-3*, its ligand *galectin-9*, and *VISTA* were highly expressed in the T-cell–exhausted (mesenchymal) subtype, as well as TGF-β1, suggesting an immune suppressive microenvironment.[7] In addition, GCPM with higher proportions of resting memory CD4 T cells tended to be associated with a more aggressive phenotype.[7]

Plasma cell homing through epithelial-resident *KLF2* in diffuse-type GC tumors was reported in one of the largest scRNA-seq data sets of GC reported to date, including GCPM samples.[64] Perturbation of this interaction may present a potential therapeutic target for GCPM. Omental neutrophils have been shown to generate extracellular traps, involving the release of a protein-rich chromatin web that functions as a premetastatic niche.[65,66]

Macrophages found to be residing in serous cavities such as the peritoneum have been found to have unique characteristics through *GATA6*-mediated homeostasis.[67] Cavity-resident macrophages within the peritoneum have high levels of Tim-4, which has been shown to mediate sequestration of CD8 T cells, thereby limiting antitumor activity in PM.[68] This suggests a possible strategy of using the Tim-4 blockade to enhance efficacy of CD8 T-cell–based immunotherapies in the treatment of malignant ascites. In addition, tumor-associated macrophages were found to promote PM via IL-6 and a potential therapeutic vulnerability.[69]

Vascular microenvironment. Milky spots are regions of lymphoid tissue found on the omentum in the peritoneal cavity. These tend to have dense capillary networks, forming a proangiogenic habitat for metastases, driven through CD105-positive vessels.[70] Oncogenesis may be further propagated by tumor and mesothelial secretion of VEGFs such as VEGF and platelet-derived growth factor, which lead to abnormal, hyperpermeable blood vessel formation. Several studies have associated changes in the tumor vasculature with the immune microenvironment and oncogenic signaling, suggesting an interplay between various biologic hallmarks.[71]

Physical Factors

As an enclosed space, the peritoneal cavity is subject to biomechanical forces, which were shown to affect tissue homeostasis. Imbalances to this tensional homeostasis have been associated with the pathogenesis of PM. These forces have also been associated with induction of EMT or mesothelial mesenchymal transition.[72] Leaky vasculature associated with PM, along with a deficient lymphatic drainage, leads to an elevated fluid pressure in the interstitium. The increased pressures within the fluid and the PM increases epithelial cell shedding and metastasis, leading to decreased diffusion and convection within the tumor and resulting in poor drug penetration.[73]

Although described individually, the multiple biologic hallmarks are interconnected, with several overlapping biologic programs regulating and signaling pathways. For example, the mesenchymal subtype of GCPM (*v* epithelial subtype) was found to have a T-cell–exhausted phenotype with increased expression of immune checkpoint *TIM-3*, its ligand *galectin-9, VISTA*, and TGF-β1.[7] Other groups, sampling either primary GC tumors or GCPM, have also described molecular subgroups. An overarching similarity across these studies is the dichotomization of GCPM into

EMT and non-EMT subgroups (Appendix Table A2, online only). Tumors with active EMT tend to have poorer survival, but more importantly, EMT-specific novel and potential therapeutic targets have been identified. Collectively, a deeper understanding of the unique biologic and molecular networks driving GCPM has identified therapeutic vulnerabilities that could be harnessed either through systemic or locoregional therapies or by a combination of both.

MOLECULAR BIOMARKERS PREDICTIVE OF GCPM

Given the poor prognosis of GCPM, significant research efforts were put into identification of biomarkers that predict the emergence of GCPM. Conventional serum tumor markers such as carcinoembryonic antigen, cancer antigen (CA) 19-9, CA 72-4, and CA125 can modestly predict GCPM recurrence.[74]

High mesothelin protein expression in primary GC tumors, measured by immunohistochemistry, is associated with GCPM recurrence.[75] A series of studies, on the basis of bulk RNA-Seq data of primary GC tissue, showed a significant association between higher expression of *SYT8*,[76] *SYT13*,[77] and *TNNI2*[78] and the risk of developing metachronous GCPM. Other groups have studied specific patterns of the TME to develop metabolic,[79] immune,[80] and collagen[81] signatures predictive of GCPM. In a more comprehensive, transcriptome-wide analysis, a six-gene panel predictive of both synchronous and metachronous GCPM has been identified.[82] This signature consists of genes such as *CAVIN2*, part of the TGF-β pathway and associated with EMT.

Several studies have tried to identify predictive biomarkers for GCPM recurrence in intraoperative peritoneal lavage samples. Positive *SYT13* mRNA in peritoneal lavage fluid was found to be an independent prognostic factor for peritoneal recurrence.[83] *MMP-7*,[84] *CK20*, *FABP1*, and *MUC2*[85] in peritoneal washings have also been identified as potential biomarkers for identifying patients at risk of peritoneal recurrence after gastrectomy. More recently, reduced expression of miR-29s in peritoneal exosomes was identified as a strong risk factor for GCPM development.[86] However, most studies evaluating these biomarkers were retrospective in nature, with varying definitions of PM recurrence end points, and further prospective large-scale validation studies are required before these can be incorporated into clinical practice.

RISK FACTORS FOR DEVELOPMENT OF GCPM

Risk Factors

Patient characteristics such as female gender[3,24,87] and primary GC tumor characteristics including more advanced T stage,[24,25,28,87] nodal involvement,[24,25,27,28] and distal gastric (*v* proximal or gastroesophageal junction) location[27,87] have been identified as clinical risk factors for the development of GCPM in both metachronous and synchronous settings.

Diffuse-type GCs by Lauren's classification, most often composed of SRCs, are more biologically aggressive than intestinal-type GCs, and correspondingly, diffuse/mixed type tumors and the presence of SRC histology have been shown to be associated with increased risk of developing PM, in both the synchronous[3,23,24] and metachronous settings.[25,87]

Role of Adjuvant Systemic Therapy in Preventing GCPM Recurrence

Systemic chemotherapy is commonly administered in either the perioperative or adjuvant setting for patients with GC undergoing curative resection.[88-92] In the ACTS-GC trial, adjuvant S-1 significantly lowered the PM recurrence rate (15% *v* 19% in the surgery-alone group, hazard ratio 0.69).[89] However, in the CLASSIC trial, adjuvant capecitabine plus oxaliplatin had only a small, nonsignificant effect on PM recurrence,[90] whereas the addition of adjuvant docetaxel to S-1 in the JACCRO GC-07 trial did not further lower the incidence of PM recurrence.[92] Various cohort studies from both Western and Asian populations found that the use of systemic therapy was not associated with a lower risk of metachronous PM after curative-intent gastrectomy.[25,27-29,87] Therefore, although adjuvant chemotherapy in GC prevents distant metastases and prolongs survival, the efficacy of systemic therapy to prevent PM remains uncertain.

PROGNOSIS OF GCPM AND THE EFFECT OF SYSTEMIC THERAPY

Prognosis of GCPM

Both synchronous GCPM and metachronous GCPM portend a poor prognosis. Studies evaluating synchronous GCPM showed a dismal survival, ranging between 3 and 15 months,[2,22,24,93] whereas the median survival ranged between 3 and 9 months in patients with metachronous GCPM (Appendix Table A1).[28-30,33] Patients with peritoneal recurrence had shorter survival compared with patients with nonperitoneal (distant and locoregional) recurrences.[27-31]

Patients with synchronous PM as the only metastatic site tend to have marginally better survival compared with patients with PM with concomitant extra-PMs.[3,24] The prognosis of patients with GCPM is also dependent on the PM disease burden. The Peritoneal Cancer Index (PCI) and the Japanese Gastric Cancer Association classification are two commonly used metrics to quantify GCPM.[22,93] The Japanese Gastric Cancer Association classification[94] describes PM as peritoneal lavage cytology–negative (CY0) and peritoneal lavage cytology–positive (CY1) and the absence (P0) or presence of macroscopic PM (P1), whereas the PCI takes into account the extent of PM by calculating the size of PM lesions across 13 pelvic-abdominal regions within the abdominal cavity.[95] Regardless of the metric used, survival of patients with synchronous GCPM worsens with increasing PM burden.[22,93,96,97]

Role of Systemic Therapy in the Treatment of GCPM

Several systemic therapies have been introduced in the past 2 decades for the treatment of metastatic GC, including combinations of chemotherapeutic agents,[98-100] targeted therapies such as trastuzumab[101] or ramucirumab,[102,103] and immune checkpoint inhibitors,[104,105] leading to a clinically meaningful improvement in survival.[25] Yet, there are several challenges in the use of systemic chemotherapy in the treatment of patients with GCPM. The presence of the plasma-peritoneal barrier and the poor blood supply of PM limit the tissue penetration and therapeutic effect of systemic agents.[106,107] Patients with GCPM may also develop complications such as intestinal obstruction and, in turn, poor nutrition and performance status, which may preclude them from systemic treatment.[108] Furthermore, because radiologic studies such as CT scans cannot consistently and accurately identify low-volume PM, objective assessment of treatment response remains a challenge.[109,110]

Within the limited number of randomized controlled trials that performed subset analysis of survival on the basis of the presence or absence of PM, patients with GCPM benefit from systemic therapies such as cisplatin plus S-1 (first line; SPIRIT[99]), ramucirumab monotherapy (second line; REGARD[102]), paclitaxel plus ramucirumab (second line; RAINBOW[103]), TAS-102 (trifluridine/tipiracil) (third line; TAGS[111]), and nivolumab monotherapy (second line; ATTRACTION-2[112]), similar to patients with metastatic GC without PM. However, the magnitude of benefit is lower in patients with PM in many of these studies compared with those without PM, confirming that PM is a negative prognostic marker among patients with inoperable metastatic GC.[102,103,111,112] Furthermore, two large-scale cohort studies found that the prognosis of GC patients with synchronous and metachronous GCPM has not improved significantly over time, despite an increasing proportion of patients who received systemic therapy in the past 2 decades.[2,25] These results suggest that solely using systemic therapy may inadequately treat patients with GCPM. These also highlight the need for better detection, risk stratification, and therapeutic strategies in patients with GC. In particular, patients with early-stage disease, treated with curative intent, may benefit from earlier identification of those at risk for peritoneal recurrence and interventions to prevent or at least delay the development of metachronous GCPM.

INTRAPERITONEAL THERAPEUTIC STRATEGIES FOR GCPM AND THEIR ROLE IN THE PREVENTION AND TREATMENT OF GCPM

Given the dismal prognosis of GCPM, novel peritoneal-directed strategies for the prophylaxis of metachronous GCPM and treatment of synchronous GCPM are areas of active research and clinical trials. Various modalities, in conjunction with surgery and systemic therapy, have been developed with ongoing evaluation to determine their role in the management of patients with GCPM (Fig 4). These strategies have been used as prophylactic strategies to prevent GCPM recurrence or conversion strategies to allow surgical resection of primary tumor and GCPM or incorporated into palliative/disease control approaches with systemic therapy.

Extensive Intraoperative Peritoneal Lavage: Primary Prevention

Since free intraperitoneal cancer cells exfoliate from the primary gastric tumor and result in PM formation, the hypothesis that repeated intraoperative peritoneal lavages (extensive intraoperative peritoneal lavage [EIPL]) with saline solution during primary resection might reduce GCPM was formulated. Three randomized controlled trials failed to demonstrate significant improvement in both overall survival (OS) and peritoneal recurrence-free survival.[113-115] Furthermore, patients in the EIPL arm of the EXPEL trial experienced a higher risk of adverse events compared with the standard surgery group.[114] Currently, there is no established role for the use of EIPL as a prophylactic strategy in the prevention of metachronous GCPM.

HIPEC: Primary Prevention and/or Conversion to Resectable Disease

Pre-emptive, intraoperative HIPEC (most commonly with oxaliplatin, mitomycin, or cisplatin as single agent or in combination with other drugs) may eliminate progression of peritoneal implantation after curative surgery and reduce metachronous PM recurrence. A meta-analysis evaluating the role of HIPEC in addition to gastrectomy in patients with advanced GC without PM showed a significant reduction in rates of PM recurrence (risk ratio = 0.63) compared with gastrectomy alone. However, HIPEC was associated with significantly higher risk of postoperative complications, in particular, renal dysfunction.[116] The ongoing multicenter phase III GASTRICHIP randomized trial (ClinicalTrials.gov identifier: NCT01882933) aims to develop definitive evidence evaluating the role of adjuvant HIPEC with oxaliplatin in patients with locally advanced GC without gross PM undergoing curative gastrectomy.[117]

HIPEC in addition to cytoreductive surgery (CRS) remains contentious as a treatment strategy for synchronous GCPM. The CYTO-CHIP study, an observational cohort study, demonstrated that patients with GCPM who underwent complete CRS with curative intent with HIPEC (using various agents including oxaliplatin, mitomycin, and cisplatin) had significantly longer survival compared with patients who underwent CRS alone, with similar morbidity rates across both groups.[118] In particular, patients with only microscopic PM or positive peritoneal cytology (ie, PCI score 0) who underwent CRS plus HIPEC had a longer median OS than those who underwent CRS alone although the difference was not statistically significant. In a follow-up study, poorly cohesive carcinoma (including SRC histology)

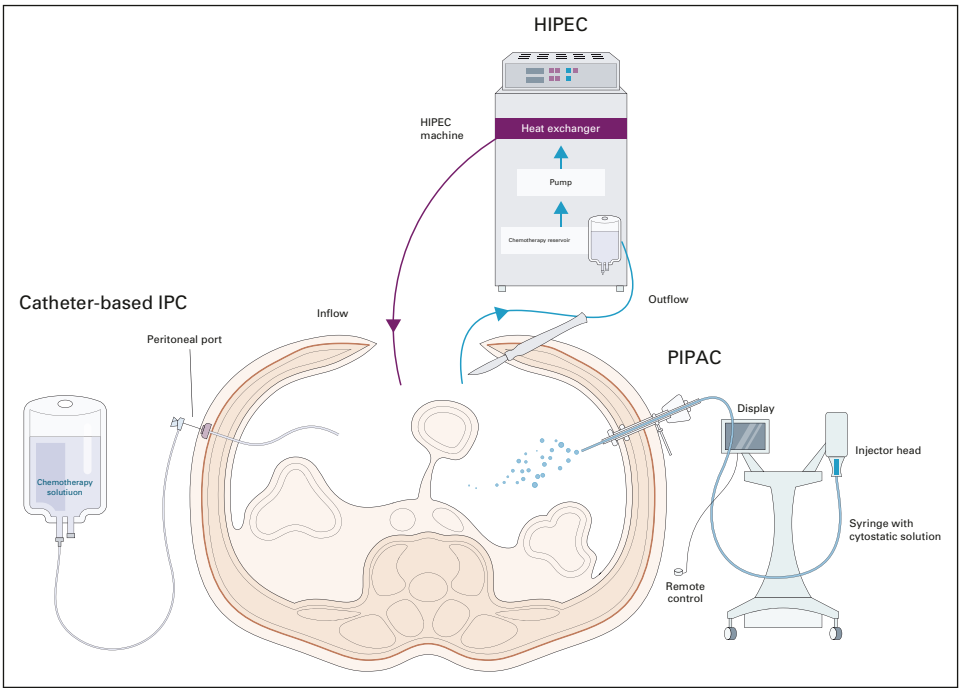

FIG 4. Peritoneal-directed modalities and their roles in treatment and prophylactic strategies of GCPM. Catheter-based IPC in combination has been evaluated in both adjuvant and neoadjuvant settings in the management of GCPM. Adjuvant combination of systemic and intraperitoneal chemotherapy may help downstage PM, allowing for conversion gastrectomy, whereas the role of adjuvant early postoperative intraperitoneal chemotherapy in prevention of metachronous PM remains unclear. HIPEC is most commonly carried out in conjunction with cytoreductive surgery as a potentially curative strategy in patients with low-volume PM and potential for complete cytoreduction. A potential role exists for prophylactic HIPEC in patients with GC undergoing gastrectomy to prevent or reduce metachronous PM recurrence, with ongoing studies underway. Studies of PIPAC have thus far been limited to palliative treatment for patients with PM; the role of PIPAC in treatment of GCPM requires further evaluation and is currently limited to the settings of clinical trial. GCPM, gastric cancer peritoneal metastasis; HIPEC, hyperthermic intraperitoneal chemotherapy; IPC, intraperitoneal chemotherapy; PIPAC, pressurized intraperitoneal aerosol chemotherapy.

was shown to be associated with poorer prognosis. CRS plus HIPEC conferred a longer median OS in this group of patients, compared with CRS alone.[119] The GASTRIPEC trial (ClinicalTrials.gov identifier: NCT02158988), which compared CRS plus HIPEC (with mitomycin C and cisplatin) with CRS alone with pre- and postoperative systemic chemotherapy, reported no significant difference in OS nor treatment-related adverse events.[120] Subgroup analysis demonstrated a significant improvement in OS in patients in whom complete cytoreduction (CC) was achieved in the HIPEC arm. In addition, progression-free survival was significantly longer in the HIPEC arm compared with that in the non-HIPEC arm (7.1 months *v* 3.5 months, $P = .0472$). Importantly, this trial was closed early because of poor patient recruitment and is underpowered for OS. On the other hand, a meta-analysis demonstrated that CRS plus HIPEC, although superior to control, was not superior to systemic chemotherapy alone.[116] Furthermore, HIPEC was associated with a significantly higher risk of postoperative complications including respiratory failure and renal dysfunction. The benefits of CRS plus HIPEC need to be balanced against the risks; patients with low-volume PM (by PCI score) and possibility for CC are most likely to benefit from CRS plus HIPEC.[118-122]

Catheter-Based Intraperitoneal Chemotherapy

The implantation of a peritoneal port is considerably less invasive than HIPEC, allows for repeated IP 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.[123,124] Therefore, catheter-based intraperitoneal chemotherapy (IPC; most commonly with taxane-based drugs) plus systemic chemotherapy presents a theoretical advantage over HIPEC plus systemic chemotherapy.[125]

Early postoperative intraperitoneal chemotherapy: Primary prophylaxis. There are little data on the use of adjuvant early postoperative intraperitoneal chemotherapy (EPIC) after curative gastrectomy in patients at high risk of PM recurrence. A randomized study of EPIC (using mitomycin C and fluorouracil), immediately postgastrectomy, compared with surgery alone, demonstrated a clinically meaningful

reduction in the rate of PM recurrence.[126] However, there was a significantly higher incidence of postoperative complications in the EPIC group, including intra-abdominal bleeding and sepsis. By contrast, the more recent INPACT trial comparing adjuvant IP paclitaxel versus intravenous paclitaxel demonstrated that postgastrectomy, IP paclitaxel did not confer any survival or PM-recurrence benefit over the intravenous group.[127] In view of these findings, the role of EPIC in the prevention of PM recurrence remains uncertain. The ongoing Japanese multicenter, randomized phase III PHOENIX-GC2 trial (JPRN-jRCT2031200087) aims to evaluate the role of IPC, in addition to gastrectomy and systemic chemotherapy, in patients with diffuse GC without distant metastasis or macroscopic PM.[128]

Combination of systemic and intraperitoneal chemotherapy: Conversion to resectable disease; palliative disease control. Several phase II trials evaluating systemic and intraperitoneal chemotherapy (SIPC) in patients with GCPM using IP taxanes demonstrated high rates of conversion to negative peritoneal cytology (71%-86%) and 1-year survival rates of more than 70%.[125] Although primary analysis of the phase III RCT (PHOENIX-GC) comparing S-1/systemic paclitaxel/IPC paclitaxel versus S-1/systemic cisplatin reported no statistical advantage of the IP paclitaxel group (IP *v* non-IP group, median OS 18 *v* 15 months, $P = .080$), exploratory analysis adjusting for an imbalance in ascites between the two groups demonstrated an adjusted hazard ratio of 0.59, suggesting possible efficacy of the IP regimen.[129] Other groups have reported successful downstaging of PM (disappearance of macroscopic GCPM and conversion to negative peritoneal cytology) after combined SIPC, allowing for conversion gastrectomy in those without extraperitoneal unresectable metastases and leading to a median OS ranging between 21.6 and 34.6 months.[130-132] These data suggest a role for combined SIPC and subsequent conversion gastrectomy in the treatment of GCPM in selected patients.

PIPAC: Palliative Disease Control

PIPAC is a novel method of intraperitoneal chemotherapy administration.[133] During PIPAC, aerosolized chemotherapy is directly administered to the peritoneum through a laparoscope. Various studies have shown that PIPAC (most commonly using cisplatin, doxorubicin, or oxaliplatin) in combination with systemic chemotherapy is safe and feasible in GCPM and has shown promise in improving outcomes.[134-137] Within the limited existing literature, studies on PIPAC are mostly limited to palliative treatment for patients with PM.[138] The role of PIPAC in the treatment of GCPM requires further evaluation and should only be performed within the framework of clinical trials. Numerous trials are underway in Europe, Singapore, and the International PIPAC Registry, which will provide more conclusive evidence on the role of PIPAC in GCPM.[134,139,140]

Geographical Differences in Treatment Strategies of GCPM

Major guidelines around the world consider synchronous GCPM to be metastatic disease and recommend palliative systemic chemotherapy (Fig 1).[10,20,141,142] Although there are differences in the management of GCPM across the world, whether this is necessary because of geographical or ethnic variations in GC biology remains an area of controversy.[143] In patients who have incidentally discovered GCPM during index surgery, the Korea Gastric Cancer Association guidelines recommend considering radical gastrectomy (gastrectomy with D2 lymphadenectomy) and limited CRS if CC can be achieved.[144] If systemic chemotherapy leads to complete resolution of PM, conversion gastrectomy is recommended by guidelines from the National Health Commission of the People's Republic of China and Korea Gastric Cancer Association.[11,144] Although catheter-based IPC is administered in combination with systemic chemotherapy by several academic groups in Japan, Singapore, and Korea, it remains experimental.[129,131,145,146] In patients with good response to this treatment and minimal residual GCPM, conversion gastrectomy is considered. In specialized centers in the United States, GCPM patients with good response to systemic chemotherapy and low PCI proceed with laparoscopic HIPEC.[141] Those with good response to systemic chemotherapy and laparoscopic HIPEC, with a low PCI score, are considered for radical surgery with CRS. By contrast, patients with good response to systemic chemotherapy with low PCI scores are subsequently offered CRS and HIPEC in specialized centers in Europe.[20] Of note, European and US guidelines do not require complete resolution of GCPM and see a benefit in limited CRS if CC can be achieved. There is no consensus on the role of intraperitoneal chemotherapy after curative surgery (either conversion surgery or radical gastrectomy with CRS). A number of groups from Asia continue catheter-based IPC in the postoperative period.[129,131,145,146]

DISCUSSION

In conclusion, we describe GCPM as a distinct clinical entity with significant mortality and morbidity and an area of unmet clinical need. Despite earlier diagnosis of GCPM and the introduction of new systemic treatment agents, outcomes remain poor. Novel modalities of peritoneal-directed therapies are being extensively evaluated and are gradually being adopted in various countries. Concurrently, in addition to conventional clinicohistopathologic risk factors, molecular profiling of GCPM has uncovered subtypes with varying molecular biologies and disease behaviors. Importantly, several novel therapeutic targets specific to GCPM have been identified. These advances will pave the way for the integration of molecular information into prognostication, follow-up, and treatment strategies of GCPM. It is likely that future studies will consider incorporation of

peritoneal-directed treatment with systemic therapy. One example is the PIANO study (ClinicalTrials.gov identifier: NCT03172416), which is evaluating the role of PIPAC-delivered oxaliplatin, in combination with systemic nivolumab in patients with GCPM. In principle, immunogenic cell death induced by PIPAC with oxaliplatin in a conventionally immune-cold cancer niche may render lesions hot, thereby inducing a response to systemic immune checkpoint inhibition. It is fathomable that in the future, more sophisticated intratumoral agents (such as STING agonists)[147] may also be delivered intraperitoneally through either PIPAC or other methods, opening the door to several other combination treatment strategies that are currently being pursued in other tumor types such as melanoma.[148] These integrated combination strategies are the most plausible way through which patients with this dreadful illness may finally have better therapeutic options.

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EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Integration of Genomic Biology Into Therapeutic Strategies of Gastric Cancer Peritoneal Metastasis

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APPENDIX

TABLE A1. Prevalence and Prognosis of Patients With Gastric Cancer With Peritoneal Metastases by Geographical Region

Author	Year	Country	Study Population	Rates of PM, %/No. of Patients	Survival of Patients With GCPM
Synchronous GCPM					
Americas					
Shiozaki et al[93]	2016	United States	145 patients diagnosed with GCPM and treated at a single institution between 2000 and 2014	Not applicable	Median OS 15 months Patients with a lower burden of PM had longer OS
Fanelli et al[23]	2009	Brazil	186 patients diagnosed with GC and treated at a single institution between January 1994 and December 2004	12.9/24	Not available
Europe					
Gretschel et al[22]	2006	Germany	660 patients diagnosed with GC and treated at a single institution between January 1992 and June 2004	16.7/110	Median disease-specific survival (according to first edition JGCA classification): P1 disease 9.9 months (95% CI, 7.9 to 11.9) P2 disease 8.2 months (95% CI, 7.3 to 9.0) P3 disease 7.6 months (95% CI, 4.7 to 10.8)
Seyfried et al[25]	2015	Germany	1,108 patients diagnosed with GC and treated at a single institution between January 1986 and July 2013	14.7/158	Not available
Thomassen et al[24]	2014	the Netherlands (Southern)	5,220 patients diagnosed with GC in the Eindhoven Cancer Registry between 1995 and 2012	13.5/706	With PM as the only metastatic site 4.6 months (95% CI, 4.0 to 5.2) With PM + other sites of metastases 3.3 months (95% CI, 2.8 to 4.0)
Koemans et al[2]	2021	the Netherlands	3,733 patients diagnosed with GC in the Netherlands Cancer Registry between 1999 and 2017	Range between 17.9% and 26.5% (from 2008 to 2017)	Median OS 3.6-4.4 months
Asia					
Abbasi et al[149]	2010	Jordan	162 patients with advanced, inoperable GC treated at a single institution between January 2004 and December 2008	42.6/69	Not available
Katai et al[26]	2017	Japan	118,367 patients with GC who underwent gastric resection between 2001 and 2007 across 367 institutions in Japan	5.3/6,310	5-year OS 9.5% (95% CI, 8.7 to 10.3) 5-year DSS 11.9% (10.9 to 12.9) By contrast, patients with no peritoneal involvement at the point of surgery had a 5-year OS of 74.6% (95% CI, 74.4 to 74.8) and a 5-year DSS of 82.9 (95% CI, 82.7 to 83.1)

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TABLE A1. Prevalence and Prognosis of Patients With Gastric Cancer With Peritoneal Metastases by Geographical Region (continued)

Author	Year	Country	Study Population	Rates of PM, %/No. of Patients	Survival of Patients With GCPM
Tan et al[3]	2017	Singapore	271 patients with GCPM diagnosed at initial metastatic presentation and treated at a single institution between January 2010 and December 2014	Not applicable	Median OS 8.7 months (95% CI, 7.1 to 10.1)
Metachronous GCPM					
Americas					
Spolverato et al[29]	2014	United States	817 patients who underwent curative gastrectomy among 7 major academic institutions between 2000 and 2012	11.3/92 37.7% of all recurrence	Median peritoneal RFS 8.5 months Median survival after recurrence 2.7 months Worse compared with locoregional recurrence 9.1 months and hematogenous recurrence 4.8 months, $P = .01$
Ikoma et al[30]	2017	United States	488 patients who underwent curative resection in a single institution between January 1995 and December 2014	12.5/61 49% of all recurrence	Median peritoneal RFS 1.3 years (95% CI, 0.7 to 1.7) Median OS after PM recurrence 0.6 years (95% CI, 0.4 to 0.9) versus locoregional recurrence 1 year (95% CI, 0.3 to 3.1) and distant nonperitoneal recurrence 0.8 years (95% CI, 0.5 to 1; $P = .05$)
Mizrak Kaya et al[31]	2017	United States	164 patients who underwent curative resection in a single institution between January 2002 and December 2014	13.4/22 45.8% of all recurrence	Median peritoneal RFS 15.6 months (range 8.5-81.7 months) Median OS 1.9 years Significantly lower compared with those without PM (median 1.9 years *v* 10.2 years, HR 7.26 [95% CI, 4.07 to 12.95]; $P < .001$)
Europe					
Honoré et al[27]	2013	France	424 patients with esogastric carcinoma who underwent curative resection across 19 surgical centers	19.1/81	Median peritoneal RFS 15.1 ± 8.5 months Median OS 17.2 months Significantly lower when compared with patients with locoregional recurrence (23.5 months, $P = .015$)
Seyfried et al[25]	2015	Germany	1,108 patients diagnosed with GC and treated at a single institution between January 1986 and July 2013	16/64 44.3% of all recurrence	Median peritoneal RFS 17.7 (15.1 to 20.3) months
Asia					
Sasako et al[32]	2008	Japan	523 patients who underwent curative resection (D2 lymphadenectomy alone or D2 lymphadenectomy plus para-aortic lymph node dissection) across 24 institutions between July 1995 and April 2001	15.7/82 38.1% of all recurrences	Not available

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TABLE A1. Prevalence and Prognosis of Patients With Gastric Cancer With Peritoneal Metastases by Geographical Region (continued)

Author	Year	Country	Study Population	Rates of PM, %/No. of Patients	Survival of Patients With GCPM
Deng et al[33]	2011	China	308 patients who underwent curative resection in a single institution between January 1997 and December 2000	31.8/98 58.0% of all recurrences	Median DFS 26 months Median survival after recurrence 6 months
Lee et al[28]	2014	Korea	805 patients who underwent curative resection in a single institution between May 2003 and December 2009	17.9/144 58.8% of all recurrence	Median survival time after recurrence 9.4 months Significantly lower compared with patients with nonperitoneal recurrence (14.6 months)
Katai et al[26]	2017	Japan	118,367 patients who underwent gastric resection between 2001 and 2007 across 367 institutions in Japan	6.56/7,769 44.3% of all recurrence	Not available

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; GCPM, gastric cancer peritoneal metastasis; HR, hazard ratio; JGCA, Japanese Gastric Cancer Association; OS, overall survival; RFS, recurrence-free survival.

TABLE A2. Comparison of Studies Investigating Gene Expression Profiles of GC and/or PM Samples

Author	Year	Sample Sequenced	Non-EMT	EMT	Potential Treatment Target(s) in the EMT Subtype
ACRG Cristescu et al[37]	2015	Primary GC	MSI MSS/TP53+ MSS/TP53–	MSS/EMT subtype Develop PM more frequently and poorer prognosis compared with all other subtypes	Not applicable
Kurashige et al[42]	2016	Primary GC		Patients with PM tended to show a more pronounced GDES. Patients with higher GDES also had poorer prognosis	DDR2
Wang et al[7]	2019	PM	E.a and E.b	M Patients with the M subtype were shown to be less responsive to chemotherapy compared with patients with the E subtypes	TGF-β1, immune checkpoint TIM-3 and its ligand galectin-9 and another immune checkpoint VISTA
Tanaka et al[38]	2021	PM	Non-EMT group	EMT group Poorer prognosis compared with the non-EMT group	TEAD

NOTE. Findings across the various studies broadly dichotomize GC and GCPM into two groups: EMT and non-EMT, with the EMT subtype predisposed to PM, poorer prognosis, and poorer response to chemotherapy.

Abbreviations: ACRG, Asian Cancer Research Group; DDR2, discoidin domain receptor 2; E.a, epithelial-like, a; E.b, epithelial-like, b; EMT, epithelial-mesenchymal transition; GDES, gastric dissemination expression signature; GC, gastric cancer; M, mesenchymal-like; MSI, microsatellite instability; MSS, microsatellite stable; PM, peritoneal metastasis; TGF, transforming growth factor.