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Cytoreductive surgery and HIPEC in peritoneal metastases: from Sugarbaker's concept to modern evidence*

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ABSTRACT

Peritoneal metastases (PM) are a common manifestation of advanced gastrointestinal and gynecological cancers and are traditionally associated with poor prognosis. Historically, the peritoneal–plasma barrier and limited drug diffusion have restricted the efficacy of systemic chemotherapy, resulting in short survival times. Since the 1980s, the treatment landscape has been transformed by the locoregional approach introduced by Paul H. Sugarbaker. The combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has redefined peritoneal surface malignancies as a potentially local-regional disease entity. Recent phase III trials [PRODIGE-7 (colorectal), OVHIPEC-1 (ovarian), and GASTRIPEC-I (gastric)] have refined the evidence base, showing that CRS remains the strongest prognostic factor, while HIPEC may provide survival benefits in carefully selected cases, depending on primary tumor type and protocol parameters. Despite persistent heterogeneity in HIPEC regimens, growing efforts in biomarker-guided patient selection, AI-assisted imaging, and international data-sharing networks (e.g., PSOGI, RENAPE) are expected to improve standardization and predictability. These developments may optimize both safety and long-term outcomes in the management of peritoneal metastases.

Keywords: Cytoreductive surgery, HIPEC, peritoneal carcinomatosis

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INTRODUCTION

Peritoneal metastases (PM) are a common clinical presentation in advanced stages of gastrointestinal and gynecological malignancies, often associated with poor prognosis. The presence of PM, particularly in colorectal and gastric cancers, has historically been associated with short survival and limited treatment options.[1,2] Population-based studies in this patient group have reported median survival remaining at the level of months, even during the era of widespread palliative chemotherapy.[3] The peritoneal-plasma barrier inherent in PM and limited drug diffusion to tumor nodules have historically limited the effectiveness of systemic chemotherapy on peritoneal surfaces.[4,5]

This bleak picture has changed fundamentally since the 1980s with the locoregional treatment approach pioneered by Paul H. Sugarbaker. Sugarbaker conceptualized peritoneal surface malignancies as a potentially "local-regional" disease area with distinct biology from systemic metastasis; he defined a treatment paradigm involving the removal of macroscopic tumor burden through CRS and the targeting of residual microscopic disease with hyperthermic intraperitoneal chemotherapy (HIPEC).[6] The pharmacological rationale for this approach is based on the high peritoneal/blood exposure ratio of intraperitoneal administration and the cytotoxic enhancing effect of hyperthermia.[4,7]

Disease burden is scored by the Peritoneal Cancer Index (PCI) (0-39 across 13 regions), and surgical efficacy by the completeness of cytoreduction (CC) score; detailed definitions are provided in Section 2.1.[8,9]

In current practice, CRS±HIPEC is applied in carefully selected cases-particularly in PM associated with colorectal, ovarian, and gastric cancer-based on the decision of multidisciplinary tumor boards. However, global standardization has not been achieved in areas such as agent selection, temperature-time parameters, and perfusion technique.

The 2022 PSOGI (Peritoneal Surface Oncology Group International) consensus gave a weak-positive vote for MMC-based HIPEC regimens (particularly the "Dutch protocol") in PM-CRC, while expressing a strong-negative opinion on the short-course high-dose oxaliplatin protocol; it emphasized that advanced studies clarifying the role of HIPEC should be a primary research priority[10]. Similarly, in other primaries, patient selection, tumor biology, and protocol-specific variables emerge as the main factors determining survival contribution.[1]

Most reviews in the current literature address CRS+HIPEC therapy solely from a surgical and chemotherapeutic perspective. This study, however, offers a multidisciplinary

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perspective by examining the historical framework from Sugarbaker to the present day, biomarker-based selection, artificial intelligence-supported patient assessment models, and data standardization initiatives together. The aim of this review is to evaluate the historical development of CRS and HIPEC, starting from the conceptual foundation laid by Sugarbaker, their biological and technical principles, current clinical evidence, and future research agenda through an interdisciplinary and critical lens. Within this framework, the following sections will detail primary-specific evidence (colorectal, ovarian, and gastric), randomized trials and meta-analyses, protocol parameters, and nuances related to patient selection.

THE HISTORICAL DEVELOPMENT AND FUNDAMENTAL PRINCIPLES OF CYTOREDUCTIVE SURGERY AND HIPEC

The concept that peritoneal surface malignancies have a distinct disease biology from systemic metastasis emerged in the 1980s as a conceptual revolution pioneered by Paul H. Sugarbaker. Sugarbaker redefined the peritoneal cavity as a "treatable anatomical compartment," thereby developing a locoregional approach aimed at overcoming the limitations of systemic treatment.[6]

Historical Development

Sugarbaker's first applications were extensive surgical procedures involving peritoneal stripping and organ resection performed at the Washington Cancer Institute in the late 1980s. During this period, the concept of the "peritoneal-plasma barrier" defined the limited passage of systemic agents into the peritoneal cavity and formed the pharmacological rationale for the idea of intraperitoneal (IP) chemotherapy[7].

By the 1990s, Sugarbaker[11] had systematized the strategy of surgically removing the macroscopic tumor burden (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), bringing the concept of combined therapy into clinical practice. The pharmacokinetic rationale for HIPEC is based on the advantages of intraperitoneal administration, such as creating a high local drug concentration compared to systemic circulation, increasing tissue penetration with heat, and keeping systemic toxicity relatively limited.[5,12]

Since the mid-1990s, the CRS+HIPEC concept has begun to be applied clinically, and during this period, the concepts of PCI and CC have gained widespread acceptance. The PCI, developed by Jacquet and Sugarbaker,[13] quantifies tumor burden by scoring lesion size across 13 abdominal regions, with a total range of 0-39 points. The CC score, on the other hand, grades the amount of residual disease after surgery (CC-0: no macroscopic disease, CC-1: residual nodules ≤2.5 mm, CC-2/3: >2.5 mm). Both indices are key prognostic determinants and guide treatment planning in CRS + HIPEC. Jacquet and Sugarbaker presented the methodology in this field in detail in their study "Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis". Multicenter data from Glehen[14] and Gilly[15] showed that better survival was achieved in cases where cytoreduction was performed at the CC-0/1 level.

Since the mid-2000s, CRS+HIPEC has begun to show curative potential in selected patient groups. Particularly in colorectal and appendix-derived peritoneal metastases, median survival has reached 30-40 months, with 5-year survival rates of 30-40% in some series.[16]

These successes have led to the international acceptance of the concept and the establishment of peritoneal surface oncology centers (such as the PSOGI, BIG RENAPE, and PERISCOPE II networks).[10]

Basic Biological and Pharmacological Principles

The therapeutic success of HIPEC is based on the pharmacokinetic profile that limits systemic toxicity through the biochemical and immunological effects of hyperthermia.

The increase in temperature accelerates cell death through DNA damage, increases the permeability of the tumor cell membrane, and facilitates the diffusion of agents such as cisplatin and mitomycin-C into the cel.[14]

Hyperthermia also enhances antitumor activity in the peritoneal microenvironment by activating the local immune response.[17]

Pharmacokinetically, intraperitoneal administration provides 20-100 times higher local drug concentrations compared to systemic circulation, creating cytotoxic concentrations in residual tumor clusters.[5]

Surgical Principles and Technical Approach

Cytoreductive surgery aims to systematically remove peritoneal surfaces (peritonectomy procedures) and achieve macroscopic clearance of the tumor. The six basic peritonectomy areas defined by Sugarbaker-anterior parietal, diaphragmatic, pelvic, omentectomy, spleen resection, and segmental colon resection-form the basis of CRS today.[6]

The degree of surgical completion (CC score) is one of the factors that directly determines the effectiveness of HIPEC; even in the presence of microscopic residue, the penetration depth of HIPEC is limited to 1-3 mm.[4]

In current approaches, CRS+HIPEC is no longer a single procedure but a multidisciplinary treatment algorithm. It requires integration between surgical oncologists, medical oncologists, anesthesiologists, and intensive care teams; in this respect, it is the central practice of modern peritoneal oncology.[1]

CURRENT EVIDENCE-BASED CLINICAL RESULTS

The combination of CRS (cytoreductive surgery) and HIPEC is an approach aimed at achieving local-regional control in peritoneal metastases, but its efficacy is sensitive to the primary tumor type, tumor burden (PCI), degree of surgical completeness (CC score), the HIPEC protocol used, and center experience. This section summarizes current evidence in peritoneal metastases associated with colorectal, ovarian, and gastric cancers (CRC-PM, EOC-PM, GC-PM).

Peritoneal Metastases Caused by Colorectal Cancer (CRC-PM)

PM can be observed at a significant rate in the diagnosis or follow-up of colorectal cancer; a population-based study based on Swedish national registries has detailed the incidence and risk factors of peritoneal carcinomatosis in CRC.[18]

In the PRODIGE-7 study (265 cases), one of the strongest randomized trials evaluating the added benefit of CRS+HIPEC in CRC-PM, the addition of short-course oxaliplatin-based HIPEC (460 mg/m², 30 min, ~43 °C) did not show superiority in overall survival compared to CRS alone, with a median OS of approximately 41 months in both arms. Late (post-60 days) complications were reported more frequently in the HIPEC arm. Although the study has been debated methodologically (agent/duration selection, etc.), it is a turning point that questions the "HIPEC for everyone" approach.[19]

The reflection of these results in clinical practice has also been incorporated into international consensus documents. The 2022 PSOGI consensus (HIPEC regimens for CRC-PM) takes a "conditionally positive" approach to mitomycin-C-based, longer-duration protocols under conditions of low PCI and complete cytoreduction (CC-0/1), while expressing clear reservations about the short-duration oxaliplatin protocol.[10]

On the other hand, large multicenter cohort and systematic reviews reiterate that survival can be significantly improved with CRS±HIPEC in the presence of successful adjuvant surgery (CC-0/1) and low tumor burden (low PCI); however, due to heterogeneity in the agent (mitomycin-C/oxaliplatin), temperature, and duration, it is emphasized that the benefit is strictly dependent on patient- and protocol-selection.[10]

Beyond efficacy, evidence comparing long-term morbidity and health-economic outcomes between CRS alone and CRS±HIPEC remains limited and heterogeneous. Preliminary analyses suggest increased procedural costs and late complications in the HIPEC arm, yet prospective cost-effectiveness evaluations are warranted to contextualize these findings.

Clinical implication: CRS retains its position as the primary treatment in CRC-PM; the role of HIPEC should be individualized, particularly in cases with low PCI and CC-0/1, favoring mitomycin-C-based protocols, taking into account center experience and morbidity management.[10,19]

Peritoneal Metastases Caused by Ovarian Cancer (EOC-PM)

Peritoneal spread is part of the natural course of advanced epithelial ovarian cancer. In the OVHIPEC-1 phase III randomized trial, the addition of intraoperative HIPEC (cisplatin 100 mg/m², 90 min, 40°C) significantly improved progression-free and overall survival compared to surgery alone (initial report in NEJM 2018). A final survival analysis was published in 2023, reporting an increase in median OS from 33.3 months to 44.9 months and a hazard ratio (HR) of 0.70 (p=0.011) for the risk of death. This high-level evidence strongly supports the addition of HIPEC to interval surgery in appropriately selected stage III patients.[20,21]

These findings suggest that HIPEC may add value to the standard of care in platinum-sensitive, well-selected EOC-PM cases; however, careful standardization of hydration and heat-duration parameters is required to mitigate renal toxicity and perioperative morbidity.[20,21]

Peritoneal Metastases Caused by Stomach Cancer (GC-PM)

The prognosis for peritoneal metastasis associated with gastric cancer is generally poor, and survival with systemic treatments is limited. In the GASTRIPEC-I phase III trial, the effect of adding HIPEC after CRS in synchronous GC-PM cases was evaluated; the published results of the study did not show a significant superiority in OS, but details on endpoints and safety profile were provided. This randomized data indicates that additional evidence is needed to support the routine use of HIPEC in GC-PM.[22]

The European multicenter PERISCOPE II (phase III) study was designed to compare gastrectomy + CRS + HIPEC after neoadjuvant systemic therapy with systemic chemotherapy alone in cases of GC with limited peritoneal spread and/or cytology-positive GC. As the final results are awaited, patient selection and center experience remain decisive factors in clinical practice.[23,24]

Clinical implication: CRS+HIPEC should still be considered an investigational option in GC-PM; cases with low PCI, high likelihood of R0/R1 resection, and appropriate performance status should be evaluated in prospective protocols at experienced centers.[22,24]

General Evaluation

The total body of evidence indicates that CRS is the primary curative component; HIPEC, however, can provide additional benefit in primary-specific, PCI-dependent, and CC-0/1 cases when the agent/duration/temperature parameters are appropriately selected. Oxaliplatin-short-course protocols have not shown an OS benefit in colorectal cancer; in ovarian cancer, an OS gain with cisplatin-HIPEC in interval surgery has been confirmed; in gastric cancer, results are heterogeneous, and the approach will become clearer as phase III data mature.[19-22]

Key phase III randomized trials across different primary tumors are summarized in Table, highlighting study designs, HIPEC regimens, and main survival outcomes to facilitate direct comparison of evidence.

Table. Key phase III trials and outcomes of CRS±HIPEC in peritoneal metastases

Trial	Primary Cancer	Design/N	HIPEC Regimen	Primary Endpoint	Main Results (OS/PFS)	Notes
PRODIGE-7	Colorectal (CRC-PM)	RCT/265	Oxaliplatin 460 mg/m², 30 min at ~43°C	OS	No OS benefit vs CRS alone (median OS ~41 months both arms; HR≈1.00; p=0.99)	Late (≥60 d) complications higher in HIPEC arm
OVHIPEC-1	Ovarian (EOC, stage III, interval)	RCT/245	Cisplatin 100 mg/m², 90 min at 40°C	PFS	Improved PFS & OS (median OS 44.9 vs 33.3 m; HR 0.70; p=0.011)	Final survival analysis (2023) confirms long-term OS benefit
GASTRIPEC-I	Gastric (GC-PM)	RCT	MMC/Cisplatin-based HIPEC after CRS	OS	No OS advantage; **PFS and MFS improved** in CRS+HIPEC	Safety acceptable; further exploration warranted
PERISCOPE II	Gastric (limited PM/positive cytology)	RCT	Gastrectomy + CRS + HIPEC vs systemic chemotherapy	OS	ESMO 2025 presentation: **no OS advantage** for CRS+HIPEC vs chemotherapy	Awaiting peer-reviewed full publication

CRS: Cytoreductive surgery, HIPEC: Hyperthermic intraperitoneal chemotherapy, PFS: Progression-free survival, RCT: randomized controlled trial, OS: Overall survival, CRC-PM: Peritoneal metastases caused by colorectal cancer

DISCUSSION AND FUTURE PERSPECTIVES

Clinical Significance and Current Interpretation

CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) have created a paradigm shift in the treatment of peritoneal metastases over the past thirty years. The concept of "locoregional disease," defined by Paul H. Sugarbaker[25] in the 1980s, challenged the understanding of systemic metastasis and demonstrated the need to consider peritoneal surfaces as a separate biological environment.

Today, CRS is accepted as a fundamental treatment component with curative potential in selected cases. However, the contribution of HIPEC to survival is tightly linked to the primary tumor type, tumor burden (PCI), degree of surgical completeness (CC), and the protocol used. The results of randomized controlled trials clearly demonstrate this variability.

In colorectal cancers, the PRODIGE-7 study showed that adding short-term (30 min) oxaliplatin-based HIPEC after CRS did not improve overall survival (median OS was 41 months in both groups, HR: 1.00; p=0.99).[19] However, it has been suggested that the study did not fully reflect the pharmacokinetic advantage of HIPEC due to agent selection and duration limitations.

The OVHIPEC-1 study in ovarian cancer and the long-term follow-up analysis published in 2023 demonstrated that HIPEC significantly prolonged progression-free and overall survival in platinum-sensitive stage III patients.[20,21] These results suggest that CRS+HIPEC in ovarian cancer may provide added value to the standard of care in appropriately selected cases.

In the phase III GASTRIPEC-I trial conducted in gastric cancer with peritoneal metastasis, the addition of HIPEC did not have a significant effect on overall survival; however, the safety profile and subgroup analyses revealed that HIPEC remains an area for further investigation.[22]

These three high-level studies show that the curative potential of CRS is more decisive than that of HIPEC; HIPEC, however, may improve local control and disease-free survival in selected cases with low PCI and complete cytoreduction (CC-0/1).

Limitations in the Literature

The current literature presents difficulties in comparison due to the heterogeneity in HIPEC applications. Agent selection (mitomycin-C, oxaliplatin, cisplatin), temperature range (41-43°C), application duration (30-120 min), and perfusion technique (open or closed system) vary between centers. This complicates standardization in survival analyses.[10] This multidimensional variability is summarized schematically in Figure, which illustrates the key domains of protocol heterogeneity and the steps toward standardized, comparable HIPEC datasets.

Furthermore, many studies are single-center or retrospective in design, carrying a risk of bias in patient selection. The heterogeneity in HIPEC protocols, with different combinations of agent-duration-temperature used in studies, limits the comparability of results.26 Reviews on ovarian cancer also frequently highlight platinum-sensitive patient selection, HIPEC regimen variations, and study design heterogeneity as methodological limitations.[27]

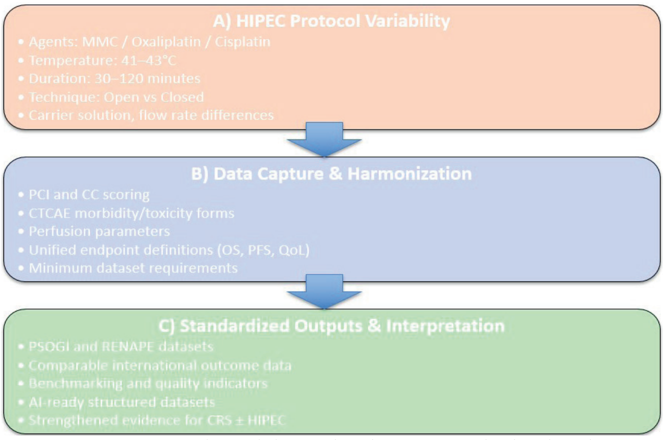

Figure. HIPEC protocol variability and pathway to standardized evidence

(A) HIPEC protocol variability ("chaos"): Across centers, agents (e.g. mitomycin-C, oxaliplatin, cisplatin), temperature (41-43 °C), perfusion duration (30-120 minutes), technique (open vs closed), and additional parameters (carrier solution, flow rate, dosing) differ substantially.

(B) Data capture and harmonization ("process"): Systematic documentation of PCI and CC scores, standardized morbidity/toxicity reporting, and recording of perfusion and protocol parameters within a minimum dataset and unified endpoint framework (OS, PFS, QoL) allows cross-study comparability.

(C) Standardized outputs and clinical interpretation ("solution"): Multicenter registries (PSOGI, RENAPE and others) integrate these harmonized data into comparable international datasets, enabling benchmarking, quality indicators, and AI-ready structured data that strengthen evidence generation for CRS±HIPEC.

Finally, the PSOGI 2024 consensus report states that international standardization of HIPEC agent, duration, and temperature parameters has not yet been achieved, and therefore protocols must be adapted on a center-by-center basis.[10]

From a meta-analytic standpoint, substantial between-study heterogeneity (high I^2) and non-uniform endpoint definitions (OS, PFS, morbidity) reduce the certainty of pooled estimates and limit the strength of recommendations.

Research Areas for the Future

The future direction in the treatment of peritoneal metastases is focused on developing more biologically based and individualized approaches.

PIPAC (pressurized intraperitoneal aerosol chemotherapy): This is a repeatable, minimally invasive method that aims to achieve more homogeneous distribution and tissue penetration by delivering normothermic, pressurized aerosolized chemotherapy into the peritoneal cavity. Clinical use today is mostly for symptom/ascites control in cases refractory to systemic therapy and for "bridge-to-CRS" purposes in selected patients. Multicenter experience and phase II data show that PIPAC is feasible and safe; it can provide measurable disease control and quality of life gains in groups such as CRC-PM. Current consensus provides practical recommendations regarding agent/protocol standardization (oxaliplatin or cisplatin+doxorubicin), pressure, and cycle planning; however, randomized comparative data are still needed.[28-30]

At present, PIPAC should be regarded as an adjunct or bridge strategy, primarily in refractory disease or for downstaging before CRS, rather than a standard-of-care alternative to CRS±HIPEC.

Normothermic intraperitoneal infusion and immunotherapy combinations: Normothermic intraperitoneal chemotherapy (NIPEC) is being investigated as a sequential regional approach to systemic therapy, particularly in gastric-derived peritoneal metastases; ongoing phase II protocols in Western cohorts (e.g., STOPGAP) are evaluating the feasibility and potential bridging effect of this strategy.[31] Early-phase evidence is also emerging for locoregional combinations with immunotherapies: a phase 1b study of intraperitoneal nivolumab+ipilimumab in gynecologic malignancies reported safety/lesion response signals; and in a phase I expansion cohort receiving intraperitoneal nivolumab after CRS+HIPEC, the approach was found to be feasible, suggesting that antigen release induced by CRS/HIPEC may enhance the immune response.[32,33] These early results support the investigation of normothermic IP infusion strategies in combination with checkpoint inhibitors, particularly in selected cases with reduced tumor burden; however, randomized comparative studies are still needed.

NIPEC and locoregional immunotherapy combinations remain investigational, and their transition into routine clinical practice will depend on forthcoming randomized data and long-term safety confirmation.

Molecular biomarker-based patient selection: Survival in CRS+HIPEC treatment depends not only on surgical completeness and tumor burden, but also on the molecular biology of the tumor. In colorectal peritoneal metastases, the BRAF mutation in particular has been identified as one of the strongest biomarkers associated with poor prognosis.[34,35]

In these studies, survival in BRAF-mutant cases was found to be significantly shorter. In contrast, results for KRAS mutations are more heterogeneous; no significant prognostic effect has been demonstrated in most series. However, it has been suggested that some subtypes (e.g., KRAS G12V and G12D) may exhibit more aggressive biological behavior.[36]

A study by Larsen et al.[37] reported that the adverse effect of BRAF mutation may be partially offset in the presence of the MSI-H phenotype.

These data suggest that molecular profiling may play an important role in personalizing patient selection for CRS+HIPEC strategies in the future.

Artificial Intelligence and machine learning-based prediction models: In recent years, radiomics analyses based on quantitative data extraction from medical images and deep learning-based models have reported promising results for predicting the risk of PM and the PCI from pre-treatment images.

For example, a radiomics-boosted deep learning model derived from PET/CT data has accurately predicted synchronous colorectal PM risk.[38]

Similarly, CT-based radiomic PCI models have shown significant agreement with surgical PCI scores and have surpassed conventional imaging assessments in distinguishing between low and high tumor burden.[39]

Furthermore, machine learning-based radiomics nomograms developed to predict occult PM in gastric and ovarian cancers also show high accuracy signals.[40,41]

Despite encouraging accuracy metrics, radiomics- and AI-based models are not ready for clinical translation; deployment should await multicenter external validation with prespecified endpoints, robust calibration and decision-curve analyses, and prospective demonstrations of clinical impact.

Standardization and international databases: One of the most significant limitations in CRS+HIPEC applications is protocol differences and data heterogeneity. Variability in the agent used, temperature, perfusion time, and evaluation criteria makes it difficult to compare results in the literature.

Therefore, in recent years, organizations such as the Peritoneal Surface Oncology Group International (PSOGI) and the French RENAPE network have established multicenter databases aimed at strengthening data standardization and quality control processes. Through these platforms, clinical and surgical data obtained from different centers are collected in a common format; thus, treatment efficacy, toxicity profile, and survival analyses can be evaluated more reliably with real-world data.[10]

In the future, the integration of these international data infrastructures with phase III clinical trials and the execution of agent-duration comparisons under standardized designs will further strengthen the evidence-based foundations of CRS+HIPEC applications.

CONCLUSION

Current evidence indicates that CRS is the strongest prognostic factor in the management of peritoneal metastases, while HIPEC may provide additional survival benefit in carefully selected cases with appropriate agent, temperature, and duration parameters. However, current data remain limited due to protocol heterogeneity, agent differences, and variability in patient selection criteria. In the future, the CRS+HIPEC approach will become much more individualized, predictable, and standardized thanks to molecular biomarker-based selection strategies, artificial intelligence-assisted imaging analyses, and the integration of international data sharing networks (e.g., PSOGI, RENAPE). Ultimately, the integration of molecular biomarkers, AI-assisted imaging analytics, and real-world multicenter data will redefine patient selection, procedural precision, and long-term outcomes in CRS±HIPEC, steering peritoneal metastasis management toward a more personalized and evidence-based era.

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This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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