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Management of peritoneal surface malignancies. (cytoreductive surgery, HIPEC, PIPAC, and beyond), 2nd Edition

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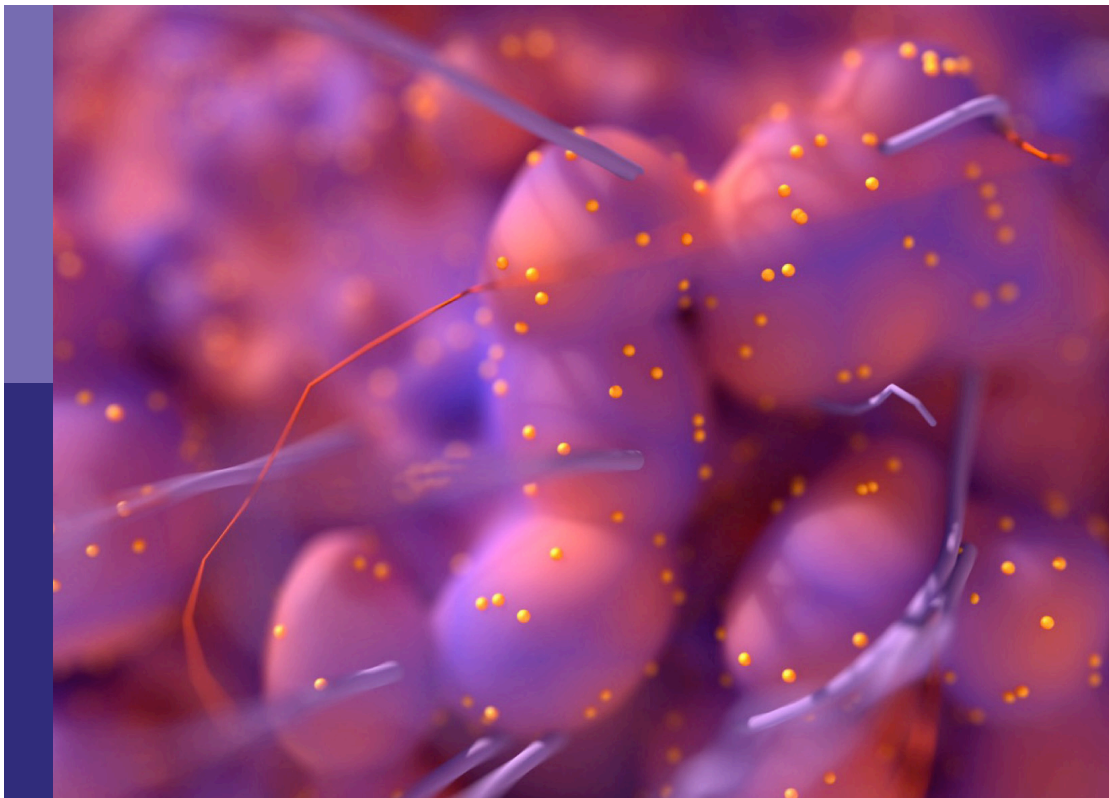

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Management of peritoneal surface malignancies. (cytoreductive surgery, HIPEC, PIPAC, and beyond), 2nd Edition

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Editorial: Management of peritoneal surface malignancies. (cytoreductive surgery, HIPEC, PIPAC, and beyond)

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Editorial on the Research Topic
Management of peritoneal surface malignancies. (cytoreductive surgery, HIPEC, PIPAC, and beyond)

Managing patients afflicted with peritoneal metastases stands as a formidable challenge within the realm of oncology. These individuals grapple with significant tumor growth that infiltrates multiple abdominal organs, leading to a spectrum of symptoms ranging from mild discomfort and early satiety to more severe complications such as ascites, bowel obstruction, and a drastic decline in their overall quality of life.

In recent years, strides in innovative systemic therapies, surgical techniques, and patient selection criteria have markedly improved outcomes for those facing this dire condition. (Mangieri and Levine) The focal point of this Research Topic lies in a comprehensive exploration of peritoneal metastasis treatment, spanning from the broader context of public health, (Aquina et al.) to the intricate molecular levels of intervention. (Breusa et al.).

Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have transitioned from being niche procedures offered by a select group of dedicated surgeons and institutions to becoming globally accessible techniques. The trend towards standardization, exemplified by collaborative efforts such as the study by Bhatt et al., (1) has ushered in a new era in the treatment landscape. Over the past two decades, the number of CRS/HIPEC-performing surgeons has significantly increased worldwide. However, disparities in care provision persist, as evidenced by Aquina et al' s investigation into patient access in the United States and Tan et al's study on the incidence and outcomes of delayed treatment of peritoneal metastasis in Singapore.

While the effectiveness of systemic therapies has been substantiated through rigorous phase III randomized trials, evidence supporting CRS/HIPEC primarily stems from extensive retrospective studies and consensus among expert groups. Notably, CRS/HIPEC has demonstrated remarkable efficacy in managing rare tumor types like

appendix and mesothelioma. Ovarian cancer occupies a pivotal position in this narrative, emerging as a quintessential example of peritoneal surface malignancy. (2) Despite initial resistance from influential figures, it has gained widespread acceptance and found its place in prominent guidelines such as NCCN, ESGO, and the French Guidelines for irresectable disease (3). Recent international collaborative endeavors, such as the Consolidation HIPEC study (CHIPOR), have underscored a substantial survival advantage, particularly in patients with previously platinum-exposed disease. (4) The molecular rationale underpinning this benefit lies in hyperthermia's role, impairing homologous recombination and DNA replication—a topic thoroughly explored by Breusa et al's review on the molecular rationality of locoregional approaches in ovarian cancer. (5). Additionally, the critical question of secondary cytoreductive surgery for recurrent ovarian cancer, as raised by de Bree et al adds depth to our understanding of this evolving field.

Encouragingly, recent surgical outcome data affirm the safety of CRS/HIPEC, aligning it with routinely performed complex oncologic surgeries. This approach has been formally integrated into surgical oncology fellowship training programs, reflecting its growing significance. One notable area of focus revolves around early detection of postoperative complications and the subsequent development of specialized center procedures to rescue patients—a testament to the evolving expertise in this domain.

In navigating this multifaceted terrain of peritoneal metastases, collaborative efforts, innovative techniques, and a relentless commitment to research underscore our progress. As we delve deeper into understanding the molecular intricacies and refine our surgical approaches, the collective aim remains steadfast: to offer not just treatment, but genuine hope and improved quality of life to those bravely battling this complex condition.

Amidst the revolutionary landscape of peritoneal surface malignancy management, a groundbreaking technique has emerged, promising a paradigm shift in the way we approach treatment: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). While still in its developmental phase, PIPAC represents a beacon of hope, offering a highly targeted and minimally invasive alternative for patients battling peritoneal surface metastases (PSM). The ongoing trials and research endeavors surrounding PIPAC signify a promising future, where patients might experience treatments characterized by fewer side effects and quicker recovery times.

A recent retrospective cohort study, (Kefleyesus et al.) conducted across 18 international centers, delved into the realm of PIPAC as a treatment modality for peritoneal surface metastases originating from recurrent or progressive ovarian cancer (OC).

Remarkably, the study demonstrated low morbidity and mortality rates associated with PIPAC, affirming its safety as a palliative treatment option. The promising outcomes observed after three PIPAC cycles not only validated its efficacy but also hinted at the possibility of refining treatment strategies to optimize patient outcomes further.

Looking ahead, collaborative efforts, rigorous research, and a commitment to refining our understanding of molecular intricacies are paramount. By delving deeper into the molecular underpinnings and continuously refining our surgical techniques, we are not

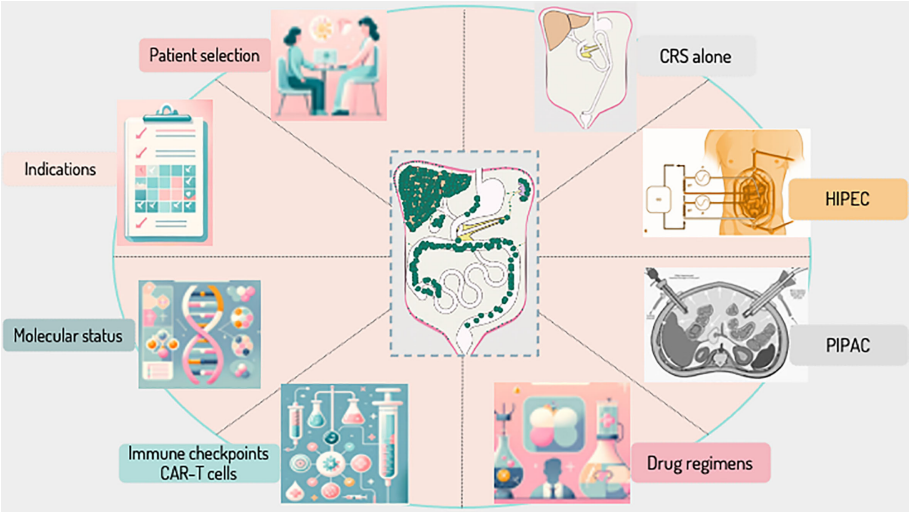

FIGURE 1
Navigating the Uncharted Waters of Peritoneal Surface Malignancy Management – Key Unresolved Questions. This figure delineates the principal uncertainties and ongoing debates in the treatment of peritoneal surface malignancies. It encompasses a spectrum of critical aspects, from patient selection to the intricacies of surgical and chemotherapeutic interventions. Each segment reflects a pivotal area of inquiry: **Patient Selection**: The enigma of creating robust, universally applicable criteria for patient eligibility for advanced treatments. **Complete Cytoreductive Surgery**: The challenge in defining and achieving complete cytoreduction, and the quest for predictive accuracy in preoperative evaluations. **HIPEC**: The pursuit of standardizing Hyperthermic Intraperitoneal Chemotherapy parameters to balance efficacy and safety. **PIPAC**: The exploration of long-term efficacy and safety profiles for Pressurized Intraperitoneal Aerosol Chemotherapy. **Drug Regimen**: The conundrum of optimizing chemotherapeutic agents and regimens tailored to individual patient and tumor profiles. **CAR T-Cells and Checkpoint Inhibitors**: The exploration into identifying predictive markers for responsiveness to CAR T cells and checkpoint inhibitors in the treatment of peritoneal surface malignancies. **Molecular Status**: The challenge of integrating molecular diagnostics into personalized treatment strategies. **Indication of Each Procedure**: The ongoing debate over the specific indications and comparative effectiveness of various treatment modalities.

merely offering treatment but also genuine hope and an improved quality of life to those bravely facing peritoneal surface metastases. The ongoing trials and research endeavors surrounding PIPAC, along with the evolution of established treatments like CRS/HIPEC, underscore our collective dedication to advancing the field. As we navigate this multifaceted terrain, our goal remains steadfast: to enhance not just survival rates but the overall well-being and resilience of patients battling this complex condition.

As we chart the course of progress in the management of peritoneal metastases, numerous unresolved questions emerge, casting a spotlight on the intricacies and challenges inherent in this field. First and foremost, patient selection remains a critical yet ambiguous area, where defining the ideal candidate for advanced interventions like CRS, HIPEC, and PIPAC continues to elude consensus. Additionally, the nuances of complete cytoreductive surgery (CRS) and the optimal parameters for Hyperthermic Intraperitoneal Chemotherapy (HIPEC) present a complex puzzle, one that intertwines surgical precision with therapeutic efficacy. The evolving landscape of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) adds another layer to this multifaceted scenario, promising a less invasive yet equally potent approach but leaving us with questions about its long-term outcomes and optimal application. Furthermore, as we delve into the realm of drug regimens, immunotherapy, and molecular profiling, we confront a myriad of uncertainties about the best treatment combinations, patient-specific therapies, and the molecular underpinnings that could guide our clinical decisions (Figure 1).

In conclusion, as we stand at the intersection of innovative therapies and evolving surgical approaches, the future of peritoneal surface malignancy management holds the promise of personalized, precise, and compassionate care. Our journey is far from over; instead, it is a continuum of discovery and dedication, fueled by the shared vision of a future where peritoneal metastases are not just treatable but conquerable, and where every patient receives the best care possible, regardless of their geographical location or socioeconomic status.

Author contributions

AS: Writing – original draft, Writing – review & editing. NB: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognosis for Young Females with Pseudomyxoma Peritonei of Appendiceal Origin and Unilateral or Bilateral Ovaries Preserved During Cytoreductive Surgery

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Objective: To determine prognosis for young female patients with peritoneal pseudomyxoma (PMP) of appendiceal origin and unilateral or bilateral ovaries preserved during cytoreductive surgery (CRS).

Methods: Clinical data of female patients treated with CRS with or without hyperthermic intraperitoneal chemotherapy (HIPEC) at the Aerospace Center Hospital, Beijing between January, 2009 and December, 2019 were retrospectively reviewed. Patients had no changes in the bilateral ovaries on gross pathological observations or biopsy during CRS, and normal ovarian function. The demographic and clinical characteristics and prognosis of women with ovaries preserved (ovarian preservation group) or resected (ovarian resection group) during CRS were compared. Independent prognostic factors for survival were identified using univariate and multivariate analysis.

Results: 40 patients were included in the final analysis. 19 patients chose ovarian preservation while 21 patients underwent ovarian resection. Completeness of cytoreduction (CCR) scores were CCR-0/1. There were significant differences in age (<40 vs. ≥40), symptoms, intraoperative HIPEC (Y vs. N), and histopathologic subtype of PMP (low-grade vs. high-grade) ($p < 0.001$) between patients in the ovarian preservation and ovarian resection groups. In the ovarian preservation group, median overall survival (OS) was 59 months (range, 53–65 months), and the 5-year survival rate was 37.9%. Median disease-free survival (DFS) was 13 months (range, 9–17 months), and the 5-year recurrence rate was 87.4%. In the ovarian resection group, the 5-year survival rate was 87.7%, and the 5-year recurrence rate was 18.3%. Median OS and median DFS were not reached. In patients with low-grade PMP, median DFS was significantly longer in patients with ovarian resection compared to ovarian preservation ($p < 0.001$). Univariate analysis showed histopathologic subtype of PMP (low-grade vs. high-grade, $p < 0.001$) was significantly associated with OS and

DFS. On multivariate analysis, high-grade histopathologic subtype of PMP was an independent predictor of poor prognosis (OS and DFS).

Conclusion: Histopathologic subtype of PMP represents an independent predictor of prognosis in female patients with PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS. These findings imply that ovarian preservation is a more suitable option for young females with low-grade PMP compared to high-grade PMP. Further prospective studies should be done investigating the role of resection of uninvolved ovaries in PMP.

Keywords: pseudomyxoma peritonei of appendiceal origin, ovarian involvement, CRS and HIPEC, prognostic prediction, female

INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare clinical syndrome that occurs with an incidence of 2 cases per 100 million individuals (1, 2). Most PMP arise from perforation of a primary appendiceal cancer and seeding of tumor cells within the peritoneal cavity (3). The gold standard curative treatment for PMP is complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CCRS/HIPEC) (4, 5).

The majority of women with PMP have involvement of the ovaries due to direct invasion from the adjacent appendix or redistribution of PMP within the peritoneal cavity (6, 7); therefore, ovariectomy is often recommended. However, surgical menopause occurs after bilateral ovariectomy. This can have a negative impact on patient quality of life, especially in young women who wish to have children. There remains an unmet clinical need for effective strategies that preserve fertility in young women with PMP of appendiceal origin and to build consensus on management in cases where the ovaries appear normal during CRS. The objective of this study was to determine prognosis for female patients with PMP of appendiceal origin and unilateral or bilateral ovaries preserved during complete cytoreductive surgery (CCRS). Findings will inform clinicians who manage women with PMP.

MATERIALS AND METHODS

Ethical Approval

The protocol for this study was approved by the Ethics committee of the Aerospace Center Hospital, Beijing, China (No. 20161109-ST-07). Written inform consent for publication of clinical data was obtained from all included patients.

Patient Population

Clinical data of patients with PMP treated at the Aerospace Center Hospital, Beijing between January, 2009 and December, 2019 were retrospectively reviewed. Inclusion criteria were: (1) female; (2) aged 20 to 60 years; (3) diagnosis of PMP of appendiceal origin on histology; (4) initial CRS (radical resection; completeness of cytoreduction [CCR] 0/1) performed at our hospital; and (5) no changes in the bilateral ovaries on gross pathological observations or biopsy during CRS, and normal ovarian function. Exclusion criteria were: (1) PMP derived from other organs or disease (e.g., colon, urachus, and pancreas); (2) previous removal of one or both ovaries; (3) incomplete medical records; or (4) loss to follow-up or death.

A total of 40 patients were included in the final analysis. Patients were divided into two groups: ovarian preservation group, comprising 19 patients who retained at least one ovary during CRS, and ovarian resection group, comprising 21 patients who underwent bilateral ovariectomy during CRS (**Figure 1**).

Surgical Treatment

Patients were treated with CRS with or without HIPEC. Patients underwent CRS to remove visible tumors (6). At our centre, criteria for considering patients for CRS include: (1) aged 20 to 75 years; (2) diagnosis of PMP with histopathologic subtype confirmed by two experienced pathologists; (3) normal liver and kidney function; (3) Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1; (4) history of severe disease affecting other organs; and (5) presence of distant metastasis or another malignant tumor prior to CRS for PMP.

Patient's care goals, personal values, and wishes were incorporated into HIPEC decision-making. For patients undergoing HIPEC, inflow and two outflow catheters were placed in the peritoneal cavity and connected to the HIPEC machine (Jilin Minda Company products, China, Model: RHL-2000B). Cisplatin 60–80 mg or mitomycin (20 mg/m^2) was warmed to 41°C–42°C and circulated intraperitoneally for 60–90 min using a closed-abdomen technique.

Study Parameters

Patients' clinicopathological parameters were recorded, including gender; ECOG performance status; age at diagnosis of PMP; symptoms; time from diagnosis of PMP to CRS for PMP; presence/absence of mucus in the abdominal and/or pelvic cavity; intraoperative peritoneal cancer index (PCI); residual disease following CRS measured as CCR; intraoperative HIPEC; pathological grade of PMP; 5-year survival rate; 5-year recurrence rate; Median overall survival (OS); Median disease-free survival (DFS); and follow-up time.

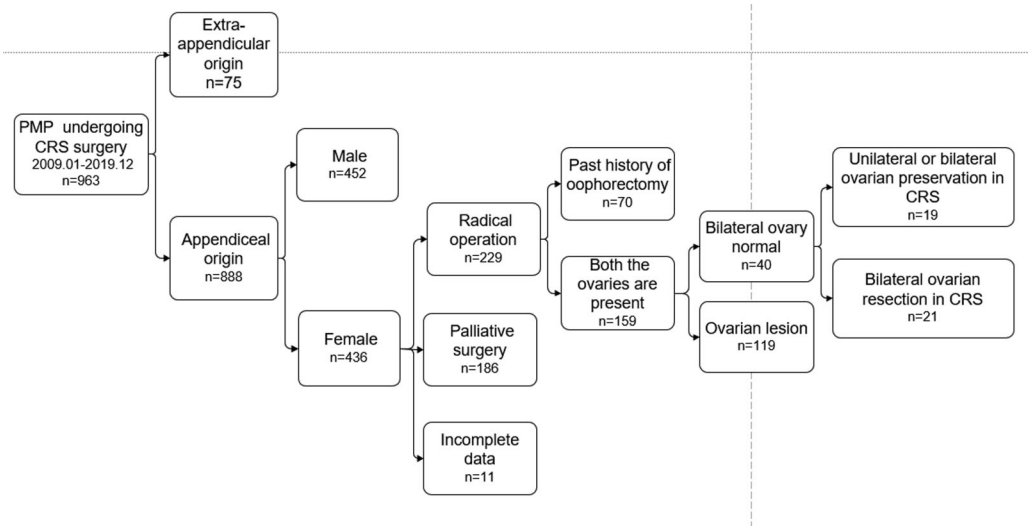

FIGURE 1 | Flow chart of patient selection.

Intraoperative PCI was determined based on tumor size and extent in nine regions in the abdomen and four regions in the small bowel, which were scored on a scale from 0 to 3 and summed (4).

CCR was scored as CCR-0, no macroscopic residual disease, CCR-1, residual disease <2.5 mm, CCR-2, residual disease 2.5 mm–2.5 cm, and CCR-3, residual disease >2.5 cm (5).

Pathological diagnosis was classified according to the 2016 Peritoneal Surface Oncology Group International (PSOGI) criteria (8) as acellular mucin (AC), low-grade mucinous carcinoma peritonei (LG-MCP), high-grade mucinous carcinoma peritonei (HG-MCP), or high-grade mucinous carcinoma peritonei with signet ring cells (HGMC-S).

OS was calculated from the date of CRS/HIPEC to the time of death or last follow-up. DFS was calculated from the date of CRS/ HIPEC to the time of recurrence or last follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS 24.0 (IBM Corporation, Armonk, NY, USA). Continuous data are expressed as medians and range (min, max). Categorical data are expressed as number and percentages. For categorical variables, data were compared using the χ^2 or Fisher's exact test. For continuous variables, normally distributed data were compared with the independent-sample t-test, and non-normally distributed data were compared the Mann-Whitney U test. Independent prognostic factors for survival were identified using univariate survival analysis, which was performed with the Kaplan-Meier method and the log-rank test, and multivariate analysis, which included statistically significant variables in a Cox proportional hazards model. All live patients were censored. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological Characteristics

Among 963 patients with PMP who were treated at the Aerospace Center Hospital, Beijing between January, 2009 and December, 2019, 888 (92%) patients had PMP of appendiceal origin, including 436 (49%) female patients and 452 (52%) males. Among the female patients, 229 (52.5%) patients received a radical resection while 186 (42.7%) patients received palliative debulking surgery.

Patients who received a radical resection were eligible for this study. Of these, 70 patients with a history of oophprectomy and 119 (74.8%) patients with ovarian lesions identified during CRS, including 20 patients who had unilateral ovaries preserved, with macroscopic involvement of the other one, were excluded. Finally, 40 (25.2%) patients with bilateral normal ovaries identified during CRS were included in the analysis, including 19 patients who had unilateral ($n = 4$) or bilateral ovarian ($n = 15$) preservation (ovarian preservation group) during CRS and 21 patients who underwent bilateral ovarian resection (ovarian resection group) during CRS (**Figure 1**).

Patients' demographic and clinical characteristics are shown in **Table 1**. In the ovarian preservation group, patients' median age was 37 years (range, 21–45 years). Median time from diagnosis of PMP to CRS was 1 month. PCI was <20 in 12 (63.2%) patients. Ovarian preservation was bilateral in 15 (78.9%) patients and the left ovary was preserved in 4 (21.1%) patients. CCR scores were CCR-0 in all patients. Pathological diagnosis showed low-grade disease in 10 (52.6%) patients and high-grade disease in 9 (47.4%) patients. In the ovarian resection group, patients' median age was 53 years (range, 46–59 years). Median time from diagnosis of PMP to CRS was 1 month. PCI was <20 in 19 (90.5%) patients. CCR scores were CCR-0 in all patients. Pathological diagnosis showed

TABLE 1 | Patients' demographic and clinical characteristics ($n = 40$).

Characteristics	No. of Patients		*p* value
	Ovarian preservation group	Ovarian resection group	
Age at diagnosis (years)			
Median (range)	37 (21–45)	53 (46–59)	<0.001*
<40	12 (63.2%)	0	
≥40	7 (36.8%)	21 (100%)	
Time from diagnosis of PMP to CRS (months)			
<1	8 (42.1%)	11 (52.4%)	0.516
≥1	11 (57.9%)	10 (47.6%)	
Symptoms			
Abdominal distension	5 (26.3%)	1 (4.8%)	0.047*
Appendix neoplasm	3 (15.8%)	3 (14.3%)	
Appendicitis	5 (26.3%)	3 (14.3%)	
Pelvic mass	3 (15.8%)	1 (4.8%)	
Seroperitoneum	1 (.3%)	1 (4.8%)	
Abdominal pain	2 (10.5%)	12 (57.1%)	
Intraoperative HIPEC			
Yes	3 (15.8%)	21 (100%)	<0.001*
No	16 (84.2%)	0	
PCI			
<20	12 (63.2%)	19 (90.5%)	0.369
≥20	7 (36.8%)	2 (9.5%)	
Ovarian Preservation			
Bilateral	15 (78.9%)	0	
Left-side	4 (21.1%)	0	
Right-side	0	0	
CCR post CRS			
0	19 (100%)	21 (100%)	
1	0	0	
Histopathologic subtype			
LG-MCP	10 (52.6%)	19 (90.5%)	0.007*
HG-MCP	9 (47.4%)	2 (9.5%)	
IVCT post CRS			
Yes	3 (15.8%)	4 (19.0%)	0.787
No	16 (84.2%)	17 (81.0)	

PMP, pseudomyxoma peritonei; CRS, cytoreductive surgery; PSC, previous systemic chemotherapy; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; LG-MCP, low-grade mucinous carcinoma peritonei; HG-MCP, high-grade mucinous carcinoma peritonei; IVCT, Intravenous chemotherapy.

low-grade disease in 19 (90.5%) patients. There were significant differences in age (<40 vs. ≥40), symptoms, intraoperative HIPEC (Y vs. N), and histopathologic subtype of PMP (low-grade vs. high-grade) ($p < 0.05$) between patients in the ovarian preservation and ovarian resection groups. There were no patients who needed secondary surgery because of serious complications in ovarian preservation group, but one patient underwent a second operation for urinary fistula in the ovarian resection group. No patients died within 90 days after CRS in two groups.

Fertility Data

In the ovarian preservation group, most ovaries were preserved to maintain hormone production. 6 women were of child bearing age and wished to have children, and one patient was planning to undergo in vitro fertilization. At the end of follow-up, no patient achieved successful childbirth.

Survival Data

At the last follow-up in June 2021. In the ovarian preservation group, mean follow-up time was 63 months, 9 (47.4%) patients were alive. 10 patients experienced disease progression. Median OS was 59 months (range, 53–65 months), and the 5-year survival rate was 37.9%. Median DFS was 13 months (range, 9–17 months), and the 5-year recurrence rate was 87.4%. In the ovarian resection group, mean follow-up time was 31 months, 19 (90.5%) patients were alive. 2 patients experienced disease progression. The 5-year survival rate was 87.7%, and the 5-year recurrence rate was 18.3%. Median OS and median DFS were not reached (**Figures 2A,B**).

In the ovarian preservation group, patients were stratified by histopathologic subtype of PMP (LG-MCP, $n = 10$; HG-MCP, $n = 9$). Among patients with LG-MCP, median OS was 108 months, and the 5-year survival rate was 71.1%. Median DFS was 15 months (range, 0–30 months), and the 5-year recurrence rate was 75.0%. Among patients with HG-MCP, median OS was 54 months (range, 52–56 months), and the 5-year survival rate was 0%. Median DFS was 11 months (range, 8–14 months), and the 5-year recurrence rate was 100.0% (**Figures 2C,D**).

Among patients with LG-MCP ($n = 29$), median DFS was significantly longer in patients with ovarian resection compared to ovarian preservation ($p < 0.001$), but there was no significant difference in OS ($p = 0.897$). (**Figures 3A,B**). Among patients with HG-MCP ($n = 11$), there were no significant differences in DFS ($p = 0.640$) or OS ($p = 0.315$) between patients with ovarian preservation and ovarian resection (**Figures 4A,B**).

Univariate analysis showed histopathologic subtype of PMP (low-grade vs. high-grade, $p < 0.05$) was significantly associated with OS and DFS (**Tables 2**, **3**). On multivariate analysis, high-grade histopathologic subtype of PMP was an independent predictor of poor prognosis (OS and DFS) **(Tables 2**, **3)**.

DISCUSSION

PMP is a clinical entity characterized by mucinous ascites, peritoneal soft-tissue implants, omental caking, and involvement of the gastrointestinal tract and ovaries. A distinguishing feature of PMP is its redistribution within the peritoneal cavity determined by normal flow of peritoneal

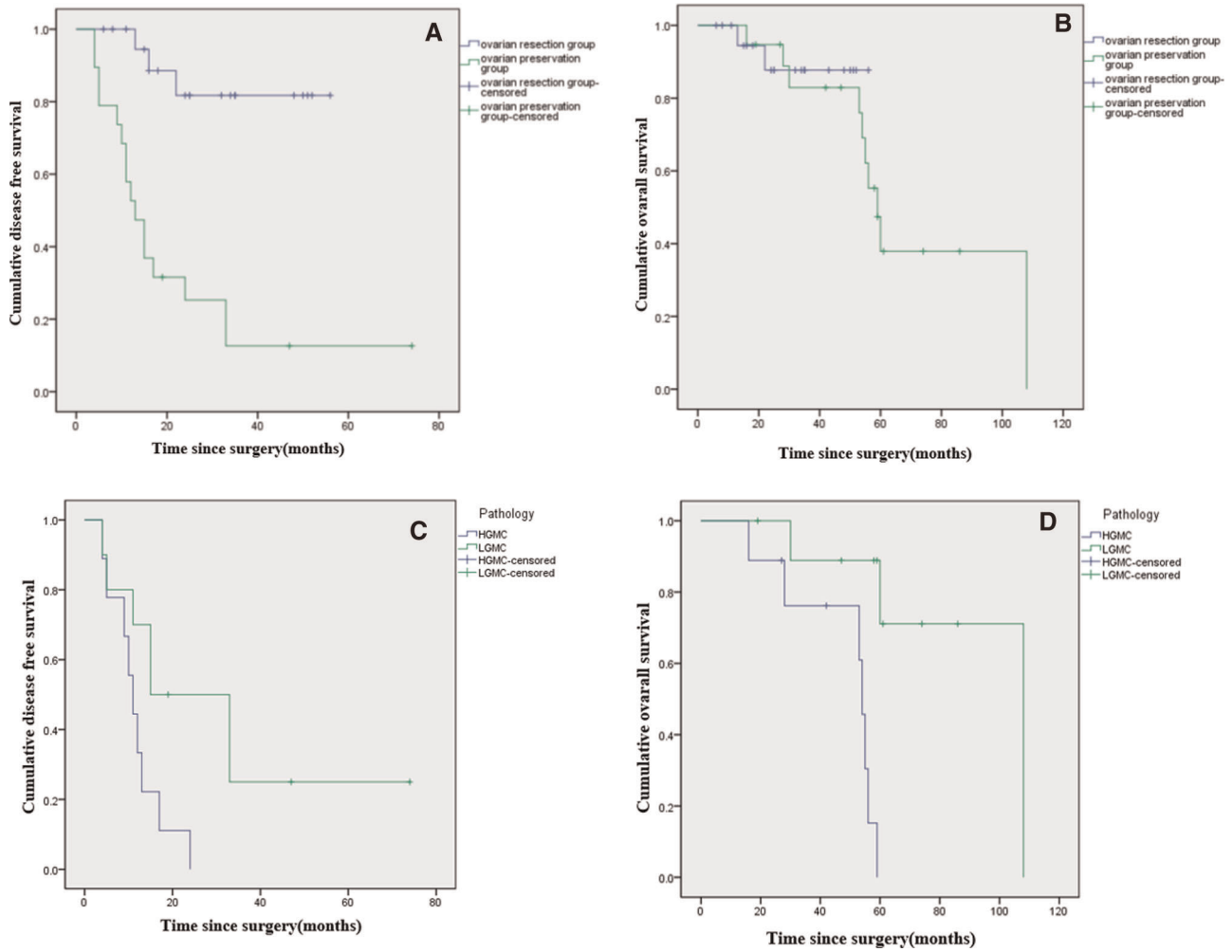

FIGURE 2 | Kaplan-Meier curves showing disease free survival (**A**) and overall survival (**B**) of female patients with PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS. Comparison of disease-free survival (**C**) and overall survival (**D***) based on histopathologic subtype of PMP (low-grade vs. high-grade). (*: $p < 0.05$).

fluid and gravity. In the present study, among the 963 patients with PMP who were treated at the Aerospace Center Hospital, Beijing between January, 2009, and December, 2019, 92% of patients had PMP of appendiceal origin. This rate is consistent with previously reported case series of patients with PMP treated with CRS/HIPEC, among which 89.6%–94% of patients with PMP had a primary appendiceal tumor (8–10). In other patients, PMP may originate from a tumor in the ovary, colon, small bowel, urachus, pancreas, bile duct, stomach, uterine cervix, fallopian tube, mesentery, kidney, extraovarian teratoma, or spleen.

In females, PMP of appendiceal origin usually metastasizes to the peritoneal surface of the ovaries and the uterus. At our center, the probability of ovarian involvement was 74.8% (119/159). A total hysterectomy with bilateral salpingo-oophorectomy may be recommended, regardless of pre-operative gynecologic organ involvement. However, young women may wish to avoid the associated iatrogenic surgical menopause and permanent infertility (11), which can have major psychosocial consequences and a negative impact on the quality of life of the patient and her family. In the present study, there was a significant difference in age between patients who chose to preserve their ovaries during CRS and those who underwent ovarian resection, with younger patients more likely to choose ovarian preservation.

Among the 19 patients with PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS included in our study, 6 desired to have children. At the end of follow-up, only one patient was planning to undergo in vitro fertilization. Our findings showed that PMP recurrence rates rose rapidly two years post-CRS, implying that women who underwent CRS with/without HIPEC for PMP with ovarian preservation should attempt to conceive as soon as possible when the recommended waiting period following therapy is complete (12, 13).

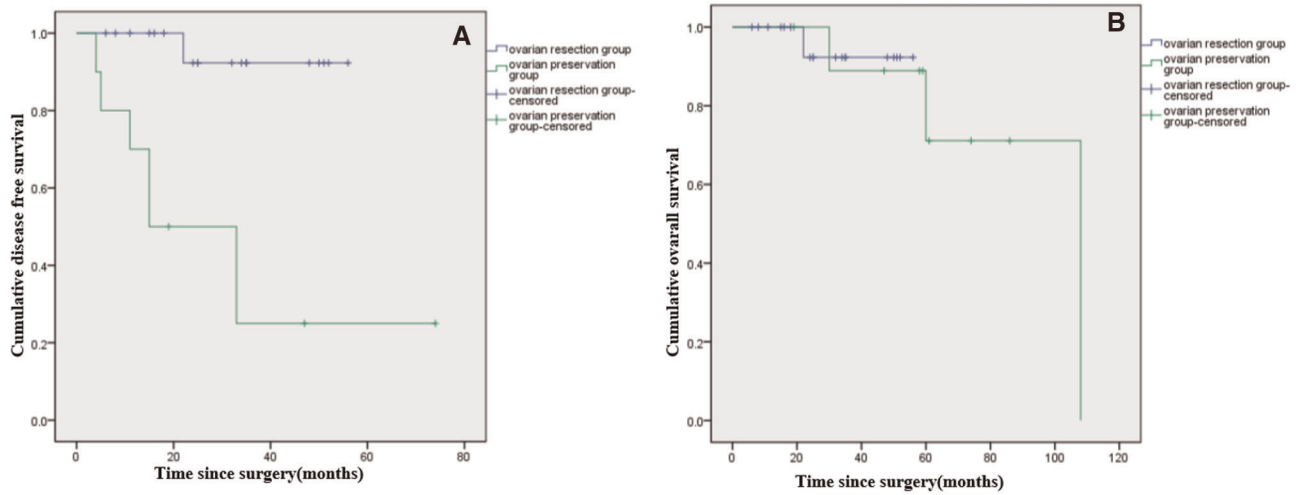

FIGURE 3 | Kaplan-Meier curves showing disease free survival (**A***) and overall survival (**B**) of female patients with low-grade PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS. (*: $p < 0.05$).

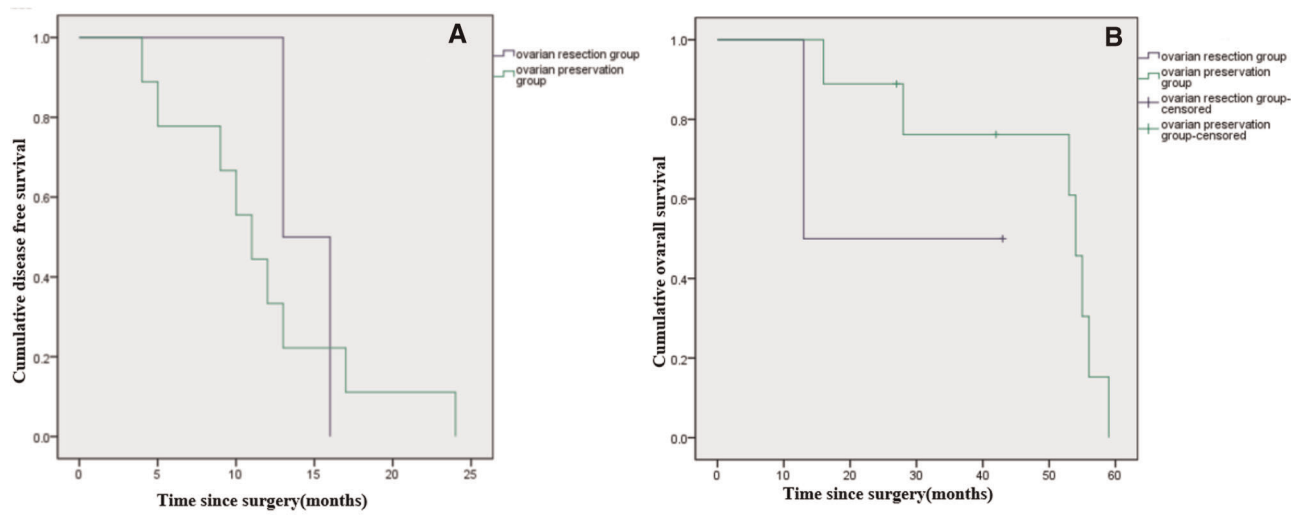

FIGURE 4 | Kaplan-Meier curves showing disease free survival (**A**) and overall survival (**B**) of female patients with high-grade PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS.

In other literature, two small retrospective studies and 5 case reports have investigated the feasibility of ovarian preservation in patients with PMP of appendiceal origin (14–20). One study in four women aged 28–35 years with PMP who sought to maintain fertility adopted a strategy that involved laparoscopy for disease staging followed by appendicectomy, irrigation of the abdominal and pelvic cavity with water, and stripping of macroscopic disease from the peritoneal surface of the pelvis and the surface of the ovaries. All patients had a low-grade appendiceal mucinous neoplasm with acellular mucin or LG-MCP in the peritoneal cavity. After the procedure, all patients conceived and gave birth to healthy babies. After 12–29 months of follow-up, all women were well with no evidence of disease recurrence on radiology or laparoscopy (21). Other women have conceived following treatment with CCRS + HIPEC. In one study, women aged <41 years with peritoneal carcinomatosis of various origins who expressed a strong desire for future pregnancy were treated with CCRS + HIPEC. At least one ovary was preserved in 21 women. Of these, 4 women developed ovarian recurrence after a median follow-up of 32 months, and two women became pregnant (14). An international survey

TABLE 2 | Univariate and multivariate analysis of factors affecting OS ($n = 40$).

Variable	Ovarian preservation group ($n = 19$)			Ovarian resection group ($n = 21$)		
	Univariate *p* value	Multivariate HR (95% CI)	*p* value	Univariate *p* value	Multivariate HR (95% CI)	*p* value
Time from diagnosis of PMP to CRS (<1 vs. ≥1, months)	0.322			0.691		
Mucus in the abdominal cavity (Yes vs. No)	0.639			0.454		
Mucus in the pelvic cavity (Yes vs. No)	0.813			0.929		
Intraoperative HIPEC (Yes vs. No)	0.428			0.528		
PCI (<20 vs. ≥20)	0.089	4.054 (2.295–7.161)	0.606	0.929		
Histopathologic subtype (LG-MCP vs. HG-MCP)	0.012	0.076 (0.008–0.701)	0.023*	0.103		
IVCT post CRS (Yes vs. No)	0.403			0.403		

Abbreviations: *PMP, pseudomyxoma peritonei; CRS, cytoreductive surgery; PSC, previous systemic chemotherapy; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; LG-MCP, low-grade mucinous carcinoma peritonei; HG-MCP, high-grade mucinous carcinoma peritonei; IVCT, Intravenous chemotherapy.*

TABLE 3 | Univariate and multivariate analysis of factors affecting DFS ($n = 40$).

Variable	Ovarian preservation group ($n = 19$)			Ovarian resection group ($n = 21$)		
	Univariate *p* value	Multivariate HR (95% CI)	*p* value	Univariate *p* value	Multivariate HR (95% CI)	*p* value
Time from diagnosis of PMP to CRS (<1 vs. ≥1, months)	0.778			0.274		
Mucus in the abdominal cavity (Yes vs. No)	0.245			0.381		
Mucus in the pelvic cavity (Yes vs. No)	0.204			0.382		
Intraoperative HIPEC (Yes vs. No)	0.174			0.499		
PCI (<20 vs. ≥20)	0.068	1.921 (0.684–5.397)	0.215	0.382		
Histopathologic subtype (LG-MCP vs. HG-MCP)	0.038	0.076 (0.098–0.968)	0.044*	0.942		
IVCT post CRS (Yes vs. No)	0.493			0.096		

Abbreviations: *PMP, pseudomyxoma peritonei; CRS, cytoreductive surgery; PSC, previous systemic chemotherapy; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; LG-MCP, low-grade mucinous carcinoma peritonei; HG-MCP, high-grade mucinous carcinoma peritonei; IVCT, Intravenous chemotherapy.*

reported seven pregnancies in women with PMP, epithelial mesothelioma, or papillary mesothelioma who underwent genital organs-preserving CRS and HIPEC, with delivery of seven newborns. Bilateral ovaries were preserved in 5 women, the left ovary was preserved in one woman, and ovocytes were harvested and cryopreserved in one woman. All women were disease free at 42–106 months of follow-up (15). In a case study, a 28-year-old patient with PMP underwent CRS + HIPEC. Bilateral ovaries were preserved, and the woman spontaneously conceived 14 months after surgery. The pregnancy was uneventful (16).

In our study, among all patients, median OS was 71 months (range, 54–88 months), and the 5-year survival rate was 37.9%. In a previous retrospective study of 2,289 patients from 16 specialized units who underwent CRS for PMP, 10- and 15-year survival rates were 63% and 59%, respectively, treatment-related mortality rate was 2%, and major operative complications occurred in 24% of patients (22). In another study of 42 patients who underwent CRS + HIPEC, 5-year survival rates after first and second CRS were 75.5% and 67.7%, respectively (23). In the present study, the incidence of serious complications and mortality rate was acceptable, but 5-year survival rate was comparatively low, potentially due to the distribution of pathological types. In the ovarian preservation group, 47.4% of patients had HG-MCP, which is associated with a poor prognosis. The ovary is a reproductive and endocrine organ that has a rich blood supply, which may promote tumor growth and metastasis. Consequently, we recommend ovarian resection during CRS in patients with HG-MCP. Meanwhile, the limitations section of our study

provides context around our patient population, stating that the majority of patients were transferred to our institution from a local hospital in poor general condition, which increased their risk of mortality. Patients in this study were treated with CRS with or without HIPEC, and patient's care goals, personal values, and wishes were incorporated into HIPEC decision-making. We believe that this treatment pathway is representative of the clinical situation in the real world.

In our study, among all patients, median DFS was 22 months (range, 12–32 months), and the 5- year recurrence rate was 87.4%, which are higher than reported elsewhere (24). Disparate findings between the present study and previous findings may be explained by differences in the patient populations. We included patients with LG-MCP or HG-MCP, while the previous report focused on patients with LG-MCP. Median DFS among our patients with LG-MCP was 32 months (range, 15–49 months), and the 5-year recurrence rate was 75.0%, which were comparable to the previous report. The present study was conducted at a referral center for myxoma, which may have led to selection bias favoring patients with more severe disease. Most notably, PMP is a rare disease; therefore, small sample size may have affected our findings.

In our study, there was no significant difference in OS in patients with LG-MCP or HG-MCP, whether ovariectomy was performed or not; however, in patients with LG-MCP, median DFS was significantly longer in patients with ovarian resection compared to ovarian preservation This suggests that ovarian preservation may increase risk for disease progression, but has little effect on the final prognosis of the patient. On multivariate analysis, high-grade histopathologic subtype of PMP was an independent predictor of poor prognosis (OS and DFS). This may be related to the growth pattern of the tumor cells and ovarian retention. Ovarian involvement is correlated with the peritoneal extent of PMP and tumor grade. Previous studies showed higher rates of ovarian invasion in patients with grade 2–3 PMP (25); specifically, 62% of ovaries were invaded in patients with grade-1 PMP, and 87.5% of ovaries were invaded in patients with grade 2–3 PMP (26). Other studies confirm these findings (27–30). Interestingly, in our study, neither PCI nor the use of HIPEC were independent predictors of prognosis. This may indicate that radical resection is more important than tumor burden and HIPEC in influencing prognosis.

This study was associated with several limitations. First, this was a retrospective study, and several clinical and histopathological data were lacking, such as the histology of the resected ovaries and intravenous chemotherapy regimen. The two groups were not homogenous to some extent. Second, most patients were transferred to our institution from a local hospital in poor general condition, which increased their risk of mortality. Last, the follow-up time was not long enough, especially for patients with preserved ovaries. Further large-scale studies are needed to confirm our results.

In conclusion, histopathologic subtype of PMP represents an independent predictor of prognosis in female patients with PMP of appendiceal origin and unilateral or bilateral ovaries preserved during CRS. These findings imply that ovarian preservation is a more suitable option for young females with low-grade PMP compared to high-grade PMP. However, the reported data were very limited and further prospective studies should be done investigating the role of resection of uninvolved ovaries in PMP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Ethics committee of the Aerospace Center Hospital, Beijing, China (no. 20161109-ST-07). The patients provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The author contributions were as follows: FF and RM conceived and designed the experiments. DL and RM provided study material or patients. HT and YL collected and assembling data FF and HT analyzed and interpreted the data. FF and HT contributed to the draft of the manuscript. FF, RM, HT, YL, and DL revised the manuscript critically for important intellectual content. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Platinum resistant recurrence and early recurrence in a multi-centre cohort of patients undergoing interval cytoreductive surgery for advanced epithelial ovarian cancer

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Background: Aggressive locoregional therapies like hyperthemic intraperitoneal chemotherapy(HIPEC) and total parietal peritonectomy(TPP) have been used to delay recurrence in patients with advanced ovarian cancer undergoing interval cytoreductive surgery(CRS). The aim of this retrospective study was to evaluate the incidence of platinum resistant recurrence (PRR) and early recurrence (ER)(recurrence within 6 months and 1 year of the last dose of platinum based therapy, respectively) in patients undergoing interval CRS. The secondary goal was to study impact of each of these therapies on PRR and ER.

Methods: One-hundred and fifty-three patients undergoing interval CRS from July 2018 to June 2020 were included. The surgical strategy was to perform a TPP in which the entire parietal peritoneum is resected irrespective of the disease extent or a selective parietal peritonectomy (SPP) in which only the peritoneum bearing visible residual disease is resected. The use of HIPEC was at the discretion of the treating oncologists.

Results: The median surgical PCI was 15 [range, 0-37]. A CC-0 resection was obtained in 119 (77.7%) and CC-1 in 29 (18.9%) patients. Eighty-one (53%) patients had a TPP and 72 (47%) had SPP. HIPEC was performed in 98(64%) patients. Bevacizumab maintenance was administered to 31(19.6%) patients. No patients received PARP inhibitors during first-line therapy. PRR was observed in 8(5.2%) patients and ER in 30(19.6%). The respective incidences of PRR and ER were 4.9% and 16% in the TPP group, 4.1% and 23.6% in the SPP group, 9% and 20% in the no-HIPEC group and 3% and 19.3% in the HIPEC groups. On multivariate analysis,

CC-0(p=0.014) resection and HIPEC(p=0.030) were independent predictors of a low ER. All patients with PR and 70% with ER had peritoneal recurrence with or without extra-peritoneal sites of recurrence.

Conclusions: The incidence of PRR and ER in this cohort was low as compared to historical data. This low incidence could be attributed to the use of aggressive locoregional therapies like TPP and HIPEC. In future, studies should be conducted to confirm these findings and evaluate the potential additive benefit of TPP and HIPEC coupled together as well as their combination with maintenance therapies.

KEYWORDS

advanced ovarian cancer, interval cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy (HIPEC), total parietal peritonectomy, early recurrence, platinum resistant recurrence

Introduction

Advanced ovarian cancer remains an incurable disease despite the advances in surgical strategies and systemic therapies. In stages III-C and IV-A that are treated with a combination of cytoreductive surgery(CRS) and systemic chemotherapy, the sequencing of these treatments has been a topic of debate and research for the past couple of decades (1). Nevertheless, many patients who present with advanced unresectable disease are treated with neoadjuvant chemotherapy(NACT) followed by interval CRS. The reported incidence of platinum resistant recurrence(PRR) is higher in patients undergoing NACT compared to those undergoing primary CRS (2).

The complete resection of macroscopic disease (CC-0 resection) or a complete gross resection (CGR) is one of the most important prognostic factors in ovarian cancer (3). In case of interval CRS, the conventional strategy is to resect only sites of residual macroscopic disease. Some researchers suggested that such a strategy could be insufficient since areas that have responded to NACT may harbor occult disease that has a high likelihood of harboring chemotherapy resistant cells and could increase the risk of recurrence (4, 5). The proposed alternative strategy is to systematically resect the entire parietal peritoneum (total parietal peritonectomy-TPP), that is invariably involved prior to NACT in patients presenting with unresectable disease (6). Though there is no robust evidence demonstrating the benefit of such extensive surgery, early reports show that the morbidity of TPP is acceptable and the incidence (40%) of occult disease in high (7–9). The distribution of residual disease in the peritoneal cavity (significantly higher incidence of both occult and overt disease in the parietal peritoneum compared to the visceral peritoneum) favors this approach (7–9).

The OVHIPEC-1 trial demonstrated the benefit of adding hyperthermic intraperitoneal chemotherapy (HIPEC) to interval CRS (10). The underlying mechanism is probably the ability of HIPEC to address microscopic residual disease more effectively and prevent implantation of free intraperitoneal cancer cells shed during surgery.

Maintenance therapy with the anti-VEGF agent bevacizumab has shown a significantly longer progression-free survival in patients with advanced ovarian cancer, with a benefit in overall survival mainly in patients with suboptimal surgery and stage IV disease (11, 12). For patients with BRCA mutations and mismatch-repair deficiency, the use of Poly ADP-Ribosyl Polymerase(PARP) inhibitors has been associated with a significant benefit in the progression-free (PFS) but overall-survival (OS) results are awaited (13, 14). The role of such maintenance therapies in patients undergoing aggressive locoregional therapies like HIPEC and TPP has not been evaluated.

In this study, our goal was to evaluate the incidence of platinum resistant recurrence and early recurrence (recurrence within 6 months and 1 year of the last dose of platinum based therapy, respectively) in a multi-center cohort of patients undergoing interval CRS. The secondary aim was to study the impact of various prognostic factors including the type of peritonectomy and HIPEC on PRR and early recurrence (ER).

Methods

This is a retrospective analysis of prospectively collected data. Four centers contributed to this study: three from India and one from France. Ethical approval was obtained at all four participating centers (Institutional review board (IRB) no A15-

128 for Hospital Lyon-Sud; specific IRB numbers are not allotted at the three Indian centers). Written informed consent was obtained from all patients. Patients with advanced epithelial ovarian, fallopian tube and primary peritoneal cancer (stage IIIC) undergoing interval CRS following NACT were included in the study. Patients undergoing upfront CRS, second look surgery or those who did not undergo surgery after NACT were excluded. At all centers, patients in whom a CC-0 resection was not deemed possible after the initial work-up that included a staging laparoscopy were treated with NACT. Interval CRS was performed after 3-6 cycles NACT. Imaging comprised of one or more of the following – CT scan, MRI and PET CT and was performed within 15 days of the planned surgical procedure. A re-staging laparoscopy was performed at the discretion of the operating surgeon.

Surgical intervention

All surgical procedures were performed with the goal of obtaining a complete cytoreduction (no visible residual disease). Briefly, a midline incision from the xiphoid to the pubis was employed irrespective of the disease extent. The disease was quantified using Sugarbaker's peritoneal cancer index (PCI) (15). For all patients, the falciform and the umbilical round ligament were systematically resected and visceral resections were performed for organs involved by tumor (16). There were two surgical strategies for addressing the peritoneal disease. At the French center, a selective parietal peritonectomy (SPP) comprising resection of disease bearing areas of the peritoneum and a systematic supracolic omentectomy were performed. At the three Indian centers, a total parietal peritonectomy (TPP) was systematically performed, irrespective of the disease extent, as part of a registered protocol (CTRI 2018/12/016789) (7). TPP comprised the following peritonectomies: pelvic, antero-parietal, right and left upper quadrant together with a total omentectomy (greater and lesser omentectomy). A total mesenteric peritonectomy was not part for that protocol.

The completeness of cytoreduction was reported using the completeness of cytoreduction score (CC-score) (15). A bilateral pelvic and retroperitoneal lymphadenectomy was performed in case of suspicious lymph nodes on imaging or intraoperatively, as per the recommendations after the LION trial.

HIPEC

At the French centre, HIPEC was performed using the OVIHIPEC-1 protocol (Cisplatin 100mg/m² for 90min, combined with intravenous Sodium Thiosulfate), by the closed method, unless there was a contraindication to the procedure (10). HIPEC is an out-of-pocket expenditure for patients in India and was performed only for those who could afford that additional cost and consented for the procedure. HIPEC was performed with cisplatin 75mg/m^2 for 90 minutes by the open (2 centres) or closed method (1 centre). The dose of 100mg/m2 was not used due to the non-availability of sodium thiosulfate (10).

Evaluation of morbidity

The 90-day morbidity and mortality were recorded. The common toxicology criteria for adverse events (CTCAE) version 4.3 classification was used to record the morbidity (17). Grades 3 and 4 were considered major morbidity.

Pathological evaluation

The pathological evaluation was performed using a previously defined protocol for peritonectomy specimens and based on the existing guidelines for the ovarian primary and regional nodes (18, 19). Appropriate immunohistochemistry markers were used to confirm the presence of disease when required. The PeRitOneal MalIgnancy Stage Evaluation online application (e-PROMISE) was used to define anatomical structures in each region of the peritoneal cancer index (20). The peritoneal cavity was divided into 4 regions: the upper region comprising regions 1,2,3, middle region comprising regions 0, 4, 8, the lower region comprising regions 5,6,7 and the small bowel regions (9-12).

The pathological PCI was calculated on the lines of the surgical PCI (21). The retroperitoneal nodes and those dissected with the resected segments of bowel and omentum were analyzed.

The pathological response to chemotherapy was graded based on the chemotherapy response score developed by Bohm et al. (22).

BRCA mutation testing was performed for all patients at the French centre and for selected patients at the Indian centres.

Adjuvant chemotherapy and maintenance therapies

Adjuvant chemotherapy was started within 4-6 weeks of surgery and continued up to 6 cycles. For patients receiving all 6 cycles before surgery, an additional 2 to 3 cycles were administered at the discretion of the treating oncologist. Maintenance therapy with bevacizumab was also at the discretion of the oncologist.

Follow-up

Routine 3-monthly follow-up included clinical exam, CA-125 dosage and cross-sectional imaging studies as deemed suitable for the first two years and 6-monthly thereafter. The diagnosis of recurrence was made according to the Gynecologic Cancer Inter Group (GCIC) criteria (23). Recurrence within 6 months (platinum resistant recurrence) and within 12 months (early recurrence) of completion of the last dose of platinum-based chemotherapy was recorded.

Statistical analysis

Categorical data were described as number (%). Abnormally distributed continuous data were expressed as the median and range. Categorical data were compared with the x2 test. For comparison of means, the independent sample t test was used and for medians, the Mann-Whitney U test was used. A p-value of <0.05 was considered statistically significant. The impact of various prognostic factors on recurrence within 12 months was evaluated using logistic regression analysis. This analysis was only performed on patients who had completed 12 months of follow-up. The prognostic factors that were evaluated were the surgical and pathological PCI, number of NACT cycles, CC-score, HIPEC, lymph node involvement, extent of peritoneal resection (TPP or SPP), chemotherapy response grade (the term is used instead of chemotherapy response score to avoid confusion with CRS), grade 3-4 complications rates and the use of maintenance bevacizumab.

Results

From July 2018 to June 2020, 153 patients undergoing interval CRS with or without HIPEC and having a minimum follow-up of 6 months from the last dose of platinum based chemotherapy were included. All patients had serous carcinoma of the ovary, fallopian tube or that arising from the peritoneum. 101 (66%) patients received 3-4 cycles of NACT and 52 (34%) received more than 4 cycles. The median surgical PCI was 15 [range, 0-37]. A CC-0 resection was obtained in 119 (77.7%) and CC-1 in 29 (18.9%) patients.

HIPEC was performed for 98 (64%) patients (Table 1). 81 (53%) patients had a TPP and 72 (47%) had SPP (Table 2). The 90-day major morbidity was 29.4% (45 patients) and 3 (1.9%) patients died within 90 days of surgery. The details of the complications and a comparison between the HIPEC and non-HIPEC groups are provided in Table 3. Adjuvant chemotherapy was started within 6 weeks for the 147 (96%) patients who received it and 145(94.7%) patients completed the stipulated adjuvant chemotherapy. Bevacizumab maintenance was administered to 31(19.6%) patients. BRCA 1 or 2 mutations were seen in 10/80 (12.5%) patients. No patients received PARP inhibitors.

Pathological findings

The median pathological PCI was 8[range, 0-26] (Table 1). A complete pathological response to NACT was observed in 4 (2.6%) patients and a near complete response in 23 (15.0%). Regional lymph nodes were involved in 46(30.0%) patients. There was residual disease in the upper regions in 94(61.4%) patients and in the small bowel mesentery in 55(35.9%) on pathological evaluation.

Early recurrence

At a median follow-up of 16 months (range, 0-33 months), 46(30.0%) patients developed recurrence or disease progression. Of these, 10(6.5%) patients died of progressive disease. Platinum resistant recurrence (PRR) was observed in 8(5.2%) patients and recurrence within 6-12 months in 22(14.3%). Thus, 30(19.6%) patients developed early recurrence/disease progression (ER). Overall, 134 (87.5%) patients had completed 12 months of follow-up and in these, ER was seen in 23(17.1%) of these 134 patients. The ER of 17.1% in patients with 12 months of follow-up was lower than that of the whole cohort (19.6%) as patients with recurrence within 6-12 months who had not completed 12 months were excluded. Of the 19(12.5%) patients who did not have 12 months of follow-up, 3(1.9%) were dead due to postoperative complications and 4(2.6%) had died of progressive disease. The incidence of PRR and ER in different subgroups in shown in Figure 1.

Factors affecting early recurrence (ER)

On multivariate logistic regression analysis, CC-0 (p=0.014) resection and HIPEC (p=0.030) were associated with reduced recurrence within 12 months (Table 4). This analysis was performed only on the 134 patients that had a 12-month follow-up. A comparison of PRR and ER observed in this study with published literature is provided in Table 5. Though 25% of the patients had a PCI>20 and 75% had a PCI>10, PCI had no impact on the ER (only the comparison between PCI<20 and >20 is presented in this manuscript). Similarly, though a chemotherapy response grade of 3 was significant in the univariate analysis, it was not an independent predictor of ER. Due to the small number of patients, the factors affecting platinum resistant recurrence could not be evaluated.

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TABLE 1 Comparison between patients treated with or without HIPEC.

Clinical parameter		All patients n = 153 (%)	No HIPEC N = 55 (%)	HIPEC N = 98 (%)	p-value
Age	<50	28 (18.3)	12 (21.8)	16 (16.3)	0.399
	>50	125 (81.7)	43 (78.2)	82 (83.7)	
Number of NACT cycles	3-4	101 (66.0)	37 (67.2)	64 (65.3)	0.805
	>4	52 (34.0)	18 (32.8)	34 (34.7)	
Surgical PCI	0-9	37 (24.1)	17 (30.5)	20 (20.4)	0.400
	10-19	77 (50.3)	26 (47.2)	51 (52.0)	
	20-29	36 (23.5)	12 (21.8)	24 (41.3)	
	30-39	3 (1.9)	2 (3.6)	1 (1.7)	
Median surgical PCI		15 [0-37]	13 [0-37]	15 [3-30]	0.540
CC-score	CC-0	119 (77.7)	42 (76.3)	77 (78.5)	0.007
	CC-1	29 (18.9)	8 (14.5)	21 (21.4)	
	CC-2/3	5 (3.2)	5 (9.0)	0 (0.0)	
Peritonectomy approach	SPP	72 (47.0)	8 (14.5)	64 (65.3)	<0.001
	TPP	81 (53.0)	47 (85.5)	34 (34.7)	
Number of peritonectomies	0-6	54 (35.2)	8 (14.5)	46 (46.9)	<0.001
	7	99 (64.8)	47 (85.5)	52 (53.1)	
Organ resections	0-3	71(46.4)	23 (41.8)	48 (48.9)	0.695
	4 -5	59 (38.5)	23 (41.8)	36 (36.7)	
	>5	23 (15.0)	9 (16.3)	14 (14.2)	
Grade 3-4 complications		45 (29.4)	9 (16.3)	36 (36.7)	0.002
90-day mortality		3 (1.9)	0 (0.0)	3 (3.0)	0.643
Pathological PCI	0-9	85 (55.5)	30 (54.5)	55 (56.1)	0.922
	10-19	61 (39.8)	22 (40.0)	39 (39.7)	
	20-29	7 (4.5)	3 (5.4)	4 (4.0)	
	30-39	0 (0.0)	0 (0.0)	0 (0.0)	
Median pathological PCI		8 [0-26]	9 [0-26]	8 [0-26]	0.430
Involvement of upper regions		94 (61.4)	33 (60.0)	61 (0.0)	0.784
Small bowel involvement		55 (35.9)	17 (30.9)	38 (38.7)	0.330
Chemotherapy response score	CRG	4 (2.6)	1 (1.8)	3 (3.0)	0.887
		23 (15.0)	8 (14.5)	15 (15.3)	
		126 (82.3)	46 (83.6)	80 (81.6)	
Regional lymph node involvement		46 (30.0)	14 (25.4)	32 (32.6)	0.351
BRCA 1 or 2 mutations*		10 (6.5)*	1(1.8)	9 (9.1)	0.076
Bevacizumab		31 (19.6)	2 (1.8)	29 (29.5)	<0.001
Recurrence within 6 months of surgery		8 (5.2)	5 (9.0)	3 (3.0)	0.107
Recurrence in 6-12 months		22 (14.3)	6 (10.0)	16 (16.3)	0.359
Recurrence in 0-12 months		30 (19.6)	11 (20.0)	19 (19.3)	0.972

*10/80 (12.5%) patients in whom BRCA testing was done.

Patients treated with or without HIPEC

There were more CC-2/3 resections in patients not undergoing HIPEC (p=0.007) (Table 1). The proportion of patients undergoing SPP (p<0.001) and receiving maintenance bevacizumab (p<0.001) was higher in the HIPEC group. Major complications (including the systemic toxicity caused due to HIPEC) were significantly higher in the HIPEC group (Table 3). Platinum resistant recurrence (p=0.107) as well as early recurrence (p=0.972) were similar in the two groups.

Patients treated with TPP or SPP

Patients treated with TPP were younger (p=0.009) and this group had more patients with a surgical PCI>10 (p=0.060)(Table 2). The number of peritonectomies (p<0.001) and visceral resections (p=0.004) was higher in the TPP group. More patients undergoing SPP were treated with HIPEC (p<0.001) and maintenance bevacizumab (p<0.001). The incidence of platinum resistant recurrence (4.9% versus 4.1%; p=0.577) and early recurrence (16.0% versus 23.6%; p=0.436) was similar in the two groups. However, recurrence within 6-12 months was higher in the SPP

TABLE 2 Comparison of patients treated with TPP and SPP^.

Clinical parameter		All patients n = 153 (%)	TPP N = 81 (%)	SPP N = 72 (%)	p-value
Age	<50	28 (18.3)	21 (25.9)	7 (9.7)	0.009
	>50	125 (81.7)	60 (74.1)	65 (90.3)	
Number of NACT cycles	3-4	101 (66.0)	59(72.8)	42 (58.3)	0.058
	>4	52 (34.0)	22 (27.2)	30 (41.7)	
Surgical PCI	0 - 9	37 (24.1)	15 (18.5)	22 (30.5)	0.060
	10 - 19	77 (50.3)	38 (46.9)	39 (54.1)	
	20 - 29	36 (23.5)	25 (30.8)	11 (15.2)	
	30 - 39	3 (1.9)	3 (3.7)	0 (0.0)	
Median surgical PCI		15 [0-37]	15 [0-37]	13 [0-28]	0.131
CC - score	CC-0	119 (77.7)	58 (71.6)	61 (84.8)	0.133
	CC - 1	29 (18.9)	18 (22.2)	11 (15.2)	
	CC - 2/3	5 (3.2)	5 (6.1)	0 (0.0)	
HIPEC		98	34 (41.9)	64 (88.8)	<0.001
Number of peritonectomies	0 - 6	54 (35.2)	0 (0.0)	54 (75.0)	<0.001
	7	99 (64.8)	81 (100.0)	18 (25.0)	
Organ resections	0 - 3	71(46.4)	29 (35.8)	42 (58.3)	0.004
	4 - 5	59 (38.5)	34 (41.9)	25 (34.7)	
	>5	23 (15.0)	18 (22.2)	5 (6.9)	
Grade 3-4 complications		45 (29.4)	15 (18.5)	30 (41.6)	0.001
90-day mortality		3 (1.9)	3 (3.7)	0 (0.0)	0.363
Pathological PCI	85	85 (55.5)	39 (48.1)	46 (63.8)	0.142
	61	61 (39.8)	38 (46.9)	23 (31.9)	
	7	7 (5.5)	4 (4.9)	3 (4.1)	
	0	0 (0.0)	0 (0.0)	0 (0.0)	
Median pathological PCI		8 [0-26]	10 [0-26]	7 [0-21]	0.080
Involvement of upper regions		94 (61.4)	52 (64.1)	42 (58.3)	0.456
Small bowel involvement		55 (35.9)	27 (33.3)	28 (38.8)	0.474
Chemotherapy response score		4 (2.6)	2 (2.4)	2 (2.7)	0.928
		23 (15.0)	13 (16.0)	10 (13.8)	
		126 (82.3)	66 (81.4)	60 (83.3)	
Regional lymph node involvement		46 (30.0)	27 (33.3)	19 (26.3)	0.349
BRCA 1 or 2 mutations		10 (6.5)*	2 (2.4)	8 (11.1)	0.998
Bevacizumab		31 (19.6)	0 (0.0)	31 (43.0)	<0.001
Recurrence in 0-6 months of surgery		8 (5.2)	5 (4.9)	3 (4.1)	0.577
Recurrence in 6-12 months		22 (14.3)	8 (6.1)	14 (19.4)	0.092
Recurrence in 0-12 months		30 (19.6)	13 (16.0)	17 (23.6)	0.436

^TPP was performed at the 3 Indian centers and SPP at the French center.
*10/80 (12.5%) patients in whom BRCA testing was done.

group (6.1%versus 19.4%; p=0.092) though this difference was not statistically significant.

Patients treated with and without bevacizumab

The 31 patients who received maintenance therapy with bevacizumab were all treated with SPP and 29 of these patients were treated with HIPEC. Further details have been provided in Table 6.

Site of recurrence

Due to the retrospective nature of this study, the description of sites of recurrence differed among different centers. At one center, they were reported as peritoneal and extra-peritoneal (included nodal and visceral metastases) whereas the other centers recorded every site of disease recurrence. All eight patients with PRR had peritoneal involvement of which half the patients had isolated peritoneal recurrence (Table 7). Of the 30% that developed ER, 40% had isolated peritoneal recurrence, 30% had only extra-peritoneal recurrence while 30% had peritoneal and extraperitoneal recurrence both (Table 8). There was no significant difference in the peritoneal and non-peritoneal recurrence between patients undergoing TPP and SPP and those receiving and not-receiving HIPEC (Table 9).

Discussion

In this study incidence of platinum resistant recurrence (5.2%) and early recurrence(19.6%) following the last dose of

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TABLE 3 Major complications occurring within 90-days of surgery in patients undergoing interval cytoreductive surgery with or without HIPEC.

Complication	All patients n = 153 (%)	No HIPEC N = 55 (%)	HIPEC N = 98 (%)	p-value
Total number of patients with major complications	45 (29.4)	9 (16.3)	36 (36.7)	0.002
Haemorrhage	6 (3.9)	1 (1.8)	5 (5.1)	0.315
Bowel fistula	6 (3.9)	3 (5.4)	3 (3.0)	0.507
Intestinal perforation	0 (0.0)	0 (0.0)	0 (0.0)	.
Anastomotic leak	0 (0.0)	0 (0.0)	0 (0.0)	.
Other GI complications	6 (3.9)	1 (1.8)	5 (5.1)	0.097
Respiratory complications	9 (5.8)	4 (7.2)	5 (5.1)	0.583
Cardiac complications	7 (4.5)	1(1.8)	6 (6.1)	0.221
Urologic complications	0 (0.0)	0 (0.0)	0 (0.0)	.
Nephrotoxicity	2 (1.3)	0 (0.0)	2 (2.0)	0.924
Hematologic toxicity	15 (9.8)	0 (0.0)	15 (15.3)	0.052
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	.
Systemic sepsis	3 (1.9)	1 (1.8)	2 (2.0)	0.924
Surgical site infection	3 (1.9)	0 (0.0)	3 (3.0)	0.650
Wound dehiscence	2 (1.3)	2 (3.6)	0 (0.0)	0.262
Intrabdominal abscess	1 (0.6)	1 (1.8)	0 (0.0)	0.656
Post op ascites/fluid collection	9 (5.8)	5 (9.0)	4 (4.0)	0.206
90-day post-operative mortality	3 (1.9)	0 (0.0)	3 (3.0)	0.650

platinum based therapy was low compared to historical data from randomized trials that included patients undergoing interval CRS (Table 5). HIPEC and CC-0 resection were the only independent predictors of a low ERR.

PRR is an important end-point in ovarian cancer as it is associated with a poorer response to subsequent chemotherapy and a poorer overall survival (28). Though patients with asymptomatic recurrence may have a better outcome than those with symptomatic recurrence, the overall prognosis of these patients is poorer compared to those with platinum sensitive disease (28). Similarly, patient who recur from 6-12 months have partially platinum sensitive disease that has a poorer outcome compared to platinum sensitive recurrence.

The impact of aggressive/extensive surgery

There were two surgical strategies– resecting only sites of residual disease and resecting the entire parietal peritoneum along with viscera bearing residual disease. In this regard, only patients with stage III-C that have unresectable disease at presentation are

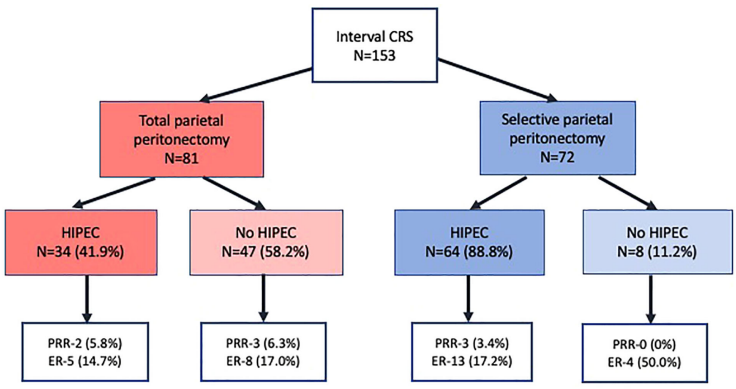

FIGURE 1
Platinum resistant recurrence and early recurrence in 153 patients undergoing interval cytoreductive surgery.

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TABLE 4 Factors affecting recurrence within 12 months of surgery (logistic regression analysis)*.

Prognostic variable (N)		Univariate analysis	Multivariate analysis	
		p-value	Hazard ratio [95% CI]	p-value
Surgical PCI	<20 >20	0.510		
CC-score	CC-0 CC-1-3	0.001	2.98 [2.5-38]	0.014
Pathological PCI	<15 >15	0.331		
HIPEC	Yes No	0.121		
Grade 3-4 complications	Yes No	0.121		
Lymph node involvement	Yes No	0.490		
Chemotherapy response grade	3** 1-2	0.031	NS^	
Extent of peritoneal resection	TPP SPP	0.570		
HIPEC	Yes No	0.020	1.77 [1.1-20]	0.030
Use of maintenance bevacizumab	Yes No	0.590		

*This analysis was performed on 134 patients who had completed 12 months of follow-up.
**Includes patients with a complete and near complete response.
^NS, Not significant.

included in the study and the entire parietal peritoneum is usually involved in these patients. Thus, in patients treated with TPP, peritoneum that was never involved is not removed. Previous studies on the distribution of residual disease have shown that following NACT, the parietal peritoneum is the most common site of occult disease (7). The visceral peritoneum (except the omenta) has less occult and overt disease both. Occult disease following NACT harbors chemotherapy resistant stem cells that may not be eradicated completely with adjuvant chemotherapy and TPP is performed to address this disease more effectively (4).

TABLE 5 Platinum resistant recurrence and early recurrence observed in the current study and that reported in published literature.

Sub-group [ref]	N	CC0/1	Optimal debulking	Platinum resistant recurrence N (%)	Early recurrence N(%)
Current study All patients	153	96.6%	100%	8 (5.2)	30 (19.6) 23(17.1%)/134 with 12 months follow-up
SOLO-1 trial Interval CRS (Olaparib arm) (24)	94	81%	–	12 (12.7)	23 (24.4)
SOLO-1 trial CC-0 resection (Olaparib arm) (24)	200	100%	–	23 (11.5)	33(16.5)
SOLO-1 trial -BRCA mutations (Olaparib arm) (24)	257	76.6%	–	31(12.0)	56 (21.7)
PRIMA trial (Niriparib arim) (14)	487	–	–	175 (35.9)	320 (65.7)
PAOLA-1 -BRCA mutated tumors (olaparib arm)	157	–	–	7 (3.8)	13 (8.2)
EORTC-NCIC trial NACT arm (25)	334	45.5%	80.6%	–	179 (53.5)
CHORUS trial NACT arm (26)	274	39%	73%	76 (27.7)	155 (56.5)
SCORPION trial (NACT arm) (27)	87	77%	98.6%	–	24(27.5)
OVIHIPEC-1 trial; HIPEC arm (10)	122	69%	98%	–	55 (45.0)

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TABLE 6 Comparison between patients treated with and without bevacizumab.

Clinical parameter		All patients N = 153 (%)	With Bev N = 31 (%)	Without Bev N = 122 (%)	p-value
Age	<50	28 (18.3)	1 (3.2)	27 (22.1)	0.015
	>50	125 (81.7)	30 (96.8)	95 (77.9)	
Number of NACT cycles	3-4	101 (66.0)	20 (64.5)	81 (66.3)	0.843
	>4	52 (34.0)	11(35.5)	41 (33.7)	
Surgical PCI	0-9	37 (24.1)	9 (29.0)	28 (22.9)	0.442
	10-19	77 (50.3)	18 (58.0)	59 (48.3)	
	20-29	36 (23.5)	4 (12.9)	32 (26.2)	
	30-39	3 (1.9)	0 (0.0)	3 (2.4)	
Median surgical PCI		15 [0-37]	13 [3-28]	14 [0-31]	0.110
CC-score	CC-0	119 (77.7)	25 (80.6)	94 (77.0)	0.967
	CC-1	29 (18.9)	6 (19.4)	23 (18.8)	
	CC-2/3	5 (3.2)	0 (0.0)	5 (4.0)	
HIPEC		98	29 (93.5)	69 (56.5)	<0.001
Peritonectomy approach	TPP	81(53.0)	0 (0.0)	81(66.3)	<0.001
	SPP	72 (47.0)	31 (100.0)	41 (33.7)	
Number of peritonectomies	0-6	54 (35.2)	19 (61.2)	35 (28.6)	<0.001
	7	99 (64.8)	12 (38.8)	87 (71.4)	
Organ resections	0-3	71(46.4)	18 (58.0)	53 (43.4)	0.208
	4-5	59 (38.5)	11(35.5)	48 (39.3)	
	>5	23 (15.0)	2 (6.4)	21 (17.2)	
Grade 3-4 complications		45 (29.4)	5 (6.1)	40 (32.7)	0.069
90-day mortality		3 (1.9)	0 (0.0)	3(2.4)	0.811
Pathological PCI	0-9	85 (55.5)	17 (54.8)	68 (55.7)	0.853
	10-19	61 (39.8)	12 (38.8)	49 (40.1)	
	20-29	7 (5.5)	2 (6.4)	5 (4.0)	
	30-39	0 (0.0)	0 (0.0)	0 (0.0)	
Median pathological PCI		8 [0-26]	7 [0-21]	9 [0-26]	0.540
Involvement of upper regions		94 (61.4)	19 (61.2)	75 (61.4)	0.984
Small bowel involvement		55 (35.9)	13 (41.9)	42 (34.4)	0.436
Chemotherapy response score		4 (2.6)	0 (0.0)	4 (3.2)	0.991
		23 (15.0)	5 (16.1)	18 (14.7)	
		126 (82.3)	26 (83.9)	100 (81.9)	
Regional lymph node involvement		46 (30.0)	9 (29.0)	36 (29.5)	0.958
Recurrence in 0-6 months of surgery		8 (5.2)	1 (3.2)	7 (6.5)	0.574
Recurrence in 6-12 months of surgery		22 (14.3)	7 (22.5)	15 (12.2)	0.144
Recurrence in -12 months		30 (19.6)	8 (36.3)	22 (18.0)	0.330

The SPP performed in this study was performed at an expert center where the entire peritoneal region in which the disease bearing peritoneum region lies is resected. This surgery is likely to be more extensive than the SPP performed at many other gynecologic oncology units considering that nearly 80% of patients had a diaphragmatic peritonectomy in the SPP group. Upper abdominal procedures were performed in 37.8% patients in the NACT arm of the SCORPION trial (29).The surgeons also systematically resected the lesser omentum, the falciform and umbilical round ligament that are common sites of residual

TABLE 7 Sites of recurrence in 8 patients who developed platinum resistant recurrence.

	Peritoneum alone	Peritoneal and extraperitoneal	Peritoneal and pleural	Peritoneal and nodal
All patients (n = 8)	4	2	1	1
TPP (N = 5)	2	1	1	1
SPP (N = 3)	2	1	0	0
HIPEC (N = 5)	3	1	0	1
No HIPEC (N = 3)	1	1	1	0

TPP, total parietal peritonectomy; SPP, selective parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

TABLE 8 Sites of recurrence in all 30 patients who developed early recurrence.

Treatment group	Peritoneum alone N (%)	Peritoneal and extraperitoneal N (%)	Extraperitoneal alone N (%)	Nodal alone* N (%)	Peritoneal and pleural* N (%)	Peritoneal and nodal* N (%)	Liver alone* N (%)
All patients (N = 30)	12 (40)	4 (13.3)	7 (23.3)	1(3.3)	2 (6.6)	3 (10)	1(3.3)
TPP (N = 13)	5 (38.4)	0 (0.0)	1 (7.6)	1 (7.6)	2 (15.3)	3(23.0)	1(7.6)
SPP (N = 17)	7 (41.1)	4 (23.5)	6 (35.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HIPEC (N = 18)	7 (38.8)	3 (16.6)	6 (33.3)	0 (0.0)	0 (0.0)	1(5.5)	1(5.5)
No-HIPEC (N = 12)	5 (41.6)	2 (16.6)	1 (8.3)	1 (8.3)	2 (16.6)	1(8.3)	0 (0.0)

*Some of these recurrences were reported as extra-peritoneal or peritoneal and extra-peritoneal.
TPP, total parietal peritonectomy; SPP, selective parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

disease. Another difference was the significantly higher number of patients receiving both HIPEC and bevacizumab in the SPP group. These could be some of the reasons for the lack of difference in PRR and ER between the TPP and SPP groups.

It has been clearly demonstrated that there is benefit of having no residual disease (complete gross resection-CGR) following NACT over optimal cytoreduction (<1cm residual disease) (3, 27). And it may be questioned why the benefit should stop at a CGR and not be obtained when the occult disease is resected more completely. Even with a TPP, it is impossible to identify and resect all sites of occult disease but the amount of occult residual disease can be substantially reduced.

HIPEC

HIPEC has shown a benefit in PFS and OS both in addition to CRS alone in the interval setting (10). HIPEC addresses microscopic residual disease and the combination of cisplatin with heat has the potential to overcome platinum resistance (30). A significantly higher proportion of patients in the SPP group received HIPEC, which could be another factor responsible for the similar rates of PRR and ER in the two groups. Assumedly, HIPEC should add to the benefit of TPP and may not be replacement for it. Whereas a TPP removes occult disease from the parietal peritoneum more effectively, HIPEC has the additional benefit of addressing free intraperitoneal cancer cells shed during surgery and preventing their implantation at sites of resection. The benefit of the combination of TPP and HIPEC should be evaluated in future studies.

Impact of other prognostic factors

Though PCI is not an established prognostic factor in advanced ovarian cancer, several studies have shown an inferior survival in patients with a high PCI (31–33). This factor had no impact on ER in this study. Thus, even patients with more extensive surgery (25% with PCI>20 in this study) had a low PRR and ER in this study.

Chemotherapy response grade was not an independent predictor of ER and it may be inferred that TPP and HIPEC

TABLE 9 Peritoneal and non-peritoneal recurrence in 8 patients that developed platinum resistant recurrence and 30 patients that developed early recurrence.

Treatment group	All sites of recurrence	Peritoneal recurrence	Non-peritoneal recurrence	p-value
Platinum Resistant Recurrence				
All patients (N = 153)	8 (5.2%)	8 (100%)	0 (0.0)	
TPP (N = 81)	5 (3.7%)	5 (100%)	0 (0.0)	0.673
SPP (N = 72)	3 (4.1%)	3 (100%)	0 (0.0)	
HIPEC (N = 98)	3 (3.0)	3 (100%)	0 (0.0)	0.709
No- HIPEC (N = 55)	1 (1.8)	1 (100%)	0 (0.0)	
Early Recurrence				
All patients (N = 153)	30 (19.6)	21 (70.0)	9 (30.0)	
TPP (N = 81)	13 (16.0)	10 (76.9)	3 (23.1)	0.469
SPP (N = 72)	17 (23.6)	11 (64.7)	6 (35.3)	
HIPEC (N = 98)	18 (18.3)	11 (61.1)	7 (38.9)	0.193
No- HIPEC (N = 55)	12 (21.8)	10 (83.3)	2 (16.7)	
PCI	15 [0-37]	18 [5-37]	10 [2-19]	0.213

TPP, total parietal peritonectomy; SPP, selective parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal cancer index.

could delay recurrence in sub-groups of patients that have a poorer response to systemic chemotherapy (22).

Morbidity and mortality

The overall major morbidity of 30% and mortality of 1.9% compares well with published literature and could be considered acceptable (24, 25, 34). The 90-day morbidity was considered and even the systemic toxicity was included in this evaluation which explain the incidence of 30%. The morbidity was significantly higher in the HIPEC group (Table 3). This was mainly due to the hematological side effect of HIPEC which are not observed in patients that do not undergo HIPEC.

The morbidity in the SPP group was also higher due to more number of patients receiving HIPEC in this group. There was no mortality in the SPP group and all patients started adjuvant chemotherapy within 6 weeks of surgery. Three deaths occurred in the TPP group and all three patients received HIPEC. This is the average rate of post-operative mortality at Indian centers as reported in previous studies (7, 26). One patient died of hemorrhagic shock and two others of systemic sepsis that occurred in absence of gastrointestinal complications.

Maintenance therapy with bevacizumab

Maintenance therapy with bevacizumab has shown a benefit in overall-survival in patients with suboptimal debulking and those with stage IV disease (11, 12). In all the trials evaluating the role of maintenance bevacizumab, It's benefit in patients who have a complete cytoreduction has not been demonstrated (11, 12). The use of bevacizumab was at the discretion of the treating physician in this study and in the univariate analysis it had no impact on ER. It has been shown that the benefit of bevacizumab is short lived and wears of soon after discontinuation of therapy. The optimal duration of maintenance therapy with bevacizumab has still not been determined. We presume that bevacizumab should be an adjunct to aggressive locoregional therapies and not a substitute for them and its role in patients undergoing TPP and/or HIPEC should be evaluated in future studies.

Maintenance therapy with PARP inhibitors

Similarly, PARP inhibitors were not used for all patients, even those with BRCA mutations as the evidence for its benefit in different subgroups was only evolving at the time of this study. For Indian patients, the cost is the main limiting factor. In patients with BRCA 1 and 2 mutations in different randomized trial, the PRR and ER rates were similar or more than those in our study(Table 5). This comparison is not ideal considering that the intention-to-treat population is considered in the survival analysis in these trials and that includes approximately 10-15% of the patients that never had surgery. But even if these patients were excluded, the reduction in the PRR and ER would not be more than 2-3%. Thus, similar rates of ER and PRR were achieved with our locoregional strategies without the maintenance therapies. In the subgroup analysis of the SOLO 1 trial, 11.5% of the patients with a CGR recurred at 6 months and 16.7% at 12 months which is similar to the results in this study (Table 5) (35). The benefit of aggressive locoregional therapies in patients with BRCA mutations who receive maintenance therapy needs further evaluation; our presumption is that the benefit could be additive.

Site of PRR and ER

Though the reporting of sites of recurrence was not uniform, we were able to distinguish between the peritoneal and non-peritoneal recurrences. All patients with PRR had peritoneal recurrences while 70% of the ERs were peritoneal with or without extra-peritoneal recurrences. There is limited information on the sites of recurrence in patients with PRR in literature. Petrillo et al. found peritoneal recurrence in nearly 50% and isolated nodal recurrence in the remaining 50% of the patients undergoing secondary CRS for PRR (36). They did not report the sites of recurrence in the whole cohort of 268 patients with PRR and hence our findings cannot be compared to this study. The incidence of isolated nodal recurrences in this study was low though we have not been able to capture the exact incidence. It has been shown that patients with isolated nodal recurrences are more likely to undergo secondary CRS and these recurrences are less chemosensitive (37). There was no difference in the peritoneal recurrence rate in patients undergoing TPP and SPP though this comparison is not ideal since a significantly higher number of patients in the SPP group received HIPEC. TPP and HIPEC should both reduce the incidence of peritoneal recurrence and thus, prolong survival. Our findings however cannot be generalized to all patients in this study as the sites of late recurrence may not be the same as that of early recurrence. Moreover, not all peritoneal recurrences are the same- there are isolated recurrences that are amenable to surgery, non-isolated asymptomatic recurrences and more widespread recurrences that produce symptoms early on. The pattern of recurrence following TPP should be an area of future study.

Strengths, limitations and future directives

This study has many limitation beginning with the inherent bias that exists in all retrospective studies. The number of

patients in different subgroups is small (TPP versus SPP and HIPEC versus no-HIPEC). The major shortcoming of this study is the comparison of different populations: the SPP patients were French, and routinely underwent HIPEC after CRS. In the Indian population, which is fundamentally different in terms of the healthcare system, HIPEC was only performed in patients who can afford the cost of treatment. The use of maintenance therapies was not uniform which adds to the heterogeneity in the patient population. The main strengths of this study are that data were collected prospectively and surgery was performed according to predefined protocols at all centers. Meticulous disease mapping was done during surgery and on pathology using the PCI. The study included patients with extensive disease- over 60% had residual disease in the upper abdominal regions and 35% on the small bowel mesentery on pathology. Despite the limitations of this study, the reduction in both PRR and ER is significant (75%) compared to that reported in randomized trials on interval CRS which is the main reason for presenting these results early on (Table 5) (38, 39). These results need to be confirmed in larger and more homogeneous patient cohorts. The follow-up is short but is adequate to evaluate the incidence of PRR and 87.5% had completed 1 year of follow-up which is sufficient to evaluate ER. Both PRR and ER are important end-points in ovarian cancer as delaying recurrence is essential associated with a longer platinum-free interval that is a robust prognostic factor in advanced ovarian cancer (28). The benefit of aggressive locoregional therapies is that they are 'single-shot' treatments and can provide a longer 'treatment-free' and 'platinum-free' interval compared to conventional surgery but the role of these treatments in the light of maintenance therapies needs further evaluation. For TPP, the impact on PFS and OS has still not be demonstrated. This study is retrospective and the results are applied to generate new hypotheses and we do not recommend any practice changes based on these results.

Conclusions

The incidence of PRR and ER in this cohort was low compared to historical data. HIPEC and CC-0 resection were independent predictors of a low ER. These results should be confirmed in larger and more homogeneous patient cohorts. Future research should evaluate the potential additive benefit of aggressive locoregional therapies like TPP and HIPEC coupled together as well as their combination with maintenance therapies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Zydus Hospital Ethics Committee, India. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All the authors have made a substantial contribution to this manuscript as described below. Study concept: AB, OG, VK, and SSi. Study design: AB, OG, VK, and SSi. Data collection: AB, SSi, SSh, PK, WG, VK, OG, NB, and SM. Data analysis and interpretation: AB and SSi. Statistical analysis: SSi and AB. Manuscript preparation: AB, VK, and OG. Manuscript editing: All authors. Manuscript review: All authors. The final version of the manuscript was approved by all the authors. All the authors agree are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

OG is a consultant for Gamida Tech.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The current role of secondary cytoreductive surgery for recurrent ovarian cancer

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Ovarian cancer represents worldwide the second most frequent and the most fatal gynecological malignancy, with approximately two thirds of the patients presenting with advanced disease. Cytoreductive surgery, primary or after neoadjuvant chemotherapy, in combination with platinum-based chemotherapy is the standard of care for these patients. Despite the improvement in quality of cytoreductive surgery as well as development of novel drugs and chemotherapy regimens, still most women with ovarian cancer will ultimately develop recurrent disease and die of their disease. In contrast to the management of primary disease, the standard treatment of patients with recurrent ovarian cancer remains a topic of debate. While platinum-based or second line systemic chemotherapy, depending on the time after last platinum treatment, is standard of care, the role of secondary cytoreductive surgery has been a controversial issue for the last decades. Potential outcome benefit must be also weighed against the risk of severe surgical morbidity, impairment of quality of life and costs. In platinum-resistant recurrent disease, i.e., relapse after less than 6 months from the last platinum-based chemotherapy for primary disease, secondary cytoreduction seems generally not to be indicated due to its aggressive biological behavior and the absence of effective systemic treatment. In this comprehensive review, the current role of cytoreductive surgery in platinum-sensitive recurrent ovarian cancer is discussed thoroughly in view of the results of most recent randomized trials and a meta-analysis. There seems to be definitely a role for secondary cytoreductive surgery in selected patients with ovarian cancer recurrence in whom complete resection of macroscopic disease is feasible. However, its role should be continuously reviewed due to the changing systemic treatment of patients with ovarian cancer recurrence over time.

KEYWORDS

ovarian cancer recurrence, secondary cytoreductive surgery, patient selection, platinum-sensitive, predictive tools

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Introduction

In recent global cancer statistics, ovarian cancer represents the third most frequent gynecological malignancy and the second cause of death from gynecological cancer (1). It has been estimated that in 2022 almost 20.000 women will be newly diagnosed with ovarian cancer and almost 13.000 will die from this disease in the U.S.A (2). The vast majority of ovarian cancer patients have already advanced disease with peritoneal metastases at diagnosis (2). The treatment of choice for primary advanced ovarian cancer has been the combination of primary (or interval) cytoreductive surgery (CRS), aiming for complete resection of all visible disease, and systemic chemotherapy (3, 4). Whereas the standard chemotherapy has been the combination of carboplatin and paclitaxel (3, 4), more recent studies have demonstrated an increase of progression-free survival by additional systemic treatment with bevacizumab or a PARP inhibitor (5–11). In meta-analyses (12, 13), primary complete CRS, without macroscopic residual disease, has been associated with a significant survival benefit. Outcome after incomplete primary CRS was substantially inferior. The theoretical benefit from CRS relates to removing large tumor volumes that have a decreased growth fraction and poor blood supply, thereby improving the efficacy of chemotherapeutic agents. Additionally, CRS is believed to remove chemo-resistant clones of cancer cells by eradicating as much as possible tumor masses and to enhance host immunological response. Complete CRS may circumvent acquired drug resistance after adjuvant chemotherapy (14, 15). Despite the improvement of the quality of primary CRS and the development of new systemic treatment regimens, resulting in a high percentage of clinical remission after completion of initial treatment, approximately 80% of the women with advanced epithelial ovarian cancer will ultimately develop recurrence (1, 16, 17). Only 15% of patients with early ovarian cancer experience recurrent disease (18). The standard of care in recurrent ovarian cancer has mainly consisted of systemic treatment, with eventually palliative surgery for complications as bowel obstruction, whereas the role of CRS in this setting has not been well defined yet. In this comprehensive review the current role of secondary CRS in patients with recurrent ovarian cancer will be discussed, especially in view of data of recent randomized controlled studies.

Secondary cytoreductive surgery

In view of the widespread adoption of primary CRS, it is not unexpected that secondary CRS is strongly considered for patients with recurrent ovarian cancer. This is particular the case for patients with potentially platinum-sensitive disease (i.e., those with recurrence at least 6 months after the last platinum containing therapy) and patients with relatively limited-volume recurrent disease. Platinum-resistant disease represents aggressive biological behavior and in absence of effective systemic treatment secondary CRS is generally considered not to be beneficial. In the past, several retrospective studies and meta-analyses have demonstrated a benefit from secondary CRS, most obviously for patients with platinum-sensitive recurrence and when macroscopic residual disease is very small (optimal CRS) or absent (complete CRS) (17, 19–22). Among all studies, the definition of optimal CRS varies widely from residual disease smaller than 0.25 cm to residual tumor up to 2.5 cm. In an earlier meta-analysis (19), the weighed mean proportion of patients undergoing complete and optimal secondary CRS was 52.2% and 70.3%. In multivariate analysis, the only statistically significant clinical variable independently associated with post-recurrence survival time was the proportion of patients undergoing complete secondary CRS (p=0.019) (19). After controlling for confounding variables, each 10% increase in the proportion of patients undergoing complete CRS was associated with a 3.0 month increase in median cohort overall survival time. The impact of optimal CRS on survival was less obvious. Moreover, in another previous systematic review and meta-analysis (23), overall survival was higher after complete than after optimal CRS, whereas larger residual disease was associated with poorer outcome. The difference in impact on survival between complete and optimal secondary CRS may be caused by the fact that residual disease drives an early development of drug resistance or that recurrent disease that cannot be complete resected, even by an expert team, represent an aggressive tumor biology that can cannot be altered by surgery.

In selected patients, laparoscopic CRS appears to be a feasible and safe approach to complete removal of recurrent ovarian cancer (24). In the case of isolated lymph node recurrence, salvage lymphadenectomy as secondary CRS seems beneficial with a median progression-free survival of 27 months, especially when the platinum-free is longer and the number of involved lymph nodes low, but independently of BRCA mutational status (25). In selected patients, salvage lymphadenectomy may be also performed in a minimal invasive manner (26, 27). Even when recurrent disease involves major vascular structures, vascular procedures can be safely performed with a proper pre-operative planning and may not be an impediment to major gynecological oncological surgery (28).

Randomized trials

Despite the encouraging results of retrospective studies and meta-analyses, a patient selection bias might have been considerable in these studies and consequently randomized studies are

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warranted. Moreover, in the era of bevacizumab and PARP inhibitors, which addition to systemic chemotherapy appear to improve progression-free survival significantly among patients responding to salvage treatment for platinum-sensitive relapse (29), the role of secondary CRS may have to be redefined. Recently, five randomized trials were initiated to assess the role of secondary CRS in recurrent ovarian cancer. Unfortunately, two of them, the Dutch SOCCER trial and the EORTC 55963 trial, were prematurely closed due to low recruitment. The most recently published results of the remaining three randomized trials will be discussed below (Table 1).

The GOG-0213 trial

The Gynecological Oncology Group (GOG) performed the multinational multicenter GOG-0213 trial to assess the role of bevacizumab in recurrent ovarian cancer and whether secondary CRS would increase overall survival among ovarian cancer patients with platinum-sensitive relapse and who were potential surgical candidates (30). Patients with platinum-sensitive recurrent epithelial ovarian cancer considered to be amenable to complete CRS by the surgeon were enrolled in the study. The patients should have had a complete clinical response after the initial treatment and recurrent disease should have been diagnosed at least 6 months after the last chemotherapy. Patients who were not medical fit for major surgery and those with diffuse carcinomatosis, ascites or extra-abdominal disease were excluded. No other specific selection criteria were used. In a 10-year period, 485 patients were randomly assigned to secondary CRS followed by systemic treatment (240 patients) or systemic treatment only (245 patients). Systemic treatment consisted of paclitaxel-carboplatin or gemcitabine-carboplatin. As part of the chemotherapy component of the randomized trial all patients were randomized to the addition of bevacizumab or not to the chemotherapy regimen.

Two hundred twenty five of the 240 patients assigned to surgery actually underwent CRS. In 67% of the cases complete CRS was achieved. The median estimated blood loss was 200 ml and blood transfusion only necessary in 8% of the patients. Bowel resection was performed in 28%, a stoma was created in 2% and the procedure was aborted in 4% of the cases. The 30-day surgery related morbidity was only 9% and the 30-day mortality only 0.4%, whereas no patient underwent repeat laparotomy for complications. Patients in the CRS group experienced a significant decrease in quality of life immediately after surgery. However, after recovery from surgery, there was no difference in quality of life between both groups at time points up to 12 months.

After a median follow-up period of 48.1 months, no significant differences in outcome between both groups were observed. The median overall survival, counted from the time of randomization, was 50.6 months and 64.7 months for the CRS group and no surgery group, respectively (adjusted hazard ratio [HR] 1.29, 95% confidence interval [CI] 0.97-1.72, p=0.08), whereas the progression-free survival was 18.9 months and 16.2 months, respectively (HR 0.82, 95% CI 0.66-1.01). The 3-year overall survival rates were 67% and 74% and the 3-year progression-free survival rates 29% and 20%, respectively. In subgroup analysis, no patient and treatment variables could be identified that were associated with improved overall survival following secondary CRS. In the small group of patients (n=77, 15,9% of the patients) that did not receive bevacizumab after randomization, patients who underwent secondary CRS (n=38, 15.8% of the patients) experienced worse overall survival than those treated by chemotherapy only (n=39, 15,9% of the patients. In the CRS group, complete CRS, when compared with incomplete CRS, was associated with longer overall (HR 0.61, 95% CI 0.40-0.93, median 56.0 vs. 37.8 months) and progression-free survival (HR 0.51, 95% CI 0.36-0.71, median 22.4 vs. 13.1 months). Although patients with complete CRS did not experience an improved overall survival when compared with those who did not undergo surgery (HR 1.03, 95% CI 0.74-1.46, median 56.0 vs. 64.7 months), a benefit regarding progression-free survival was observed after complete CRS (HR 0.62, 95% CI 0.48-0.80, median 22.4 vs. 16.2 months).

TABLE 1 Results of randomized controlled trials on secondary cytoreductive surgery for recurrent ovarian cancer.

Study	Year	Sec. CRS	N	Selection criteria	Complete CRS	PFS* (months)	HR, p-value	OS* (months)	HR, p-value	Survival for completevs. incomplete CRS*
GOG-0213 (30)	2019	Yes	240	Clinical opinion	67%	18.9	HR=0.82	50.6	HR=1.29	PFS 22 vs. 13 months, HR=0.51
		No	245			16.2	NS	64.7	p=0.08	OS 56 vs. 38 months, HR=0.61
SOC-1 (31)	2021	Yes	182	Tian/iMODEL	77%	17.4	HR=0.58	58.1**	HR=0.82	PFS 19 vs. 13 months
		No	175	score		11.9	p<0.001	53.9	NS	OS >72 (NR) vs. 35 months
DESKTOP III (32)	2021	Yes	206	AGO score	75.5%	18.4	HR=0.66	53.7	HR=0.75	PFS 21 vs. 12 months
		No	201			14.0	p<0.001	46.0	p=0.02	OS 62 vs. 28 months

Sec, secondary; CRS, cytoreductive surgery; N, number of patients; PFS, progression-free survival. OS, overall survival, * median values, ** interim analysis, NR, not reached; HR, hazard ratio.

The SOC-1 trial

The Chinese multicenter SOC-1 trial (31) investigated the same hypothesis, i.e. whether secondary CRS is of benefit in platinum-sensitive ovarian cancer recurrence that is potentially completely resectable. Completeness of resectability was predicted by the Tian score, or otherwise called iMODEL score, and PET-CT imaging. The Tian score uses six variables, including FIGO stage, residual disease after primary surgery, platinum-free interval, ECOG performance status, serum level of CA-125 and presence of ascites at recurrence (Table 2). A value of ≤ 4.7 is considered to predict a potentially complete CRS (33). Patients with a higher score and a CA-125 >105 U/mL could be included when the principal investigator deemed the disease completely resectable at PET-CT. In a 7-year period, 357 patients were randomized to secondary CRS and systemic chemotherapy (182 patients) or systemic chemotherapy only (175 patients). The chemotherapy regimen consisted of paclitaxel or docetaxel combined carboplatin. Maintenance treatment with bevacizumab or PARP inhibitors was allowed. Patients were excluded when complete CRS was deemed impossible according to the Tian score and PET-CT, in case of re-recurrence, when the patient had received more than first-line chemotherapy only and when comorbidity did not allow major surgery or chemotherapy. Patients were stratified according to participation center, Tian score, completeness of primary CRS and enrollment in the SUNNY study (primary versus interval CRS for primary disease).

In 77% of the patients, secondary CRS was considered complete, with no gross residual disease. Five percent of the patients who underwent secondary CRS experienced grade 3-4 30-day surgical morbidity, while no patient had died at 60 days in either group. After a median follow-up of 36.0 months, median progression-free survival, counted from the day of randomization, was 17.4 months in the secondary CRS group and 11.9 months in the chemotherapy only group (HR 0.58, 95% CI 0.45-0.74, p<0.0001). In subgroup analysis, the statistically significant progression-free survival benefit of secondary CRS remained in almost all subgroups and in none of the subgroups the outcome was worse after secondary CRS. Whereas complete CRS was associated with better progression-free survival than chemotherapy only (HR 0.50, 95% CI 0.37-0.66), incomplete CRS and chemotherapy only displayed similar progression-free survival curves (HR 0.91, 95% CI 0.61-1.36). While the investigators planned to assess definite overall survival outcome after further maturation of data, a prespecified interim overall survival analysis showed no statistically significant difference between both groups, with a median overall survival of 58.1 and 53.9 months, respectively (HR 0.82, 95% CI 0.57-1.19). However, patients with complete CRS experienced a better overall survival (HR 0.59, 95% CI 0.38-0.91) and patients with incomplete CRS a worse overall survival than patients who received chemotherapy only (HR 1.79, 95% CI 1.07-2.99). Time intervals to first and second subsequent systemic treatment, key endpoints between progression-free and overall survival, were also longer in the secondary CRS and chemotherapy group when compared with the chemotherapy only group. From the 130 patients in the chemotherapy only group who had a subsequent relapse, 48 (37%) underwent surgery. Assessment of quality of life did not show differences among both groups of patients.

The DESKTOP III trial

In the third international multicenter randomized study, the DESKOP III trial (32), 407 ovarian cancer patients with a first platinum-sensitive relapse (i.e., with an interval of at least 6 months without platinum-based chemotherapy) and a positive AGO score, to assure a high likelihood of complete secondary CRS, were allocated to undergo secondary CRS and subsequently to receive platinum-based chemotherapy (206 patients) or to receive platinum-based chemotherapy alone (201 patients). A patient with a positive AGO score should have platinum-sensitive relapse, an ECOG performance status of 0, ascites of less than 500 ml and complete primary CRS at initial treatment (34) (Table 3).

Complete secondary CRS was achieved in 76% of the patients who underwent surgery. The median operation time was 222 minutes, raging from 150 to 300 minutes. Bowel

TABLE 2 Tian or iMODEL score system. Score ≤4.7 represents low-risk and score > 4.7 high-risk for not achieving complete secondary CRS (33).

Impact factors	Scoring					
	0	0.8	1.5	1.8	2.4	3.0
FIGO stage	I/II	III/IV				
Residual disease after primary CRS	0		>0			
Progression-free interval (months)	≥16				<16	
ECOG performance status	0-1				2-3	
Ca-125 level at recurrence (U/mL)	≤105			>105		
Ascites at recurrence	absent					present

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; CRS, cytoreductive surgery; ECOG, Eastern Cooperative Oncology Group.

resection was performed in 36%, a stoma was created in 8% and partial hepatectomy was performed in 5% of the patients. The median estimated blood loss was 250 ml and blood transfusion only necessary in 17% of the patients. No perioperative death was recorded. Reoperation for complications had to be performed in 3.7% of the patients. The majority of patients in both groups received at least five cycles of platinum-based chemotherapy postoperatively. In each group, 47 patients received bevacizumab as part of the systemic treatment.

After a median follow-up of 69.8 months, overall survival was significantly higher in the group of patients who underwent secondary CRS, with a median overall survival of 53.7 months versus 46.0 months (HR 0.75, 95% CI 0.59-0.96, p=0.02). Median progression-free survival was also superior after secondary CRS (HR 0.66, 95% CI 0.54-0.82, 18.4 vs. 14.0 months). Subgroup analysis, considering age, initial disease stage, histological subtype, the administration of maintenance therapy and duration of platinum-free interval, did not identify patients who did not benefit from secondary CRS. Complete CRS when compared with incomplete CRS was associated with a highly increased median overall survival (61.9 months, 95% CI 55.3-78.9 vs. 27.7 months, 95% CI 23.5-38.7). Notably, the median overall survival in non-operated patients was significantly higher (46.0 months, 95% CI 39.5-52.6) than the patients with incompletely resected recurrent disease. The median progression-free survival was almost two times higher after complete versus after incomplete CRS, with non-operated patients exhibiting a slightly higher progression-free survival than the patients in whom complete CRS could not be achieved. Regarding quality-of-life analysis, there were no substantial differences at 6 and 12 months after randomization. In the group of patients who underwent secondary CRS, the insomnia and constipation score were slightly higher at 6 months, but similar at 12 months. This might be attributed to the fact that at 6 months more patients in the CRS group were still receiving chemotherapy (38% vs. 11%).

Comparison of randomized studies

In two of the three randomized trials (31, 32), the addition of secondary CRS to systemic chemotherapy appeared to be beneficial in patients with platinum-sensitive recurrence of ovarian cancer. In all three studies (30–32), secondary CRS was associated with acceptable surgical morbidity and did not appear to have a negative impact on quality of life. The median follow-up period was much longer in the DESKTOP III trial (69.8 months) than the GOG-0213 trial (48.1 months) and SOC-1 trial (36.0 months), making its results possibly more consistent. Progression-free survival was significantly improved by secondary CRS in the SOC-1 and DESKTOP III trials (31, 32), while in the GOG-0213 trial (30) no significant impact, neither negative nor positive, was observed after secondary CRS. Overall survival was significantly improved in the DESKTOP III (32), while in the SOC-1 trial (31) secondary CRS had no effect on overall survival, but the data were considered still immature for definite overall survival analysis and the high cross-over rate from the no surgery group to surgery at subsequent relapses might extend the median overall survival in the no surgery group and consequently result in limited statistical power to demonstrate potentially a reduced overall survival for the non-surgery group. In the GOG-0213 trial (30), no overall survival benefit was observed for secondary CRS. The discrepancy between GOG-0213 study (30) and the DESKTOP III trial (32) regarding the 3-year overall survival, with the GOG-0213 study exhibiting a lower rate in the complete secondary CRS group (76% vs. 84%) and at the same time a much higher in the no CRS arm (75% vs. 62%), suggests that there were some fundamental differences in the patient and treatment profile across the studies.

The lack of improvement of overall and progression-free survival in the GOG-0213 trial (30) may call into question the merit of secondary CRS in patients with platinum-sensitive ovarian cancer recurrence that appears preoperatively to be completely resectable. However, as discussed by the investigators, various factors may have diluted and masked an incremental benefit from secondary CRS. Firstly, the patients enrolled had considerably limited tumor load, with more than half of the patients having only one or two sites involved. In the GOG-0213 study (30) only 5% of the patients had peritoneal carcinomatosis, whereas in the SOC-1 (31) and the DESKTOP III trials (32) two third of the patients presented with multifocal disease relapse, including peritoneal carcinomatosis. The overall survival after secondary CRS is considerable higher when a single site is involved when compared with the case of multiple lesions or carcinomatosis. In a series of the Memorial Sloan Kettering Cancer Centre (22), secondary CRS for a single-site lesion multiple lesions and carcinomatosis (≥20 nodules)

TABLE 3 AGO score.

Predictive parameters for complete secondary cytoreductive surgery
Platinum-sensitive recurrent ovarian cancer (interval of ≥6 months without platinum-based chemotherapy
ECOG performance status of 0
No residual disease after primary surgery (or, alternatively if information not available, FIGO I/II)
Ascites of less than 500 ml at preoperative imaging

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; ECOG, Eastern Cooperative Oncology Group.
The AGO score is positive when all parameters are encountered (22, 34).

resulted in a median overall survival of 60, 42 and 28 months, respectively. Secondly, the patients in the GOG-0213 study had substantially platinum-sensitive disease, with a median platinum-free interval of 20.4 months, which is expected to make systemic treatment more effective. Thirdly, in the GOG-0213 trial (30) 84% of the patients received also bevacizumab, whereas in the SOC-1 (31) and the DESKTOP III trials (32) only in 1% and 23% of the patients this biological agent was administered. The highly effective systemic treatment regimen leading to a median overall survival of the entire study population being almost three times longer than expected, may definitely have diluted an independent effect of secondary CRS. Among the small group of patients who did not initially receive bevacizumab, secondary CRS was associated with worse overall survival. However, it is unknown who of the patients received the effective bevacizumab at a later point of treatment, resulting potentially in a treatment imbalance that could affect overall survival outcome. Whereas after secondary CRS the progression-free survival was slightly, non-significantly, better in the entire group and even statistically significantly better in the large subgroup of patients treated by paclitaxel-carboplatin and bevacizumab, overall survival was not improved by secondary CRS. Extended post-progression survival by improved clinical care and highly effective consecutive treatment regimens may have diluted the effect of secondary CRS measured according to progression-free survival by reducing statistical power to assess overall survival and enabling a higher probability of intervening treatment (35, 36). The differences in disease burden, use of biological agents and maintenance regimens across the three studies make a direct comparison very challenging.

Differences in outcome between the trials may also be attributed to the lack of standardization of surgical technique and surgical quality assurance among the participating centers as well as the difference in patient selection, causing heterogeneity of the study cohorts. In the GOG-0213 trial (30), the percentage of complete CRS was 67%, while in the other studies 77% (31) and 76% (32). The surgical skill and the ability of achieving complete CRS may differ considerably among centers and countries (37). In the GOG-0213 (30) participated 51 centers, from which 18 with 5 cases or less. Low volume centers may have more difficulty in achieving complete CRS (see 'Referral centers'). The substantial difference in selection of patient for potentially complete secondary CRS among the randomized trials will be discussed below.

Patient selection and prediction models

Appropriate patient selection is of paramount importance, performing secondary CRS only in those patients who may benefit and omitting secondary CRS in those who are not considered to benefit, avoiding unnecessary risk of surgical morbidity and costs. Firstly, patients should have platinum-sensitive disease, i.e being diagnosed with recurrence at least 6 months after the last platinum-based primary chemotherapy. Secondary CRS is generally not offered for resistant disease with evidence of progression during first line platinum-based chemotherapy (platinum-refractory), or recurrent disease within less than six months of completion of primary treatment (platinum-resistant). These women typically have poor prognosis and do not benefit from further surgical attempts at CRS (38, 39). Even if it has been possible to perform optimal or complete CRS, contrary to the case of 'platinum-sensitive' recurrent disease surgical treatment cannot be completed with effective chemotherapy. Hence, these patients may be exposed to unnecessary surgical morbidity and impairment of quality of life, without any significant survival benefit and are not to be considered candidates for secondary CRS.

Secondly, it appeared from above mentioned randomized trials (30–32) that only patients in whom complete CRS was achieved may benefit. Complete CRS, when compared with incomplete CRS, was associated with improved overall survival in the SOC-1 (31) and DESKTOP III (32) trials and improved progression-free survival in all three randomized trials (30, 31, 32). In the SOC-1 (31) and DESKTOP III (32) trials, patients who had undergone incomplete CRS, when compared with those receiving systemic treatment alone, exhibited a similar or slightly worse progression-free survival and even a significantly worse overall survival. In the GOG-0213, such a comparative analysis was not reported. This reduced survival in patients with incomplete CRS most probably reflects the aggressive biological behavior of the recurrent disease that prohibited complete CRS.

In a recent meta-analysis (40), the impact of the quality of secondary CRS on the survival of patients with platinum-sensitive recurrent ovarian cancer was studied. The meta-analysis comprised of 36 studies, published between 1995 and 2021, and a total of 2,805 patients. The majority of studies included were of retrospective nature. The median major surgical complication rate was 16.4% (0-44%), whereas a mean 30-day postoperative mortality of 0.7% was recorded. A significant heterogeneity among the studies was observed. The definition of optimal CRS varied considerably, from residual disease smaller than 0.25 cm to even residual tumor up to 2.5 cm. The median rate of complete and optimal CRS was 69.8% (9.4-100%) and 85.7% (43.5-100%), respectively. A meta-regression analysis to determine the cause of heterogeneity demonstrated the proportion of complete and optimal CRS to be statistically significant. Nevertheless, complete and optimal CRS were independent significant moderators of overall survival ($p<0.001$ and $p=0.04$, respectively). Studies with a complete CRS rate of higher than 70% reported a pooled overall survival rate of 65% in comparison with 46% in studies with an optimal

CRS rate higher than 70% or less. For a cut off rate of 85% optimal CRS, the pooled overall survival rates were 63% and 47%, respectively. In multivariable analysis, with adjustment of the other variables, an increase of 10% in complete and optimal CRS was associated with respectively an increase of 8.97% and 7.04% in median overall survival. Hence, when secondary CRS is performed, a maximal effort should be made to accomplish complete or optimal disease resection in order to improve survival in patients with platinum-sensitive ovarian cancer recurrence. During the progress in systemic treatment the benefit of secondary CRS appeared to exist even more obviously in more recent years (p<0.001). For each 1-year increase in year of publication of the study, overall survival increased independently with 3.11% and 3.49% after complete and optimal CRS, respectively.

From the above it appeared of paramount importance to identify preoperatively the patients in whom complete or optimal secondary CRS can be performed, offering those patients the probable benefit of secondary CRS and avoiding potential surgical morbidity and costs in those who may not benefit since complete or optimal secondary CRS seems unfeasible. Various models for the prediction of complete secondary CRS in patients with recurrent ovarian cancer have been developed in order to have an objective tool that is more effective than just the individual surgeon's opinion (41). In the three randomized trials the criteria for patient selection with respect to the probability of complete secondary CRS differed. In the GOG-0213 trial (30), while patients with preoperative evidence of ascites and/or diffuse peritoneal carcinomatosis were excluded, the platinum-sensitive recurrent disease was just 'deemed by the investigator to amenable to complete gross resection'. With a considerably limited initial tumor load, as earlier mentioned, a complete CRS was reported in 67% of the cases. In the SOC-1 trial (31), completeness of CRS was predicted by a Tian or iMODEL score of ≤4.7 and, when the score was >4.7 and the tumor marker CA-125 >105 U/mL, by PET-CT imaging. As mentioned above, the Tian Score System, uses six variables, including FIGO stage, residual disease after primary surgery, platinum-free interval, ECOG performance status, serum level of CA-125 and presence of ascites at recurrence (33) (Table 2). In the original study (33), a value of ≤4.7 predicted a potentially complete resection rate of 53% vs. 20% for a higher score. In the SOC-1 study, complete secondary CRS was achieved in 77% of the cases, more frequently than in the GOG-0213 study. A recent retrospective, propensity score-matched analysis demonstrated that in Tian-model low-risk patients secondary CRS was associated with increased survival outcome when compared with chemotherapy only (42). In the DESKTOP III trial (32), the AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) score had been used to select patients for secondary CRS and in 76% of the selected patients macroscopically complete resection of recurrent disease could be performed. This score was initially developed by the Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) study (34). Retrospective analysis in databases from multiple centers determined objective selection criteria to identify patients with platinum-sensitive recurrent ovarian cancer that may benefit from secondary surgery. Complete secondary CRS was associated with a significantly longer median survival than incomplete secondary CRS (45.2 vs. 19.7 months, HR 3.7, 95% CI 2.27-6.05, p<0.0001). Variable associated with complete secondary CRS included ECOG performance status (0 vs. >0, p<0.001), FIGO stage at initial diagnosis (I/II vs. III/IV, p=0.036), residual tumor after primary CRS (absent vs. present, p<0.0001) and absence of ascites >500 ml (p<0.001). A positive AGO score, being a combination of performance status ECOG 0, complete primary CRS in the past (or when data not available initial FIGO I/II disease), and absence of ascites >500 ml, could predict complete secondary CRS in 79% of the patients with platinum-sensitive ovarian cancer relapse (Table 3). In the DESKTOP II trial (43), this AGO score was prospectively validated to predict completeness of secondary CRS. Two-hundred and sixty-one of the 516 screened patients (51%) had a positive AGO score. Complete secondary CRS was achieved in 76% of the 129 patients with a positive AGO score who underwent secondary surgery, while surgical morbidity and mortality were acceptable. Consequently, this prospective study verified the value of the AGO score in patient selection for secondary CRS. However, in an exploratory analysis by the same group the complete CRS rate for a positive AGO score was 89.3% and for a negative AGO score still 66.7%, underlining its suboptimal negative predictive value (44). Another prediction model for complete secondary CRS that has been externally validated in clinical studies has been developed at the Memorial Sloan Kettering Cancer Centre (22). The MSK Criteria are based on disease-free interval (6-12, 12-30, >30 months), single vs. multiple recurrence sites and evidence of carcinomatosis (≥20 nodules) (Table 4). The effectiveness of those three prediction models have been tested retrospectively and compared with each other in various studies (45–49). In patients with platinum-sensitive recurrent ovarian cancer who were initially treated with primary systemic chemotherapy and interval CRS instead of primary CRS followed by systemic chemotherapy, these predictive models have similar efficacy (50). While their positive predictive value for complete CRS was generally high (73-86%), unfortunately the false negative rate of those models was relatively high (55-70%). Hence, these prediction models may be too strict and exclude patients who may have a chance of successful secondary CRS. Consequently, further studies are warranted so as not to prohibit patients from undergoing potential life-extending surgery. The addition of preoperative imaging and/or staging laparoscopy to the criteria of those prediction models may be beneficial.

Regarding the preoperative radiological workup, contrast enhanced computed tomography (CT) is usually the technique of choice for follow-up of patients with ovarian cancer, but its efficacy is limited by its low soft-tissue contrast in evaluating disease in the pelvis and on visceral surfaces (51). Magnetic resonance imaging (MRI) has excellent soft-tissue resolution and the capacity to discriminate between post-treatment

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TABLE 4 The MSK criteria (22).

Disease-free interval	Single site of recurrence	Multiple sites of recurrence but no carcinomatosis	Peritoneal carcinomatosis
6-12 months	Offer sCRS	Consider sCRS	No sCRS
12-30 months	Offer sCRS	Offer sCRS	Consider sCRS
>30 months	Offer sCRS	Offer sCRS	Offer sCRS

MSK, Memorial Sloan Kettering; sCRS, secondary cytoreductive surgery, * ≥ tumor 20 tumor nodules at time of surgery.

changes and tumor recurrence, but its diagnostic accuracy is limited in small-volume recurrent lesions and in sites where the lesions are contiguous to tissues with similar signal intensity (52). Diffuse weighted imaging MRI seems promising to identify small peritoneal and nodal lesions (53). Combining anatomical and functional imaging through positron emission imaging (PET)/CT may help evaluate patients with suspected ovarian cancer recurrence but negative or indeterminate CT findings. In a recent meta-analysis of 34 studies (54), the pooled area under the curve (AUC) of PET/CT for detecting ROC was significantly higher than that of CT or MRI. PET-CT and staging laparoscopy may be helpful in identification of patients in which complete CRS may be feasible (55–57). Staging laparoscopy is feasible in the vast majority of patients with recurrent ovarian cancer, despite the major abdominal surgery that usually has preceded (55). While their negative and positive predictive value, sensitivity and specificity in assessing the possibility of complete CRS are quite similar, PET-CT and staging laparoscopy should be considered complementary modalities (56). The combination of these preoperative examinations seems better than the AGO-score in patient selection for complete or optimal CRS. In a comparative study (55), approximately 20% of patients with negative AGO score achieved actually successful secondary CRS after preoperative evaluation with PET–CT and staging laparoscopy, whereas almost one of three positive AGO score patients, who had however a negative assessment with PET-CT and staging laparoscopy, would be submitted to an unnecessary explorative laparotomy.

Moreover, the identification and incorporation of predictive biomarkers to tailor the medical and surgical approach, including secondary CRS, is paramount to the success of treatment of recurrent ovarian cancer. BRCA mutation status is a potential selection parameter for secondary CRS in the future, although its role is still to be defined. Women with BRCA mutation are likely to receive a new emerging treatment with PARP inhibitors that has notably improved progression-free survival, as mentioned previously. In a recent multicenter study (58), germline BRCA mutation carriers were more likely to undergo secondary cytoreduction. This may be mediated in part by lower volume disease at recurrence. In a multicenter study (59) to assess the role of BRCA mutation status in personalizing the management of recurrent ovarian cancer, BRCA mutation patients had the best prognosis regardless of secondary CRS, whereas post-recurrence survival in BRCA wild type women was improved by complete secondary CRS. In another study, however, the benefit of secondary CRS was similar for both groups of patients (60). Similarly, in a similar case-control study (61) ovarian cancer patients with a BRCA mutation who underwent secondary CRS and subsequently received chemotherapy and a PARP inhibitor experienced a better survival than those who received chemotherapy and a PARP inhibitor only. Moreover, resection of hepatic recurrences, isolated or with concomitant peritoneal disease, seem to be associated with a favorable outcome only in patients with BRCA mutations (62). As mentioned previously, salvage lymphadenectomy as secondary CRS seems beneficial independently of BRCA mutational status (25).

Referral centers

CRS is a demanding and complex procedure, which may include specific surgical techniques such as peritonectomies, may require a multidisciplinary surgical team and may expose the patient to an increased risk of surgical morbidity. The procedure is associated with a long learning curve for a center in order to achieve a high complete CRS rate with synchronously low major surgical morbidity and mortality, less blood loss, shorter operation time and shorter hospital stay (63). The number of cases to overcome the learning curve varied from 130 to 220 in series of patients with peritoneal carcinomatosis from various origins, of whom most underwent besides CRS also HIPEC (63–67). In another study (68), the learning curve with respect to operation time and total blood loss was considered significantly longer for high-complexity procedures with bowel resection and upper abdominal surgery for primary advanced ovarian cancer than for moderate-complexity procedures. While the learning curve for the complete primary CRS rate was not examined, no typical learning curve was observed concerning the occurrence of severe complications. A mentorship model by surgeons with a large experience and knowledge of CRS should be paramount to reduce the prolonged learning curve for the achievement of proficiency considering radicality and safety (63, 69–71).

Advanced surgical skills as applied in referral centers might be one step towards increasing the complete CRS rate and consequently the proportion of patients who might benefit from surgery for primary and recurrent ovarian cancer. In

primary surgery for advanced ovarian cancer, a paradigm shift toward more aggressive surgery as well as training in and incorporation of extensive upper abdominal procedures resulted in a higher chance on complete CRS in referral centers (71–74).

There are, as far as we know, no data published regarding learning curves and surgical skills in secondary CRS for recurrent ovarian cancer. While expertise and surgical skills are important in order to offer the highest chance of complete CRS and synchronously low surgical morbidity in primary ovarian cancer, this should be even more the case for secondary CRS in women who have already been operated, usually extensively, for primary ovarian cancer. The maximal effort to achieve complete secondary CRS may require collaboration of various surgical specialists such gynecological and surgical oncologists, gastrointestinal surgeons, urologists, hepatobiliary surgeons, vascular surgeons and other. Such a multidisciplinary surgical team is preferably created in a referral center in order to obtain adequate experience.

Secondary cytoreductive surgery and HIPEC

CRS is also mandatorily performed when intraperitoneal chemotherapy is applied for ovarian cancer. Intraperitoneal chemotherapy has a pharmacological advantage above systemic, intravenous chemotherapy (75–77). Due to the slow absorption of chemotherapeutic drugs from the peritoneal cavity and the first-pass effect in the liver, a high intraperitoneal drug concentration can be achieved with simultaneously low systemic drug toxicity. Intraoperative application of HIPEC assures optimal exposure of the drug to the entire seroperitoneal surface and early treatment of (microscopic) residual disease before re-growth can occur. Heating the drug solution as in intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) increases the efficacy of intraperitoneally administered drugs, while heat itself may have a direct cytotoxic effect. However, the penetration depth of intraperitoneally delivered drugs into tumor nodules is very limited and hence thorough resection of macroscopic peritoneal disease, i.e. complete or optimal CRS, should precede intraperitoneal chemotherapy (75, 76).

During the last decades, CRS and HIPEC has been applied in various primary and secondary peritoneal malignancies, among which advanced ovarian cancer (78, 79). Only a few randomized trials on HIPEC for ovarian cancer have been reported. The recently published Korean randomized KOV-HIPEC-1 trial (80) did not show benefit of the addition of HIPEC to primary CRS and systemic chemotherapy for primary advanced ovarian cancer. In the Dutch multicenter randomized OVHIPEC trial (81), in the Spanish multicenter randomized CARCINOHIPEC trial (82) and in the subgroup analysis of the KOV-HIPEC-1 trial (80), an evident benefit was observed for the addition of HIPEC to interval CRS after primary chemotherapy in primary ovarian cancer. In the largest of the randomized trials, the Dutch OVHIPEC study (81), only patients with at least stable disease during primary chemotherapy and complete or optimal interval CRS were enrolled in the study.

Regarding secondary CRS and HIPEC for relapsed ovarian cancer, a Greek single-center randomized trial (83) reported improved overall survival for the patients who underwent secondary CRS and HIPEC (n=60), both in platinum-sensitive and platinum-resistant disease, when compared with CRS only (n=60). All received systemic chemotherapy postoperatively. However, the validity of the study has been contested due to significant shortcomings: the randomization process was not described in detail, primary end points were not clearly defined, there was no information provided regarding disease-free survival, complications, postoperative systemic chemotherapy and follow-up, and the study had not been registered in an international clinical trial database (84). Moreover, others raised that the statistical analysis performed in the study was not clearly described and inappropriately applied, mean instead of median OS was used, reported data were inconsistent with provided graphics and their recalculation of the statistics demonstrated the outcome after HIPEC to be not statistically significantly superior to the control group (85, 86). Most recently, the results of the Memorial Sloan Kettering (MSK) Team Ovary randomized phase II study have been reported (87). Ninety-eight patients with ovarian cancer recurrence were randomly assigned to secondary CRS and HIPEC or secondary CRS only, in both groups followed by systemic chemotherapy. Although complete CRS had been more frequently achieved in the HIPEC group (94% vs. 82%), the addition of HIPEC to secondary CRS did not improve disease progression-free or overall survival. In both randomized trials secondary CRS was performed in both arms and therefore a potential partial role of secondary CRS cannot be determined in this setting.

Conclusions and future directions

As discussed above, two of the three recently reported randomized trials (31, 32) have demonstrated that a definite role exists for secondary CRS in patients with recurrent ovarian cancer with respect to survival improvement, but only when complete resection of macroscopic disease can be achieved. Complete CRS was associated with significantly better survival outcome than after incomplete CRS in recent randomized trials and meta-analyses, with incomplete CRS be associated with worse survival than chemotherapy only (19, 30–32, 40). Patient selection is of paramount importance to identify those patients in whom complete secondary CRS seems to be feasible. Various models for this patient selection have been developed with an adequate preoperative prediction of achievement of complete secondary CRS (22, 33, 34, 41). However, the negative predictive rate is relatively high. Hence, these prediction models may be too strict

and exclude patients who may have a chance of successful secondary CRS. Consequently, further studies are warranted to improve these prediction models with respect to their negative predictive value, so that patients who may benefit are not prohibited from undergoing potential life-extending surgery.

CRS is a demanding and complex procedure with a long learning curve to accomplish a high complete CRS rate and low surgical morbidity (63). When performed by experienced teams, secondary CRS is safe and without a negative impact on quality of life (40). Therefore, secondary CRS is preferably performed in referral centers with ample experience. It is crucial to develop standardized training programs and mentorships to shorten the long learning process to reduce morbidity and mortality, and improve oncologic outcomes (63, 69–71). The impact of the multidisciplinary effort in the treatment of ovarian cancer relapse is being indirectly reflected by the increasing survival outcomes in more recently published studies on secondary CRS (40), which is result of the significant improvement in both surgically and systemically management over the last decades.

The role of secondary CRS should be continuously reviewed considering the changing systemic treatment of patients with ovarian cancer recurrence over time. A well-designed biomarker-driven randomized trial with prespecified subgroup analysis seems rather ambitious, but will certainly reveal further the true effect of secondary CRS in the various ovarian cancer subgroups. As discussed previously, some recent retrospective studies have assessed the impact of biological features, such as the BRCA status and the use of PARP inhibitors, on the potential benefit of secondary CRS in patients with platinum-sensitive ovarian cancer relapse with yet inconclusive data (25, 58–62). The results of the randomized phase II SGOG SOC-3 study (88) on the benefit of CRS before receiving platinum-based chemotherapy and a PARP inhibitor in patients with a secondary platinum-sensitive ovarian recurrence are eagerly awaited. Further studies should be conducted to determine the benefits of secondary CRS with respect to the molecular characteristics (BRCA or homologous recombination deficiency status) and the use of PARP inhibitors and/or bevacizumab. The forthcoming research trend is to achieve a more accurate, individualized treatment approach of recurrent ovarian cancer.

Author contributions

All of the coauthors listed meet the criteria for authorship. EB provided the concept and guidance. EB and EA reviewed the literature. EB wrote and DM critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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Predictive value of C-reactive protein levels for the early and later detection of postoperative complications after cytoreductive surgery and HIPEC

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Synopsis: C-reactive protein (CRP), white blood cells and procalcitonin (PCT) participate in the systemic response to inflammation and increase after postoperative infective complications. Postoperative complications after CRS and HIPEC could be predicted using the CRP cut-off value (169 mg/L at PODs 3-5 and 62 mg/L at PODs 7-10).

Background: Postoperative elevation of C-reactive protein (CRP) can be used in order to predict the postoperative complications in many indications. Cytoreduction surgery (CRS) associated with hyperthermic intraperitoneal chemotherapy (HIPEC) is associated with high morbidity.

Objectives: The aim of the study was to demonstrate the CRP predictive value for the occurrence of complications.

Methods: All patients who had CRS and HIPEC, regardless of the origin of peritoneal metastasis, were included in this retrospective study. Postoperative complications and CRP and white blood cell (WBC) counts were recorded from postoperative day (POD) 1 through 10.

Results: Among the 127 patients included, 58 (45.7%) had no complications (NCs), 53 (41.7%) had infective complications (ICs), and 16 (12.6%) had non-infective complications (NICs). The IC group had a higher CRP value than the NC group, which was statistically significant from POD7 to POD10 (41.1 versus 107.5 p = 0.023 and 77.8 versus 140 p = 0.047, respectively). A cut-off CRP value was 169 mg/L at PODs 3-5 and 62 mg/L at PODs 7-10. The area under the curve (AUC) at POD5 was 0.56 versus 0.76 at POD7, p=0.007. The sensibility, specificity, positive and negative predictive values of these cut-offs were 55%, 83%, 74% and 67%, respectively. Moreover, 17 patients (32%) with ICs had a CRP value higher than these cut-offs before the diagnosis was made by the medical team.

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Conclusion: This study suggested that postoperative complications could be predicted using the CRP cut-off value on PODs 3-5 (169 mg/l) and PODs 7-10 (62 mg/l) after CRS and HIPEC.

KEYWORDS

postoperative complications, C-reactive protein, peritoneal metastasis, non-infective complications, infective complications, HIPEC, cytoreductive surgery

Introduction

Over the past decade, cytoreduction surgery (CRS) associated with hyperthermic intraperitoneal chemotherapy (HIPEC) has been used to treat peritoneal metastasis (PM) originating from different tumours. Its usefulness is less proven in other types of digestive cancers and is discussed on a case-by-case basis in multidisciplinary oncological meeting for PM from gastric or biliary cancers (1, 2). It is a heavily skilled surgical procedure that can lead to complications secondary to surgery (anastomotic leakage, intra-abdominal abscesses) and chemotherapy (thrombocytopenia, haemorrhage), and the complication rate is estimated to be 24% at 2 months postoperatively (3).

C-reactive protein (CRP), white blood cells and procalcitonin (PCT) participate in the systemic response to inflammation and increase after postoperative infective complications (4). The usefulness of CRP as a marker of septic complications has been demonstrated by several authors (5, 6). Most of these studies have found a cut-off value of CRP at a concrete postoperative day (POD) that predicts postoperative complications, especially infective complications.

The use of CRP, PCT and white blood cell (WBC) in postoperative monitoring has been poorly assessed after HIPEC (7). Currently, no study has established a CRP « cut-off » that can lead the surgeon to search for postoperative complications, and the HIPEC procedure produces an inflammatory response in all patients undergoing cytoreductive surgery (8). The utility of a CRP cut-off value for predicting which patients are at greatest risk of complications following peritoneal metastasis surgery is an important topic that has not been evaluated and can help the peritoneal surgeons. The aim of this study was to evaluate the predictive value of CRP for detecting postoperative infectious complications following CRS and HIPEC and to establish clinically valuable cut-off values for CRP levels.

Materials and methods

Study population

All patients over 18 years of age who had undergone HIPEC associated with cytoreduction surgery at our university hospital, regardless of the origin of peritoneal metastases, were included between 01/2010 and 02/2020 in this retrospective study.

Inclusion and exclusion criteria

Patients were selected after preoperative radiological examinations and all cases are discussed in a multidisciplinary oncology meeting. Only patients with limited resectable MP (i.e. with PCI < 15 for colorectal origin, ovarian origin or with resectable mesothelioma or pseudomyxoma) according to the French recommendations (9, 10), had a cytoreduction surgery and HIPEC. If the patient had extensive or non-resectable PM on the preoperative work-up including CT-Scan +- MRI +- PET Scan +- Laparoscopy, he received palliative treatment.

Perioperative care and HIPEC procedure

All participants underwent a median laparotomy, and explorative laparotomy was performed first to evaluate the peritoneal cancer index (PCI). Complete, visible resection of all PMs, when needed, visceral resection, and multiorgan resection, e.g., the liver and spleen, were performed in order to achieve curative surgery. Then, HIPEC procedure was performed with Oxaliplatin, Mitomycin, Doxurubicin or Cisplatin.

Initial data analysis

The following data were recorded: age, sex, body mass index (BMI), American Society of Anesthesiology (ASA) score, primary tumour site, surgical procedures (digestive resection, stoma, estimated blood loss), PCI, chemotherapy used during HIPEC, and CC score.

Postoperative follow-up

All patients were followed up and examined at each visit, every day, by the surgeon and anaesthetist. If the patient had symptoms,

the medical team performed a specific exam (urinary test, radiological exams) according to French guidelines (Annex 2).

Postoperative complications were recorded during 3 months. CRP level and the WBC count were recorded from postoperative day (POD) 1 through 10, as well as the mean length of stay (LOS) and mortality at 3 months.

Definitions of complications

All patients were examined daily and were divided into three groups:

- without complications (no complications (NCs)),
- group with infective complications (ICs) according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (11), including pneumonia, subcutaneous abscess, urinary tract infection, anastomotic leakage, intra-abdominal abscess and central venous catheter infection. These ICs were confirmed by clinical and radiologic or bacteriological exams.
- group with non-infective complications (NICs) to Common Terminology Criteria For Adverse Events (CTCAE) Version 5.0 (11), such as postoperative bleeding, digestive occlusion, respiratory failure, acute renal failure, thrombocytopenia, venous thrombosis, pulmonary embolism, and peripheral neuropathy. These NICs were confirmed by clinical and radiological or biological exams.

Endpoints

The objective was to analyse the ability of CRP to predict ICs and NICs in the first 10 PODs.

To improve the comparison of tested values, we summarized the values of POD 3 and 5 (very early complications) and of POD 7 and 10 (later complications) and used the highest measured value. Moreover, we calculated the optimal cut-off values using ROC analysis.

The secondary endpoints were the incidence of postoperative ICs, according to the WBC levels. All procedures were in accordance with the Helsinki Declaration.

Statistical analysis

Data are shown as means ± SD for quantitative variables or numbers and percentages for qualitative variables. The baseline data and the occurrence of endpoints were analyzed using the parametric t test or the nonparametric U test for continuous variables. The Chi-squared test or Fisher's exact test was used for categorical variables as appropriate. An ANOVA parametric test was used as well, to compare between the two groups (No complication versus with ICs), and between the two others groups (No complication versus with NICs). A multivariate logistic regression analysis was further performed, confuting the PCI and the origin of PM as a confounder, affecting the CRP statistical correlation with infective complications. Statistical analysis was performed with GraphPad Prism v8.0. The cut-off value for the CRP ratio was determined using receiver operating characteristic (ROC) curves. The area under the curve and 95% confidence interval of the ROC curve were calculated using Stata 11. Values of $p< 0.05$ were considered statistically significant. To evaluate the predictive value of these cut-offs on the occurrence of complications, we also calculated the sensitivity, specificity, positive predictive value and negative predictive value.

Results

Patient characteristics and postoperative complications

A total of 166 patients were initially eligible for inclusion in the study. Of these, 5 patients received 2 HIPEC and were therefore included twice. Forty-four patients were excluded: 34 due to a lack of data (no CRP values collected in 10 days), 5 because surgical exploration did not allow curative management and received intravenous chemotherapy (high PCI, metastasis, local invasion), and 5 patients who had CRS without HIPEC. Annex 1

A total of 127 patients who had undergone HIPEC were included. Table 1 The study population consisted of 88 women (69.3%) and 39 men (30.7%). All patients with colorectal and ovarian PMs received preoperative IV chemotherapy. Patients with primary peritoneal cancer received surgery treatment in front line.

Of the patients analyzed, the global morbidity rate was 54.3%: 45.7% (58 of 127) presented with no complications (NCs), 41.7% (53 of 127) had infective complications (ICs), and 12.6% (16 of 127) had non-infective complications (NICs). Table 2

Table 1 presents the descriptive data of the 3 groups (NCs versus ICs and NCs versus NICs groups) and the perioperative data.

The length of hospital stay was significantly higher in the ICs group than in the NCs group (31 to 15.1 days [3.77; 10.89] $p= 0.0001$), whereas there was no significant difference between the NICs and the NCs groups (26 to 15.1 days [4.72; 26.80] $p= 0.2$). No patient died during the three postoperative months.

CRP value in the three groups (NCs versus ICs and NCs versus NICs groups)

ICs patients had a higher CRP value than NCs patients, which was statistically significant from POD 7 to POD 10 (41.1 versus 107.5 $p = 0.023$ and 77.8 versus 140 $p = 0.047$,

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TABLE 1 Patients characteristics and postoperative complications.

Characteristic	No Complication N = 58	Infective complications N = 53	P (No complications group vs Infective complications group)	No infective complications N = 16	P (No complication group vs No infective complications group)
Sex (n, %)					
Male	16 (27,6%)	19 (35,8%)	*0,4*	4 (25%)	*1*
Female	42 (72,4%)	34 (64,2%)	*0,4*	12 (75%)	*1*
Age (years) (mean-ranges)	61,4 (37-74)	59,5 (29-77)	*0,3*	61,5 (36-75)	*0,9*
BMI (kg/m2) (mean +- SD)	24,7 (3,9)	25,3 (+-4,9)	*0,5*	26,1 (+-8,4)	*0,4*
ASA Score					
ASA 1-2	32 (55,2%)	32 (60,3(%)	0,7	7 (43,7%)	0,4
ASA 3-4	26 (44,8%)	21 (39,7%)	0,7	9 (56,3%)	0,4
Origin of PM (n, %)					
Colorectal	21 (36,2%)	31 (58,5%)	***0,02***	6 (37,5%)	*1*
Ovarian	23 (39,7%)	13 (24,5%)	*0,1*	6 (37,5%)	*1*
Peritoneum	12 (20,7%)	6 (11,3%)	*0,2*	4 (25%)	*0,7*
Neoadjuvant chemotherapy (n, %)	49 (71%)	48 (90,6%)	*0,4*	10 (62,5%)	*0,08*
PCI (mean, +- SD)	7 (+- 6.3)	8,9 (+-6.5)	*0,1*	9,1 (+- 6.1)	*0,4*
HIPEC (n, %)					
Oxaliplatine	35 (60,3%)	36 (67,9%)	*0,7*	10 (62,5%)	*0,9*
Mitomycine	16 (27,6%)	12 (22,6%)	*0,7*	5 (31,2%)	*0,8*
Cisplatine	7 (12,1%)	4 (7,6%)	*0,5*	1 (6,3%)	*0,7*
CC score (n, %)					
CC0	51 (87,9%)	41 (77,4%)	*0,2*	11 (68,8%)	*0.1*
CC1	4 (6,9%)	9 (16,9%)	*0,1*	3 (18,7%)	*0,2*
CC2	3 (5,2%)	3 (5,7%)	*1*	2 (12,5%)	*0,3*
Operative procedure (n, %)					
Resection and digestive anastomosis	19 (32,8%)	26 (49,1%)	*0,08*	11 (68,7%)	***0.01***
Digestive resection without anastomosis	9 (15,5%)	13 (24,5%)	*0,2*	1 (6,2%)	*0,7*
Gallbladder resection	47 (81%)	43 (73,6%)	*1*	9 (56,3%)	***0,05***
Omentectomy	47 (81%)	43 (73,6%)	*1*	11 (68,8%)	*0,3*
Liver resection or radiofrequency	5 (8,6%)	9 (17%)	*0,25*	1 (6,3%)	*1*
Diaphragm resection	1 (1,7%)	1 (1,9%)	*1*	0 (0%)	*0,4*
Total Peritonectomy	12 (20,7%)	6 (11,3%)	*0,2*	4 (25%)	*0,7*
Ovariectomy	15 (25,9)	18 (34%)	*0,4*	5 (31,3%)	*0,7*
Vaginal resection	2 (3,5%)	1 (1,9%)	*0,6*	1 (6,3%)	*0,5*
Hysterectomy	8 (13,8%)	6 (11,3%)	*0,7*	3 (18,8%)	*0,7*
Appendectomy	16 (27,6%)	7 (13,2%)	*0,1*	2 (12,5%)	*0,4*
Splenectomy	3 (5,2%)	0 (0%)	*0,1*	2 (12,5%)	*0,3*
Bladder resection	1 (1,7%)	1 (1,9%)	*1*	0 (0%)	*0,4*
Estimated blood loss (ml) (mean +- SD)	525 (+- 450)	478 (+- 301)	*0.3*	285 (+- 177)	*0.3*

ASA Score, American Society of Anesthesiologists; BMI, body mass index; CC score, completeness of Cytoreduction score; HIPEC, hyperthermic intraperitoneal chemotherapy; n, number; PCI, peritoneal cancer index; PM, peritoneal metastasis; SD, standard deviation.
Bold values = p values < 0.05.

TABLE 2 Postoperative complications according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

	Infective complications	No infective complications
Any grade ≥2 adverse event n (%)		
Grade II n (%)		
Pneumonia	3 (5,7%)	
Colitis	3 (5,7%)	
Urinary tract infection	**22 (41,4%)**	
Wound abscess	7 (13,2%)	
Infection of central venous catheter	6 (11,3%)	
Fever of Unknown Origin	6 (11,3%)	
Phlebitis		1 (6,2%)
Respiratory complication		**3 (18,9%)**
Acute kidney failure		**4 (25%)**
Others		4 (25%)
Grade III n (%)		
Anastomosis leakage	3 (5,7%)	
Intra abdominal abscess	3 (5,7%)	
small bowel obstruction		2 (12,5%)
Post operative bleeding		1 (6,2%)
Grade IV n (%)		
Pulmonary embolism		1 (6,2%)

Bold values = p values < 0.05.

respectively). Figure 1 NICs patients had a higher CRP value than NCs patients on POD 5 (48.7 versus 100.3 p = 0.036). A CRP peak occurred during the 72 hours for the three groups.

In contrast to the NICs and NCs groups, in the ICs group, the CRP level increased progressively between POD 3 and POD 10. A progressive increase was observed in the NICs group at POD 10. The means and values are shown in Table 3. No significant difference between CRP values was found between the NCs versus ICs groups, and NCs versus NICs groups.

WBC counts in the three groups (NCs versus ICs and NCs versus NICs groups)

For the three groups, the white blood cell counts decreased gradually from POD1 to POD 5, then increased until POD 10. The only significant difference between the groups with infective complications and no complications occurred at POD 10 (9.1 versus 11.9 p= 0.008). Figure 2

Postoperative laboratory data and predictive value of CRP for patients with infective complications

We performed a univariate analysis of the highest CRP level in order to search for a predictive value and we divided patients into two groups: those with very early ICs (PODs 3-5) and those with ICs from the second week (PODs 7-10). We analyzed the ROC curve from PODs 3-5 and PODs 7-10. A cut-off CRP value of 169 mg/L had a sensitivity of 26.3% and a specificity of 88.1% for postoperative infective complications at PODs 3-5. A cut-off CRP value of 62 mg/L at PODs 7-10 represented the optimal cut-off (69.2% sensitivity and 80% specificity). The area under the curve (AUC) was significantly lower at PODs 3-5 than at PODs 7-10 (0.56, 95% Confidence. Interval: [0.41108-0.70961] versus 0,76, 95% Confidence Interval: [0.63086-0.88523], p=0.007). Figures 3A–C

Among the 53 patients with ICs, 29 patients had a CRP value higher than these cut-offs (True positive, sensibility = 55%). The percentage of patients who had CRP values above that threshold at any point and with ICS (positive predictive value) was 74%. Moreover, 17 patients (32%) with ICs had a CRP value higher than these cut-offs before the diagnosis was made by the medical team. The mean of delay between the date of "predictive CRP value" and the date of "diagnosis" was 2.9 days (Range 1 - 7). The 3 patients with anastomotic leak and 2 of the 3 patients with intrabdominal abscesses had a delay in diagnosis of 1 to 4 days.

Among 58 patients of NICs group, 10 patients without infective complication had CRP value higher than these cut-offs (False positive, 17%). The specificity and negative predictive value were 83% and 67%, respectively.

Multivariable analysis included PCI (p = 0.003), ovarian PM (p = 0.03), Pseudomyxoma and mesothelioma (p=0,003) in the final model. All three variables are demonstrated to be independent risk factors for the occurrence of IC (p value <0.05).

Discussion

Some inflammatory markers, such as CRP and WBCs, have been used as useful tools to observe postoperative evolution and to diagnose postoperative complications after oncological surgery. We investigated the reliability of CRP and WBC values for predicting ICs after CRS and HIPEC for peritoneal metastases of diverse origins. To our knowledge, our study represents in the literature, the second work assessing the usefulness of CRP in PM from digestive and ovarian origins. These results suggested a significant association between postoperative complications after CRS and HIPEC and postoperative CRP elevation from POD3 to POD10. Moreover, the CRP cut-off value on PODs 3-5 (169 mg/l) and PODs 7-10 (62 mg/l) represented a risk factor for postoperative infective complications. The area under the curve (AUC) was significantly higher at PODs 7-10 than at PODs 5-7 (0,76 versus 0.56, p=0.007).

This study suggests that CRP cut-off may be used in clinical practice after CRS and HIPEC, specifically after POD7, before

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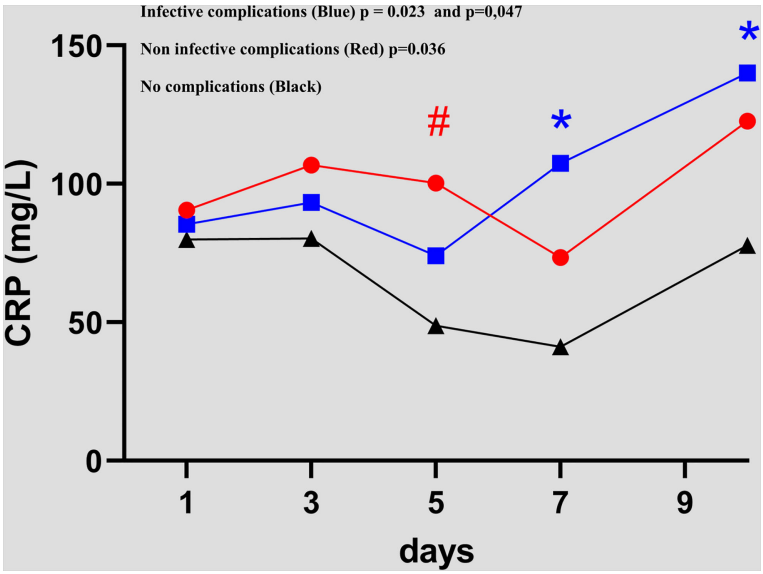

FIGURE 1
Evolution of C-reactive protein value between day 1 and day 10 in the 3 groups *(NCs* versus *ICs and NCs* versus *NICs groups)*.. #, * = statistically significant.

TABLE 3 Postoperative values of CRP and the WBC count in the 3 groups.

Variable	No complication (N = 58) Mean +/- SD	Infective complications (N = 53)		No Infective Complications (n = 16)	
		Mean +/- SD	*P (No complication group* vs *Infective complications group)*	Mean +/- SD	*P (No complication group* vs *No Infective complications group)*
CRP Value					
POD 1	79,9 +/- 29,1	85,4 +/- 41	*0,5*	90,6 +/- 37,2	*0,3*
POD 3	80,3 +/- 60,8	93,3 +/- 80	*0,4*	106,8 +/- 67,9	*0,3*
POD 5	48,7 +/- 46,2	74,1 +/- 78,8	*0,2*	100,3 +/- 70,8	***0,04***
POD 7	41,1 +/- 40,8	107,5 +/- 104,1	***0,02***	73,4 +/- 45,8	*0,1*
POD 10	77,8 +/- 81,8	140 +/- 107,9	***0,047***	122,6 +/- 126,2	*0,3*
WBC count					
POD 1	11,1 +/- 3,3	11,2 +/- 4,2	*0,9*	11,5 +/- 5,5	*0,7*
POD 3	8,8 +/- 3,1	8,6 +/- 3	*0,7*	9,5 +/- 4,4	*0,5*
POD 5	7,9 +/- 2,5	8,6 +/- 3,6	*0,3*	8,1 +/- 2,6	*0,9*
POD 7	9,5 +/- 3,2	11,2 +/- 5,3	*0,08*	10 +/- 2,6	*0,6*
POD 10	9,1 +/- 3	11,9 +/- 6,1	***0,008***	10 +/- 2,7	*0,4*
Length of stay (mean)	15,1	31	***0,0001***	26,1	*0,2*
Mortality < 3 months	0	0	1	0	*1*

CRP, c reactive protein; POD, postoperative day; WBC, white bloods cells.
Bold values = p values < 0.05.

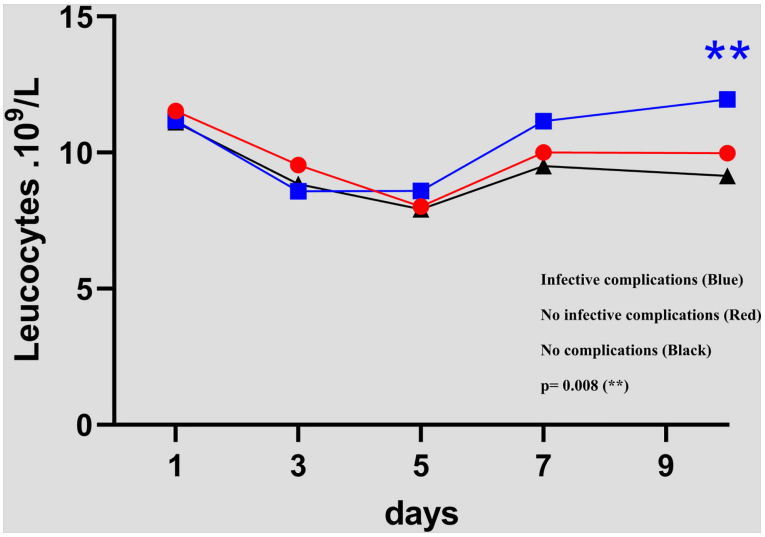

FIGURE 2
Evolution of white blood cell count between day 1 and day 10 in the 3 groups *(NCs versus ICs and NCs versus NICs groups)*..

any symptoms appear. In practice, if the CRP value is higher than these cut-off values, the medical team should perform the appropriate biological or radiological exams to diagnose and treat postoperative complications earlier.

The study population encompasses the large spectrum of patients undergoing CRS and HIPEC, as our study was a consecutive series, and global postoperative complications occurred in 54.3% of the patients, which is similar than the published complication rates (3).

CRP is a nonspecific inflammatory protein synthesised by the liver and has a short half-life (~19 h) such that the serum level quickly returns to normal when patients recover (12). It is produced in response to proinflammatory cytokines that pivotal role in the amplification of the inflammatory response and can increase in many different situations, such as cancer (13), infection, inflammatory disease (14), and thrombosis. Thus, it can be tested easily at low cost and with good reliability. In digestive surgery, it can be used as a marker of postoperative complications, specifically infective complications such as anastomosis leakage after colorectal (5, 6), pancreatic (15) or oesophageal (16), bariatric (17) surgery or even infectious complications in mesh repair in ventral hernia (18).

However, the systemic inflammatory response can be secondary to HIPEC chemotherapy (19, 20). This study confirmed the conclusion of Roth et al. (19) and more recently Van Kooten et al. (21). We found a peak of postoperative inflammation after the HIPEC procedure in patients without postoperative complications in the first 3 days. Nevertheless, we did not compare the different HIPEC protocols, and this CRP increase was more significant after HIPEC with mitomycin or cisplatin. Moreover, the systemic inflammatory response after CRS can be correlated with surgical stress parameters such as blood loss, surgical dissection, open surgery (22) and operation time (23), which is particularly long in peritoneal surgery. This may explain our results at PODs 3-5 (CRP cut off = 169 mg/L).

Nevertheless, to our knowledge, this is the first study that evaluated CRP cut-off values after CRS and HIPEC in order to analyse infective/non-infective complications and early/later complications.

The value was 62 mg/L on PODs 7-10. This low value is comparable to the study of Pochhammer et al. but unusual compared to other studies, and we were expecting a higher cut-off point for patients who had HIPEC (18). For example, the CRP cut-off value was 125 mg/mL at POD4 for the detection of anastomotic leakage in colorectal surgery, for Lagoutte et al. (5), and for Ortega-Deballon et al. (24). In the literature, there are few data on the use of the CRP cut-off value after peritoneal surgery. In addition, there is heterogeneity of cut-off values and days of CRP measurement, ranging from the day of surgery to POD30. Finally, it is difficult to compare all these studies in view of the various criteria used to predict postoperative complications, such as procalcitonin, cytokines, the CRP/WBC ratio and even the CRP/albumin ratio (25, 26).

We included all complications of the use of the CRP cut-off value in clinical practice in order to analyse separately the infective and non-infective complications. For example, anastomotic leakage could induce a stronger inflammatory response than non-infective complications as pulmonary

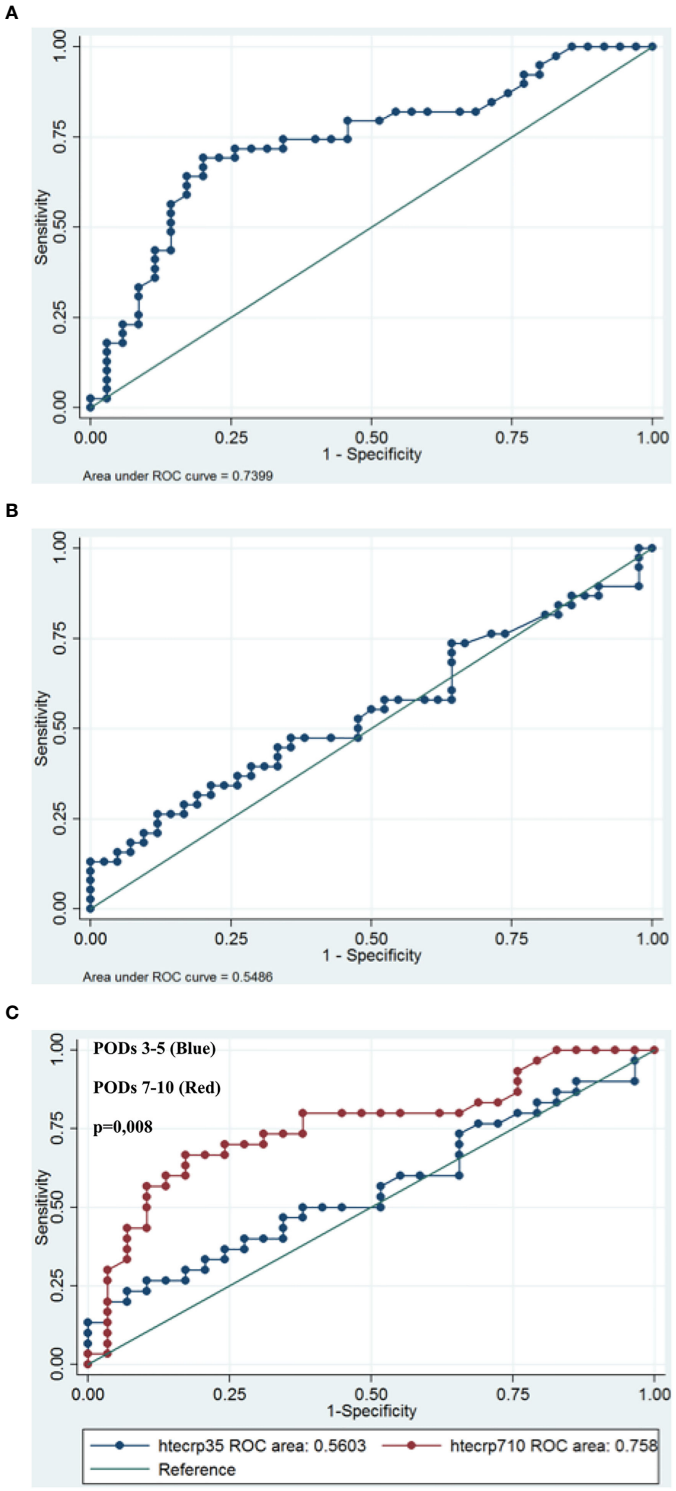

FIGURE 3
Receiver operating characteristic (ROC) curves for CRP on postoperative day (PODs) 3-5 **(A)** and PODs 7-10 **(B)** for patients with infective complications. An investigation of cut-off scores showed that the optimal CRP cut-off value was 169 mg/l on PODs 3-5 (sensitivity 26.3%; specificity 88.1%) and 62 mg/l on PODs 7-10 (sensitivity 69.2%, specificity 80%). The area under the ROC curve was 0,56 on PODs 3-5 and 0,76 on POD 7-10, p=0.0071 **(C)**.

embolism (21) and may explain this CRP cut-off rate difference between the literature and our study.

Although, some of authors aimed to predict all severe postoperative complications including non-infective complications, such as Van Kooten et al. (21). However, non-infective complications rate represented 10.3% in their study, and this low rate could explain the same CRP cut-off on PODs 3-5 with these both studies (166 mg/L on POD 3 (21) versus 169 mg/L on PODs 3-5 in our study).

The more representative infectious complication in our study was urinary tract infection, which can be an explanation for the low CRP cut-off value on PODs 7-10. This high rate can be explained by the use of morphine (27); the RAAC protocol (early mobilization), which was implemented only recently in our centre; and, finally, the duration of the bladder survey that could exceed 1 week after peritonectomy of the bladder peritoneum.

The most common medical complication was acute renal failure (3.1%, 4/127), probably secondary to cisplatin. Indeed, the main side effect of cisplatin, commonly used in HIPEC (9% in this study), is nephrotoxicity (28). Nevertheless, to prevent acute renal failure, many authors use recently sodium thiosulfate during cisplatin-HIPEC (29). All respiratory complications accounted for 4.7% of cases (6/127), including pneumonia, atelectasis, and pleural effusion, which is similar to that of the literature (30). This rate can be explained by the peritonectomy of the two diaphragmatic domes and of the operating time, which regularly exceeds 10 hours after CRS and HIPEC (31, 32).

Limitations

Several limitations to this study must be considered. Our study is limited by its retrospective, single-centre design, and a small number of subjects constituted the groups, especially with non-infective complications. Nevertheless, the study population represents the complete spectrum of patients with PM at a large-volume oncological centre and were followed every day by peritoneal surgeons and anaesthetists. Hence, these results seem to be applicable to surgical practice but need to be confirmed in prospective studies, including the use of other parameters such as the CRP-to-albumin ratio, platelet-to-lymphocyte ratio, procalcitonin, and cytokines.

Conclusion

In conclusion, our findings suggest that routine measurement of CRP after POD3 can provide information for oncological surgeons to guide postoperative management. The CRP cut-off value on PODs 3-5 (169 mg/l) and PODs 7-10 (62 mg/l) can be useful for the early diagnosis of postoperative infectious complications after CRS and HIPEC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

AR: Study concepts and design, data acquisition, quality control of data and algorithms, data analysis and interpretation, manuscript preparation, editing and review. VD: Manuscript preparation, editing and review. EA: Quality control of data and algorithms, data analysis and interpretation. SB: Quality control of data and algorithms, data analysis and interpretation. SD: Study concepts and design, data analysis and interpretation, manuscript preparation, editing and review. AT: Study concepts and design, data acquisition, quality control of data and algorithms, data analysis and interpretation, manuscript preparation, editing and review.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.943522/full#supplementary-material

ANNEX1
Flow chart.

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Disparities in access to care among patients with appendiceal or colorectal cancer and peritoneal metastases: A medicare insurance-based study in the United States

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Background: Prior studies attempting to identify disparities in the care of patients with appendiceal (AC) or colorectal cancer (CRC) with peritoneal metastasis (PM) are limited to single-institution, highly selected patient populations. This observational cohort study sought to identify factors associated with specialty care for Medicare beneficiaries with AC/CRC-PM.

Materials and methods: Patients >65 years old in the United States diagnosed with AC/CRC and isolated PM were identified within the Medicare Standard Analytic File (2013-2017). Mixed-effects analyses assessed patient factors associated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) and outpatient consultation with a peritoneal surface malignancy (PSM) surgeon, and Cox proportional-hazards analysis compared 3-year overall survival (OS) between patients receiving CRS/HIPEC versus systemic therapy alone.

Results: Among 7,653 patients, only 250 (3.3%) underwent CRS/HIPEC. Among those individuals who did not undergo CRS/HIPEC (N=7,403), only 475 (6.4%) had outpatient consultation with a PSM surgeon. Patient factors independently associated with lower odds of CRS/HIPEC and PSM surgery consultation included older age, greater comorbidity burden, higher social vulnerability index, and further distance from a PSM center (p<0.05). CRS/HIPEC was

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independently associated with better 3-year OS compared with systemic therapy alone (HR=0.29, 95%CI=0.21-0.38).

Conclusion: An exceedingly small proportion of Medicare beneficiaries with AC/CRC-PM undergo CRS/HIPEC or even have an outpatient consultation with a PSM surgeon. Significant disparities in treatment and access to care exist for patients with higher levels of social vulnerability and those that live further away from a PSM center. Future research and interventions should focus on improving access to care for these at-risk patient populations.

KEYWORDS

appendiceal cancer, colorectal cancer, peritoneal metastases, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), healthcare disparities, access to cancer care

Introduction

Colorectal cancer (CRC) remains the third most common cause of cancer in the United States with an incidence of 149,500 cases per year and was the third-leading cause of cancer death expected in 2021 (1). Approximately 10-15% of patients will present with peritoneal metastasis (PM) at the time of diagnosis (2). An additional 20-50% of patients will eventually develop metachronous PM (2). Although current therapies provide excellent outcomes for early-stage cancers, systemic chemotherapy is less effective for advanced stage disease, especially for PM (3). Patients with PM experience a median survival of approximately 6-8 months if untreated and approximately 16 months if treated with systemic chemotherapy (3, 4). Alternatively, cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to be efficacious in select patients with a median survival of up to 41 months (5–7).

Due to the complexity of patients with PM, optimal disease management requires access to multiple specialists to formulate and execute a detailed treatment plan. Nevertheless, multiple barriers exist to ensuring equitable access to specialty care and oncologic outcomes. For example, previous studies have demonstrated significant gaps in access to specialty care for oncology patients across various disease sites including cervical, breast, non-small cell lung cancer, and CRC (8–11). Even after treatment, patients require frequent visits to specialists for post-treatment evaluation and cancer surveillance. For patients in vulnerable populations, which includes individuals with lower socioeconomic status, underserved ethnic minority status, and residence in rural areas, initial access to care and subsequent adherence to post-treatment care remain significant challenges (9). Given the complexity and rarity of CRS/HIPEC compared to more common oncologic operations, access to care may be even more inequitable.

Several prior studies have attempted to identify and address possible disparities related to specialty care for patients with appendiceal cancer (AC)/CRC-PM. However, these analyses were largely based on single-institution data with inherent selection bias, including pre-screening of patients prior to care, type of insurance accepted, and patients already having received care at a quaternary center (12–15). As such, a better understanding of how many patients with AC/CRC-PM are receiving specialty care and which patient factors are associated with access to referral and treatment using a non-biased approach remains crucial. In the United States, Medicare health insurance serves as universal coverage for seniors over the age of 65. Using 100% capture Medicare claims data, this study sought to identify patient factors that contributed to specialty care for patients diagnosed with AC/CRC-PM and to examine the outcome of patients following treatment.

Materials and methods

Data sources

Medicare

The Medicare 100% Inpatient Standard Analytic File (SAF) (2012-2017) was utilized to identify Medicare beneficiaries >65 years old in the United States with an initial diagnosis of AC or CRC between January 1st, 2013 and March 31st, 2017 using *International Classification of Diseases, Ninth Edition* (ICD-9) and *Tenth Edition* (ICD-10) codes. The SAF is managed by the Centers for Medicare & Medicaid Services (CMS) and includes patient-level demographics, diagnoses, procedures, and costs data

from inpatient, skilled nursing facility, and hospice claims covered by Medicare Part A and outpatient and home health claims covered by Medicare Part B. The claims are linked to the Medicare Limited Data Set Denominator and Master Beneficiary Summary Files to obtain insurance status and mortality data. Medicare SAF data were available from January 1st, 2012 through December 31st, 2017. Therefore, each patient had at least one year of "look back" claims to identify the initial diagnosis of AC or CRC. The study cohort was then restricted to patients with an initial diagnosis of PM between January 1st, 2013 and March 31st, 2017 and either 60 days prior to or within 3 years following the initial diagnosis of AC or CRC. Further exclusion criteria included: 1) a diagnosis of distant metastases at other sites prior to, at the time of, or within 180 days of the initial diagnosis of PM; 2) a diagnosis of primary esophageal, gastric, small bowel, hepatopancreaticobiliary, or gynecologic cancer prior to or within 180 days following the initial diagnosis of PM; 3) non-continuous enrollment in Medicare Part A/B; 4) enrollment in a Health Maintenance Organization (HMO) health insurance plan from the date of the initial diagnosis of AC or CRC through the date of death or the end of the study period on December 31, 2017; and 5) missing county of residence for the patient. All administrative coding utilized for the study are listed in Table 1.

Outcomes

The primary outcome was treatment with CRS/HIPEC within 365 days of the date of the initial PM diagnosis. Because there are no specific ICD-9 procedure codes for CRS/HIPEC, a combination of hyperthermia and/or intraperitoneal chemotherapy procedure codes and at least one procedure code for an abdominal operation were utilized to identify CRS/HIPEC cases for inpatient claims with a discharge date prior to the implementation of ICD-10 codes on October 1st, 2015 as published previously in the surgical literature (16). For inpatient claims with a discharge date of October 1st, 2015 or later, specific ICD-10 codes for HIPEC were utilized to identify CRS/HIPEC cases (Supplementary Table 1).

Secondary outcomes included outpatient evaluation by a peritoneal surface malignancy (PSM) surgeon and 3-year overall survival (OS). A PSM surgeon was defined as a surgeon who performed at least one CRS/HIPEC case for a Medicare beneficiary during the study period and had a specialty taxonomy in the CMS National Plan and Provider Enumeration System (NPPES) of general surgery, surgical oncology, or colon & rectal surgery. Surgeons were matched to the NPPES using the National Provider Identifier number of the primary surgeon within the Medicare claim for the CRS/HIPEC procedure (17, 18). Three-year OS was defined as death from any cause within 3 years of the initial diagnosis date of PM. To limit heterogeneity with respect to patient fitness and treatment intent, the survival analyses only included patients who either underwent CRS/HIPEC or who received at least one cycle of systemic chemotherapy, targeted biologic therapy, or immunotherapy within 90 days of the initial diagnosis date of PM. These analyses were restricted to patients with information on CRS/HIPEC or systemic therapy within the Medicare Physician Supplier Part B/Carrier, Inpatient, and Outpatient claims.

Covariates

Patient factors included in the study are listed in Table 2. "Other" race included those that were coded as other, Asian, Hispanic, or North American Native within the Limited Data Set Denominator and Master Beneficiary Summary Files. The van Walraven Elixhauser Comorbidity Score is a validated modification of the thirty Elixhauser binary comorbidity measures that uses a weighted score for each of the comorbidities to compute a single numeric score for administrative data using ICD-9/ICD-10 diagnosis codes (19, 20). The CDC Social Vulnerability Index is a county-level estimate of the population's social vulnerability based on 15 United States census variables including socioeconomic status, household composition and disability, minority status and language, and housing type and transportation (21). Primary cancer site was categorized into appendiceal, right colon, left colon, unspecified colon site, and rectal cancer. Synchronous PM was defined as an initial PM diagnosis date within 180 days of the initial AC or CRC diagnosis date, and metachronous PM was defined as an initial PM diagnosis date 180 days or more after the initial AC or CRC diagnosis date. Distance to the nearest PSM center was estimated using the great-circle distance in miles from the county centroid of the patient's primary residence at the time of diagnosis to the county centroid of the nearest PSM center using the Haversine formula. This information was available through the National Bureau of Economic Research (NBER) and based upon the Federal Information Processing Standard Publication (FIPS) United States county codes using 2010 U.S. census data (22). PSM centers were identified within the Medicare data and defined as hospitals that performed an average of ≥1 CRS/HIPEC cases per year for appendiceal neoplasm, CRC, gastric cancer, ovarian cancer, primary peritoneal malignancy, or PM during the study period (Supplementary Table 1).

Statistical analysis

Bivariate analyses were performed using chi-squared and Mann-Whitney U tests, and clinically appropriate factors were manually entered into multivariable analyses for the outcomes of CRS/HIPEC, outpatient evaluation by a PSM surgeon, and 3-year OS. Two-level mixed-effects multivariable analyses accounted for

TABLE 1 Bivariate analysis of factors associated with CRS/HIPEC.

Factor	Overall study cohort (N=7,653)	No CRS/HIPEC (N=7,403) (96.7%)	CRS/HIPEC (N=250) (3.3%)	*P*
Age				<0.001
66-69	1,517 (19.8)	1,398 (18.9)	119 (47.6)	
70-79	3,340 (43.6)	3,215 (43.4)	125 (50.0)	
≥ 80	2,796 (36.5)	2,790 (37.7)	6 (2.4)	
Sex				0.01
Male	3,426 (44.8)	3,295 (44.5)	131 (52.4)	
Female	4,227 (55.2)	4,108 (55.5)	119 (47.6)	
Race				0.93
White	6,737 (88.0)	6,515 (88.0)	222 (88.8)	
Black	558 (7.3)	541 (7.3)	17 (6.8)	
Other	358 (4.7)	347 (4.7)	11 (4.4)	
van Walraven Elixhauser Comorbidity Score				<0.001
Median (IQR)	25 (19-33)	26 (19-33)	22 (16-30)	
CDC Social Vulnerability Index				<0.001
Median (IQR)	52.4 (30.4-71.3)	52.6 (30.6-71.6)	40.6 (23.2-63.5)	<0.001
1st quintile (least vulnerable)	1,068 (14.0)	1,021 (13.8)	47 (18.8)	
2nd quintile	1,607 (21.0)	1,532 (20.7)	75 (30.0)	
3rd quintile	1,930 (25.2)	1,870 (25.3)	60 (24.0)	
4th quintile	1,866 (24.4)	1,821 (24.6)	45 (18.0)	
5th quintile (most vulnerable)	1,182 (15.4)	1,159 (15.7)	23 (9.2)	
Distance to Nearest PSM Center				0.005
Median (IQR)	46.6 (17.1-101.2)	47.0 (17.1-101.7)	34.2 (10.9-87.0)	0.01
< 30 miles	2,856 (37.3)	2,741 (37.0)	115 (46.0)	
30-119 miles	3,346 (43.7)	3,245 (43.8)	101 (40.4)	
120-239 miles	1,140 (14.9)	1,111 (15.0)	29 (11.6)	
≥ 240 miles	311 (4.1)	306 (4.1)	5 (2.0)	
Year of Diagnosis				0.006
2013	2,129 (27.8)	2,081 (28.1)	48 (19.2)	
2014	1,908 (24.9)	1,851 (25.0)	57 (22.8)	
2015	1,806 (23.6)	1,738 (23.5)	68 (27.2)	
2016	1,479 (19.3)	1,415 (19.1)	64 (25.6)	
2017	331 (4.3)	318 (4.3)	13 (5.2)	
Primary Cancer Site				<0.001
Appendix	678 (8.9)	522 (7.0)	156 (62.4)	
Right colon	3,202 (41.8)	3,154 (42.6)	48 (19.2)	
Left colon	2,109 (27.6)	2,073 (28.0)	36 (14.4)	
Colon of unspecified site	925 (12.1)	922 (12.4)	3 (1.2)	
Rectum	739 (9.7)	732 (9.9)	7 (2.8)	
Timing of Carcinomatosis				0.007
Synchronous	6,027 (78.7)	5,813 (78.5)	214 (85.6)	
Metachronous	1,626 (21.2)	1,590 (21.5)	36 (14.4)	

CRS/HIPEC, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy; PSM, peritoneal surface malignancy; CDC, Centers for Disease Control and Prevention.

clustering of patients at the county level while evaluating factors associated with the outcome measures (23, 24).

For the binomial outcomes of CRS/HIPEC and outpatient evaluation by a PSM surgeon, Bayesian mixed-effects multivariable analyses were performed. Weakly informative independent normal priors were specified for the log odds ratio, variance parameters were set to 1, co-variances to 0, and the degree of belief to 0.002, and the Gibbs sampler was utilized to run Bayesian models for 13,000 Monte Carlo Markov chain iterations with a burn-in of 3,000 iterations (18, 25).

For the time-to-event outcome of 3-year OS, mixed-effects propensity-adjusted Cox proportional-hazards analysis was performed. Given the observational nature of the data and non-random assignment of treatment with CRS/HIPEC, a propensity score for each patient was estimated from the Bayesian mixed-effects multivariable analysis as the probability of undergoing CRS/HIPEC. To avoid reduction in study cohort size, the propensity score was entered as a continuous variable in the Cox proportional-hazards model as previously described (26, 27). All patients who were alive at the end of the study period, which was December 31st, 2017, were censored.

Bayesian mixed-effects logistic regression analyses were performed using the *MCMCglmm* package, and mixed-effects Cox proportional-hazards analyses were performed using the

TABLE 2 Mixed-effects multivariable analysis of factors associated with CRS/HIPEC.

Factor	Odds ratio (95% CI)	*P*
Age		
66-69	Reference	
70-79	0.46 (0.32-0.64)	<0.001
≥ 80	0.03 (0.01-0.06)	<0.001
Sex		
Male	Reference	
Female	0.69 (0.50-0.95)	0.02
Race		
White	Reference	
Black	1.06 (0.58-1.78)	0.82
Other	0.74 (0.33-1.55)	0.45
van Walraven Elixhauser Comorbidity Score	0.98 (0.96-1.00)	0.04
CDC Social Vulnerability Index		
Continuous (per 10th percentile increment increase)*	0.87 (0.82-0.93)	<0.001
1st quintile (least vulnerable)	Reference	
2nd quartile	1.08 (0.66-1.82)	0.81
3rd quartile	0.77 (0.48-1.23)	0.29
4th quintile	0.53 (0.32-0.89)	0.01
5th quintile (most vulnerable)	0.45 (0.24-0.85)	0.01
Year of Diagnosis		
2013	Reference	
2014	1.35 (0.85-2.05)	0.21
2015	1.49 (0.93-2.24)	0.10
2016	1.68 (1.03-2.64)	0.04
2017	1.44 (0.67-2.83)	0.34
Primary Cancer Site		
Appendix	Reference	
Right colon	0.05 (0.04-0.07)	<0.001
Left colon	0.05 (0.03-0.08)	<0.001
Colon of unspecified site	0.01 (0.003-0.03)	<0.001
Rectum	0.03 (0.01-0.05)	<0.001
Timing of Carcinomatosis		
Synchronous	Reference	
Metachronous	0.85 (0.55-1.37)	0.46
Distance to Nearest PSM Center		
Continuous (per 30 mile increment increase)*	0.97 (0.93-1.00)	0.09
< 30 miles	Reference	
30-119 miles	0.78 (0.56-1.10)	0.17
120-239 miles	0.63 (0.36-1.04)	0.07
≥ 240 miles	0.37 (0.13-0.93)	0.04

CRS/HIPEC, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy; CI, confidence interval; CDC, Centers for Disease Control and Prevention; PSM, peritoneal surface malignancy.
*Separate multivariable models were used to estimate continuous variable measures for CDC Social Vulnerability Index and distance to nearest CRS/HIPEC center.

coxme package in R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) (25, 28). All other analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The study was approved by the Institutional Review Board at the Ohio State University Wexner Medical Center.

Results

Cohort characteristics

A total of 7,653 patients met inclusion criteria. Among 22,669 patients with an initial diagnosis of AC/CRC-PM, 11,064 were excluded due to distant metastatic disease at other sites, 2,199 were excluded due to a diagnosis of another primary abdominal malignancy, 1,272 were excluded due to non-continuous enrollment in Medicare Part A/B or HMO enrollment, and 26 were excluded due to missing county of residence.

The most common primary cancer site was right-sided colon cancer (41.8%; N=3,202) followed by left-sided colon cancer (27.6%; N=2,109), unspecified colon cancer site (12.1%; N=925), rectal cancer (9.7%; N=739), and AC (8.9%; N=678). The median age of the study cohort was 76 (interquartile range [IQR]=71-83). A higher proportion of patients were female (55.2%; N=4,227), White (88.0%; N=6,737) versus Black (7.3%;

N=558) or another race (4.7%; N=358), and had synchronous PM (78.7%; N=6,027) versus metachronous disease (21.2%; N=1,626). There were 83 PSM centers identified between 2013 and 2017 across the United States, and the median patient distance to the nearest PSM center was 46.6 miles (IQR=17.1-101.2).

CRS/HIPEC

Overall, only 3.3% (N=250) of patients underwent CRS/HIPEC. When stratified by cancer type, 23.0% (N=156) of patients with AC and 1.3% (N=94) of patients with CRC underwent CRS/HIPEC. Among patients with CRC, patients with left-sided colon cancer were more likely to undergo CRS/HIPEC (1.7%; N=36) compared with right-sided colon cancer (1.5%; N=48) and rectal cancer (0.9%; N=7) (p<0.001). Patients of older age, female sex, higher comorbidity burden, higher social vulnerability, who lived further away from a PSM center, who had an earlier year of diagnosis, and who had metachronous versus synchronous PM were less likely to undergo CRS/HIPEC (all p<0.05) (Table 1). Patient race was not associated with CRS/HIPEC (p=0.93). Factors independently associated with lower odds of CRS/HIPEC on multivariable analysis included older age, female sex, higher comorbidity burden, higher social vulnerability, CRC compared with AC, and further distance from the patient's residence to the nearest PSM center (all p<0.05) (Table 2).

Outpatient visit with a peritoneal surface malignancy surgeon

Overall, there were 269 PSM surgeons across 83 PSM centers identified within the 2013-2017 Medicare SAF claims. Among the 7,403 patients who did not undergo CRS/HIPEC, only 6.4% (N=475) had an outpatient visit with a PSM surgeon. When stratified by cancer type, 31.2% (N=163) of patients with AC and 4.5% (N=312) of patients with CRC had an outpatient visit with a PSM surgeon. Factors independently associated with lower odds of an outpatient visit with a PSM surgeon among those who did not undergo CRS/HIPEC were older age, higher comorbidity burden, higher social vulnerability, CRC compared to AC, synchronous PM compared to metachronous PM, and greater distance from the patient's residence to the nearest PSM center (all p<0.05) (Table 3).

Three-year overall survival

Overall, 1,848 patients were treated with CRS/HIPEC and/or systemic therapy. Comparing individuals who underwent CRS/HIPEC (13.5%; N=250) to systemic therapy alone (86.5%; N=1,598), CRS/HIPEC was associated with better 3-year OS (74.4% vs 35.1%; log-rank p<0.001). When stratified by cancer type, CRS/HIPEC was associated with better 3-year OS for both AC (78.2% vs 33.1%; log-rank p<0.001) and CRC (68.1% vs 35.3%; log-rank p<0.001) (Figures 1–3). After propensity and risk-adjustment, CRS/HIPEC was independently associated with better 3-year OS (hazard ratio [HR]=0.29, 95% confidence interval [CI]=0.21-0.38) compared to systemic therapy alone (Table 4).

Discussion

Among Medicare beneficiaries in the United States, only 1 in 30 patients underwent CRS/HIPEC for AC/CRC-PM between 2013 and 2017. While the rate of CRS/HIPEC was higher among patients with AC-PM at 23%, the rate of CRS/HIPEC for CRC-PM was only 1.3%. Furthermore, patients with higher social vulnerability or who lived further away from a PSM center were less likely to undergo CRS/HIPEC or have outpatient consultation with a PSM surgeon. These findings highlight disparities in access to care for AC/CRC-PM patients with higher social vulnerability and/or increased travel burden. Given the recent findings from the PRODIGE-7 trial demonstrating a clear long-term survival benefit associated with CRS+/-HIPEC compared to survival data from other trials in which patients received systemic therapy alone, these findings highlight the need for future research focusing on interventions to improve access to care for this at-risk patient population (3, 4, 7).

This study is the first observational study to the authors' knowledge to assess healthcare disparities in care for AC/CRC-PM using a national study cohort in the United States. Two prior studies investigated possible treatment-related disparities for AC/CRC-PM using the National Cancer Database (NCDB) (13, 14). However, the NCDB is not population-based as it is limited to cases diagnosed or treated at Commission-on-Cancer (CoC)-accredited institutions in the United States. In a study by Byrne et al. that included 18,055 patients with AC, White patients, non-Hispanic ethnicity, and private insurance were associated with receipt of CRS/HIPEC (13). However, the study included patients without peritoneal metastasis, and neighborhood-level socioeconomic characteristics were not assessed. In a study by Goldberg et al. that included 6,634 patients diagnosed with ovarian or CRC-PM, the rate of CRS was 18.1%, and older age, male sex, lymph node metastasis, and community hospitals versus academic centers were associated with lower odds of receiving CRS (14). Interestingly, patient median household income, education status, distance to the reporting hospital, and treatment at facilities with higher-income patient populations were not associated with receipt of CRS. However, as aforementioned, the study was limited to those treated at CoC-accredited centers.

TABLE 3 Mixed-effects multivariable analysis of factors associated with an outpatient visit with a peritoneal surface malignancy (PSM) surgeon.

Factor	Odds ratio (95% CI)	*P*
Age		
66-69	Reference	
70-79	0.50 (0.39-0.65)	<0.001
≥ 80	0.16 (0.12-0.24)	<0.001
Sex		
Male	Reference	
Female	0.84 (0.68-1.07)	0.11
Race		
White	Reference	
Black	0.77 (0.48-1.19)	0.20
Other	1.43 (0.93-2.18)	0.11
van Walraven Elixhauser Comorbidity Score	0.97 (0.96-0.99)	<0.001
CDC Social Vulnerability Index		
Continuous (per 10th percentile increment increase)*	0.90 (0.86-0.95)	<0.001
1st quintile (least vulnerable)	Reference	0.008
2nd quartile	0.53 (0.35-0.81)	0.05
3rd quartile	0.67 (0.43-0.96)	0.006
4th quintile	0.57 (0.38-0.86)	<0.001
5th quintile (most vulnerable)	0.44 (0.29-0.73)	
Year of Diagnosis		
2013	Reference	
2014	1.21 (0.88-1.60)	0.25
2015	1.09 (0.80-1.54)	0.57
2016	1.20 (0.84-1.67)	0.30
2017	0.92 (0.52-1.83)	0.78
Primary Cancer Site		
Appendix	Reference	
Right colon	0.07 (0.5-0.09)	<0.001
Left colon	0.08 (0.06-0.11)	<0.001
Colon of unspecified site	0.06 (0.04-0.10)	<0.001
Rectum	0.06 (0.04-0.10)	<0.001
Timing of Carcinomatosis		
Metachronous	Reference	
Synchronous	0.73 (0.56-0.96)	0.02
Distance to Nearest PSM Center		
Continuous (per 30 mile increment increase)*	0.97 (0.94-1.00)	0.02
< 30 miles	Reference	
30-119 miles	0.56 (0.42-0.76)	<0.001
120-239 miles	0.30 (0.20-0.48)	<0.001
≥ 240 miles	0.34 (0.16-0.66)	0.002

CRS/HIPEC, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy; CI, confidence interval; CDC, Centers for Disease Control and Prevention.
*Separate multivariable models were used to estimate continuous variable measures for CDC Social Vulnerability Index and distance to nearest peritoneal surface malignancy center.

Other prior studies were limited to single-institution data with inherent selection bias that included pre-screening of patients prior to care, types of insurance accepted, and patients already having received care at specialized centers. In a case-control study by Tabrizian et al. comparing all patients with CRC-PM who had undergone CRS/HIPEC between 1993 and 2013 (N=112) and patients who underwent either colectomy for non-metastatic colon cancer or hepatectomy for colorectal cancer liver metastasis, patients who underwent CRS/HIPEC were more likely to be White, English speaking, privately insured, have higher mean income, and travel further distances for treatment compared with the control groups (12). In a separate study by Rieser et al. that included 226 patients who underwent CRS/HIPEC for CRC-PM between 2000 to 2018 at a high-volume tertiary CRS/HIPEC center, patients with high socioeconomic status were more likely to be White, privately insured, and travel further distances for treatment compared to those with low socioeconomic status (15). Following CRS/HIPEC, patients with low socioeconomic status had worse outcomes, including longer length of stay, higher rates of 90-day readmission and 30-day mortality, and lower median OS.

Another possible disparity that was identified was related to patient sex. While the association between female sex and outpatient consultation with a PSM surgeon did not reach statistical significance (p=0.11), female sex was independently associated with lower odds of CRS/HIPEC compared to male

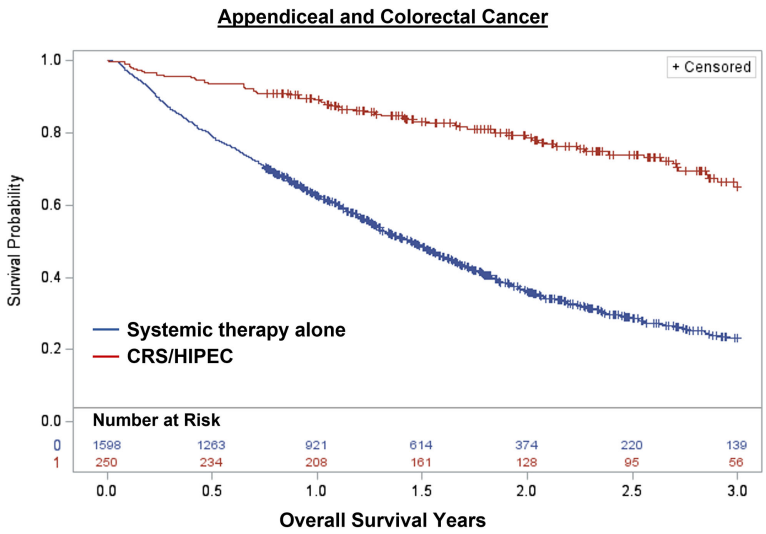

FIGURE 1
Kaplan-Meier 3-year overall survival of 1,848 patients with appendiceal or colorectal cancer and peritoneal metastasis stratified by treatment with CRS/HIPEC +/- systemic therapy or systemic therapy alone.

sex. Interestingly, this difference was also observed by Byrne et al. in which male patients were 33% more likely to undergo CRS/HIPEC for appendiceal cancer compared to female patients (13). Unfortunately, the reasons for this association cannot be elucidated from the Medicare data. Possible explanations include an underlying disparity or more advanced disease at time of diagnosis. Future research is needed to better understand this association.

While the rate of CRS/HIPEC was much higher for AC-PM compared to CRC-PM (23% versus 1.3%), the reasons for the overall low rate of CRS/HIPEC in the current study are likely multifactorial. Medicare beneficiaries >65 years of age are likely to have an increased risk of postoperative complications and mortality secondary to a higher comorbidity burden and less functional reserve which may influence their perceived ability to tolerate a high-risk operation (29). However, only 5% of the 66-69

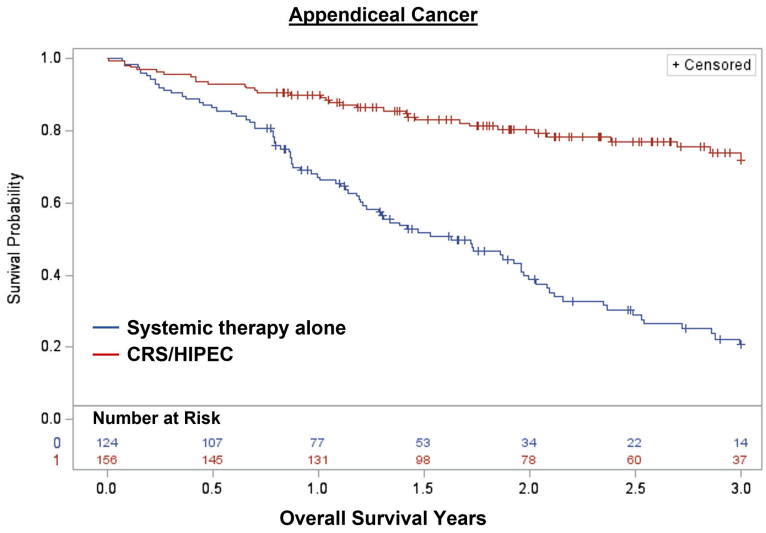

FIGURE 2
Kaplan-Meier 3-year overall survival of 280 patients with appendiceal cancer and peritoneal metastasis stratified by treatment with CRS/HIPEC +/- systemic therapy or systemic therapy alone.

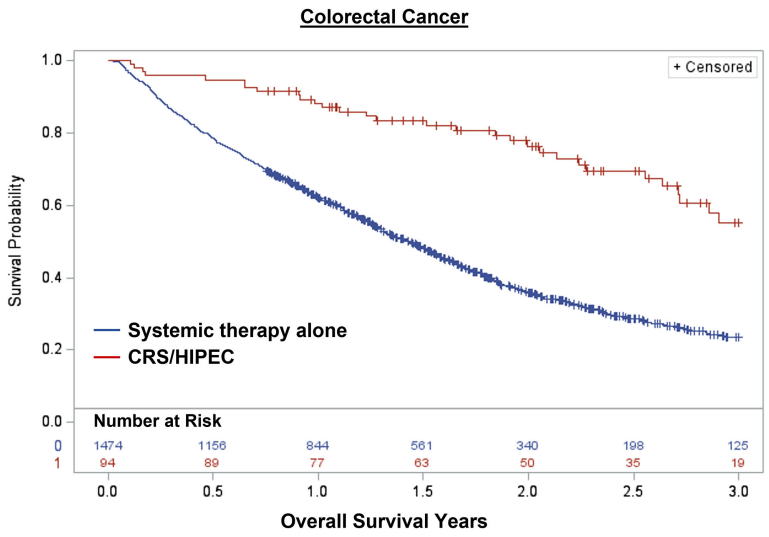

FIGURE 3
Kaplan-Meier 3-year overall survival of 1,568 patients with colorectal cancer and peritoneal metastasis stratified by treatment with CRS/HIPEC +/- systemic therapy or systemic therapy alone.

age group within the study underwent CRS/HIPEC, suggesting that the low rate of utilization also occurred across younger age groups. The availability of CRS/HIPEC was also limited, as reflected by only 83 hospitals being identified as PSM centers in the study. Of note, the median distance from the patient residence to the nearest PSM center across the study cohort was 46.6 miles. In addition, there was underutilization of referral to PSM surgeons, which is likely related to both lack of access to PSM specialists and limitations in knowledge among providers related to the postoperative outcomes and efficacy of CRS+/-HIPEC in the treatment of PSM. Furthermore, as a higher proportion of providers view CRS/HIPEC as an appropriate treatment modality for AC-PM compared to CRC-PM, a limitation in knowledge may at least partially explain the higher rates of CRS/HIPEC (23% versus 1.3%) and outpatient consultation with a PSM surgeon (31% versus 4.5%) for AC-PM compared to CRC-PM (30–32).

These suspected reasons for low rates of CRS/HIPEC and referral to PSM surgeons are supported by provider survey data. In a study by Bernaiche et al, medical oncologists and general surgeons in Virginia, Maryland, and Washington, D.C. who treated patients with gastrointestinal cancer were asked questions regarding access to centers that performed CRS/HIPEC, prior referral to PSM centers, opinions regarding efficacy of CRS/HIPEC, and knowledge with respect to postoperative outcomes following CRS/HIPEC (30). Among 116 respondents, 41% indicated that multidisciplinary tumor board discussion of patients with PM occurred ≤50% of the time, and 34% stated that PSM specialists were not easily available to their patients. For specific cancer types, CRS/HIPEC was considered an appropriate therapeutic option for AC and CRC among 75% and 50% of respondents, respectively. More than a quarter of respondents had never referred a patient to a PSM specialist in the past due to lack of access to a specialist (47%), perceived lack of efficacy of CRS/HIPEC (31%), and a belief that the morbidity and mortality of CRS/HIPEC is too high (16%). Furthermore, OS was underestimated among 48% of respondents for low-grade appendiceal mucinous neoplasm and 39% of respondents for colon cancer, and 30-day

TABLE 4 Mixed-effects propensity-adjusted Cox proportional-hazards analysis of association between CRS/HIPEC and overall survival*,†.

	Overall study cohort (N = 1, 848)		Appendiceal cancer (N = 280)		Colorectal cancer (N = 1, 568)	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Systemic therapy alone	Reference		Reference		Reference	
CRS/HIPEC	0.29 (0.21-0.38)	<0.001	0.22 (0.14-0.32)	<0.001	0.35 (0.24-0.51)	<0.001

CRS/HIPEC, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy; HR, hazard ratio;
CI, confidence interval.
*To limit study cohort heterogeneity with respect to patient fitness and treatment intent, the analysis only includes patients who underwent CRS/HIPEC or systemic therapy.
†Models also control for patient age, sex, race, van Walraven Elixhauser comorbidity score, CDC social vulnerability index quintile, year of diagnosis, primary cancer site, synchronous vs metachronous carcinomatosis, and distance to nearest peritoneal surface malignancy center.

mortality at experienced PSM centers was overestimated by the majority of respondents. Similar results were observed in Ontario, Canada where only 46% of respondents were aware that CRS/HIPEC is a therapeutic option in patients with CRC-PM; in the Netherlands, 32% of providers did not view CRS/HIPEC as an accepted treatment modality for CRC-PM (31, 32).

Regardless of the possible etiologies – given the estimated annual incidence in the United States of 10,620-22,550 for CRC-PM and 600 for AC-PM – CRS/HIPEC clearly appears to be underutilized (33). There are several potential strategies to improve referral rates and access to PSM specialists for patients. Under ideal circumstances, all patients with isolated PM or PM with limited, resectable extraperitoneal metastatic disease should undergo formal multidisciplinary review with surgeons, medical oncologists, and a trained PSM surgeon. In geographic areas where there is no qualified PSM surgeon, virtual tumor board or telemedicine referral and evaluation, which has been shown to be a cost-effective modality for specialized care, are alternative options (34, 35). In light of improved perioperative outcomes and a long-term survival benefit from CRS/HIPEC in carefully selected patients, education of various stakeholders including medical providers, patients, policy makers, and payers regarding the efficacy of CRS/HIPEC for AC/CRC-PM may also lead to higher referral rates (7, 36). Furthermore, the creation of financial assistance programs with travel and lodging vouchers for disadvantaged patients with limited financial means and higher travel burden to the nearest PSM center will help reduce disparities in access to care.

While this study is the first national observational cohort study investigating factors associated with receipt of CRS/HIPEC for AC/CRC-PM, there are several limitations. Medicare SAF is susceptible to medical coding errors since it is comprised of administrative data. In addition, TNM staging is not available within the data. However, validation studies have demonstrated low false positive rates with the use of ICD-9/ICD-10 diagnosis coding algorithms to identify metastatic disease in colorectal cancer with a specificity > 90% (37, 38). Similarly tumor histology, differentiation, and disease burden as measured by the peritoneal carcinomatosis index are also not available which influences the decision on whether a patient may benefit from CRS/HIPEC. Because these factors are not available within the data, the 3-year overall survival analyses had to be limited to those who underwent CRS/HIPEC or systemic therapy alone to reduce heterogeneity among patients. Furthermore, because there are no specific codes for CRS, it was not possible to identify patients who underwent CRS without HIPEC which can also lead to long-term survival (7). However, CRS is rarely performed without HIPEC for AC/CRC-PM (39). Finally, the study cohort was necessarily restricted to patients > 65 years old with Medicare insurance. The rates of CRS/HIPEC are likely higher in younger patient populations who are healthier and have better functional status.

Conclusion

An exceedingly small proportion of Medicare beneficiaries with AC/CRC-PM undergo CRS/HIPEC or even have an outpatient consultation with a PSM surgeon. Significant disparities in treatment and access to care were evident for patients with higher levels of social vulnerability and who live further away from a PSM center. Future research should focus on interventions to improve referral rates to PSM centers and appropriate access to care for these at-risk patient populations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The Medicare Standard Analytical claims data contain patient-level health information and are considered identifiable files. Therefore, access to these data requires a data use agreement and institutional review board approval. Requests to access these datasets should be directed to https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board at the Ohio State University Wexner Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CA and AK contributed to the conception and design of the work. CA, ZB, JB, AE, JC, OE, JM, SR, GK, MA, SO-G, TP, and AK contributed to acquisition, analysis, and/or interpretation of data for the work. CA and AK contributed to drafting of the work. ZB, JB, AE, JC, OE, JM, SR, GK, MA, SO-G, TP, and AK contributed to revising the work for important intellectual content. CA, ZB, JB, AE, JC, OE, JM, SR, GK, MA, SO-G, TP, and AK provided approval for publication of the work and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author AE was employed by Natera, Inc. and Delcath, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.970237/full#supplementary-material

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Management of peritoneal surface metastases from colorectal cancer: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, pressurized intraperitoneal chemotherapy, and beyond

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This article provides a contemporary review of the current surgical management of peritoneal surface malignancy (PSM) of colorectal origin. A brief review of the founding history of surgical intervention for PSM is followed by a focused review of the level I evidence, current clinical questions, and evolving advancements. While not intended to address all the facets of PSM, this review aims to provide the reader with the essential knowledge and resources to effectively provide surgical care for carcinomatosis due to colorectal malignancies.

KEYWORDS

colorectal cancer, peritoneal surface malignancies (PSM), cytoreductive surgery and HIPEC, PIPAC, surgical standard

Introduction

The management of peritoneal surface malignancy (PSM) has significantly changed in both clinical attention and complexity over the past decade. PSM encompasses a broad range of etiologies to include rare primary peritoneal malignancies as well as the more commonly encountered secondary peritoneal metastatic disease. This is primarily due to the pioneering efforts establishing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) as an accepted therapeutic intervention within the oncologic community. While CRS-HIPEC constitutes the focus of the majority of research regarding surgical management of PSM, additional modalities such as

adjuvant HIPEC and pressurized intraperitoneal aerosol chemotherapy (PIPAC) have also been investigated.

The heterogenicity of PSM, coupled with limited level I evidence, has made definition of the optimal management of PSM a difficult standard to define. The objective of this review is to provide a concise review regarding the history, current clinical research data, and future targets for surgical management of PSM, with the targeted audience being physicians who manage PSM to provide them with current standards within this evolving clinical field. The focus of this manuscript is for PSM of gastrointestinal origin, specifically colorectal and appendiceal primaries. Using the PICO (patient, intervention, comparison, outcomes) format, this literature review aims to educate the reader on current standard of care for patients with PSM secondary to appendiceal and colorectal primaries (P), undergoing CRS-HIPEC (I), evaluating the only published level I data (C), and establishing the standards of care (O).

Subsections

The origin of CRS-HIPEC

CRS-HIPEC has become the cornerstone for surgical management of PSM. CRS-HIPEC is currently the most utilized surgical intervention for PSM. Therefore, the overwhelming majority of basic science and clinical research data reside within the scope of CRS-HIPEC. The treatment tenet of CRS-HIPEC is two-pronged: the cornerstone being the removal of all gross tumor (CRS), and then utilizing "local" intraperitoneal adjuvant therapy, such as HIPEC, to effectively treat residual microscopic disease.

The genesis of CRS can be traced back to the 1930s with Dr. Meigs' publication on his experience with cytoreduction for ovarian cancer (1). Further work in the 1960s–1970s by Dr. Griffiths' National Cancer Institute group, investigating ovarian cancer, and Dr. Long's Alabama group, investigating mucinous neoplasms, provided the first modern scientific evidence that CRS significantly increased survival for patients with PSM (2, 3). Both the research by Dr. Griffiths' and Dr. Long's collaboratives found that the addition of adjuvant systemic therapy improved outcomes (4, 5). The conceptual basis of CRS is quite elementary; if all gross diseases can be resected, than there will be significant benefit. Those inceptive efforts with CRS provided the "proof of concept" work facilitating the evolution of surgical management of PSM.

The practice of combined CRS-HIPEC was spearheaded by Dr. Paul Sugarbaker's experience with the Washington Cancer Institute in the 1980s. That pioneering work combining CRS with HIPEC established the conduct of CRS-HIPEC as it is utilized currently. Progressing the landmark work by Dr. Spratt and colleagues from the University of Louisville, who developed a human delivery system for HIPEC, Dr. Sugarbaker's group became the lead academic research team evaluating CRS-HIPEC providing critical prospective data to legitimize CRS-HIPEC (6–9). Several benefits of HIPEC over adjuvant systemic therapy have been proposed. HIPEC has been touted as having a superior therapeutic effect within the peritoneal cavity where systemic therapy penetration is limited (10). Further, intracavitary administration of chemotherapy is able to achieve higher, more tumoricidal, levels of chemotherapy at the site of the disease than can be accomplished with even the most aggressive dosing of systemic drug can achieve without undue toxicity (10). Lastly, the one-time dosing of HIPEC is more cost effective (compared with repeated systemic chemotherapy dosing) and is not associated with the compliance issues or tolerability of multicycle therapy (10). That collective early CRS-HIPEC endeavor by the multiple founding PSM surgeons has served as the standard for surgical management of peritoneal carcinomatosis for nearly 40 years. Only recently with the results from the PRODIGE7 trial has the decoupling of CRS and HIPEC been seriously reconsidered.

The ability to efficiently and accurately quantify the volume of peritoneal metastatic disease across multiple pathologies and applying that metric to clinical decision making was also established by Sugarbaker and his colleagues. They developed the peritoneal cancer index (PCI) score which allowed PSM surgeons to reliably quantify burden of disease on a point spectrum from 1 to 39 based on standardized anatomical locations (11, 12). The PCI is the standard currently utilized at most larger centers for quantification of the amount of disease present at the start of CRS.

The completeness of the cytoreduction (CC) score was invented by Dr. Glehen and Dr. Gilly to grade the quality of CRS (13). Slight technical variations of that CC score, R score (from the AJCC staging manual), are used at differing PSM centers, but the primary gradation scheme is similar, with a complete cytoreduction (CC-0, R1) defined as no gross residual tumor, a near-complete cytoreduction (CC-1, R2a) with less than 2.5 mm of gross residual disease remaining, and two incomplete cytoreduction scores for residual disease between 2.5 mm and 2.5 cm (CC-2, R2b) and residual disease in excess of 2.5 cm (CC-3, R2c). Similar to how CRS-HIPEC is a bimodal intervention, the PCI-CC score provides two complimentary data points. The PCI score provides guidance for PSM surgeons regarding the likelihood of achieving a complete cytoreduction based on the underlying tumor biology, while the CC score has become the main determining factor to proceed with HIPEC at the time of CRS. The collection of promising initial phase I and II trials evaluating CRS-HIPEC paired with the reproducible PCI-CC scoring scheme provided the requisite groundwork for the subsequent phase III studies validating surgical management of PSM.

CRS as standard oncologic therapy for PSM for colorectal and appendiceal primaries and utility of HIPEC in flux

CRS-HIPEC has been frequently performed at leading academic centers worldwide since the 1990s, but it took nearly two decades for the oncologic community to embrace surgical management of PSM as standard of care. Despite positive basic science and clinical data with CRS-HIPEC, surgical management of PSM was often labeled radical therapy leading to limited utilization. The inertia to CRS-HIPEC was multifaceted. One of the major hurdles was the general therapeutic nihilism with treating diffusely metastatic diseases. Despite objective effectiveness with CRS-HIPEC, that evidence was frequently trivialized within the oncologic academic oncologic community (14, 15). The general negative bias toward CRS-HIPEC was further reinforced by the initial morbidity and mortality associated with the procedure that was in the 60% and 20% range, respectively (16). Like with most initially labeled radical therapies, persistent hesitance is only overcome with establishing gold standard, phase III, trial data, despite the fact that the median survival with PSM from GI primaries prior to the turn of the century was a mere 6 months.

To date, there have only been four completed and reported randomized control trials (RCTs) evaluating the primary surgical management of PSM for colorectal cancer, and one for appendiceal. All of those trials involved secondary metastatic disease to the peritoneal cavity, of which three studies focused on colorectal and appendiceal primaries with the remaining study evaluating carcinomatosis due to ovarian cancer. As will be detailed in the succeeding text, those RCTs, particularly the trials involving colorectal primaries, have definitively established CRS as standard-of-care oncologic management for patients with carcinomatosis. However, the most recently published trial, PRODIGE7, has now reintroduced additional discussions on the surgical management of PSM. Does HIPEC after CRS provide any additional benefit? The level I data for CRS-HIPEC for PSM secondary to gastrointestinal cancer, colorectal, and appendiceal tumors will be evaluated in detail, specifically examining each published individual RCT followed by a discussion of the current quandary regarding the benefit of HIPEC.

The Dutch trial

The first RCT was by Verwaal et al., from the Netherlands Cancer Institute, published in 2003 (17). In that trial, 105 patients with peritoneal carcinomatosis due to colorectal primary tumors, of which approximately 85% were colorectal cancer and 15% were appendiceal cancer, were equally randomized to a control standard chemotherapy-alone group and an experimental CRS-HIPEC group. The control group received 5-FU and leucovorin alone (standard systemic chemotherapy at the time the trial was started). Patients randomized to CRS-HIPEC were to undergo an optimal cytoreduction, defined for this study protocol as R2a or better, with mitomycin C as the HIPEC agent.

The median follow-up was 21.6 months, and the primary outcome was survival. For the CRS-HIPEC cohort, an R1 resection was achieved in 33%, R2a in 39%, and R2b in 18% with a surgical mortality rate of 8%. The CRS-HIPEC group had significantly improved survival with a median OS of 22.4 vs. 12.6 months (HR = 0.55, 95% CI 0.32–0.95, P = 0.032). Subgroup analysis based on sex, age, tumor site, and either primary or recurrent disease revealed no heterozygosity from the main results, and CRS-HIPEC was significantly beneficial across all subgroups. Further evaluation of CRS-HIPEC stratified by burden of disease and completeness of cytoreduction, R1/R2a vs. R2b, demonstrated improved survival with decreased disease burden and optima cytoreduction with median OS of 29 vs. 5.4 months ($P < 0.0001$) and 20 vs. 5 months ($P < 0.0001$), respectively. Of note, PCI scoring was not utilized in this trial. Burden of disease was quantified by abdominal regions, ≤5 or 6–7, containing disease. Long-term trial data analysis found that CRS-HIPEC had persistent utility with improved DFS and PFS of 22.2 vs. 12.6 months (P = 0.028) and 12.6 vs. 7.7 months (P = 0.020), respectively (18). Also for those achieving an R1 cytoreduction, the 5-year OS rate was 45% on that 8-year follow-up which was remarkably improved survival compared to historical data with standard chemotherapy alone.

The Dutch trial was a true landmark study in several regards. It provided the first level I evidence evaluating CRS-HIPEC and most importantly produced favorable data demonstrating improved survival with CRS-HIPEC. However, critics of the trial suggested that the improved survival with CRS-HIPEC compared to the control group was due to utilization of an outdated less efficacious chemotherapy regimen. At the time of the publication of the trial, newer oxaliplatin and irinotecan-based chemotherapies FOLFOX and FOLFIRI were becoming the standard of care for systemic treatment of metastatic colorectal cancer based on their superior results (19). Despite those study critiques, the Dutch trial was instrumental in validating CRS-HIPEC as both a therapeutic intervention with true utility and as a surgery that could be safely performed.

The Swedish trial

The next RCT was performed by Cashin et al., as a study involving several academic centers within Sweden (20).

Unfortunately, the trial was terminated early due to poor accrual with only 48 patients recruited at the time of study closure. Publication of the trial data occurred in 2016. All the study participants had secondary peritoneal carcinomatosis with a near-identical distribution of primary etiology to the Dutch trial, approximately 85% being colorectal tumors and 15% being appendiceal tumors. Each study group contained 24 patients who were equally randomized. The control group received contemporary standard systemic chemotherapy with FOLFOX. The experimental CRS-HIPEC group had the same objective as the Dutch trial with trying to achieve an optimal cytoreduction of CC-0 or CC-1. However, the HIPEC protocol in the Swedish trial was performed in an adjuvant technique utilizing an abdominal port to infuse 5-FU with leucovorin every 4–5 weeks for a total of 6 cycles.

The median follow-up was 78 months with survival as the primary outcome. For the CRS-HIPEC group, the mean PCI was 18 and 79% of cases achieved either a CC-0 or CC-1 cytoreduction. The surgical mortality and morbidity, defined as Clavien–Dindo III/IV complications, rates were 0% and 33%, respectively. For the entire study population, the CRS-HIPEC group had superior survival with a median OS of 25 vs. 18 months and 2-year OS rates of 54% vs. 38% (HR = 0.51, 95% CI 0.27–0.96, P = 0.04). Yet, for the entire study population on multivariate analysis, CRS-HIPEC was not independently associated with improved OS (HR = 2.17, 95% CI 0.77–1.61, P = 0.14). Adjusting only for patients who achieved an optimal cytoreduction, CC-0 or CC-1, CRS-HIPEC significantly improved OS on both univariate (HR = 0.20, 95% CI 0.09–0.45, P = 0.0001) and multivariate (HR = 0.11, 95% CI 0.04–0.34, P = 0.0005) analyses. The median OS was 40 months with a 5-year OS rate of 40% in those achieving an optimal cytoreduction. There was no significant difference in PFS with a median PFS of 12 vs. 11 months, but based on 5-year PFS rates, there was a trend toward improved outcomes with CRS-HIPEC at 17% vs. 0% (P = 0.16).

The Swedish trial justifiably received less acclaim than the Dutch trial due to the fact that it failed to accrue the required number of participants to satisfy its study design. Despite the early termination, this incomplete study still provided objective data that further supported CRS-HIPEC. Again, a statistically significant survival benefit was demonstrated with CRS-HIPEC in the Swedish trial. Those findings strengthened the results from the Dutch trial since the control group participants in the Swedish trial received the contemporary standard of FOLFOX systemic therapy. Therefore, the criticism of improved survival with CRS-HIPEC levied in the Dutch trial due to the use of non-contemporary chemotherapy regimens was mitigated with the Swedish trial results. Evaluating the Swedish trial with the perspective of the PRODIGE7, PROPHYLOCHIP, and COLOPEC trial data, which will be subsequently discussed, these study results suggest that CRS alone is the principal factor in improved survival with surgical management of PSM.

The French PRODIGE7 trial

The most recent RCT evaluating CRS-HIPEC for colorectal cancer was PRODIGE7 performed by Quénet et al. and published in 2021 and is arguably the most influential trial regarding surgical management of PSM (21). PRODIGE7 is the largest trial being a multicenter study, involving French PSM institutions, of 265 patients with peritoneal carcinomatosis all due to colorectal adenocarcinoma alone. There were no appendiceal cancer cases allowed in PRODIGE7, which differentiated it from the previously performed Dutch and Swedish trials. Another critical distinguishing feature of PRODIGE7 was it equally randomized patients to a CRS-alone group and a CRS-HIPEC group. The final study population consisted of 133 patients in the CRS-alone group and 132 patients in the CRS-HIPEC group. All study participants had to have a PCI ≤25 and undergo an optimal cytoreduction defined as no gross residual disease or remaining tumor implants of ≤1 mm, modified CC-1/R2a cytoreduction, in order to be included in the final analysis. The study HIPEC protocol significantly differed from many other PSM centers with a shortened 30-min perfusion of oxaliplatin that was combined with an IV dose of 5-FU. Lastly, nearly the entire study populace, over 95% received systemic therapy either preoperatively or as a postoperative adjuvant, with approximately 65% of patients receiving both preoperative and postoperative adjuvant systemic chemotherapies.

The median follow-up was 63.8 months, and the primary endpoint was OS with RFS as a secondary outcome. Both cohorts had excellent cytoreductions with approximately 90% of all patients achieving an CC-0/R1 cytoreduction with the remaining 10% undergoing a modified optimal cytoreduction. The median PCI scores were 9 and 10 for CRS and CRS-HIPEC, respectively. There was no difference in survival outcomes between the cohorts. The median OS was 41.2 vs. 41.7 months and 5-year OS rates of 36.7% and 39.4% (HR = 1.0, 95% CI 0.63–1.58, P = 0.99) for CRS alone and CRS-HIPEC, respectively. Likewise, there was no difference in RFS with median RFS of 11.1 vs. 13.1 months and 5-year RFS rates of 13.1% vs. 14.8% (HR = 0.91, 95% CI 0.71–1.15, P = 0.43) for CRS and CRS-HIPEC, respectively. On subgroup analysis to include sex, primary location, nodal status, neoadjuvant versus adjuvant chemotherapy, and completeness of cytoreduction, there was no heterozygosity with the main analysis. The only subgroup that benefited from CRS-HIPEC, for OS alone, was for cases with an intermediate PCI score of 11-15 (HR = 0.44, 95% CI 0.21–0.99). There was no significant difference in mortality rates between CRS and CRS-HIPEC, 4.5% vs. 6%, as well as no difference in 30-day complication rates at 32% vs. 42% (P = 0.083). However, CRS-HIPEC was associated with an increased long-term—31–60 days—complication rate at 26% vs. 15% (P = 0.035).

To date, the survival results from PRODIGE7 are the best for any prospective study evaluating metastatic colorectal cancer regardless of intervention. However, the results of PRODIGE7 have become a flashpoint subject within the academic oncology

community. Generally speaking, the medical oncology community has viewed the study results as a negative trial since there was no overall survival benefit with HIPEC. However, within the surgical oncology viewpoint of the study, it is more appropriately evaluated as the trial that has clearly established CRS as the optimal oncologic therapy for appropriate candidates. As previously mentioned, the median OS times within PRODIGE7 have not been rivaled by any other therapeutic intervention. While there was no difference in survival between CRS alone and CRS-HIPEC, all patients underwent cytoreduction; therefore, it is the CRS that improves survival. That finding is strengthened by the fact that nearly all patients received systemic therapy. Further, the OS benefit seen in the intermediate PCI range of 11–15 suggests an effect of the HIPEC. Hence, it is the combination of systemic therapy and CRS that produces the best survival for patients with metastatic colorectal cancer limited to the peritoneal cavity. While HIPEC was not found to add any benefit in the entire population of PRODIGE7 patients, the specific HIPEC study protocol has been strongly criticized for being an outlier from many leading PSM centers (22). Due to that concern with the HIPEC protocol, the French Cancer Consortium (PRODIGE) is currently establishing another RCT to replicate the PRODIGE7 trial with a HIPEC protocol that is more consistent with PSM center norms, particularly longer HIPEC treatment time. Despite the legitimate concerns about PRODIGE7 questioning the utility of HIPEC, the consensus of expert PSM surgeons is that PRODIGE7 has unequivocally established CRS, combined with systemic therapy, as the standard of care for carcinomatosis of colorectal origin for appropriate CRS candidates.

The appendiceal randomized trial

To date, there has been a single completed and reported prospective randomized trial for PSM from appendiceal sources. That study by Levine et al. was a prospective randomized trial evaluating the utility of mitomycin vs. oxaliplatin in the HIPEC perfusate after CRS (23). The study was performed at Wake Forest University, M.D. Anderson, and the University of Pittsburgh Medical Center. Principal endpoints were survival, quality of life (24) and hematologic toxicity of the two agents. Patients with mucinous appendiceal neoplasms with evidence of peritoneal dissemination were consented and underwent cytoreductive surgery and HIPEC using a closed technique for 120 min. Patients were randomized intraoperatively to HIPEC using mitomycin (40 mg) or oxaliplatin (200 mg/M^2). Follow-up included daily blood counts and toxicity assessments using CTCAE criteria (volume 3.0) and quality-of-life measures.

A total of 121 analytic patients were accrued to the trial over 6 years at three sites. The cases were 57% women, with an average age of 55.3 years (range 22–82). The disease was low grade in 77% and high grade in 23%. There were no significant differences in hemoglobin or platelet counts. The WBC was significantly lower in the mitomycin group between postoperative days 5–10. Quality-of-life scores were better in the oxaliplatin group for physical wellbeing (24.2 vs. 22.4, p = .015) and emotional wellbeing (19.4 vs. 18.0, p = .048) through 1 year after surgery. Overall survival and disease-free survival at 3 years were similar at 83.7% and 66.8% for mitomycin and 86.9% and 64.8% for oxaliplatin, respectively.

This study represents the first completed prospective randomized trial of cancer of the appendix in any setting and shows that despite their rarity, multicenter trials for appendiceal neoplasms are feasible. Both mitomycin and oxaliplatin are associated with minor hematologic toxicity. However, mitomycin has slightly higher hematologic toxicity and lower QOL than oxaliplatin in HIPEC. The overall survival was similar with the two agents. This similar survival suggests either equal efficacy or the lack of efficacy for either agent. Consequently, if HIPEC is to be delivered after CRS for appendiceal PSM, oxaliplatin may be preferred in patients with leukopenia and mitomycin preferred in patients with thrombocytopenia due to prior chemotherapy. However, based upon the superior quality-of-life data and lower cost, oxaliplatin is considered the default agent for HIPEC for appendiceal cancer by the authors (23, 24).

The future of HIPEC

The PRODIGE7 results have returned clinical scrutiny to the efficacy of HIPEC for PSM due to colorectal tumors (21). Since the emergence of standardized surgical therapy for PSM, the pairing of CRS-HIPEC has been an unquestioned pairing with accepted synergy. The initial endeavors by the pioneer PSM surgeons to have therapeutic surgical management of carcinomatosis considered acceptable and efficacious required legitimization of CRS-HIPEC as dual therapy *via* prospective randomized trials. Now with the reverberations of the PRODIGE7 results, combined with the other level I evidence, there is no question about the utility of CRS. However, the current clinical conundrum is: should we continue with the longstanding approach of pairing CRS with HIPEC?

There are several reasons to temper the inclination to dismiss the role of HIPEC based on the PRODIGE7 results. First, as mentioned previously, there is sound critical concern of the HIPEC protocol utilized with PRODIGE7. The incredibly short perfusion time of 30 min, nearly all leading HIPEC centers perfusing for 1–2 h, and the choice of oxaliplatin as the perfusate are grounds enough to question the clinical applicability of PRODIGE7 when it comes to evaluating the role of HIPEC. While mitomycin C is the most commonly selected HIPEC

agent, there are prospective randomized data that demonstrate no survival difference between mitomycin or oxaliplatin HIPEC (23), albeit for appendiceal and not colorectal cancer. With the planed performance of another PRODIGE RCT to better evaluate the true efficacy of HIPEC using a more accepted protocol, future study results will better delineate the future of HIPEC.

Another fundamental question when applying the PRODIGE7 results to the utility of HIPEC is: how does the completeness of cytoreduction influence the efficacy of HIPEC? There is a large volume of high-quality data corroborating a complete cytoreduction, CC-0/R1, as the most prognostic independent variable for survival (24–27). One of the true feats of the PRODIGE7 trial was that 90% of study participants underwent a CC-0/R1 cytoreduction, while subgroup analysis revealed no difference with the main results. Specifically, regardless of the completeness of cytoreduction, an outcome variable, an argument can be made that with so few CC-1/R2a cases in the PRODIGE7 population, a true determination of HIPEC efficacy with residual disease cannot be determined.

Despite years of research, there is an ongoing debate regarding the mechanism of effectiveness of HIPEC in clinical practice. Data on tissue penetration of HIPEC are acquired from animal studies where the maximum depth into the peritoneum was measured between 1 and 5 mm (28, 29). There are limited human data on the effective therapeutic penetration of HIPEC (30, 31). Thus, since the advent of CRS-HIPEC, a residual tumor goal of less than 2.5-mm implants, CC-1/R2a or better cytoreduction, has been the threshold to proceed with HIPEC with an expected therapeutic effect (32). We clearly have suboptimal understanding of the extent of efficacy with HIPEC. In fact, recent analysis has even found that HIPEC may hold a survival benefit for incomplete cytoreductions, CC-2/R2b and CC-3/R2c, for certain patient populations (33). HIPEC already has a well-established role as palliative treatment for management of malignant ascites (33–35).

Until there is more definitive level I evidence to adjudicate the utility of HIPEC in this setting, it is expected that most PSM centers will continue to perform CRS-HIPEC as opposed to CRS alone. Further, scientific evaluation of HIPEC itself is certainly required to ensure it has a meaningful benefit in the oncologic management of PSM. However, it should be stated that the authors feel that continuing to pair CRS with HIPEC is likely a favorable risk–benefit ratio. The individual HIPEC component is a limited factor in the associated morbidity of CRS-HIPEC compared to the major visceral resections and anastomoses involved with the actual cytoreduction (36, 37). Considering all of the knowns and unknowns with HIPEC, it seems prudent for the PSM surgeon to continue with the established coupling of CRS-HIPEC. However, preoperative discussions with patients of the risk and benefits of the HIPEC component of this treatment are in order.

Adjuvant HIPEC, PIPAC, and future therapy

With the positive results from the Dutch and Swedish RCT data in conjunction with the additional literature on the benefit of HIPEC, there was keen academic interest to determine if adjuvant HIPEC had the potential to prevent carcinomatosis, particularly with the application of adjuvant HIPEC in those cases assessed at high risk for the subsequent development of PSM. There was sound basic science and clinical reasoning underlying the premise of adjuvant HIPEC, as well as promising initial research data (38, 39). However, the final results of two RCTs found that adjuvant HIPEC lacked any demonstrable efficacy.

The first adjuvant HIPEC RCT was COLOPEC. This trial was a multicenter study of 204 patients with resected colorectal cancer that were assessed as high-risk for peritoneal recurrence based on advanced stage disease (T4N0-2M0) or primary tumor perforation (40). Patients were equally randomized to a control group of structured surveillance or experimental adjuvant HIPEC group. There was no difference in survival outcomes between the cohorts. The 18-month peritoneal metastasis-free survival rates were 80.9% vs. 76.2% (P = 0.28) for HIPEC and surveillance, respectively. There was also no difference in 18-month DFS (69% vs. 69.3%, P = 0.99) and OS (93% vs. 94.1%, P = 0.82). The second published RCT was PROPHYLOCHIP, another multicenter trial involving 150 patients with resected high-risk colorectal cancer based on either a perforated primary tumor or a small-volume peritoneal disease at the index surgery that was completely resected (41). Again, patients were equally randomized to either a control structured surveillance group or an experimental second-look surgery adjuvant HIPEC group. After a median follow-up of over 50 months, there was no difference in the primary outcomes of 3-year DFS and OS rates. The negative results of both COLOPEC and PROPHYLOCHIP essentially quelled the performance of adjuvant HIPEC after resection of high-risk colorectal cancer. Those combined trial findings suggest that HIPEC is ineffective when no gross residual disease is present. Interestingly, if you apply the PROPHLYOCHIP and COLOPEC conclusions, HIPEC is ineffective when no gross residual disease remains, to the PRODIGE7 results that lack of utility with HIPEC in PRODIGE7 may be confounded by the fact that the majority of patients had no residual disease at the time of actual HIPEC. Although the COLOPEC and PROPHYLOCHIP trials found no benefit with adjuvant HIPEC, the initial results from the HIPECT4 RCT demonstrated that there was utility with adjuvant HIPEC for T4 colorectal tumors that underwent an oncologic resection (42).

The most recent advancement with surgical management of PSM is the development of pressurized intraperitoneal chemotherapy (PIPAC). The theoretical basis of PIPAC is the potential ability to deliver more efficacious intraperitoneal chemotherapy treatments repeatedly *via* an intraperitoneal nebulizer device. Proponents of PIPAC claim that approach superior to HIPEC *via* the ability of PIPAC to improve peritoneal distribution with enhanced tissue uptake while also being better tolerated than HIPEC with the ability for the procedure to be serially repeated in a minimally invasive fashion (43, 44). Additionally, PIPAC is touted as a therapeutic intervention for all patients with PSM, regardless of etiology or functional status, as opposed to HIPEC which is typically limited to patients with certain etiologies who are good surgical candidates for a major operative procedure. Currently, PIPAC is limited to palliative therapy with the rationale being that most patients with carcinomatosis will never be appropriate candidates for CRS-HIPEC and therefore will be limited to systemic therapy which has limited therapeutic effect on peritoneal-based metastatic disease. PIPAC allows direct delivery of the same chemotherapy agents to PSM which enhances effectiveness. A European collaborative group published the first basic science experience with PIPAC in an animal model in 2000, but it took that same group nearly a decade to develop a delivery system appropriate for human clinical use (45, 46). Currently, there is only one manufactured nebulizer device (CapnoPen® Villingendorf, Germany) available for clinical application which must be delivered in a minimally invasive fashion utilizing CO^2 insufflation. The clinical experience with PIPAC was principally in Europe. While the collective experience with PIPAC is significantly more limited compared to HIPEC, a recent systematic review, including over 1,800 cases, suggested that there was oncologic efficacy in 50%–80% of cases that were previously refractory to standard systemic therapy (47). PIPAC has definite potential to be a more encompassing therapeutic option for surgical management of PSM but it may be associated with increased complications compared to HIPEC (48). Prospective trials are ongoing to provide required high-level evidence to support more ubiquitous use of PIPAC. Although PIPAC is delivered *via* minimally invasive techniques, there is additional risk of aspiration of vaporized chemotherapy to operative teams and the agent is commonly delivered after all personnel leave the operative theater until the vapor is likely cleared.

A conundrum with intraperitoneal chemotherapy has always been, which is the optimal perfusate agent for a particular histology. Since coveted level I evidence is quite limited for intraperitoneal chemotherapy as a whole, PSM surgeons are rather handicapped in accurate prognostic therapeutic choices for individual patients. Due to the inherent difficulties in completing RCTs for PSM, there likely may never be adequate level I data to support the multitude of clinical decision points (47, 49). Therefore, non-standard approaches need to be utilized to pair the most efficacious HIPEC, or PIPAC, agent for the specific tumor characteristics of the patient. As modern oncologic care becomes exponentially more technically advanced, the treatment paradigm is shifting from "one-size fits all" to precision medicine. The use of organoids as a therapeutic treatment platform has the potential to completely change cancer care by providing real-time treatment data for how a patient's unique tumor will respond to a plethora of agents (50). Validating the use of organoid-derived treatment data for clinical application in PSM has been published with promising results (51–54). With further "proof of concept" and clinical data, organoid platforms could become the critical tool to providing reliable treatment guidance that likely will never be obtainable with level I evidence for PSM.

Consensus management standards

An Achilles' heel regarding management of PSM has been the lack of recognized clinical practice guidelines by an accepted expert consortium. Varying factors have contributed to that dilemma: the lack of high-quality large-volume data to extrapolate guidelines from, the fact that PSM has been a relative "orphan" disease, and the wide spectrum of different etiologies that fall under the PSM umbrella. In 2020, the Chicago Consensus Working Group published a comprehensive set of multidisciplinary clinical practice guidelines for the management of PSM (54). This was a monumentous achievement that united preeminent experts throughout North America to provide the first set of universally well-accepted standards for PSM. The Chicago Consensus guidelines not only provided guidance for general standards in the multidisciplinary management of PSM but also provided etiology-specific recommendations for management of carcinomatosis secondary to appendiceal neoplasms, colorectal cancer, peritoneal mesothelioma, gastric cancer, ovarian neoplasm, neuroendocrine tumors, and rare primaries such as breast and GIST (55–62). In addition to recommendations for therapy with curative intent, the Chicago Consensus Working Group provided guidance for palliative management of PSM as well (63). Any physician who manages patients with PSM should be well versed in the Chicago Consensus guidelines as they are considered a current standard. While the field of PSM remains dynamic, it is anticipated that the Chicago Consensus Working Group will remain a central authority in compiling leading data and expertise to provide recommendations that are applicable to the entire spectrum of PSM centers.

Conclusions

This review article provides physicians who manage PSM, primarily of colorectal origin, with the landmark trial data and current guiding standards. It is beyond the scope of this manuscript to comprehensively address every subset of PSM. The reader is strongly encouraged to examine the references. The authors recommend the Chicago Consensus Guidelines, for

further guidance of the subject matter. While the full extent of PSM management cannot be adequately covered in a review article, the quintessential principles and resources have been discussed.

The field of therapy for PSM continues to expand and become a more commonly treated cancer. No longer is therapeutic nihilism appropriate when peritoneal metastases are encountered. The surgical management of PSM/carcinomatosis should no longer be considered a radical procedure. CRS has clearly been proven through level I evidence to provide a significant survival benefit for appropriate patients. Until there is definitive evidence that HIPEC is not beneficial, CRS-HIPEC will continue to be paired together to provide the optimal curative therapy for patients with PSM due to colorectal malignancies. Additionally, innovative advances like PIPAC and organoid platforms and genomics could provide the framework to expand surgical management of PSM to a larger patient pool. Lastly, what previously was a discipline of often non-networked experts, without clear field defining standards, now has a collective and well-recognized community, as the Chicago Consensus Working Group has shown.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Temperature management during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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In addition to attaining complete or near complete cytoreduction, the instillation of select heated chemotherapeutic agents into the abdominal cavity has offered a chance for cure or longer survival inpatients with peritoneal surface malignancies. While the heating of chemotherapeutic agents enhances cytotoxicity, the resulting systemic hyperthermia has been associated with an increased risk of severe hyperthermia and its associated complications. Factors that have been associated with an increased risk of severe hyperthermia include intraoperative blood transfusions and longer perfusion duration. However, the development of severe hyperthermia still remains largely unpredictable. Thus, at several institutions, cooling protocols are employed during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Cooling protocols for CRS-HIPEC are not standardized and may be associated with episodes of severe hyperthermia or alternatively hypothermia. In theory, excessive cooling could result in a decreased effectiveness of the intraperitoneal chemotherapeutic agents. This presumption has been supported by a recent study of 214 adults undergoing CRS-HIPEC, where failure to attain a temperature of 38° C at the end of chemo-perfusion was associated with worse survival. Although not statistically significant, failure to maintain a temperature of 38° C for at least 30 minutes was associated with worse survival. Although studies are limited in this regard, the importance of maintaining a steady state of temperature during the hyperthermic phase of intraperitoneal chemotherapy administration cannot be disregarded. The following article describes the processes and physiological mechanisms responsible for hyperthermia during CRS-HIPEC. The challenges associated with temperature management during CRS-HIPEC and methods to avoid severe hypothermia and hyperthermia are also described.

KEYWORDS

HIPEC, hyperthermia, temperature control, cooling protocols, chemotherapy, peritoneal disease

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Introduction

Peritoneal dissemination of disease is a common manifestation of gastrointestinal and gynecological malignancies including those of ovarian, colon, gastric, small intestine and appendiceal origin (1). Among the peritoneal surface malignancies, disease of colorectal origin is most common with an estimated prevalence of about 5% (2).

According to a recent study published in the Journal of the American Medical Association, approximately 60,000 patients are diagnosed with peritoneal disease in the United States every year (3). However, over the last couple of decades, there has been an increase in the incidence of the disease, which can be explained by the improvement and accessibility to diagnostic imaging (computed tomography and ultrasound) and the introduction of screening colonoscopy for high-risk patients (4).

The presence of peritoneal disease is associated with more rapid disease progression, poor prognosis, and a significant decrease in survival. As expected, survival rates differ according to the location and histology of the primary tumor. For instance, according to the multicentric prospective study EVOCAPE I (Evolution of Peritoneal Carcinomatosis), the median survival in patients with peritoneal disease is 2.1 months for those with pancreatic cancer, 5.2 months for advanced colorectal cancer and 3.1 months in patients with advanced gastric cancer (5).

Despite significant advances in treatment, systemic chemotherapy alone has shown to have minimal effect on the progression of certain types of peritoneal disease (6). Furthermore, systemic chemotherapy is often associated with severe dose-limiting toxicity in many patients and as a result cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has become a more popular treatment. CRS-HIPEC offers an opportunity for the eradication of macroscopic disease and treatment of microscopic disease, with a benefit of a decreased risk of systemic toxicity and prolongation of survival.

CRS-HIPEC is an extensive surgical procedure that has become part of the standard of care for patients with a select group of peritoneal surface malignancies (7). The procedure typically involves multiple organ resections, peritonectomies, and the instillation of heated chemotherapy (up to 42o C) into the abdominal cavity for up to 120 minutes. The goal of intra-abdominal hyperthermia during CRS-HIPEC is to enhance the cytotoxicity and penetration of chemotherapeutic agents into malignant disease (8, 9). The mechanism for this synergistic effect may be related to 1) hyperthermia-induced increased permeability of chemotherapeutic agents into tumor cells, 2) increased drug-induced DNA damage, 3) inhibition of the repair of drug-induced DNA damage, 4) and the expression of heat shock proteins by tumor cells which ultimately potentiates the effect of Natural Killer cells (antitumor response) (10, 11).

HIPEC technique

HIPEC is typically delivered to the patient in the operating room after cytoreduction surgery has been completed and hemostasis is confirmed. The procedure involves placement of cannulas that introduce (inflow) and remove (outflow) fluid from the abdominal cavity, which is then recirculated through a perfusion circuit driven by a roller pump. To ensure adequate flow between the inflow and the outflow cannulas, the peritoneal cavity it filled with fluid (filling phase) and the perfusion machine adjusted to keep a steady flow between the reservoir and the patient (12). Occasionally, the perfusionist may need to add fluid to the circuit in order to achieve this goal. The heat exchanger keeps the perfusate temperature at 43 to 45°C. The goal of this is to maintain the intraperitoneal temperature between 41 and 43°C. Once the in/out flow and temperatures are relatively stable, the chemotherapeutic agent is added to the pump primer (12, 13). This solution, also known as the perfusate, is circulated between the patient and the machine for up to 120 minutes. During this time, temperature probes within the abdominal cavity provide information regarding the degree of hyperthermia. There are two methods to administer HIPEC (Figure 1): the open coliseum technique and the closed abdomen technique (13–17). During the open technique, the abdominal wall skin edges are elevated with a retractor and the abdominal contents are directly agitated manually. In contrast, in the more popular closed technique, the skin is completely sutured closed along the laparotomy incision and the abdominal wall is manually agitated during the perfusion time to promote uniform heat distribution throughout the peritoneal cavity.

Although each technique possesses unique advantages (Table 1), such as the capacity to manually stir the fluid in the open technique or the ability to rapidly achieve and maintain hyperthermia in the closed technique, neither has demonstrated superior outcomes compared to the other (12, 14, 18). In recent years, following the increasing use of minimally invasive surgery, some patients have received laparoscopic HIPEC, avoiding the need of a midline laparotomy to place the cannulas by using the initial laparoscopy ports (7, 24–26).

The chemotherapeutic agents administered during HIPEC include cisplatin, oxaliplatin, mitomycin C, paclitaxel, and doxorubicin. These chemotherapeutic agents are employed during HIPEC procedures since they are stable at high temperatures and have a synergic effect with heat (8). Noticeably, the cytotoxic effect of intraperitoneal chemotherapy depends on the concentration of the drug and the duration of chemotherapy instillation. The former, depends on the pharmacokinetic properties of the drug (e.g., half-life), the type of fluid administered along with chemotherapy (isotonic saline or dextrose containing solution), and the volume infused (7).

The most common core target temperature during HIPEC is 42°C. However measurements at different sites in the abdomen can be highly variable (20). For instance, inflow temperatures in recent trials have ranged from 41 to 45°C, while aiming for target intra-abdominal fluid temperatures between 40 and 43°C (27–29).

HIPEC machines available are either custom-made commercial devices (e.g., ThermoChemTM, Hyperthermia PumpTM, PerformerHTTM), or 'homemade' devices (cardiopulmonary bypass machine used in conjunction with a water bath) (7, 30). Some commercial machines heat the solution through a water bath, while others use electromagnetic induction. As mentioned before, all devices have a reservoir that helps adjust the fluid volume to the peritoneal cavity, compensates for variable outflow volume, prevents the circulation of air, and quickly removes the solution from the abdomen in case of emergency (12). Anecdotally, the volume of this

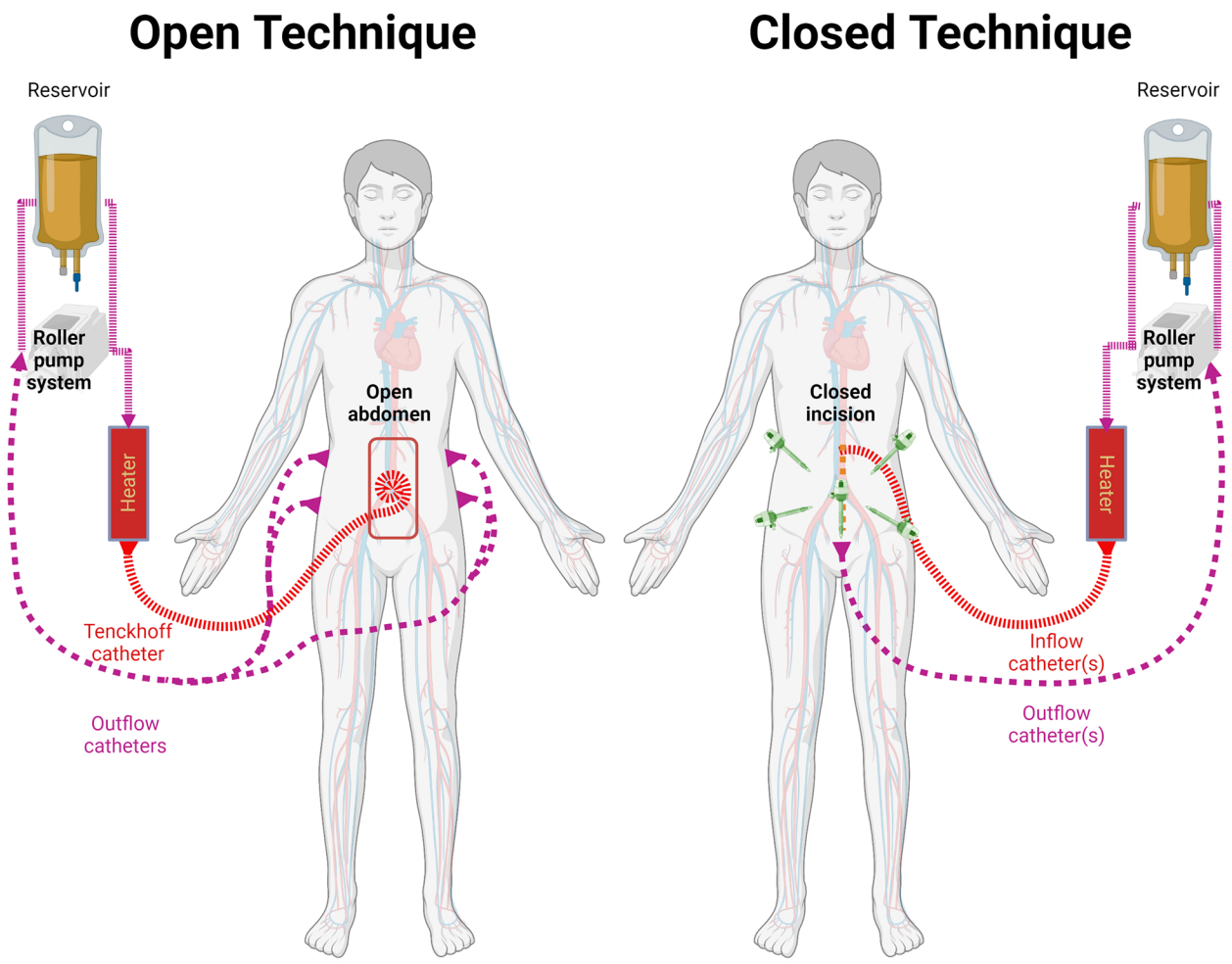

FIGURE 1
Methods for HIPEC administration. Both methods involve the use of a reservoir, roller pump system, heater, and connecting circuits. Temperature is monitored through the HIPEC procedure. Left: the open technique keeps the cavity open and retracts the wall to increase its filling capacity.Typically uses a Tenckhoff catheter for inflow and 2 catheters on each side for outflow as described by Sugarbaker et al. Right: the cavity is closed temporarily or definitely for HIPEC. Variable number of cannulas are used. In recent years it has been used after laparoscopic cytoreductive approach.

reservoir is typically maintained at around 500 mL. Although one inflow and one outflow line are always connected to the HIPEC machine, there is a variable number of cannulas or catheters that reach the patient. According to Gronau et al., these numbers are seldom reported (31). Given that the volume of the solution held between the reservoir and circuit is variable or sometimes even unknown, the actual amount of chemotherapy in contact with the patient at a given time depends entirely on the individual HIPEC set up.

A novel approach to intraperitoneal chemotherapy instillation using pressurized aerosolized chemotherapy (PIPAC) has been described and tested in humans (32, 33). PIPAC aims to address the shortcomings of HIPEC by improving the distribution and penetration of chemotherapy and by reducing local and systemic toxicities (33). Additionally, PIPAC allows the precise determination of instant and total drug given (32). Further technological advances have also combined PIPAC with therapeutic hyperthermia (hPIPAC) (34). Proponents of this technique describe that the drug regimens used in PIPAC are more stable than those used for HIPEC (35). Currently, PIPAC is mostly perceived as a palliative or neoadjuvant therapy (in preparation for CRS/HIPEC). (PMID: 35602919. As PIPAC is not routinely administered with hyperthermia, further discussion is out of the scope of this manuscript.

Biophysical considerations of intra-abdominal hyperthermia

In order to understand the temperature changes during CRS-HIPEC, it is necessary to comprehend principles of physics and human thermoregulation. From the perspective of physics, one can describe the human body (bounded by the skin) as an open thermodynamic system. During HIPEC, this system is surrounded by the operating room, the operating table, the perfusion machine, and the cooling systems. Altogether, these comprise the thermodynamic universe in which we observe the flow of energy. In this context, a HIPEC is “simply” the flow of thermal energy through the body over a predetermined time.

Because only one inflow and one outflow line are connected to the HIPEC machine, the energy transmitted to the patient

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TABLE 1 Comparison of open and closed HIPEC techniques.

Features	Closed technique	Open technique
Technology variations	May be used with minimally invasive cytoreduction.	Traditional open coliseum, "closed technique" with open access (7).
Temperature control	Easier to achieve target temperature (18).	More difficult to reach target temperature (18).
Chemotherapy distribution	Dependent on abdominal distention, pressure, and external shaking. Pooling of chemotherapy is conceivable (18).	Manual stirring of fluid and organs is possible (7).
Temperature distribution	Follows the inflow-to-outflow gradient (at studied parameters) (19).	Manual stirring of fluid and organs is possible. Heat loss dissipates over the exposed abdomen (additional posterior-to-anterior gradient).
Volume	Limited to usual filling capacity of the cavity. Smaller variations in total volume used between studies (20).	Increased due to tenting of the abdominal wall. Larger variations in total volume used between studies (20).
Pressure	Can be increased. May improve tissue penetration (21, 22).	No additional pressure can be exerted.
Occupational hazard	Closed circuit limits agent exposure. Risk of a splash accident could still occur.	Room staff at higher risk of splash and aerosolization. Surgeon may decrease skin exposure with double gloving (23).
Visualization of cavity	Only performed at the end of perfusion. A laparoscopic HIPEC alternative for real-time assessment has been described (26917929)	Allows detection of immediate complications and continued cytoreduction (7).
Physiologic Changes	Related to core-body hyperthermia.	Related to core-body hyperthermia and intrabdominal pressure.

can be calculated by using; 1) the difference between the inflow and outflow temperatures, 2) the HIPEC flow, and 3) the specific heat capacity of the hyperthermic fluid. For distilled water and normal saline, the specific heat capacities have been estimated to be 4179 and 4139 J Kg-1°C-1, respectively (36). This energy results in a temperature change consistent with the heating properties of the tissues (37).

In general, heat transfer is the result of the balance between heat gain and heat loss. Heat gain is defined by the basal metabolic rate of the patient and the hyperthermic fluid, whereas heat loss is the result of the body's interaction with the colder surroundings, such as the cooling systems, clothing, and the operating room. Over the last few decades, extensive research in thermal engineering has improved our knowledge of the human thermal responses to different environmental conditions, which has resulted in multiple predictive thermophysical and mathematical models (38–40). As explained by Stolwijk, a human thermophysical model consists of a *passive* (*controlled*) and an *active (controlling)* system. The *passive* system is composed of the tissues (and their respective heating properties) and the circulatory system (41). Within the body, heat is transferred by conduction between adjacent tissue layers and by convection *via* the blood flow as a central blood compartment. It is well known that anthropometric and demographic variables (age, sex, body-mass index) directly affect the heat characteristics of the human body (42), which explains why these variables have been found to independently predict hyperthermia during HIPEC (43, 44). The *active* system, in contrast, describes the thermoregulatory system. For example, common auto-regulatory responses to hyperthermia are vasodilatation and sweating, thereby increasing the heat redistribution to superficial areas of the body and the evaporative heat losses (Figure 2) (45). Ultimately, the computational models integrate these systems to predict temperature responses after heat or cold exposures in humans.

Only a few authors have approached HIPEC with mathematical or physical models of intra-abdominal hyperthermia. Examples include the mathematical human model proposed by Ladhari et al. and the animal treatment planning software model of Loke et al. (46, 47) Remarkably, these studies highlight the importance of patient and perfusion characteristics in the resultant intra-abdominal and core temperatures during HIPEC. Unfortunately, none of these models constitute a complete thermo-physical model, nor have they considered the effects of anesthesia in the thermoregulatory system (45, 48, 49).

The efficacy of CRS-HIPEC is directly related to the capacity to reach and maintain a target peritoneal temperature for as long as possible. However, with the continuous infusion of the heated perfusate, systemic hyperthermia is very likely to develop. While intra-abdominal hyperthermia may offer survival benefits, high core temperatures can lead to physiological derangements. Mild core (esophageal) hyperthermia is defined by core temperatures greater than 38°C, while moderate to severe hyperthermia begins at temperatures greater than 39°C. Patients undergoing CRS-HIPEC are at risk of moderate-to severe hyperthermia which is associated with several adverse effects (Figure 3) (50). These side effects are secondary to the close contact of the heated perfusate with the peritoneal cavity or are related to the systemic hyperthermia. In regard to direct effect of the heated perfusate, side effects include edema of the intestinal wall, ileus, bowel perforation, fistula and reduced cytotoxicity of some chemotherapeutics agents like mitomycin C (51). With regard to systemic hyperthermia, side effects include; cardiac arrhythmias, intravascular depletion, cardiovascular collapse, immunosuppression, poor neurologic outcomes, renal failure, coagulopathies, seizures and an increased risk of severe 30-day postoperative complications (44, 52–55). For instance, Hendrix et. al., found that patients undergoing CRS-HIPEC who reached severe hyperthermia (esophageal temperature of

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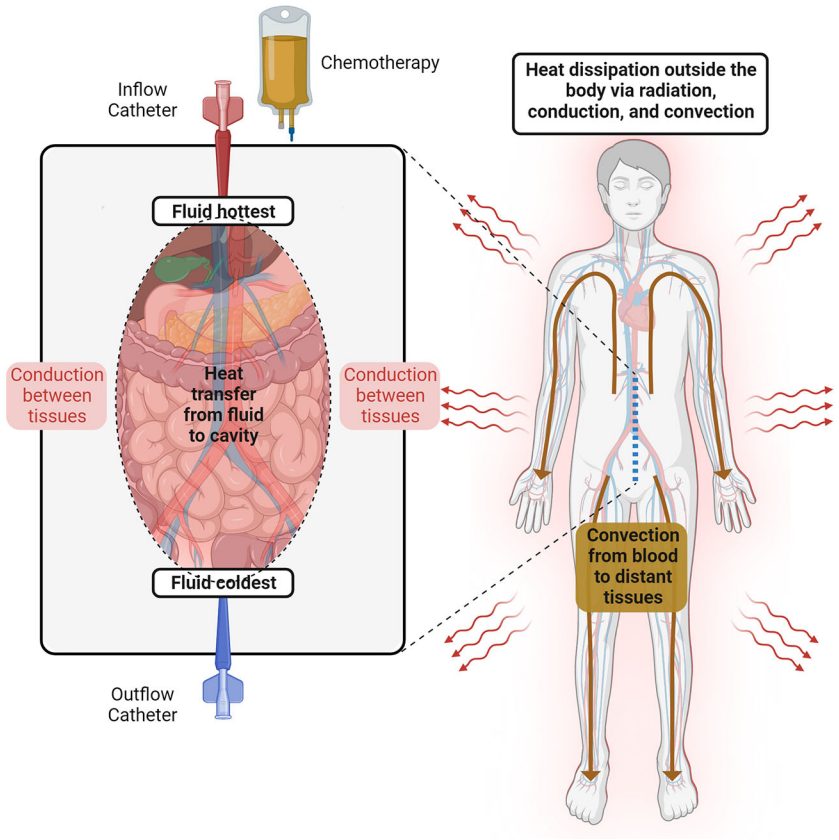

FIGURE 2
Temperature behavior during HIPEC. The heated perfusate is recirculated through the abdominal cavity. The fluid temperature follows a gradient between the inflow and the outflow catheters. Inside the cavity, the heat is dissipated between adjacent tissue layers via conduction, while distant tissues receive heat via convection from the blood flow. Thermoregulatory responses to hyperthermia (e.g., vasodilatation and sweating) allow heat dissipation outside the human body.

≥39.5°C) at any time were more likely to develop postoperative complications (HR= 3.77, 95% CI 1.56-9,14), and this complication was most likely to be severe according to Clavien-Dindo classification (HR= 3.46, 95% CI 1.10-10.95) (44).

The central nervous system is particularly vulnerable to hyperthermia. Hyperthermia decreases cerebral perfusion when core temperature increases by more than 1.2°C (56). Patients who become acutely hyperthermic might experience cognitive dysfunction, seizures and change in consciousness (from lethargy to coma and death). Interestingly, hyperthermia can cause changes in memory even if the hyperthermic event is short (1 hour) and mild (body core temperature 38.8°C) (57, 58). Additionally, hyperthermia can also affect attention and processing information (59). A temperature above 40°C can be associated with a permanent neurological damage. This effects seems to be secondary to cellular changes and/or cell death. Other mechanism of central nervous system disarrangement includes direct neurotoxicity from hyperthermia combine with inflammation (60).

The circulatory response to hyperthermia is secondary to increased metabolism and increased oxygen demand (61). The hyperthermia induced hyper-metabolic state is characterized by an increase in heart rate, cardiac output, central venous pressure, systolic function, and a decreased in systemic vascular resistance (due to redistribution of blood flow to the cutaneous vasculature) and a decrease in circulating intravascular volume (62). Hyperthermia also effects the electrical activity of the heart by increasing the discharge of the sympathetic nervous system. This inotropic effect can lead to sinus tachycardia, junctional rhythm and sustained supraventricular and ventricular tachyarrhythmia (63). Additionally, the incremental activity of the sympathetic nervous system causes vasoconstriction of the splanchnic and renal circulation which combine with hypovolemia during HIPEC increases the risk of acute kidney injury. Interestingly, preclinical data suggest that hyperthermic perfusion itself does not aggravate HIPEC-induced acute renal failure and indeed is mostly the cytotoxic side effects of chemotherapy that causes the acute kidney injury in patients undergoing CRS-HIPEC (64).

It is important to point out that the majority of the side effects of hyperthermia has been described in preclinical and clinical models of hyperthermia such as sepsis, heat stroke or malignant hyperthermia, however the specific data regarding the side effect of hyperthermia in patients undergoing CRS-HIPEC remains unknown.

Several publications have described intra-abdominal and core-body temperature changes in patients undergoing closed HIPEC. In one study, Rettenmaier et al. collected data of the intra-abdominal fluid temperature in five locations: upper left and right quadrants, lower left and right quadrants, and the suprapubic region. HIPEC was administered with two inflow and two outflow catheters, using a flow

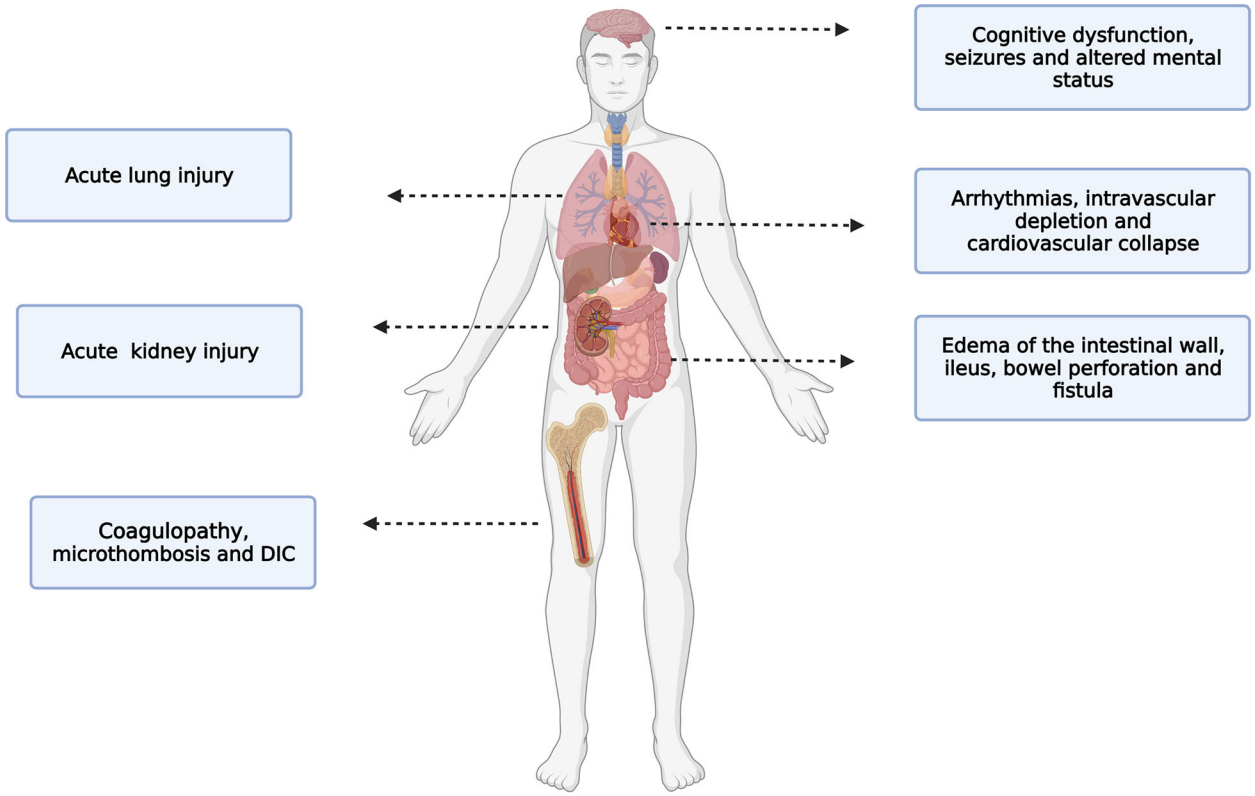

FIGURE 3
Side effects of hyperthermia. Side effects of hyperthermia during CRS-HIPEC.

rate of 1.6-1.8 L/min and aiming for an inflow-to-outflow gradient of 1.5°C. The authors found that the inflow-to-outflow gradient decreased significantly within the first 15 minutes of HIPEC and remained stable thereafter. The five regions demonstrated temperatures that followed such gradient, with minimal variation between them (19) Due to the proximity to the intra-abdominal fluid, the bladder temperatures also rose more rapidly in the initial period, and continued to show heat gain over time (43). Of note, the relationship between the perfusate and the bladder temperatures is likely to depend on the individual perfusate catheter configuration within the abdominal cavity (e.g., inflow placed in the upper or lower quadrants). These considerations are particularly relevant for closed HIPECs, given the inability to manipulate the catheter configuration once perfusion has started. Some authors have noted, a modest correlation between the change in the intraperitoneal and bladder temperatures and the change in core-body temperature (65). As such, bladder temperature changes may help clinicians guide changes in the cooling protocols to prevent unwanted systemic hyperthermia. Depending on the definition, the incidence of hyperthermia is quite variable with one third to one half of the patients experiencing it (43, 44). At the end of HIPEC, the abdominal cavity is drained of hyperthermic fluid and washed, allowing the patient to return to normothermic conditions. Hypothermia during this period is not uncommon and authors have reported the potentially devastating risks of rebound hypothermia and cardiac arrest after CRS-HIPEC (66).

The literature still needs to address several issues. First, it seems that intraperitoneal temperature stability is difficult to achieve despite established perfusion protocols (51). Exploring the potential causes of these problems (e.g., perfusion set up, patient's position, type of device) may lead to a more predictable administration of therapeutic hyperthermia. Second, thermal dosimetry principles are difficult to apply to microscopic tumor spread throughout the peritoneal cavity and further research will help to improve the safety and efficacy of this medical intervention.

Temperature management and cooling protocols during CRS-HIPEC

The HIPEC technique requires close communication between the surgical team, the perfusionist and the anesthesiologist. The role of the perfusionists is to control the temperature, the volume and the flow of the perfusate. The role of the anesthesiologist is to control body temperature necessary to maximize the effectiveness of intraperitoneal chemotherapy while avoiding adverse events associated with severe systemic hyperthermia. In an effort to avoid severe core hyperthermia, cooling protocols are widely employed during CRS-HIPEC. Unfortunately, current cooling protocols are not standardized and may involve the use of underbody cooling mattresses, ice packs around the head and axilla, and the use of forced air warmers operating at ambient room temperatures. A major disadvantage of these options is the inability to adequately cover major body surfaces and the lack of a constant closed feedback loop between the patient's temperature and the cooling device. Therefore, there is not a constant re-adjustment of the cooling system and as a

result, temperature control is unpredictable during chemoperfusion. Another technique widely used to avoid hyperthermia is to perform controlled hypothermia (by decreasing room temperature, cooling intravenous fluid and setting forced air warmers to ambient room temperature). The time for controlled hypothermia is not standardized. At our institution, it is around 30 minutes to 1 hour before the initiation of the HIPEC. The time for controlled hypothermia could be difficult to predict since the time required to achieve complete cytoreduction could be highly variable. Occasionally, severe systemic hyperthermia requires the reduction of intraperitoneal chemoperfusate temperature, potentially reducing its effectiveness.

There is relatively little data regarding temperature management during of CRS-HIPEC. For instance, the European Journal of Surgical Oncology published the Guidelines for Perioperative Care of Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy: Enhanced Recovery After Surgery (67). In this publication, the group of experts agreed to first; monitor patient's temperature during CRS-HIPEC with esophageal temperature probe, second; keep patient normothermic (36 C°) during the cytoreduction phase, third; prevent hypothermia with forced air warmers and warming mattress, fourth; actively cool *via* forced air blowers on cool or ambient setting during HIPEC phase and fifth; allow an increase core body temperature to between 36-41C ° during HIPEC phase. It should be pointed out (and as the authors mentioned on the guidelines) that while the strength of the data for active cooling and hypothermia is strong, the data regarding hyperthermia is limited and weak. The majority of the literature available describes the physiological implications of hyperthermia but none of the literature addresses or provides a more detailed guideline regarding temperature management during the hyperthermic phase of HIPEC. Several questions remain unanswered, such as what target temperature should the anesthesiologist achieve during controlled hypothermia before initiation of HIPEC? For how long does the patient need to be hypothermic before HIPEC? Does the timing of controlled hyporthermia change depending of the timing of chemopefusion? What is the target range of temperature during HIPEC? What is the maximum temperature allowed during HIPEC? How can we estimate which patients will have bigger delta changes in temperature? What about rebound hypothermia after HIPEC?

Benefits of controlling temperature during CRS-HIPEC

Survival

While several factors including gender, tumor histopathology, extra-abdominal disease, and the completeness of cytoreduction have been shown to influence survival in patients undergoing CRS-HIPEC, the role of intra-abdominal hyperthermia per se was not established until recently (68). A retrospective study of 214 patients undergoing CRS-HIPEC found that development of mild hyperthermia was associated with age and the type of chemotherapy. Prognostic factors associated with moderate to severe hyperthermia were the duration of the perfusion and blood transfusions. Interestingly, patients who were unable to achieve a bladder temperature of 38°C for 30 minutes during the perfusion had worsening recurrence free survival and overall survival (50) 9 361.

Bowel function

In regards to temperature management of the perfusion, a retrospective study involving 59 patients found that patients who had stable temperature control (defined as change of temperature not exceeding 0.5C°) during the entire HIPEC had less pain, reduced time to flatus and shortened enteral nutrition and hospital stays. Unfortunately, oncological outcomes such as survival were not improved in the stable temperature group (51).

Conclusion

In summary, the role of HIPEC is to maximize tumor cell death while minimizing systemic toxicity. Unfortunately there is no consensus regarding the optimal temperature necessary to reach the maximum benefit in regards to cancer prognosis while avoiding adverse events associated with severe local and systemic hyperthermia.

Despite protocols for cooling and warming during CRS-HIPEC, patients still develop episodes of severe hyperthermia and hypothermia. Overall, little is known about the impact of body temperature during CRS-HIPEC on oncological and perioperative outcomes. The amount of data published related to cooling protocols and cancer outcomes during HIPEC is still very limited. Standardization of temperature management and treatment during HIPEC will enhance the accuracy of scientific discussions. Ideally, data should be derived from a prospective randomized control study in which patients are kept on a constant target temperature for at least 30 minutes or more during the intraperitoneal chemotherapy. Continued research on this topic will allow HIPEC specialists to move from an empiric administration of hyperthermia to a thermophysical and evidence-based approach, which will promote the development of healthcare technologies and tools to improve the care of patients with peritoneal surface malignancies. Whether a tighter control of body core temperature during CRS-HPEC would promise improved outcomes remains unknown.

Author contributions

MR, JG-L and CG-L: discussed ideas and prepared the manuscript. MR and JG-L: prepared figures and tables. PO-A and KF: improved manuscript and edited. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Localized chemotherapy approaches and advanced drug delivery strategies: a step forward in the treatment of peritoneal carcinomatosis from ovarian cancer

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Peritoneal carcinomatosis (PC) is a common outcome of epithelial ovarian carcinoma and is the leading cause of death for these patients. Tumor location, extent, peculiarities of the microenvironment, and the development of drug resistance are the main challenges that need to be addressed to improve therapeutic outcome. The development of new procedures such as HIPEC (Hyperthermic Intraperitoneal Chemotherapy) and PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) have enabled locoregional delivery of chemotherapeutics, while the increasingly efficient design and development of advanced drug delivery micro and nanosystems are helping to promote tumor targeting and penetration and to reduce the side effects associated with systemic chemotherapy administration. The possibility of combining drug-loaded carriers with delivery via HIPEC and PIPAC represents a powerful tool to improve treatment efficacy, and this possibility has recently begun to be explored. This review will discuss the latest advances in the treatment of PC derived from ovarian cancer, with a focus on the potential of PIPAC and nanoparticles in terms of their application to develop new therapeutic strategies and future prospects.

KEYWORDS

peritoneal carcinomatosis (PC), ovarian cancer, PIPAC technique, nanomedicine, cancer treatment

1 Introduction

With 295,000 new cases and 184,000 deaths worldwide in 2018[1] ovarian carcinoma, and its most common form epithelial ovarian carcinoma (EOC), is the leading cause of death among gynecologic malignancies. Despite a high response rate to initial treatment (1), most patients develop disease recurrence within 2 years. The abdominal cavity and peritoneum are the sites most involved in the metastatic process that characterizes the advanced stages (stages III and IV) of ovarian cancer (2, 3). The five-year survival rate of ovarian carcinoma is close to 45%, however, most of these cases refer to patients diagnosed in early stages (I and II) who have 5-year survival rates of 95 and 70%, respectively. Unfortunately, only a minority of patients are diagnosed early, and the 5-year survival rate of patients with stage III or IV primary ovarian cancer drops to 25 and 15%, respectively, with the exception of patients with mutations of the *BRCA* genes who show a better response to treatment[2]. These numbers highlight the poor efficacy of current therapies in treating this deadly disease and underscore the urgent need for additional and alternative therapeutic strategies.

In this review we will focus on the treatment of high-grade ovarian cancer and PC, exploring the potential of localized chemotherapy to improve drug delivery and tissue penetration. Insights will be provided on novel locoregional delivery systems already or possibly deliverable by pressurized nebulization such as PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) and e-PIPAC (electro-Pressurized Intraperitoneal Aerosol Chemotherapy).

1.1 Development of peritoneal carcinomatosis in ovarian carcinoma

Due to late diagnosis and high heterogeneity in clinical behavior and biological properties, ovarian carcinoma is still one of the most lethal gynecological cancers (4). It exhibits extensive malignant progression, rapid development of drug resistance, and associated cross-resistance, which are major unresolved clinical problems.

Ovarian cancer exists in different histotypes depending on the type of cell that underwent the initial neoplastic mutation. More than 90% of ovarian tumors originate from the epithelial surface of the ovary, while the remaining 10% originate from the germ cells or stroma. EOC can be further identified as serous (68-71%), endometrioid (9-11%), mucinous (3%), clear cell (12-13%), and Malignant Brenner (1%) (5, 6). These subtypes differ in terms of risk factors, biological behavior, and response to treatment. Early diagnosis is hampered by the lack of appropriate tumor markers and the paucity of symptomatic manifestations until the advanced stage of the disease, therefore, most patients are diagnosed when the tumor has already spread to the abdominal area and the clinical outcome is already compromised (4).

EOC originates from the serous lining of the ovary, which is in close contact with the peritoneum, the serous lining of the abdomino-pelvic cavity. The process of deposition and colonization of cancer cells in the peritoneum is known as PC, a difficult-to-treat condition that often leads to recurrence and death. During the development of ovarian carcinoma, tumor cells may detach from the primary tumor site through a process called exfoliation, probably mediated by the downregulation of adhesion molecules, such as E-cadherin, on the surface of tumor cells (7) and facilitated by the high interstitial fluid pressure common to many solid tumors (8). These mechanisms have also been confirmed for colon (9) and gastric (10) cancer with peritoneal spread. Because of the anatomical location, gravity, peristaltic movement of the gastrointestinal tract, and negative pressure exerted by the movements of the muscles of the diaphragm, exfoliated cells commonly implant in the pelvic and subdiaphragmatic region, and their adhesion to the mesothelial layer of the peritoneum appears to be mediated by glycan-binding proteins expressed by mesothelial cells (11) and by adhesion molecules such as CD44, integrins, selectins, and a number of other leukocyte-associated adhesion molecules (12). Tumor cells then penetrate into the submesothelial basement and consequently into the subperitoneal tissue due to the contraction of mesothelial cells and the degradation of the peritoneal tissue (13) and to the degradation of the peritoneal blood barrier (14). Another possible route of peritoneal spread of cancer cells is by the transmesothelial route, in which cancer cells enter the subperitoneal lymphatic space through lymphatic stomata and milky spots (15), small structures composed of macrophages and lymphocytes that are in contact with the peritoneal membrane (16).

First-line chemotherapy for the treatment of ovarian cancer is administered systemically by intravenous (IV) infusion and is often the only option in most patients with multifocal progression in the peritoneum. Despite the high response rate to initial treatment, most patients develop disease recurrence within 2 years (1). The rationale for the use of intraperitoneal chemotherapy (IPC) stems from the observation that IV administered chemotherapy drugs have low concentrations in the peritoneum, regardless of peak serum values (17). In addition, the peritoneal cavity is identified as a virtually large area that can increase the spatial and temporal exposure of the tumor to the drugs, reducing the absorption of the drug into the systemic circulation and thus its toxicity. We will discuss these aspects later in this review.

1.2 Conventional therapeutic approaches for ovarian cancer and mechanism of resistance

Depending on the stage at the time of diagnosis, treatment of primary EOC may be limited to surgery or accompanied by chemotherapy and, in rare cases, radiation or immunotherapy. Cytoreduction surgery (CRS) is performed as first-line therapy in all stages of the tumor and includes hysterectomy, removal of the ovary, removal of the omentum, and any other site compatible with removal. PC occurs in EOC stages III and IV, when the tumor has

1 World Health Organization. International Agency for Research on Cancer_The Global Cancer Observatory_Cancer Fact Sheets. 2018.

2 Cancer Research - Ovarian Cancer Survival.

spread outside the pelvis and lymph nodes but is still within the abdominal cavity (stage III) or has distal metastases (stage IV). In these patients, the outcome of CRS has prognostic value (18, 19), patients with optimal CRS (no residual lesion is > 1 cm) have a median survival of 39 months compared with 17 months for patients with suboptimal CRS (20). For stage III patients, combination of CRS with subsequent cycles of IV and/or intraperitoneal (IP) infused chemotherapy is the main option.

Several studies have shown that IV administration of DNA cross-linking drugs such as platinum derivatives induces improved response rates in patients with EOC (21, 22). Carboplatin is currently widely used in the clinic, as it has less severe side effects than cisplatin (23) and resulting in an overall improvement in patients' quality of life (24–33). However, the development of platinum resistance is common in patients with advanced ovarian cancer. Platinum-sensitive patients who respond to the first-line chemotherapy regimen and relapse after 6 or more months have a response rate to subsequent platinum-based therapies ranging from 30 to 90% (34–37) but most of them will eventually develop platinum-resistant tumors. Patients who relapse within 6 months have a response rate to new chemotherapy of 15% and have a short progression-free survival interval (3-4 months) and a median survival of less than 1 year. Platinum resistance may be limited by the combination of taxanes (paclitaxel or docetaxel), a class of mitotic inhibitors that block cell proliferation by disrupting microtubule function. To date, carboplatin/taxane is the gold standard postoperative chemotherapy regimen worldwide, with clinical response rates > 60% and median time to recurrence usually > 1 year (23). Among taxanes, docetaxel and paclitaxel show similar efficacy and progression-free survival rates when combined with carboplatin (38). They also exhibit incomplete cross-resistance, and clinical trials have shown that docetaxel administration is effective in patients refractory to paclitaxel regimens (39). However, the 5-year survival rate of stage III and IV patients undergoing optimal CRS flanked by systemic chemotherapy is close to only 30% (39).

The emergence of platinum resistance is partly due to increased DNA repair due to the modification of key proteins associated with this mechanism (40, 41). An example of particular interest is the secondary mutation of the *BRCA1* and *BRCA2* genes that causes restoration of BRCA function and consequently reacquisition of DNA repair activity (42, 43). *BRCA1/2* function as tumor suppressor genes by playing an important role in DNA repair through homologous recombination (44–47). Approximately 15-20% of ovarian cancer patients have a germline mutation of *BRCA1/2* (48, 49). Due to the ineffectiveness of cancer cells to repair DNA damage these patients show a higher likelihood of responding to second-line platinum-based therapies than patients with wild-type *BRCA1/2* resulting in a more favorable clinical outcome and higher survival rate (50–53).

The observation of *BRCA* mutations as favorable prognostic factors led to the introduction, in 2014, of the use of poly (ADP-ribose polymerase) inhibitors (PARPi) (54). PARPi are a class of drugs systemically orally administered that, by competing with nicotinamide (NAD+) for the catalytic active site of PARP molecules, can exploit *BRCA* mutations and deficiencies in DNA damage response. PARPi induce propagation of DNA damage that cannot be repaired due to the inefficiency of *BRCA1/2* activity resulting in cell death. In 2017, after the significant improvement in progression-free survival achieved with PARPi in three randomized phase III trials: NOVA/ENGOT-OV16 (NCT01847274), SOLO-2/ENGOT-OV21 (NCT01874353) and ARIEL3 (NCT01968213) (55–57) the use of PARPi has been extended to maintenance therapy for platinum-sensitive relapsed primary ovarian, fallopian, and peritoneal cancers, regardless of *BRCA* status (56, 58, 59). To date, olaparib, rucaparib and niraparib are also approved as monotherapy for pretreated recurrent ovarian cancer (60).

1.3 The intra peritoneal path for the management of peritoneal carcinomatosis

Despite the progress made with the introduction of new drugs that can circumvent molecular-based drug resistance, the efficacy of these new therapeutic approaches in patients with peritoneal metastases is limited, suggesting that other mechanisms must be involved in the chemoresistance of these diseases (61). For example, high dosing is known to facilitate the onset of multiple drug resistance (62). In PC, high dosages of IV chemotherapy are necessary to achieve therapeutic efficacy since the presence of the peritoneal-plasma membrane prevents the passage of large molecules, and most drugs, from the bloodstream to the peritoneal cavity and vice versa (63).

However, the presence of the peritoneal-plasma membrane may be an advantage for the treatment of diseases limited to the peritoneal cavity, as an administration of chemotherapeutics directly into the peritoneum may reduce systemic toxicity (64–66). In PC, locoregional administration (IP) thus has the advantage of increasing drug concentration in the residual tumor, avoiding drug leakage and systemic adsorption, as initially demonstrated in 1978 by Dedrick and colleagues (67) and later validated by early clinical trials in which the IP route of administration showed a 10- to 20-fold higher dose of tumor chemotherapy than the IV route (17). The peritoneal-plasma barrier, consisting of the peritoneal mesothelium, subserosal tissue, and blood vessel walls, appears to be primarily responsible for maintaining high drug concentrations in the peritoneum (68–70) preventing the transfer of high molecular weight and hydrophilic drug molecules into the systemic circulation (71). Drugs administered to the peritoneum can also be adsorbed from the peritoneal cavity through the lymphatic vessels, and the hypothesis that this phenomenon may help treat retroperitoneal lymph node metastasis was demonstrated by a randomized subtrial that showed that the survival benefit of IP over IV chemotherapy in ovarian cancer was independent of the patient's lymph node status (72).

Unfortunately, less drug penetration into the tissue stroma has been observed with IP administration via catheter compared with IV administration, and its application is beneficial only for patients in whom optimal CRS has been achieved. Furthermore, although median disease-free survival was increased with IP chemotherapy compared with IV chemotherapy (73) the IP route still retains high toxicity, as demonstrated in the GOG-172 clinical trial

(NCT00003322) in which only 42% of patients receiving IP chemotherapy were able to complete their scheduled chemotherapy cycles. Most of the side effects recorded during this study were related to catheter-related problems, poor tolerance of IP treatment, complications of chemotherapy, or disease progression (74). An in-depth description and summary of these studies were comprehensively reviewed in (75).

Another problem related to catheter-IPC is that this procedure is usually performed weeks after CRS, when extensive adhesions have already developed in the peritoneal cavity as a postoperative consequence. Adhesions hinder the efficient distribution of IPC in the peritoneum, as they impair the ability of the drug solution to distribute properly in the abdomen.

Because of the problematic tolerability of IP chemotherapy administered via catheter, this approach has not been included in routine clinical practice; however, it has set the stage for the development of other techniques such as hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC).

1.4 Locoregional treatments based on intra peritoneal administration: HIPEC and PIPAC

HIPEC consists of a single administration of heated chemotherapy solution onto the peritoneal surface of the abdomen and is usually performed immediately after CRS. The purpose of HIPEC is to eradicate microscopic foci of disease that cannot be surgically removed. Unlike catheter administered IPC, in the case of HIPEC, the perfusate is administered as an intraoperative treatment after CRS, prior to the development of adhesions and provides homogeneous exposure of the entire seroperitoneal surface to both drug and heat (70). In addition, the intraoperative combination of CRS and HIPEC allows immediate treatment of the residual tumor, facilitating its eradication and removing the need to install peritoneal access devices on patients, thus eliminating the resulting catheter-related complications (76). Other advantages that make HIPEC preferable to traditional IPC are related to the temperature of the drug solution (around 42°C). Hyperthermia has direct cytotoxic activity on tumor cells and shows a synergistic effect with many antiproliferative agents such as, cisplatin and oxaliplatin, paclitaxel, and mitomycin (77). In addition, typical hypoxic tumor cells are more sensitive than normal cells to hyperthermia (78) which also enhances the penetration ability of chemotherapeutics (79, 80) contributing to increasing the sensitivity of tumor cells to drug treatment (81–83). Hyperthermia has also been linked to an enhanced antitumor immune response through Heat Shock Proteins 90 (HSP90) (84) and to an increase in lymphocyte migration and activation of antigen-presenting cells (85, 86).

Until recently, global acceptance of HIPEC has been hampered by a lack of solid evidence of efficacy, as promising data were mainly derived from small case series, nonrandomized comparative studies, and systematic reviews (87–95). In addition, these studies are not homogeneous in terms of timing of administration, disease status (primary or recurrent) active molecules, and dosage used. HIPEC performance is expected to be optimal when administered for the treatment of chemosensitive tumors both at the beginning of treatment course or as consolidation therapy, thus it can be strongly influenced from these differences. In addition, because of the high heterogeneity of ovarian cancer patients, the lack of randomization has been a major limitation. To date, there are 14 ongoing international randomized phase 3 trials investigating the use of HIPEC in the treatment of women with ovarian cancer at different time points (Table 1).

Although drugs administered by HIPEC achieve better distribution, permanence, and penetration into the tumor tissue than systemic administration, this can only be performed once, immediately after CRS. Moreover, due to the physical properties of the liquids and the location of the inflow and outflow catheters, the exposure of the peritoneal surface to liquid drugs administered by HIPEC is incomplete (96). The use of an aerosol instead of a liquid drug solution could help overcome poor drug delivery. It has been widely shown that application of increased IP pressure increases drug uptake by tumor cells in both cases (97, 98) that in humans (99–103).

Based on these premises, a new IP delivery system called PIPAC (Pressurized IntraPeritoneal Aerosol Chemotherapy) was developed (104). PIPAC was first applied in humans in Germany in 2011 (105), and several European countries are now adopting it as a palliative therapy for patients with unresectable PC. PIPAC consists of drug nebulization into the peritoneum in the form of a polydisperse aerosol with an average droplet size of 25 μm at constant pressure and normotemperature. Unlike HIPEC, PIPAC is performed as a laparoscopic technique, is minimally invasive, and can be repeated several times after CRS. The aerosol nature of the drug solution used in PIPAC provides several advantages over other localized delivery techniques, such as more homogeneous tissue distribution of chemotherapeutics and higher drug concentration in the tumor microenvironment (104, 106). As mentioned earlier, the application of a constant pressure of 12 mmHg to the peritoneal cavity overcomes the pressure of the tumor interstitial fluid, resulting in higher local drug concentration and lower plasma levels of chemotherapeutics compared with IP or systemic catheter-based chemotherapy. The combination of pressure and aerosol also allows a more homogeneous distribution of droplets containing the active ingredient within the peritoneum, reaching exposed and even partially hidden surfaces, resulting in a prolonged antitumor effect with significant benefits on overall survival using a lower drug dosage (97, 98, 107).

Many parameters, such as aerosol droplet size, flow rate and solution viscosity, play a key role in the effectiveness of PIPAC, as they influence the physical and behavioral properties of the droplets. The optimal parameters required to achieve homogeneous drug distribution were studied by computational fluid dynamics modeling (108). The ideal droplet size was estimated to be between 1 and 5 μm, since gravitational forces had less impact on homogeneous drug distribution. However, commercial nebulizers are not able to reach those size, thus particles ranged between 30 and 50 μm are considered as a good compromise. Furthermore, higher flow velocity and low fluid

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TABLE 1 Clinical trials involving the use of HIPEC for the treatment of disseminated peritoneal ovarian carcinoma.

Title	Identifier	Status	Conditions	Patients	Interventions	Drug
Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)	NCT01376752	Active, not recruiting	Recurrent Epithelial Ovarian Cancer	415	Maximal cytoreductive surgery with or without HIPEC	Cisplatin
Cytoreductive Surgery (CRS) Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) With Lobaplatin in Advanced and Recurrent Epithelial Ovarian Cancer	NCT03371693	Active, not recruiting	Ovarian Cancer, Epithelial Ovarian Cancer	112	HIPEC + CRS + CT, CRS + CT	Lobaplatin (HIPEC), Carboplatin, Paclitaxel, Gemcitabine, Liposomal Doxorubicin (HIPEC)
Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer	NCT00426257	Completed	Ovarian Cancer	242	Secondary debulking surgery, Secondary debulking surgery + HIPEC	Cisplatin (HIPEC), Carboplatin, Paclitaxel (IV)
Intraoperative Hyperthermic Intraperitoneal Chemotherapy With Ovarian Cancer	NCT01091636	Completed	Epithelial Ovarian Cancer	184	HIPEC	Cisplatin
Cytoreductive Surgery and HIPEC in First or Secondary Platinum-resistant Recurrent Ovarian Epithelial Cancer (HIPOVA-01)	NCT03220932	Not yet recruiting	Epithelial Ovarian Cancer	132	CRS + HIPEC, CT-BEV	Cisplatin, Bevacizumab
Efficacy of HIPEC as NACT and Postoperative Chemotherapy in the Treatment of Advanced-Stage Epithelial Ovarian Cancer	NCT03180177	Not yet recruiting	Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Carcinoma	263	HIPEC, Interval debulking surgery, neoadjuvant chemotherapy, adjuvant chemotherapy	Paclitaxel, Cisplatin, Paclitaxel + Carboplatin (IV)
HIPEC for Platinum-Resistant Recurrent Ovarian Cancer (KOV-HIPEC-02)	NCT05316181	Recruiting	Epithelial Ovarian Cancer	140	HIPEC	Doxorubicin, Mitomycin
Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer (CHIPPI)	NCT03842982	Recruiting	Ovary Neoplasms, Ovarian Cancer, Ovarian Carcinoma	362	HIPEC	Cisplatin
Efficacy of HIPEC in the Treatment of Advanced-Stage Epithelial Ovarian Cancer After Cytoreductive Surgery (EHTASEOCCS)	NCT03373058	Recruiting	Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Carcinoma	310	HIPEC, CRS, CT	Paclitaxel, Docetaxel, Paclitaxel + Carboplatin (IV)
A Randomized Prospective Trail of HIPEC in Recurrent Ovarian Cancer Patients With HRR Mutation	NCT04473339	Recruiting	Ovarian Cancer and Epithelial Ovarian Cancer with Homologous Recombination Repair (HRR) Gene Mutation	280	CRS, CRS + HIPEC	Lobaplatin
Hyperthermic Intraperitoneal Chemotherapy With Paclitaxel in Advanced Ovarian Cancer (hipecova)	NCT02681432	Unknown	Epithelial Ovarian Cancer	60	HIPEC, CRS only	Paclitaxel
Primary Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (OVHIPEC-2)	NCT03772028	Recruiting	Epithelial Ovarian Cancer	538	CRS + HIPEC	Cisplatin
Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer (CHORINE)	NCT01628380	Unknown	Ovarian Neoplasms	94	CRS, CRS + HIPEC	Cisplatin, Paclitaxel
Cytoreduction With or Without Intraoperative Intraperitoneal Hyperthermic Chemotherapy (HIPEC) in Patients With Peritoneal Carcinomatosis From Ovarian Cancer, Fallopian Tube or Primary Peritoneal Carcinoma (CARCINOHIPEC)	NCT02328716	Unknown	Peritoneal Carcinomatosis From Ovarian Cancer, Fallopian Tube Carcinoma, Primary Peritoneal Carcinoma	32	CRS, CRS + HIPEC	Cisplatin

viscosity are preferred because they are associated with both a reduction in particle diameter and an increase in spray cone angle, both of which promote homogeneous drug distribution (109). Several clinical trials have been performed since 2011 and more are ongoing. Phase I clinical feasibility studies of PIPAC found no signs of renal or hepatic toxicity, despite temporary impairment of portal and renal blood flows due to increased IP pressure. In addition, no signs of cumulative organ toxicity were found after repeated procedures of PIPAC (110). It has been generally observed that the dosage of doxorubicin, cisplatin and oxaliplatin administered via PIPAC is still far from the maximum tolerated dose (MTD) (107, 111–117), and in the case of oxaliplatin the dosage administered via PIPAC is approximately equal to 20 percent of the dose administered with HIPEC (107). The most recent ongoing study is still in phase of recruitment and aims to compare the efficacy of standard systemic treatments with IP aerosolization of cisplatin/doxorubicin combination (118). In this context, no systemic chemotherapy will be associated with the PIPAC procedure.

1.5 The emergence of ePIPAC

As described earlier, PIPAC is a viable alternative to conventional locoregional therapies, such as HIPEC and IPC, for patients with unresectable PC. Recent studies have shown that PIPAC can be improved by applying an electrostatic field during or after aerosolization of chemotherapeutic agents. Charged droplets precipitate electrostatically on tissues increasing cellular uptake of drugs (119). ePIPAC employs the same PIPAC equipment with the addition of an atraumatic stainless-steel brush electrode connected to a low-current generator. A weakly positively charged return electrode completes the system. Due to the collision of the emitted electrons with the aerosolized particles, the resulting negatively charged droplets are accelerated toward the peritoneum through the return electrode. The application of an electric field improves the spatial distribution of the droplets, increasing their ability to reach previously unreachable regions (119).

To date, there are only few studies in which the ePIPAC has been performed on patients. In the first human application of ePIPAC (120) only three patients with peritoneal metastases of hepatobiliary-pancreatic origin were enrolled, and although a positive response was observed, the obtained data were not sufficient to confirm the efficacy of the therapy. In 2019, ePIPAC was used in 48 patients (NCT03246321) with PM of different origin where it induced regression or pathology stabilization in about 50% of patients with no serious adverse effects (121). The safety and well tolerability of repeated ePIPAC procedures have been demonstrated in a retrospective cohort study published in 2021. The study included 69 patients treated with consecutive ePIPAC and oxaliplatin or cisplatin-doxorubicin combination in three centers from April 2019 to April 2020. About 76% of patients received concomitant treatment with systemic chemotherapy and in 38.5% and 53.8% of cases respectively, patients exhibited complete or greater histologic response (122). A new phase 1 research study (NCT05395910), initiated in October 2022 in Singapore and currently in the recruitment phase, aims to determine the safety profile and maximal tolerated dose of ePIPAC in combination with paclitaxel in pre-treated patients with PC. A summary of ongoing clinical trials involving PIPAC and ePIPAC for the treatment of ovarian cancer is summarized in Table 2.

Both PIPAC and e-PIPAC may be useful in the treatment of peritoneal metastases. However, these techniques are still considered experimental treatments. Whereas PIPAC is typically used as a second-line treatment option for patients with recurrent peritoneal metastases after failure of previous systemic chemotherapy (123), e-PIPAC is still in its early stages and, despite promising results, has not yet been widely adopted in clinical practice. e-PIPAC is being studied for its safety and efficacy, and further research is needed before it can be suggested as a conventional treatment for peritoneal metastases (121).

The choice between PIPAC and e-PIPAC will likely depend on the clinical circumstances of the individual patient and the extent of peritoneal metastases. There are no absolute contraindications to either procedure, but patients with significant abdominal adhesions may not be suitable candidates for PIPAC or e-PIPAC. Adhesions, obliteration of the peritoneal space, organomegaly, bowel distension, or portal hypertension/cirrhosis have been found to affect the abdominal access procedure (124) and can generate difficulties of achieving even distribution of chemotherapy particles in the peritoneal cavity. In addition, patients with severe cardiovascular or pulmonary disease may not tolerate the procedure well because of the need for general anesthesia.

2 Exploring innovative drug delivery formulations as therapeutic approach for peritoneal carcinomatosis

Application of innovative drug delivery systems as micro and nanomedicines for the treatment of cancer has gained tremendous interest as they increase site specific drug delivery, attenuate drug toxicity, and protect drugs from rapid clearance (125). Since Doxil®, the first FDA-approved nanomedicine, more than 20 among lipid, polymer or inorganic nano- and micro- based drug delivery systems have become available in clinic for systemic administration in both therapeutic and imaging setting (126). Among them, 14 systems are currently employed in cancer treatment (127).

In the management of PC, the use of drug delivery systems can further ameliorate the efficacy of locoregional administration, since they can be designed to prolong the residence time in the peritoneal cavity and to target tumors, leading to a better toxicity/efficacy ratio (128). Despite an increasing number of preclinical and clinical studies are investigating the applicability of different delivery systems to the IP route (129, 130), this topic is young and, to date, there are still no clinically approved drug delivery systems for locoregional IP administration. However, different carriers are been tested, providing promising results. Polymeric and lipid nanocarriers with specific surface modifications have been conceived to improve tumor targeting, accumulation and residence time, whereas microparticles and hydrogel-based nanocomposites have been tuned to increase retention in the peritoneal cavity providing a controlled and sustained drug release.

TABLE 2 Clinical trials employing the use of PIPAC and/or ePIPAC for the treatment of disseminated peritoneal ovarian carcinoma.

Phase	Title	Identifier	Status	Conditions	Patients enrolled	Procedure	Drug
1/2	Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Applied to Platinum-Resistant Recurrence of Ovarian Tumor (PARROT)	NCT02735928	Unknown	Ovarian Epithelial Cancer Recurrent and Platinum-resistant	50	PIPAC	Cisplatin, Doxorubicin
1/2	Study of Efficacy and Safety of Laparoscopic Intra-abdominal Chemotherapy (PIPAC) Performed in Patients With Peritoneal Carcinomatosis From Colorectal, Ovarian, Gastric Cancer and Primary Peritoneal Tumors (PI-CaP)	NCT02604784	Completed	Peritoneal Carcinomatosis from Ovarian, Gastric and Colorectal origin	105	PIPAC	Cisplatin (15 – 30 - 50 - 67 - 88 - 93 - 100 mg/m^2), Doxorubicin (3 - 6 - 10 - 13 - 18 - 23 - 30 mg/m^2), Oxaliplatin (100 - 135 - 155 - 180 - 200 - 235 - 270 - 300 mg/m^2)
1	PIPAC Nab-pac for Stomach, Pancreas, Breast and Ovarian Cancer (PIPAC nabpac)	NCT03304210	Completed	Peritoneal Carcinomatosis derived from Ovarian, Breast, Stomach and Pancreatic Cancer	20	PIPAC	Abraxane (nab-paclitaxel) (35 - 70 - 90 - 112.5 - 140 mg/m^2)
1	A Study With Intraperitoneal Cisplatin and Doxorubicin in Recurrent Ovarian Cancer and Peritoneal Carcinomatosis (PIPAC-OV2)	NCT02475772	Completed	Ovarian Cancer	15	PIPAC	Cisplatin (7.5 - 11.25 - 15 mg/m^2), Doxorubicin (1.5 - 2.25 - 3 mg/m^2)
1	Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Associated With Systemic Chemotherapy in Women With Advanced Ovarian Cancer (PIPACOVA)	NCT04811703	Completed	Ovarian Cancer	15	PIPAC/IV chemotherapy	Cisplatin, Doxorubicin (PIPAC), Carboplatin, Paclitaxel (IV)
1	PIPAC for the Treatment of Peritoneal Carcinomatosis in Patients With Ovarian, Uterine, Appendiceal, Colorectal, or Gastric Cancer	NCT04329494	Recruiting	Ovarian, Uterine, Appendiceal, Colorectal, Gastric Cancer	49	PIPAC/IV chemotherapy	Cisplatin, Doxorubicin, Mitomycin, Oxaliplatin (PIPAC), Fluorouracil, Irinotecan, Leucovorin (IV)
1	International Registry of Patients Treated With Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) (PIPACRegis)	NCT03210298	Recruiting	Peritoneum, Pleural, Ovarian, Gastric, Appendix, Pseudomyxoma Peritonei, Colorectal, Pancreatic, Gallbladder Cancer	1000	PIPAC	n.d.
1	PIPAC With Nab-paclitaxel and Cisplatin in Peritoneal Carcinomatosis (Nab-PIPAC)	NCT04000906	Recruiting	Peritoneal Carcinomatosis	36	PIPAC	Nab-paclitaxel (7.5 - 15 - 25 - 37.5 - 52.5 - 70 mg/m^2), Cisplatin
2	Intraperitoneal Aerosol High-pressure Chemotherapy for Women With Recurrent Ovarian Cancer (PIPAC-OV1)	NCT01809379	Completed	Recurrent Ovarian Cancer	69	PIPAC	Cisplatin, Doxorubicin
1	Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) and Electrostatic PIPAC (ePIPAC) With Paclitaxel In Patients With Peritoneal Carcinomatosis	NCT05395910	Recruiting	Peritoneal Carcinomatosis	Estimated 36	ePIPAC	Paclitaxel

Many of the features of these and others innovative drug delivery systems and their achievements are discussed in the following sections, summarized in Table 3 and illustrated in Figure 1. Description of cell line characteristic cited in Table 3 have been summarized in Table 4.

2.1 Drug delivery systems to improve tumor targeting and penetration

Passive accumulation via enhanced permeability and retention (EPR) effect or active targeting are the main drivers for delivery

TABLE 3 Nanomedicines developed for intraperitoneal delivery.

Nanocarrier	Drug	Physicochemical characterization	Cell lines	Animal model	Studies outcome		Ref.
					in vitro	*in vivo*	
Ameliorating tumor targeting and penetration							
Hyaluronic acid-polyArginine nanoparticles (DACHPt-HA-pArg NPs)	DACHPt	Size: 249 nm Surface potential: -25 mV	SKOV3	Athymic nude female rats	(+) Better stability in ascitic fluids thanks to surface potential.	(+) When aerosolized (platinum dose 5 mg/kg), better tumor growth inhibition than free drug	(131)
Silica nanoparticles internalized into neural stem cells NSCs	Cisplatin	Size: 52 nm Surface potential: -17 mV	OVCAR8 and SKOV3	Female NOD-SCID mice	(+) Drug-loaded nanoparticles were toxic for NSCs only after 72 hours (IC_{50} = 21.3 µM)	(+) Specific tumor targeting. (+) Better tumor penetration when associated to NSCs.	(132)
Polymeric expansile nanoparticles (eNPs)	Paclitaxel	Size: from 20 to 50 nm (at neutral pH) 250 nm (at acidic pH)	OVCAR3	Female nude mice	(+) Cytotoxicity not associated to eNPs alone (IC_{50} for paclitaxel loaded eNPs = 10 ng/mL).	(+) Selective localization in tumor areas. (+) Superior inhibition of tumor recurrence if compared with paclitaxel Cremophor EL® formulations (paclitaxel dose 10 mg/kg).	(133)
RGD-decorated calcium phosphate nanoparticles	Doxorubicin	Size: 122.4 nm Surface potential: -2.3 mV	SKOV3 HK2	BALB/c-nu mice	(+) RGD peptide improves NPs internalization in SKOV3 cells (IC_{50} 11.13 mg/mL for RGD-decorated NPs vs IC_{50} 24.42 mg/mL for untargeted NPs). (+) Stronger tumor killing effect than on healthy cell line (HK2)	(+) Mice overall survival increased from 29 to 59 days (doxorubicin dose 10 mg/kg three times every five days). (+) No signs of drug-related toxicity.	(134)
iRGD-decorated polymersomes	Paclitaxel	Size: 233 nm Surface potential: -2.7 mV	PPC-1, M21, MKN-45P, CT26	Athymic nude mice, BALB/c mice	(+) Enhanced cytotoxicity for active-targeted polymersomes (paclitaxel concentration of treatment 100 nM). (+) Higher cellular uptake than not-targeted polymersomes	(+) Selective uptake in neuropilin-1 rich organs. (+) Reduced tumor burden (paclitaxel cumulative dose injected 7 mg/kg). (+) In CT26 model, reduction of ascites volume.	(135)
FRRG-doxorubicin nanoparticles (PNPs)	Doxorubicin (prodrug)	Size: 101 nm	H9C2, HDF, CDD-18Co, HeyA8, SKOV3, MC38, CT26, human ovarian tumor-bearing (POX) mice and human ovarian cancer patient derived xenograft (PDX) mice	BALB/c nu/nu and BALB/c mice	(+) Drug release specific to cancer cells. IC_{50} for SKOV3, HeyA8, MC38, CT26, H9C2, HDF and CCD-18Co cells were respectively 9.11µM, 5.06 µM, 8.98 µM, 5.2 µM, 111.36 µM, 111.72 µM and 135.8 µM.	POX model: (+) Lower PCI score than with saline or free drug (2.4 vs 13.8 and 6 respectively). (+) No associated systemic toxicity. PDX model: (+) tumor regression with homogenous drug tumor penetration and negligible organ toxicity. Both POX and PDX model used a doxorubicin dose corresponding to 5 mg/kg.	(136)

(Continued)

TABLE 3 Continued

Nanocarrier	Drug	Physicochemical characterization	Cell lines	Animal model	Studies outcome		Ref.
					in vitro	*in vivo*	
Increase residence time							
NanoOlaparib (lipid-based nanoparticles)	Olaparib	Size: 72 nm Surface potential: -30.5 mV	403 and 404 tumor line, (Brca2$^{-/-}$, Tp53$^{-/-}$, Pten$^{-/-}$) 4306 and 4412 lines (K-ras$^{LSL\text{-}G12D/+}$, Pten$^{-/-}$)	Female NCr nude mice	(–) no IC_{50} difference from free drug (IC_{50} of NanoOlaparib for 4412, 404, 403 and 4306 cell lines were respectively 2.15 μM, 4.42 μM, 10.38 μM, 20.31 μM, while free olaparib IC_{50} were 2.49 μM, 3.43 μM, 10.94 μM, 19.57 and μM).	(–) Low retention time in the peritoneal cavity. (-) Daily IP administration not feasible due to systemic toxicity (NanoOlaparib injected dose 50 mg/kg).	(137)
NanoTalazoparib (lipid-based nanoparticles)	Talazoparib	Size: 71 nm Surface potential: +4 mV	mFT 3666, 3635,3665,3707 luc transfected cell lines ASC34, ASC54, ASC46 derived from ascitic fluid KURAMOCHI, OVSAHO	Female NCr nude mice	(+) IC_{50} values lower than IC_{50} of NanoOlaparib.	(+) Slow drug release. (+) 3/weekly administration sufficient to decrease tumor growth rate and ascitic fluid (NanoTalazoparib injected dose 0.33 mg/kg).	(138)
Bioadhesive polymeric nanoparticles BNPs (oxidized polylactic acid block–hyperbranched polyglycerol (PLA-HPG) copolymers)	Epothilone B	Size: 130 nm	Uterine serous carcinoma (USC)	Nude mice	(+) Lower IC_{50} than free drug after 72 hours of exposure.	(+) Bioadhesion with gradual drug release. (+) Two doses of Epothilone B were tested, 2.5 mg/kg and 0.5 mg/kg. Survival improvement (60% of treated mice alive at the end of the experiment).	(139)
Genipin-crosslinked gelatin microspheres (GP-MS)	Paclitaxel	Size: 50 μm	SKOV3 and OVCAR3	Female BALB/c Nu mice	(+) Drug-loaded-GP-MS were toxic for cells according to dose and exposure time. IC_{50} at 72 h and 168 h on SKOV3 and OVCAR3 increased from 8.6 and 9.5 nM to 4.9 and 7.1 nM respectively.	Two doses of paclitaxel tested: 7.5 mg/kg and 35 mg/kg. (+) Increase in median survival (from 33 days to 90 days). (+) Decrease in PCI score and ascitic fluid volume (comparison with ctrl and nab-paclitaxelVEG formulation)	(140)
Alginate-based cisplatin nanogel encapsulated in an *in situ* cross-linkable alginate-based hydrogel matrix	Cisplatin	Nanogel particles size: 10-30 nm	ID8-KRAS	C57BL/6 mice	(+) Lower cytotoxicity than free drug at 24 and 48 hours.	Cisplatin dose: 2 mg/kg and 10 mg/kg. (+) sustained drug release over a week. (+) increase in overall survival, reduction of VEGF expression and no observed adverse effects	(141)
Lipophilic nanocapsule loaded into PEG cross-linked hydrogel	Docetaxel	Nanocapsules size: from 174 to 250 nm Surface potential: -17 mV	–	Female BALB/c nude mice	(+) Hydrogel was stable upon dilution and ensure controlled nanocapsules release	(+) Nanocapsules incorporated in the PEG hydogel were retained in the IP cavity for 24 h after IP administration	(142)

(Continued)

TABLE 3 Continued

Nanocarrier	Drug	Physicochemical characterization	Cell lines	Animal model	Studies outcome		Ref.
					in vitro	*in vivo*	
Alendronate, calcium and cyclin-dependent kinase 7 inhibitor THZ1 self-assembled pH sensitive nanoparticles	Alendronate and THZ1	Size: 164 nm Surface potential: +12.4 mV	SKOV3, HK2, HMrSVS	BALB/c nude mice	(+) Intracellular uptake time-dependent. (+) Apoptosis induction through different mechanisms.	Administered dose: 10 mg/kg of nanoparticles. (+) Better % of apoptosis when THZ1 concentration increased. (+) Fluorescent NPs present in the tumor site 7 day after IP injection. (+) antitumor efficacy confirmed at 60 days after first treatment.	(143)
Tumor penetrating microparticles (TPM): Priming TPM (PLG 50:50 L:G) and Sustaining TPM (PLG 75:25 L:G)	Paclitaxel	Size: from 4 to 30 μm	SKOV3	Female athymic BALB/c Nu/Nu mice	–	Paclitaxel dose: 10 mg/kg. (+) Greater tumor targeting and therapeutic efficacy than paclitaxel-loaded cremophor-based formulations. (+) Better peritoneal cavity distribution for smaller particles.	(144)
Gene silencing							
Lipidoid siPARP1 nanoparticle	siPARP1	Size: 75 nm	*BRCA1* deficient ovarian cancer cell line	Nude mice	(+) Cells were efficiently transfected (65% of transfection after 24 h with 5 nM siRNA.	Total siRNA dose: 5 mg/kg. (+) PARP1 silencing confirmed by increased apoptosis, reduced tumor growth and increased mice overall survival.	(145)
HA-coated siPLK1 and sieIF3c loaded lipid-based nanoparticles	siPLK1 and sieIF3c	Size: 60 nm Surface potential: +5 mV	OVCAR8	Athymic nude female mice	(+) Synergistic antitumor efficacy of combined gene silencing. (+) Better internalization thanks to HA surface decoration.	Total siRNA dose: 1 mg/kg. (+) The combination of two siRNAs was more effective on mice overall survival (60% compared to 20 and 10% of single siRNA, PLK1 and eIF3c respectively).	(146)
Paclitaxel and siCD44 loaded polypropylenimine (PPI) dendrimer decorated with LHRH	siCD44 and Paclitaxel	Size: from 100 to 200 nm Surface potential: +1.10 mV	Human ovarian xenograft	Athymic nude mice	(+) Decoration with LHRH contributed to the antitumoral efficacy. (+) 10-fold decrease in cell viability compared to controls. 1.5-fold decrease in IC_{50} for formulate paclitaxel compared to unbound paclitaxel (from 55 μM to 34 μM).	Paclitaxel dose: 2.5 mg/kg. (+) Decrease in the invasiveness of malignant cells after CD44 suppression (+) Almost complete tumor eradication after 28 days.	(147)
Cisplatin and siDJ-1 PPI dendrimer decorated with LHRH peptide	siDJ-1 and cisplatin	Size: 145.2 nm Surface potential: +7.7 mV	ES-2 human ovarian clear cell carcinoma cells	Female athymic Nu/Nu mice	Preliminary *in vitro* studies were carried out to determine the siDJ-1 treating dose	siRNA dose: 50 μM in 0.5 mL volume. Cisplatin dose: 1.85 mg/kg. (+) After 35 weeks follow up, complete	(148)

(Continued)

TABLE 3 Continued

Nanocarrier	Drug	Physicochemical characterization	Cell lines	Animal model	Studies outcome		Ref.
					in vitro	*in vivo*	
						elimination of tumor mass without any recurrence.	
siHuR-loaded fluorescent-labeled folic acid derivatized DNA dendrimers	siHuR	Size: 70 nm Surface potential: -28 mV	A2780, OVCAR5, OVCAR3, ID8-Fluc	C57BL/6 mice	(+) Tumor growth inhibition after HuR suppression.	siHuR dose: 3 µg/ injection. (+) Tumor growth suppression and reduction in ascites formation. (+) Median life span increased from 29 to 43 days.	(149)
siTWIST-loaded hyaluronic acid conjugated mesoporous silica nanoparticles	siTWIST + cisplatin	Size: 120 nm Surface potential: +43.75 mV	F2, OVCAR8	Female NSG mice	(+) Cisplatin sensitization restored after TWIST suppression.	Nanoparticles dose: 2.5 mg/week. (+) 75% or 90% of tumor growth inhibition if compared with free drug or control group.	(150)
IRF5/IKKβ mRNA self-assembled to poly(β-amino ester) pre-functionalized with di-mannose poly glutamic acid	IRF5/IKKβ mRNA	Size: 100 nm Surface potential: +3.40 mV	ID8	Female albino B6 mice C57BL/6 mice for *ex vivo* studies.	(+) Reduction of the immune-suppressive macrophage population with increase in the M1-like macrophages fraction.	mRNA dose: 100 µg/ mouse/week. (–) mRNA was also taken up by systemic circulation. (+) Tumor regression and immune activation with an increase in overall survival (142 days for treated mice vs 60 days for control groups)	(151)
Paclitaxel-pVSVMP loaded DPP nanoparticles	Paclitaxel and pVSVMP	Size: 197 nm Surface potential: +29 mV	SKOV3, A549, MDA-MB-231, MCF-7, CT26, B16	BALB/c nude mice	(+) Paclitaxel promoted transfection. (+) Reduced cell viability in presence of paclitaxel.	Paclitaxel, DPP and pVSVMP were administered at 1 µg/ kg, 5 mg/kg and 0.2 mg/kg respectively. (+) Combination with paclitaxel enhanced gene transfection, while VSVMP antitumoral activity was confirmed.	(152)

systems accumulation in solid tumors. The EPR effect has attracted great interest because of its success in preclinical animal models (153–155), but it has failed to demonstrate greater efficacy when studied in clinical setting (156, 157). Moreover, the advantage that the EPR effect offers in facilitating the accumulation of nanosystems in the tumor is relatively low and estimated at less than 2-fold compared with normal organs, and the resulting drug concentration is insufficient to treat most tumors (158). In the particular context of PC, tumor lesions differ in size and location and often have poor vascularization and perfusion, which prevent nanoparticles from take advantage of the EPR effect (159). IP delivery represents a more appropriate administration route because it exploits the irregularities and disorganization of mesothelial tissue caused by tumor cell infiltration, a mechanism that has been described as the main responsible of drug accumulation in tumor nodules following IP delivery (160, 161). However, a formulation developed for IV administration will not necessarily demonstrate better efficacy when administered via IP. An example is given by pegylated liposomal doxorubicin (PLD). The analysis of the pharmacokinetic curves of doxorubicin in patients receiving PLD via HIPEC following CRS, suggested a slow and variable absorption into the intraperitoneal tissues (40% of the administered drug was retained) with no advantages respect to the drug administered as such (162).

The addition of specific moieties to the surface of the nanoparticles facilitates their interaction via active targeting with specific molecules overexpressed at the tumor site. CD44 has already been extensively described as a suitable antigen for tumor targeting since it is overexpressed in a plethora of cancers as lung (163, 164), prostate (165), colon (166, 167), ovarian (168) and

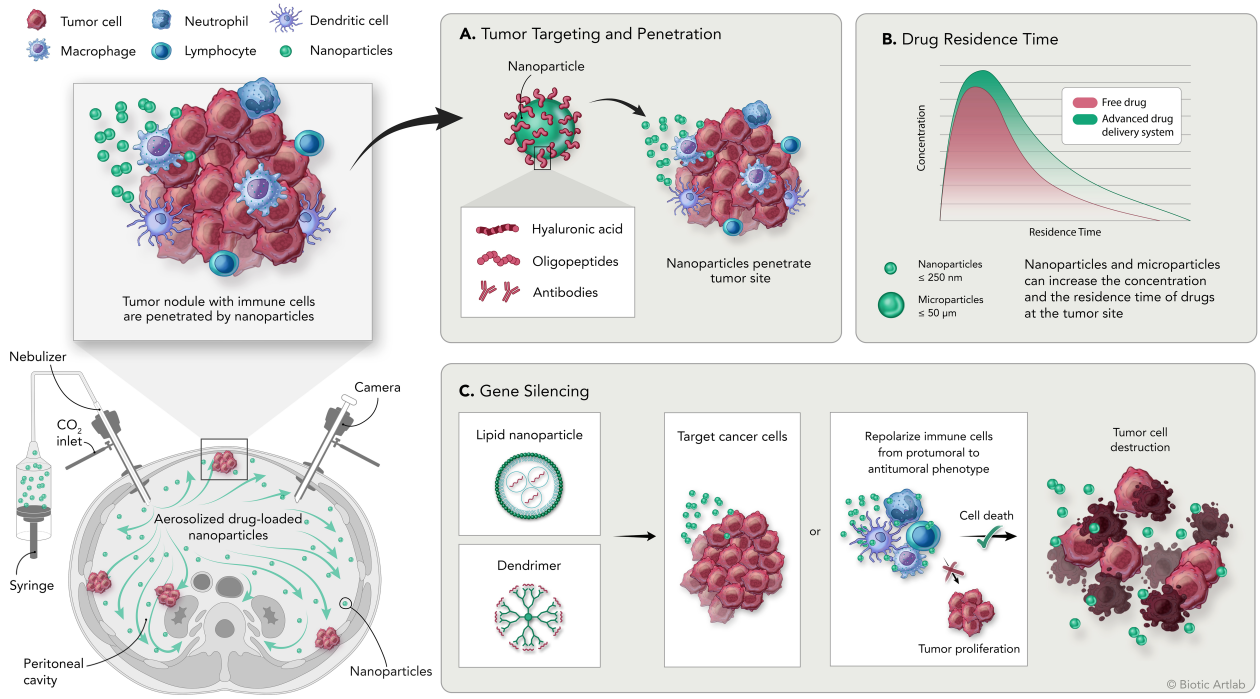

FIGURE 1
Overview of the PIPAC procedure and the application of nanomedicine for the treatment of peritoneal carcinomatosis. Bottom left: schematic representation of intraperitoneal aerosolization of nanoparticles by PIPAC; top left: schematic representation of tumor nodules with tumor infiltrating immune cell populations and delivered nanoparticles. **(A)** Nanoparticles can be modified by adding surface moieties of different origins to increase their targeting and penetration capabilities into the tumor. **(B)** Delivery systems are designed to increase the concentration and residence time of the drug at the tumor site compared with free drug. **(C)** Delivery systems designed to carry genetic material are used to induce silencing of specific genes on tumor or immune cells to promote direct or immune-mediated destruction of tumor cells.

others (169). In several human ovarian cancer models, overexpression of CD44 is linked with cancer cells adhesion to peritoneal mesothelial cells (170). As the primary ligand of CD44, hyaluronic acid (HA) as an integral part of the nanocomposite structure has been shown to be effective in promoting preferential drug accumulation at the tumor site and enhancing cellular uptake (171, 172). The interaction between HA and CD44 expressed on SKOV3 cells mediates the internalization of polymeric nanoparticles generated by the electrostatic interaction between the positively charged amine groups of poly-arginine (pArg) and the carboxylic group of HA. Indeed, in the presence of free HA, internalization of the nanoparticles into tumor cells was significantly reduced and comparable to that obtained using a CD44-negative tumor (131, 173–175). Likewise, HA surface derivatization of a lipid-based nanoparticle containing a combination of two small interfering RNAs promoted their internalization in a OVCAR8 spheroid model, enhancing the effect of the therapy (146).

Active targeting is not limited to the use of small molecules as moieties for interaction with specific ligands/targets but can also employ larger molecules or even whole cells, as in the case of neural stem cells (NSCs). The tumor tropism of NSCs has been extensively studied, as has their ability to penetrate into hypoxic tumor (176–178). Nonporous, cisplatin-loaded silica nanoparticles were conjugated to the NSCs and optimized to avoid premature drug release that could have been toxic to the NSCs themselves. Comparison of IV and IP administration showed that active targeting was effective only after locoregional treatment. In addition, preliminary studies in OVCAR8 and SKOV3 tumor-bearing mice confirmed that NSC-internalizing particles administered IP had better tumor penetration ability than free drug or particles alone (132).

Tumor targeting can also be achieved through materials-based strategies, which take advantage of the intrinsic properties of the materials used rather than surface modifications.

The tumor microenvironment is often characterized by acidification due to glycolytic metabolism of tumor cells, hypoxia, and poor blood perfusion (179–182). These characteristics can be exploited by using polymers that react to the transition from the physiological to the lower tumor microenvironment pH by swelling and gradually releasing the encapsulated drug. An interesting example is represented by expansile nanoparticles (eNPs) characterized by a hydrophobic pH-cleavable protecting group which masks the hydrophilic linker (a triol group) and the polymerizing ending group (183). This cross-linked polymer is stable at physiological pH, while it starts to gradually hydrolyze from pH 6, thus releasing the encapsulated drug (183). In OVCAR3 tumor bearing mice undergoing debulking surgery to mimic clinical conditions, eNPs encapsulating paclitaxel (pax-eNPs) resulted more efficient compared to paclitaxel-Cremophor EL® formulation in reducing tumor recurrence and biodistribution studies confirmed their specific tumor accumulation (133).

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TABLE 4 Description table of the cell lines cited in Table 3.

Cell line	Description
SKOV3	Human epithelial ovarian adenocarcinoma
OVCAR8	Human high grade serous ovarian carcinoma
OVCAR3	Human epithelial ovarian carcinoma isolated from malignant ascites
HK2	Healthy human tubular cell line from adult kidney
PPC-1	Human prostate carcinoma
M21	Human melanoma cell line
MKN-45P	Poorly differentiated human adenocarcinoma. Express wild-type p53; c-met oncogene amplification and E-cadherin promoter mutation.
CT26	Murine colorectal carcinoma cell from BALB/c mouse
H9C2	Embryonic rat cadiomyocytes
HDF	Human dermal fibroblast; skin cell line
CDD-18Co	Human fibroblast cell line isolated from normal colon tissue
HeyA8	Human epithelial low-grade serous ovarian cancer
MC38	Murine colorectal cancer
404	Murine tumor cell line with $Brca2^{-/-}$, $Tp53^{-/-}$, $Pten^{-/-}$
403	
4306	Murine tumor cell line with K-$ras^{LSL\text{-}G12D/+}$,$Pten^{-/-}$
4412	
mFT 3666 luc	Murine fallopian tube cell lines developed from *Brca;Tp53;Pten* genetically engineered mouse model of high-grade serous ovarian cancer. They express *luciferase* gene for bioluminescent assays.
mFT 3635 luc	
mFT 3665 luc	
mFT 3707 luc	
ASC34	Murine tumor lines generated by culturing ascites collected from intraperitoneal murine tumor xenograft.
ASC54	
ASC46	
KURAMOCHI	Human high-grade serous ovarian cancer
OVSAHO	Human high-grade serous ovarian cancer
ID8	Murine surface epithelial ovarian cancer
ID8-KRAS	Murine surface epithelial ovarian cancer, oncogenic KRAS-transduced
HMrSVS	Healthy human peritoneal mesenchymal cells
ES-2	Human clear cell ovarian carcinoma
A2780	Human ovarian cancer cell line from an ovarian endometroid adenocarcinoma
OVCAR5	Human high grade serous ovarian cancer with possible gastrointestinal origins
ID8-Fluc	Murine epithelial ovarian cancer expressing *luciferase* gene for bioluminescent assays
F2	Human high grade serous ovarian cancer platinum resistant
A549	Human lung cancer
MDA-MB-231	Epithelial human breast cancer cell line
MCF-7	Human breast cancer cell line expressing estrogen, progesterone and glucorticoid receptors
B16	Murine melanoma

Active and material-based targeting strategies can also be integrated to develop formulations with multiple properties, as is the case with the combination of tumor homing peptides and pH-sensitive materials. Tumor homing peptides are oligopeptides up to 30 amino acids able to be specifically and efficiently internalized by tumor cells (184, 185). Some of the most widely used are the linear peptide RGD and its cyclic form iRGD. Both peptides consist of the amino acid sequence Arg-Gly-Asp that is known to recognize and bind αvβ3 integrins, which overexpression in tumors favors survival, proliferation and metastasis in cells of many different cancer models (186). In addition, the iRGD peptide also interacts with the neuropilin-1 receptor, increasing its permeability into the tumor tissue (187). RGD and iRGD have been conjugated to different types of drug delivery systems, such as polymeric nanoparticles (187), liposomes (184), dendrimers (188), hydrogels (189, 190), etc., showing promising results in the treatment of many types of cancer (191). These results have provided the rationale for implementing the use of these peptides in the treatment of PC by locoregional administration. In a study performed on SKOV-3 tumor bearing mice, RGD was conjugated to doxorubicin-loaded calcium phosphate (CaPO) nanoparticles, allowing the nanosystem to benefit from both RGD-induced active targeting and pH-dependent solubility of the CaPO scaffold. The resulting formulation presented a hydrodynamic size of 120 nm and a slightly negative surface charge, and was able to accumulate and release the drug into the tumor tissue. In addition, Ca^{2+} ions released from the particles accumulated in the cytoplasm of tumor cells causing mitochondrial dysfunction, increased cellular stress, and apoptosis. Once injected IP in SKOV3 bearing mice these particles induced a marked delay in tumor growth after two cycles of treatment increasing mice median overall survival from 29 to 59 days, without treatment-related toxicity (134).

The cyclic form of RGD, the iRGD peptide, has increased tumor penetrating abilities compared to RGD due to its ability to efficiently bind the transmembrane glycoprotein neuropilin 1 (NRP-1) in addition to $\alpha_v\beta_3$ integrins. As well as $\alpha_v\beta_3$, NRP-1 is often overexpressed in tumors, where it is implicated in multiple processes that promote tumor growth and invasiveness (192). Binding of iRGD with NRP-1 promotes its internalization, increasing the amount and rate of entry of the iRGD-bound nanosystem into cancer cells. Conjugation of iRGD peptide to a pH-sensitive polymersome made with POEGMA-PDPA and loaded with a fluorescent dye resulted in a compound (iRGD-PS-FAM) with a size of 233 nm and a slightly negative surface charge (-2.7 mV). Biodistribution studies showed that after IP administration on MKN-45P or CT26 tumor-bearing mice, iRGD-PS-FAM formulation was mainly detected in the tumor tissue. Furthermore, in the MKN-45P tumor model, colocalization of the formulation with blood vessels suggested that penetration of the compound into the tumors occurred from both the peritoneal cavity and systemic circulation (135). The same carrier loaded with paclitaxel showed better antitumor efficacy than Abraxane®, resulting in a significant reduction in the number of tumors in both MKN-45P and CT26 models (135).

Nanomedicines can also be designed to release the drug specifically at the tumor even without specific tumor cell binding. A short peptide substrate of cathepsin-B named FRRG (Phe-Arg-Arg-Gly), conjugated with doxorubicin and self-assembled in nanoparticles in presence of Pluronic® F68 of has been used by Kim and colleagues to achieve tumor targeting via specific peptide cleavage and consequent disruption of the nanoparticles and release of doxorubicin. Cathepsin-B is a lysosomal protease constitutively expressed characterized by having either endopeptidase or exopeptidase functions at neutral or acidic pH respectively (193, 194), this enzyme is overexpressed by cancer cells and often associated with cancer progression (195). Conjugation between doxorubicin and FRRG gives rise to an amphiphilic molecule capable of self-assembly into a nanoparticle through π- π stacking and hydrophobic interactions; addition of Pluronic F68 improves *in vivo* stability, preventing immediate opsonization and particle elimination. Both IV and IP administration of the nanosystem showed good ability to accumulate in the tumor. Antitumor efficacy was confirmed in peritoneal human ovarian tumor xenograft (POX) and patient-derived xenograft (PDX) models, where treatment induced a two-fold reduction in PCI score and an increase in overall survival to more than 30 days compared with 19 days achieved with unformulated doxorubicin (136).

2.2 Drug delivery systems to increase residence time at the tumor site

Administration of chemotherapy via IP has been shown to increase drug concentration at the tumor site; however, its rapid elimination from the peritoneal cavity hinders therapeutic efficacy, which remains low. The use of nanomedicines designed specifically for IP administration is one strategy that can help overcome this problem. Still, the fate of nanoparticles after IP is as yet mostly unknown, and data on biodistribution are still limited.

To date, two main clearance mechanisms have been described for IP administration. Peritoneal absorption impacts molecules smaller than 20 kDa that, once diffused through capillaries, are drained into the portal vein, and eliminated. This size is typical of conventional chemotherapy treatments. Larger molecules and nanoparticles are drained through the lymphatic system: if the particles are larger than 500 nm, they are trapped in the lymph nodes, otherwise they can pass through the systemic circulation (196–198).

Nano-, micro- medicines and hydrogel-based nanocomposites, when properly designed, may improve the residence time of encapsulated drugs, and control their release over time. Several physicochemical features can contribute to increase residence time, as particle size, surface potential and the intrinsic properties of the material used (199).

Cationic liposomes and lipid-based nanoparticles, for example, have good peritoneal retention due to their interaction with the negatively charged peritoneal mesothelial cells, but there are also more prone to particle aggregation, which reduces lymphatic drainage (200).

A possible impact of surface charge on residence time has been found in the case of lipid-based nanoparticles loaded with olaparib or talazoparib. The two formulations, made with DPPC, cholesterol,

DOTAP and DSPE-PEG_{2000}, presented similar size around 70 nm and two different surface potentials, -30 mV for NanoOlaparib and + 4 mV for NanoTalazoparib. One hour after IP administration, majority of the olaparib was detected in the plasma, suggesting that the formulation was rapidly cleared from the IP cavity through systemic circulation. In contrast, 24 hours after the injection, 10% of NanoTalazoparib was still present in the IP cavity. The difference in clearance time is also associated with a different efficacy on tumor growth. In 404 tumor-bearing mice, NanoOlaparib treatment inhibited tumor growth only when administered daily, but caused serious side effects. However, increasing the dose and reducing the administration schedule resulted in loss of antitumor efficacy (137). IP administration of NanoTalazoparib over 3 times a week in mFT 3666 tumor-bearing mice resulted in a tumor volume reduction of more than 60%, compared to only 30% achieved by oral administration of the free drug (138).

Increased peritoneal residence time can also be achieved by using bioadhesive materials, that can help nanoparticles to interact with mesothelial cells and avoid fast lymphatic clearance (139, 201).

Polymeric nanoparticles made of polylactic acid block-hyperbranched polyglycerol (PLA-HPG) copolymers have been loaded with epothilone B, a potent microtubule-stabilizing agent targeting class III β-tubulin currently on phase II clinical trial for the treatment of ovarian cancer. Oxidation of vicinal diol groups on the surface of NPs induces their conversion to aldehyde groups that spontaneously react with amine residues of protein-rich surfaces including the peritoneal membrane and the tumor tissue (139). *In vivo* release studies performed on a xenograft model of uterine serous carcinoma, have confirmed that chemotherapy loaded on this bioadhesive formulation achieved higher drug concentration and longer peritoneal persistence leading to amelioration of mice overall survival and reduced drug-related toxicity (139).

While nanoparticles, because of their small size, need to firmly interact with the tumor microenvironment to increase their residence time in the peritoneal cavity, microparticles can simply take advantage of their size to be longer retained after IP administration (202–204). Specifically, when larger than 12 μm in size, particles can escape lymphatic duct drainage, thus avoiding being washed away and increasing its retention in the abdominal cavity (205). Also, because of their low surface area/volume ratio, the drug release of microparticles is slower than that of smaller particles, achieving better peritoneal distribution (205).

Microspheres cross-linked with genipin and loaded with paclitaxel were chosen for their biocompatibility (206). IP treatment of SKOV3-Luc-IP1 tumor-bearing mice showed an increase in median survival (from 33 days in the control group to 90 days in the treated mice), with a clear reduction in tumor burden, PCI score and ascitic fluid production (140).

Hydrogels, defined as three-dimensional, cross-linked networks of water-soluble polymers have been tested as IP administration for the treatment of PC, demonstrating antitumor efficacy (207–209). An *in situ* cross linkable hydrogel composed of alginate has been developed to effectively deliver cisplatin-loaded nanogel in disseminated PC of ovarian origin. This cisplatin-loaded nanogel was developed through a cross-linking reaction between chelating ligand and coordination metal and then loaded in the preparation of an alginate-based hydrogel. The size of the nanogel (10 to 30 nm) remained stable for 24 hours. *In vivo* antitumor efficacy was performed on ID8-KRAS tumor-bearing mice. Median overall survival increased by 10 days, with reduced VEGF expression and no signs of serious adverse effects (141). Another potential approach is represented by nanocapsule-loaded PEG cross-linked hydrogel. Nanocapsules were designed for hydrophobic drug loading, prepared using self-emulsification technique, and coated with HA through electrostatic deposition. The hydrogel matrix was based on poly-(ethylene glycol) thiol-maleimide cross-linking chemistry. Compared to thermosensitive hydrogels this preparation had better stability to dilution, often necessary in the case of preparation for peritoneal injections that require large volumes to be delivered. In addition, the IP administered hydrogel was retained in the peritoneum and able to release its load for up to one week (142).

In addition to the above-mentioned systems, the development of carrier-free nanodrugs has gained increased interest due to their easy manufacture and high drug load. Carrier-free nanodrugs can self-assemble via ionic contact, forming a polymer matrix with controlled-release features that favor high drug concentration at the target location and minimal systemic toxicity (210).

A novel pH-sensitive carrier-free nanomedicine, has been developed by combining the bisphosphonate medication alendronate, calcium ions, and THZ1. Alendronate is currently used in the treatment of osteoporosis (211), Paget's disease of bone and bone metastases (212, 213). THZ1 is an inhibitor of cyclin-dependent kinase 7 (CDK7), an enzyme involved in the regulation of cell cycle progression and linked to increased transcription of oncogenes and increased proliferation rate of cancer cells (214). Alendronate and Ca^{2+} were assembled through coordination interactions, while self-assembly of THZ1 occurred through hydrophobic interactions. The presence of Ca^{2+} ions increased nanoparticles sensitivity to the acidic pH of the tumor microenvironment, favoring targeted drug release. In addition, as seen previously, their positive surface charge (+12.4 mV) facilitated interaction with mesothelial cells in the peritoneal cavity, increasing their retention and thus their residence time at the tumor site. Biodistribution studies performed on the SKOV3 tumor model showed that the nanoparticles were already homogeneously distributed in the peritoneal cavity one hour after injection and were still detectable one week later, with a preferential distribution in the tumor microenvironment. Efficacy studies confirmed the superior ability of the nanosystem compared to free alendronate or THZ1 alone in reducing both tumor growth and ascites volume, thus prolonging the median survival (143).

As mentioned earlier, the permeation of nanoparticles by EPR effect can be limited by inhomogeneous tissue permeability. This condition is strongly influenced by the high interstitial pressure that hinders the diffusion of the particles themselves. Chemotherapeutic agents such as paclitaxel or doxorubicin can be used to restore interstitial transport, as they stimulate apoptosis and amplify interstitial spaces, resulting in increased drug diffusion into tumor nodules. This priming mechanism can be incorporated into nanocarriers and combined with sustained drug delivery. This was achieved by combining poly-lactide-co-glycolide (PLG)

copolymers with different rates of hydrolysis due to the 50:50 or 75:25 lactide:glycolide ratio. While PLG 50:50 hydrolyzes rapidly, PLG 75:25 degrades more slowly due to the lower number of glycolide monomers (215, 216). Both the formulations were loaded with paclitaxel thus allowing both rapid release of the drug resulting in a massive immediate action on the tumor and its priming, and a long-term release that sustains the chemotherapeutic action over time. Particle sizes in the μm range (4-30 μm) also helped reducing the clearance mechanism by further promoting peritoneal retention (217). Moreover, when compared with equivalent doses of active principle administered via cremophor-based preparation, these formulations demonstrated increased efficacy and lower general toxicity (144).

2.3 Delivery systems for the delivery of genetic material

Along with conventional therapeutic strategies, gene delivery technology has brought new, versatile and promising therapeutic approaches in biomedical research, especially with regard to cancer treatment. Pathological and dysfunctional states can be corrected by introducing into the cell with the necessary information to correct the expression of misleading proteins. This information is provided in the form of nucleic acid such as DNA, mRNA, siRNA, miRNA, and antisense oligonucleotide (218).

However, in most cases, genetic material cannot be directly injected into systemic circulation, as it would be easily degraded by enzymes (219) or recognized and eliminated by the immune system. Moreover, since genetic material exert its function inside the target cells, it need to safely cross numerous biological barriers, such as the endothelium and the extracellular and, in most cases, the nuclear membrane (220).To safely deliver genetic material to the cells both viral and non-viral vectors have been developed and non-viral nanoparticles, specifically lipid-based and polymer-based nanoparticles have emerged as a safer and more convenient delivery system compared to their viral counterpart (221–224).

In the case of PC in particular of ovarian origin, different pathways have been proposed as suitable target for gene silencing. For instance, siRNAs targeting the DNA repair machinery have been used to mimic the activity of PARP inhibitors and the administration of a lipidoid-siPARP1 nanoparticle in a *BRCA1*-deficient ovarian cancer mouse model successfully reduced tumor growth by causing the activation of apoptosis (145). Another lipid-based nanoparticle formulation was developed by Singh et al. to encapsulate a combination of two small interfering RNAs, eukaryotic translation-initiation factor 3c (eIF3c) and polo-like kinase-1 (PLK1), involved in the promotion of tumorigenesis and angiogenesis, and in the activation of early G2/M phase transition respectively. The strategy of simultaneously targeting two pathways has been chosen to improve efficacy of the treatment, whose effectiveness is often limited due to transitory effect of the silencing (225). Again, nanoparticles surface coating with HA moieties facilitated the internalization of the vector into the tumor cells. As expected, the combination of the two siRNAs has shown better therapeutic efficacy in increasing OVCAR8 bearing mice overall survival up to 60% compared to 20 and 10% of single siRNA, PLK1 and eIF3c respectively (146). CD44 has also been deeply investigated for its role in tumorigenesis and conferring resistance to treatments as indicated previously (226). Indeed, it has been shown that CD44 isoforms promote cancer cell survival and invasion by interacting with other molecules in the tumor microenvironment, such as fibronectin and hyaluronic acid, which promote cancer cell survival, adhesion, migration, and invasion. However, despite being a negative prognostic factor for ovarian cancer patients (227), CD44 widespread expression makes it a suitable target for nanoparticle-mediated therapy, as it can overcome drug resistance and improve drug delivery and accumulation in tumor tissue. At the same time, silencing its expression could bring significative advantages on tumor treatment. This hypothesis was tested in which a siRNA against CD44 was combined with paclitaxel and loaded in a dendrimer functionalized with the luteinizing hormone-releasing hormone (LHRH) peptide to confer the nanosystem targeting properties to cancer cells of gynecologic origin (228). *In vivo* studies on human ovarian xenografts confirmed that suppression of CD44 was responsible for increased tumor susceptibility to platinum-derived treatments leading to nearly complete tumor reduction (147). Few years later, the same research group has adopted a similar approach by silencing DJ-1 in the ES-2 metastatic human ovarian cancer IP injected in nude mice. DJ-1 is a protein expressed by more than 80% of human advanced ovarian carcinomas and linked to poor prognosis and chemotherapeutic resistance to platinum-based therapy in ovarian cancer (229). siDJ-1 was delivered using Poly (propylene imine) (PPI) generation 4 (G4) dendrimers coated with LHRH-modified PEG chains to confer targeting properties to the nanosized platform. Suppression of DJ-1 protein expression improved the antitumor efficacy of conventional therapeutic drugs, as this protein is involved in different pathways regulating oxidative stress as well as promoting survival, growth, and invasion of ovarian cancer cells (230–232). The combination of DJ-1 silencing, and cisplatin administration was sufficient to eradicate the tumor mass without any recurrence occurring in the following 35 weeks (148).

A different dendrimer-based nanosystem was used by Huang and colleagues to deliver siRNA for the silencing of human antigen R (HuR) protein to OVCAR5 human ovarian cancer injected in athymic mice. HuR is a human RNA-binding protein which main function is to stabilize mRNA to regulate gene expression (233) and that has been linked to bad prognosis in ovarian cancer patients. In this case, a novel developed double strand DNA-based dendrimer nanocarrier (3DNA, Genisphere®), functionalized with folic acid, was used to target tumor cells that highly expressed folate receptor α. HuR inhibition on ovarian ID8 tumor bearing mice resulted in decreased tumor growth and ascites formation, with consequent mice survival extension (149).

Another interest target for gene therapy is TWIST, a morphogenesis regulator gene implicated in the induction of epithelial-mesenchymal transition (EMT) in cancer cells. Acquisition of mesenchymal characteristics is a well-known mechanism associated to metastatic spreading and confers chemotherapeutic resistance to tumor cells (234). Silencing of

TWIST mediated by siRNA loaded onto HA-conjugated mesoporous silica nanoparticles was effective in restoring mice cisplatin sensitivity in OVCAR8 model. Consequently, compared to control groups, ascites volume and tumor burden were significative reduced as well as number of metastases (150).

In addition to targeting cancer cells, gene delivery can be addressed to other components of the tumor microenvironment, such as immune cells, whose activity is often critical in determining tumor outcome. Elimination of immune suppressive cells as myeloid derived suppressor cells (MDSCs) or tumor associated macrophages (TAM) can lead to the restoration of T cells anti-tumor properties, and immune cell reprogramming or repolarization from a pro-tumor to anti-tumor status has been proposed as a tool to potentiate antitumor activity (235–237).

To achieve repolarization of TAM into macrophages with antitumor activity, Zhang at al. have exploited the function of IRF5 (interferon regulatory factor 5) that serves as a molecular switch controlling the pro- or anti-inflammatory polarization of macrophages and was chosen as target (238). They developed a nanosystem in which mRNAs encoding both IRF5 and its activating kinase IKKβ were self-assembled with a positive-charged poly(β-amino ester) (PbAE) polymer. The nanosystem was then pre-functionalized with di-mannose-poly glutamic acid (PGA) that is intended both to mask the residual positive charges, thereby stabilizing the nanocarrier, and to actively target CD206 TAM mannose receptor. *In vivo* studies conducted on ID8 ovarian cancer model confirmed tumor regression and activation of the immune response, while overall median survival passed from 60 days for control groups to 142 days for treated mice (151).

Another innovative way to avoid tumor progression is gene transfection with the vesicular stomatitis virus protein matrix plasmid (pVSVMP). In fact, the expression of vesicular stomatitis virus protein matrix leads to different mechanisms of destruction of the tumoral cell. Low dose paclitaxel was used in combination to improve gene transfection. The plasmid was loaded into a self-assembled cationic nanoparticle composed by paclitaxel, MPEG-PLA and DOTAP (P-DPP). A significative antitumoral efficacy on SKOV3 tumor model was confirmed, as well as the undeniable role of paclitaxel in enhancing the extent of growth inhibition (152).

2.4 Combination of nanomedicine and peritoneal aerosolization

The benefits that the application of nanomedicine can bring to the treatment of PC could be further enhanced by the combination with advanced peritoneal delivery techniques, such as PIPAC and ePIPAC. To evaluate the feasibility of the technique, Shariati and colleagues compared IV and IP injection of Lipofectamine™ MessengerMAX™ mRNA-containing lipoplexes with IP high-pressure nebulization (PIPAC). Biodistribution results confirmed a more homogeneous IP distribution of lipoplexes after PIPAC procedure. In addition, size, surface potential, mRNA complexation capacity as well as mRNA transfection efficacy of the commercial transfection tool were not affected by high-pressure nebulization (239).

However, nebulization processes may generate stress forces on the nanoparticles that could induce damage or deterioration of the delivery systems. Therefore, delivery systems must be appropriately designed to withstand the nebulization processes without being compromised and ensure effective and accurate delivery to the intended site. Homogeneous distribution and proper drug release depend greatly on the colloidal stability of the formulation, the maintenance of which after nebulization is closely related to its composition (240). Minnaert and coworkers compared the stability of two different aerosolized siRNA-encapsulating complexes, the lipid based Lipofectamine™ RNAiMax and a polycationic amphiphilic cyclodextrin, namely ADM70, on SKOV3. The nebulization process had a more important destabilizing effect on the ADM70 complex compared to RNAiMax, impairing its transfection efficiency. Moreover, the presence of ascitic fluid, typical of PC, dramatically decreased transfection efficiency of both systems but with a higher significance in the cyclodextrin-based complex, probably due to the formation of a protein corona around the nanosystem (241). Together with colloidal stability, size and surface charge of the nanoparticles have a massive impact on the residence properties of NPs in the peritoneal cavity, and both parameters need to remain stable during the nebulization process. In addition, the application of PIPAC rather than ePIPAC may require using different particles or their specific optimization. Positively charged curcumin loaded PLGA nanoparticles showed a better tissue penetration profile when associated with ePIPAC than a similar negatively charged PLGA formulation or PIPAC performed without an electrostatic field (242).

Viscosity is another property that can have a strong impact on nebulization results and must be considered especially when using hydrogels. Indeed, high viscosity can affect the angular cone of nebulization and thus the distribution of drugs in the peritoneum. By nebulizing five different concentrations of Pluronic F127 solution, ranging from 5 to 25% w/v, Braet and colleagues have proven how the increase of formulation viscosity was strongly associated to a dramatic decrease of the angle of aerosolization from 53.2° of the 5% w/v to 1° of the 25% w/v showing that further studies need to be done to optimize hydrogel-based nanomedicines for their application in PIPAC (243).

2.5 Clinical studies for the IP delivery of nanomedicine

To date only four clinical trials have been performed using nanoparticles for the delivery of drugs directly into the abdominal cavity via peritoneal infusion mediated by catheter (NCT00666991 and NCT00825201) or employing PIPAC (NCT03304210 and NTC05285358) (Table 5). NanoTax® has been the pioneer compound used for IP administration with the double aim of offering a cremophor-free alternative to the IV administration of paclitaxel and increasing the reservoir of the drug in the peritoneal cavity. NanoTax® is a nanoparticulate form of paclitaxel made by using supercritical carbon dioxide in combination with organic solvents in a process called supercritical fluid technology (244). This process results in naked, rod-shaped particles with narrow size

TABLE 5 Clinical trials implementing the intraperitoneal delivery of nanomedicine for the treatment of peritoneal carcinomatosis.

Phase	Title	Identifier	Status	Conditions	Patients enrolled	Procedure	Drug
1	Pharmacokinetic, Safety and Efficacy Study of Nanoparticle Paclitaxel in Patients With Peritoneal Cancers	NCT00666991	Completed	Peritoneal Neoplasms	22	IP catheter	Nanoparticulate paclitaxel (NanoTax®) (50 - 82.5 - 125 - 175 - 225 - 275 mg/m^2)
1	Intraperitoneal Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Patients With Advanced Cancer of the Peritoneal Cavity	NCT00825201	Completed	Ovarian Cancer, Peritoneal Cavity Cancer, Unspecified Adult Solid Tumor, Protocol Specific	27	IP catheter	Paclitaxel albumin-stabilized nanoparticle formulation (IP administration at day 1 - 8 - 15 for 28 days and then repeated)
1	PIPAC Nab-pac for Stomach, Pancreas, Breast and Ovarian Cancer	NCT03304210	Completed	Peritoneal Carcinomatosis, Ovarian Cancer Stage IIIB, Ovarian Cancer Stage IIIC, Ovarian Cancer Stage IV, Breast Cancer Stage IIIB, Breast Cancer Stage IIIc, Breast Cancer Stage IV, Stomach Cancer Stage III, Stomach Cancer Stage IV With Metastases, Pancreas Cancer Stage III, Pancreas Cancer Stage IV	20	PIPAC	Paclitaxel albumin-stabilized nanoparticle formulation Abraxane® (35 - 70 - 90 - 112.5 - 140 mg/m^2 every 4 week for 3 cycles)
1	Pressurized Intraperitoneal Aerosolized Nab-Paclitaxel in Combination With Gemcitabine and Cisplatin for the Treatment of Biliary Tract Cancer Patients With Peritoneal Metastases	NCT05285358	Recruiting	Distal Bile Duct Adenocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma, Metastatic Malignant Neoplasm in the Peritoneum, Stage IV Distal Bile Duct Cancer AJCC v8, Stage IV Intrahepatic Bile Duct Cancer AJCC v8, Stage IV Intrahepatic Cholangiocarcinoma AJCC v8, Stage IVB Gallbladder Cancer AJCC v8	12	PIPAC	Gemcitabine + Cisplatin (IV on day 1, 3 and 5), nab-paclitaxel (PIPAC on day 3 of cycles 1, 3 and 5) repeated every 21 days up to 8 cycles

distribution and mostly (≥95%) smaller than 1 μm (245). In 2008 the first multicenter open label dose-escalating phase I trial (NCT00666991) enrolled 21 patients to evaluate the toxicity and the pharmacokinetic profile of NanoTax® by administrating a bolus injection through a previously implanted peritoneal catheter. Patients underwent six doses of NanoTax®, each one delayed of 28 days, ranging from a concentration of 50 to 275 mg/m^2. The associated toxicity profile was comparable to the IV administration of paclitaxel with patients only experiencing low grade neutropenia, thrombocytopenia, or peripheral neuropathy, typical of paclitaxel IV treatment. Compared to IV administration, the concentration of drug measured in the peritoneal fluids was 450-2900 folds higher than plasma concentrations and remained elevated through the entire dose cycle due to extremely low peritoneal clearance, providing a marked benefit in tumor exposure intensity and duration of the treatment (246). A different approach was used in a second clinical trial started in 2009 (NCT00825201) where paclitaxel was administered IP encapsulated in a Cremophor-free formulation based on albumin nanoparticles (Abraxane®). Abraxane® is currently approved by the FDA for IV administration for the treatment of breast, lung, and pancreatic cancer (247). Abraxane®, albumin-based nanocarrier (nab-paclitaxel) is an attractive system since, being physiologically present in human serum albumin can be safely considered nontoxic, non-immunogenic, biocompatible, and biodegradable (248). Due to its configuration, albumin can stably bind different drugs providing great advantages to their pharmacokinetic profile, moreover albumin mediates the drug uptake into the tumor cells by binding over-expressed receptors in tumor or endothelial cells (249). Additionally, techniques adopted for the formulation of albumin-based nanoparticles are highly reproducible and easily scalable, facilitating large scale manufacturing (248, 250). Abraxane® was repeatedly administered via IPC to 27 patients affected by advanced peritoneal malignancies. When administered at maximum tolerated dose (MTD) of 140 mg/m^2, drug plasma concentration was similar when compared to IV injection, however drug concentration in the peritoneal cavity was higher. These results were fundamental to set the basis for the study of Abraxane® aerosolization in the peritoneal cavity. A multicenter dose-escalation phase I trial took place in 2017 (NCT03304210) to evaluate the safety of PIPAC-administered nab-paclitaxel in patients with unresectable malignancies and its results have been recently published (251). Five doses were evaluated (35-140 mg/m^2), with a dose administration schedule of three times every four

weeks, repeated for three cycles (130). Side effects were limited to the higher dosage with thrombopenia and neutropenia spontaneously recovering. Peripheral neuropathy with grade ≤2 was found only in patients with the highest dose. Results of this trial confirmed that PIPAC procedure is generally well tolerated in patients and showed that the combination of PIPAC and Abraxane® has a favorable pharmacokinetics profile with an overall median survival of 10 months with 50% of patients surviving longer than 1 year. The latest clinical trial (NTC05285358) is currently ongoing on 12 patients to evaluate the safety of PIPAC nab-paclitaxel associated with systemic administration of gemcitabine and cisplatin.

Although only few clinical trials have evaluated the nanoparticles IP administration feasibility, of which two (NCT03304210 and NCT05285358) employing PIPAC procedure, many interesting nanosystems cited in the previous paragraphs could be optimized for a future nebulization approach.

3 Conclusion

In summary, PIPAC and ePIPAC are gaining interest in the medical field as promising second-line therapeutic alternatives for patients with PC from EOC, while a plethora of novel drug delivery systems are being investigated to modify their pharmacokinetics and pharmacodynamics after administration.

Currently, the use of nanomedicine to improve tumor targeting and penetration is an active area of research and development, particularly for the localized treatment of PC. More research into the safety profile of nanosystems in comparison to current conventional treatment is required to validate their efficacy in treating cancer after IP or PIPAC. Biocompatibility, *in vivo* stability, drug loading efficiency in addition to targeting ability are the requirements that nanomedicines must meet to facilitate their translation from the bench to the bedside.

Despite the fact that many studies have been conducted using conceptually and technologically diverse nanoparticles, it is still difficult to predict which of them will be the most appropriate, safe, and effective in the treatment of this type of cancer because many of them are still in development and have only been tested in preclinical models. Furthermore, preclinical models of peritoneal carcinomatosis and PIPAC are still being developed and frequently lack complete and adequate characterization, such as from an immunological standpoint. A prerequisite that has yet to be fully addressed is the development of adequate models that depict the complexity of PC and enable the correct and repeated performance of the PIPAC method.

It should also be noted that clinical development will involve the transfer from small-scale to large-scale production, which may provide a significant challenge for some more complicated drug delivery systems. Liposomes and lipoplexes, as carriers of both chemotherapeutics and genetic material, are unquestionably a class of compounds that, because they are already in clinical usage, can enter the trial phase more quickly.

It is also important to remember that to date the current standard of care for the first-line treatment of ovarian cancer is based on the use of platinum derivatives alone, which are the most active chemotherapeutic drug class in this cancer. PIPAC's research is currently focused on establishing a viable therapeutic line to address cases of recurrence that do not respond to conventional treatments. This includes not only recognizing situations in which this technique could benefit the patient, but also understanding the timing, dosages, and intervals of administration of PIPAC therapy. Currently, PIPAC is not considered a standard treatment option for ovarian cancer according to international guidelines. Therefore, it is premature to consider the use of PIPAC as first-line therapy for ovarian cancer, and no studies have been conducted in this area.

Then, innovation in PIPAC-associated nanosystems will be primarily related to the development of alternative therapies for refractory tumors. As a result, the development of nanomedicines capable of encapsulating drugs with therapeutic potential but difficult to administer in PIPAC due to chemical properties, such as hydrophobicity in the case of olaparib, or susceptibility to degradation as in the case of genetic material, may favor some nanosystems over others.

In conclusion, although this field is still young and much ground has yet to be covered there have been enormous breakthroughs and numerous novel ideas that have the potential to result in delivery methods able to improve the treatment of EOC derived PC.

Author contributions

SB, SZ, and CG drafted the first version of the manuscipt. NB supervised the clinically relevant information. SZ, GL, and DK served as overall editors. All authors have contributed to the conception of the manuscript and revised it critically. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Incidence and outcomes of delayed presentation and surgery in peritoneal surface malignancies

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Background: Peritoneal surface malignancies (PSM) present insidiously and often pose diagnostic challenges. There is a paucity of literature quantifying the frequency and extent of therapeutic delays in PSM and its impact on oncological outcomes.

Methods: A review of a prospectively maintained registry of PSM patients undergoing Cytoreductive Surgery and Hyperthermic Intra-peritoneal Chemotherapy (CRS-HIPEC) was conducted. Causes for treatment delays were identified. We evaluate the impact of delayed presentation and treatment delays on oncological outcomes using Cox proportional hazards models.

Results: 319 patients underwent CRS-HIPEC over a 6-years duration. 58 patients were eventually included in this study. Mean duration between symptom onset and CRS-HIPEC was 186.0 $\pm$ 37.1 days (range 18-1494 days) and mean duration of between patient-reported symptom onset and initial presentation was 56.7 $\pm$ 16.8 days. Delayed presentation (> 60 days between symptom onset and presentation) was seen in 20.7% (n=12) of patients and 50.0% (n=29) experienced a significant treatment delay of > 90 days between 1st presentation and CRS-HIPEC. Common causes for treatment delays were healthcare provider-related i.e. delayed or

inappropriate referrals (43.1%) and delayed presentation to care (31.0%). Delayed presentation was a significantly associated with poorer disease free survival (DFS) (HR 4.67, 95% CI 1.11-19.69, p=0.036).

Conclusion: Delayed presentation and treatment delays are common and may have an impact on oncological outcomes. There is an urgent need to improve patient education and streamline healthcare delivery processes in the management of PSM.

KEYWORDS

peritoneal malignancy, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, delay, survival

1 Introduction

Patients with peritoneal surface malignancies (PSM) represent a heterogenous group ranging from primary peritoneal cancer to peritoneal metastases secondary to various primaries. Since its introduction in the 1980s, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC) has revolutionized the management of peritoneal malignancies (1, 2). When once associated with a dismal prognosis, selected patients receiving optimal treatment now boost a 10 year survival, with rates of up to 63% reported in patients with pseudomyxoma peritonei (1, 3–6). CRS-HIPEC is now widely regarded as central to the management of PSM in selected patients (6–8).

However, PSM are frequently clinically occult with patients presenting insidiously and with nonspecific symptoms thereby posing significant diagnostic challenges (9–16). Establishing a histological diagnosis often proves challenging, and even at the tertiary level, interpretation of potentially indeterminate imaging characteristics and difficulties in determining histological characteristics result in further delay towards timely diagnosis and treatment of such malignancies (9, 17). In addition, general awareness, and knowledge amongst the physician population towards PSM is poor. In a locally conducted survey, up to 50% of survey participants acknowledged that they were unfamiliar with the disease entity and were unaware of the presence of local PSM specialist units for referrals (18), representing a potential source contributing to delayed specialist review.

Several studies suggest a significant correlation between delays incurred in diagnostic evaluation and poorer oncologic outcomes in various tumor histologies (19–25). While the current evidence in literature concurs that delivery of curative surgery in an expedient manner is crucial to the optimal management of PSM (19, 26), the causative factors and overall impact of delays incurred from patient and healthcare-related factors on oncologic outcomes has not been well-studied.

Therefore, we aim to evaluate the incidence and causes of delayed presentation and surgery and examine its impact on oncological outcomes in patients with PSM.

2 Materials and methods

2.1 Patient selection and data

The study was performed in a single tertiary institution. Data was retrieved from a prospectively maintained database of patients treated with CRS-HIPEC for PSM between January 2014 and September 2019. The study was conducted with the approval of the Centralized Institutional Review Board (CIRB) of Singapore Health Services, CIRB reference number 2018/2638.

We included patients undergoing their index CRS-HIPEC surgery after a primary diagnosis of PSM. Patients with (i) recurrent PSM on a background of previously treated peritoneal malignancy, (ii) peritoneal metastases of a previously known and treated primary tumor, or (iii) who underwent neoadjuvant chemotherapy prior to CRS-HIPEC, were excluded.

Data on patient demographics, onset and duration of symptoms attributable to their primary malignancy, preoperative clinical course and oncologic history was obtained *via* a thorough retrospective evaluation of prospectively maintained clinical records. Patients with insufficient data pertaining to symptoms prior to initial presentation on clinical records were excluded from this study. Descriptive analyses were performed on these variables and survival outcomes were evaluated. A virtual diagnostic and treatment timeline was generated for each study patient and contributory factors to treatment delays were identified by the authors on a case-by-case basis and analyzed (Figures 1A, B).

2.2 Key definitions

1. Delayed Presentation: We defined this as a duration of > 60 days between patient-reported symptom onset and 1st presentation at a healthcare institution.
2. Time to Treatment (TT): Duration between patient-reported symptom onset and CRS-HIPEC surgery.

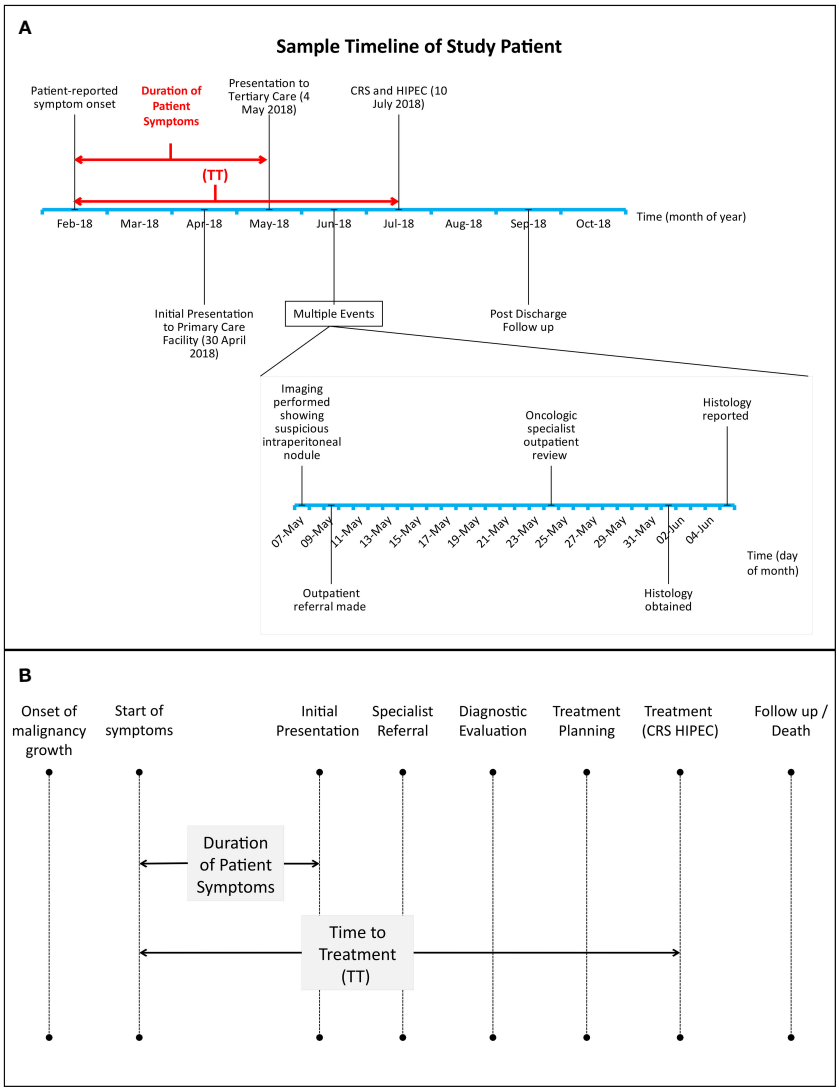

FIGURE 1
(A, B): **(A)**, sample timeline of study patient treated for high grade serous carcinoma of the fallopian tubes with peritoneal involvement. Dates of initial symptom onset, presentation to tertiary care, further diagnostic evaluation and CRS-HIPEC were recorded for every patient. CRS-HIPEC=Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy. TT=time to treatment. **(B)**, Relationship between duration of patient symptoms and time to treatment (TT) with respect to key time points in cancer-related treatment delays. Adapted from *Mou et al.* (20).

3. Delayed TT: We defined this as a Time to Treatment of > 90 days.

Given the paucity of evidence for the expected treatment timelines in peritoneal malignancies in the current literature base, the cutoffs for delayed presentation and delayed TT of 60 and 90 days, respectively, were set arbitrarily on agreement with all authors based on our institutional experience with PSM and its expected treatment course.

2.3 Factors contributing to delays

Factors contributing to delays of any duration were identified on a case-by-case basis and classified into 5 categories: Delayed presentation, healthcare provider, healthcare system, disease or patient-related (Table 1).

2.4 CRS and HIPEC

CRS and HIPEC performed at our institution included resection of the primary tumor with resection of all macroscopic peritoneal deposits combining peritonectomy procedures as well as resection of any involved intraabdominal visceral organs to achieve complete cytoreduction, with subsequent administration of HIPEC. HIPEC was performed in a closed technique, with administration of mitomycin C at 41-42°C over a duration of 60 minutes.

2.5 Statistical methods and survival analysis

Differences in characteristics were tested using the Wilcoxon rank sum test for continuous variables or Fisher's exact test for categorical variables. Kaplan-Meier survival functions were used to analyze the

TABLE 1 Factors contributing to Delayed Time to Treatment.

Factors	Explanation	Examples of Inclusions
Delayed Presentation	This is patient-driven and a result of lack of awareness and knowledge of symptoms and failure to seek appropriate medical services after onset of symptoms.	* Outright dismissal of symptoms * Perception of symptoms as mild and not warranting medical attention
Healthcare Provider	This is driven by the lack of awareness and knowledge of primary and tertiary healthcare providers such that a prompt referral to a peritoneal surgical specialist was delayed	* Elective referrals from external institutions * Elective referrals from primary care providers * Referrals made to disciplines without specialized surgical capabilities
Healthcare System	This is due to the lack of hospital-based resources e.g. operating theatre slots, long patient-waiting time prior to specialist review	* Delayed surgical case listing due to scheduling conflicts * Prolonged interval of follow up due to difficulty obtaining appointment slot
Disease-related	This is due to any disease-related complications or diagnostic difficulties encountered after presentation to a peritoneal specialist and is due to the nature of peritoneal disease and non-diagnostic findings based on radiological or histological investigations.	* Delayed reporting of diagnostic radiological or histology findings * Prolonged course of treatment planning including delays incurred by listing for and discussion at multidisciplinary team conferences * Indeterminate initial findings warranting serial monitoring for disease manifestation or progression resulting in delays * Delays incurred from an evolving disease morphology causing change in treatment plan
Patient-related	This is delay because of patient factors such as other co-morbidities that require optimization, defaulted visits or follow-up, refusal to undergo prompt surgical intervention despite medical advice.	* Treatment of other nonrelated illness * Missed follow ups due to intercurrent nonrelated illnesses * Delays incurred from initial refusal of surgery

impact of treatment delays with respect to time to treatment and symptom duration. Overall survival (OS) was defined as time from CRS-HIPEC to death from all causes or censored at last follow-up. Disease-free survival (DFS) was defined as time from CRS-HIPEC to disease progression or censored at death or last follow-up. The Cox proportional hazards model was used to model association between survival endpoints and patient characteristics, adjusted for tumor histology. Differences between groups were estimated using the log-rank test. A two-sided p-value of less than 0.05 was considered statistically significant. All analyses were performed in R software (version 4.2.0).

3 Results

3.1 Overall characteristics

319 patients underwent CRS-HIPEC at the National Cancer Centre Singapore and Singapore General Hospital between January 2014 and September 2019. 60% (n=194) underwent surgery for recurrent peritoneal disease or PM arising from a previously known and treated primary tumor and were excluded from the study. 6.3% (n=20) had insufficient data on preoperative presentation and were excluded. A further 14.7% (n=47) underwent neoadjuvant chemotherapy prior to definitive surgery, and were excluded. Finally, 58 patients were included into this study. Patients were followed up for an average of 12.4 months from time of surgery. A summary of demographic and clinical characteristics of patients studied is listed in Table 2.

3.2 Patient symptoms, incidence of delayed treatment and primary contributing factors

Common presenting complaints were varied and include abdominal discomfort, distension and constitutional symptoms including loss of weight and appetite. Patients who were asymptomatic or had extra-abdominal symptoms not attributable to PSM were assigned a symptom duration of zero days. The mean duration between patient-reported symptom onset and CRS-HIPEC (TT) was 186.0 ± 37.1 days (range 18-1494 days) and mean duration of between patient-reported symptom onset and initial presentation to any healthcare institution was 56.7 days (SD ± 16.8, range 0-730). 29(50.0%) experienced prolonged TT of more than 90 days; while 12(20.7%) patients were found to have a delayed presentation of more than 60 days. Among patients included into this study, healthcare-provider related delays (43.1%), delayed presentation (31.0%) were identified as the predominant causes of delayed TT. Among the patients who suffered healthcare provider related delays, 17(68.0%) patients were first evaluated in centers which were not specialized in treatment of peritoneal malignancies, and 6(24.0%) incurred delays after being inappropriately referred from primary care providers to disciplines not equipped to manage peritoneal disease. Patients who encountered treatment delays attributable to delayed presentation predominantly experienced protracted symptoms prior to making a decision to seek medical attention.

Less common causes for treatment delays were disease related issues (20.7%), patient related (3.4%) and healthcare system related

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TABLE 2 Demographics and clinical characteristics.

	All patients (n=58)	No Delay in TT (≤90days) (n=29)	Delayed TT (>90days) (n=29)	p-value
Age at CRS-HIPEC, years				0.963
Mean(SD)	57.2 (10.8)	57.1 (12.1)	57.3 (9.7)	
Median (IQR)	59.0 (50.9, 64.4)	59.4 (46.9, 64.4)	58.9 (52.1, 66.3)	
Range	32.0 - 77.7	32.8 - 77.7	32.0 - 72.7	
Sex				0.263
Female	39 (67.2)	22 (75.9)	17 (58.6)	
Male	19 (32.8)	7 (24.1)	12 (41.4)	
Ethnicity				0.474
Chinese	42 (72.4)	23 (79.3)	19 (65.5)	
Indian	5 (8.6)	3 (10.3)	2 (6.9)	
Malay	3 (5.2)	1 (3.4)	2 (6.9)	
Others	8 (13.8)	2 (6.9)	6 (20.7)	
ECOG performance status				0.894
1	44 (75.9)	21 (72.4)	23 (79.3)	
2	4 (6.9)	2 (6.9)	2 (6.9)	
Unspecified	10 (17.2)	6 (20.7)	4 (13.8)	
Histology				0.338
LAMN/HAMN	29 (50.0)	13 (44.8)	16 (55.2)	
PMCA	15 (25.9)	10 (34.5)	5 (17.2)	
Primary peritoneal	14 (24.1)	6 (20.7)	8 (27.6)	
PCI score				0.106
Mean(SD)	14.7 (11.0)	12.2 (10.2)	17.1 (11.4)	
Median (IQR)	15.0 (3.5, 24.0)	13.0 (2.0, 17.0)	17.0 (6.2, 27.8)	
Range	0.0 - 32.0	0.0 - 31.0	0.0 - 32.0	
Unspecified	7	4	3	
CC score				0.941
0 (No tumour)	35 (60.3)	18 (62.1)	17 (58.6)	
1 (<2.5mm)	10 (17.2)	5 (17.2)	5 (17.2)	
2 (2.5mm - 2.5cm)	3 (5.2)	2 (6.9)	1 (3.4)	
3 (> 2.5cm)	2 (3.4)	1 (3.4)	1 (3.4)	
Unspecified	8 (13.8)	3 (10.3)	5 (17.2)	
Comorbidities				
Hypertension	18 (31.0)	12 (41.4)	6 (20.7)	0.155
Diabetes	7 (12.1)	5 (17.2)	2 (6.9)	0.423
Hyperlipidemia	13 (22.4)	10 (34.5)	3 (10.3)	0.056
IHD	3 (5.2)	1 (3.4)	2 (6.9)	1.000
COPD	0 (0.0)	0 (0.0)	0 (0.0)	NA
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	NA

(Continued)

TABLE 2 Continued

	All patients (n=58)	No Delay in TT (≤90days) (n=29)	Delayed TT (>90days) (n=29)	p-value
Other malignancies	2 (3.4)	2 (6.9)	0 (0.0)	0.491
Others	31 (53.4)	18 (62.1)	13 (44.8)	0.292
None	10 (17.2)	4 (13.8)	6 (20.7)	0.730

Data presented as No. (%) unless otherwise indicated. CC, completion of cytoreduction score; COPD, Chronic Obstructive Pulmonary Disease; CRS-HIPEC, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy; GI, Gastrointestinal; HAMN, High Grade Appendiceal Mucinous Neoplasm; IHD, ischemic heart disease; IQR, interquartile range; LAMN, Low Grade Appendiceal Mucinous Neoplasm; PCI, Peritoneal Carcinomatosis Index; PMCA, Peritoneal Mucinous Carcinomatosis; SD, standard deviation; TT, Time to Treatment; NA, not applicable. NA, not applicable.

delays (1.7%) (Figure 2). A comprehensive list of factors included under each category is shown in Table 3.

3.3 Relationship between delayed presentation, time to treatment and survival

Patients with delayed presentation demonstrated poorer overall survival compared to those without (p=0.015, Figure 3A), with median overall survival (OS) being 26.0 months for patients with delayed presentation. 1- and 2- year OS was 100% (95% CI 100-100) and 71.4% (95% CI 44.7-100) versus 100% and 100% respectively for patients with and without delayed presentation. Delayed patient presentation was associated with poorer survival (HR 9.93, 95% CI 1.03-95.89, p=0.047), although this was non-significant after adjustment for tumor histology (HR 7.91, 95% CI 0.72-87.15, p=0.091).

Patients with delayed presentation similarly demonstrated lower rates of DFS (p=0.05, Figure 3B) with median disease free survival (DFS) at 12.7 months for patients with delayed presentation. 1- and 2- year DFS was 100% and 57.1% (95% CI 30.1-100) versus 93.3% (95% CI 84.8-100) and 86.1% (95% CI 71.7-100) respectively for patients with and without delayed presentation. Patients with delayed presentation demonstrated a trend towards poorer DFS (HR 3.65, 95% CI 0.91-14.62, p=0.068) which was significant after correcting for tumor histology (HR 4.67, 95% CI 1.11-19.69, p=0.036) (Table 3).

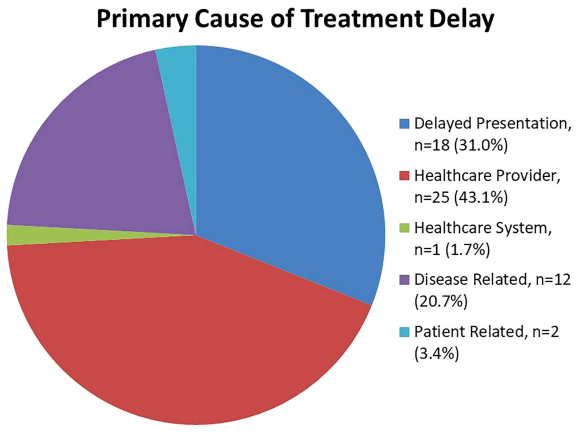

FIGURE 2
Analysis of factors contributing to treatment delays in peritoneal malignancies.

Overall survival was similar between patients with and without delayed TT (p=0.48, Figure 3C). Among patients with delayed TT, median overall survival (OS) was 26.0 months. 1- and 2- year OS was 100% and 87.8% (95% CI 73.4-100) versus 100% and 100% respectively for those with and without delayed TT. No statistical difference in overall survival was demonstrated between patients with and without delayed TT (HR 1.91, 95% CI 0.30-12.13, p=0.491) (Table 3).

No significant differences were found in disease free survival between patients with and without delayed TT (p=0.96, Figure 3D). Among patients with delayed TT, median DFS was 4 months. 1- and 2- year DFS was 100% and 81.6% (95% CI 64.7-100) versus 100% and 100% respectively for those with and without delayed TT (Table 3).

In view of the limited number of events and small sample size, 95% confidence intervals for median OS and DFS for patients with and without delayed TT, and similarly for those with and without presentation delay, could not be estimated.

4 Discussion

Our study demonstrates insight into the factors contributing to treatment delays in PSM, which consist of several potentially actionable causes predominantly attributable to provider-related delays incurred in work processes involved in transfer of care between healthcare institutions (43.1%). These findings represent, to our knowledge, the first attempt in current literature at describing actionable factors contributing to treatment delays in peritoneal malignancies. Our findings also suggest that delayed presentation may result in poorer overall survival and disease-free survival among patients with PSM. Interestingly, however, a delayed time to treatment of >90 days did not result in any significant difference in overall survival or disease-free survival in our study cohort. While the literature consistently supports the early diagnosis and treatment of peritoneal malignancies (27–29) the quantitative effect of diagnostic and treatment delays on oncologic outcomes in such patients has not been sufficiently studied. Furthermore, given the highly litigated nature of oncologic practice in general, delayed evaluation and treatment of such conditions may prove also to be a significant source of financial

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TABLE 3 Cox regression analysis of disease-free survival and overall survival by demographic and clinical variables.

	Disease-free survival			Overall survival		
	E/N	HR (95%CI)	p-value	E/N	HR (95%CI)	p-value
Delayed Presentation						
No delay (≤60 days)	5/46	1		3/46	1	
Delayed (>60 days)	4/12	3.65 (0.91-14.62)	0.0677	3/12	9.93 (1.03-95.89)	0.0473
Time to Treatment (TT)						
No delay (≤90 days)	4/29	1		3/29	1	
Delayed (>90 days)	5/29	1.04 (0.27-3.93)	0.9587	3/29	1.91 (0.30-12.13)	0.4913
Age at CRS-HIPEC, years						
<60	4/32	1		3/32	1	
≥ 60	5/26	3.76 (0.92-15.30)	0.0644	3/26	5.39 (0.84-34.72)	0.0764
Sex						
Female	4/39	1		3/39	1	
Male	5/19	2.85 (0.68-11.96)	0.1519	3/19	5.64 (0.55-58.03)	0.1457
ECOG performance status						
1	8/44	1		5/44	1	
2	1/4	1.30 (0.15-11.72)	0.8129	1/4	1.74 (0.18-17.11)	0.6364
Unspecified	0/10	Not estimable		0/10	Not estimable	
Histology						
PMCA	5/15	1		4/15	1	
LAMN/HAMN	1/29	0.12 (0.01-1.06)	0.0569	0/29	Not estimable	
Primary peritoneal	3/14	1.19 (0.27-5.34)	0.8202	2/14	2.18 (0.29-16.39)	0.4506

E/N stands for Event/Number, in the case of OS, event is the number of death, in the case of DFS, event could be relapse or death. CI, Confidence interval, CRS-HIPEC, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy; GI, Gastrointestinal; HAMN, High Grade Appendiceal Mucinous Neoplasm, LAMN, Low Grade Appendiceal Mucinous Neoplasm, PMCA, Peritoneal Mucinous Carcinomatosis.
Two patients were excluded from disease-free survival as they were lost to follow-up after CRS-HIPEC.

and legal burden to healthcare systems worldwide (30). Therefore, quantifying the causative factors of treatment delays and identifying the impact of such treatment delays on oncologic outcomes is crucial to addressing public health concerns pertaining to the evaluation and treatment of peritoneal malignancies.

A large proportion of study patients suffered delays attributable to provider-related delays incurred by processes involved in transfer of care between institutions (43.1%) and delayed presentation (31.0%) predominantly contributed by a lack of patient awareness regarding signs and symptoms of peritoneal disease. These findings suggest that treatment delays are predominantly influenced by factors within the healthcare system that can be further mitigated with improved professional education and streamlining of administrative processes. Considering the well-documented challenges involved in evaluation of peritoneal malignancies given their significant heterogeneity, varying nature of initial presentation and overall rare occurrence (14, 15, 17, 31–34), healthcare professionals at large would benefit from better awareness on the initial presentations, appropriate evaluation strategies and treatment options for peritoneal malignancies. Additionally, treatment delays incurred here are also contributed at least in part by patients' failure to recognize symptoms that suggest underlying peritoneal malignancies which resulted in delayed presentation to primary care. Findings from our study similarly highlight the importance of early patient recognition of symptoms and early appropriate clinical evaluation in optimizing treatment outcomes for peritoneal surface malignancies.

This study's findings on the association between delayed presentation and poorer overall survival and disease-free survival must be interpreted with due consideration given to the limited sample size and relatively short follow up duration of 12.4 months post CRS-HIPEC, also taking into consideration the effects of disease biology on symptom progression and presentation. The detrimental effect of delayed presentation on survival outcomes may potentially be attributable to poorer disease biology, with more indolent biology presenting with more clinically occult symptoms (28, 29) which translates to a delayed presentation to medical attention, and ultimately poorer survival outcomes. However, our study notably demonstrated that tumor histology and patient comorbidities appear relatively consistent in both non-delayed and delayed time to treatment groups (Table 2), suggesting that such factors were not likely to have influenced the duration of time to treatment. This study further demonstrated an independent association between delayed

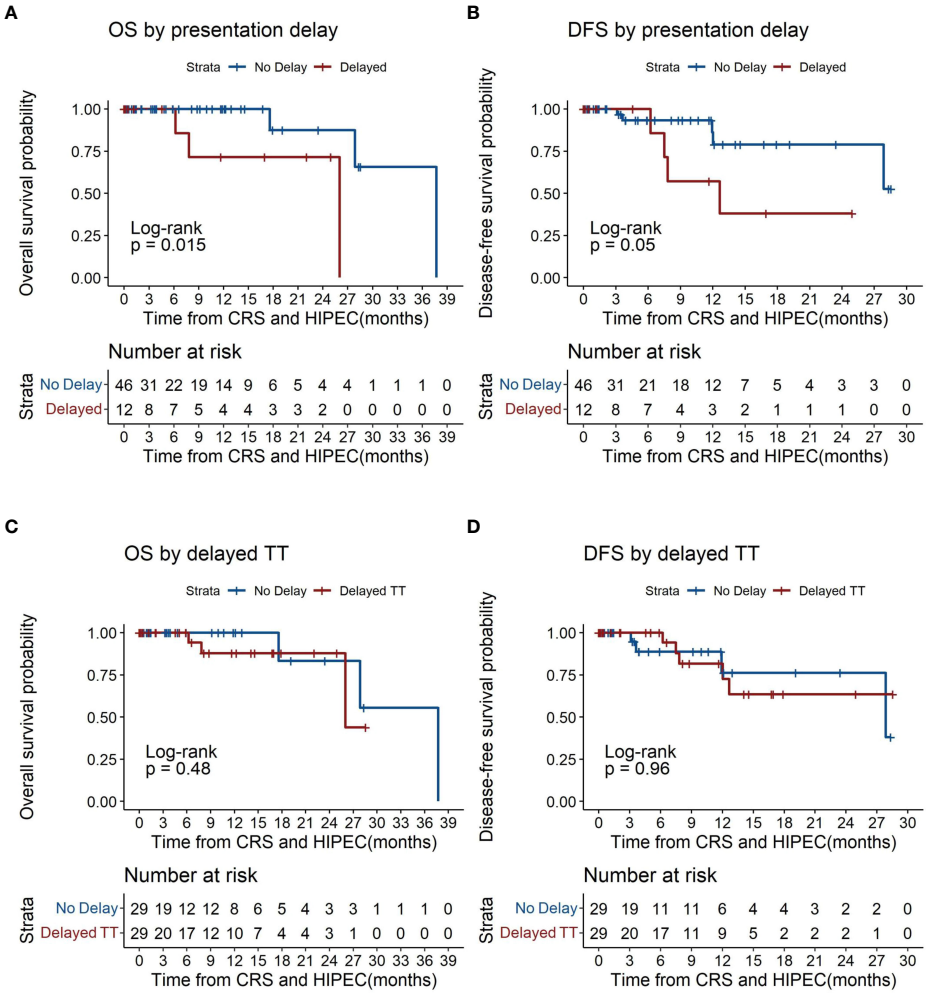

FIGURE 3
Kaplan-Meier plots of overall survival and disease-free survival by time to treatment (TT). **(A)** overall survival by presentation delay. **(B)** disease free survival by presentation delay. **(C)** overall survival by time to treatment. **(D)** disease free survival by time to treatment. CRS, Cytoreductive Surgery; HIPEC, Hyperthermic intraperitoneal chemotherapy; TT, time to treatment.

presentation and reduced disease free survival which persisted after correction for tumor histology (HR 4.67, 95% CI 1.11-19.69, p=0.036), which suggests that delayed presentation of more than 60 days may adversely impact disease outcomes in PSM regardless of the contributory primary histology. The persistent correlation between delayed presentation and poorer survival outcomes after correction for histology would, however, suggest that delayed presentation results in poorer survival due to other independent factors, which has been similarly demonstrated for some other biologically distinct malignancies, delayed presentation in soft tissue sarcoma for instance having demonstrated to be associated with higher likelihood of distal metastases on diagnosis, portending poorer prognoses and poorer survival outcomes (23).

While age does not appear to significantly influence survival outcomes in patients with PM based on our data, older patients 60 years of age and above with peritoneal malignancies demonstrate a tendency towards poorer survival (HR 5.39, 95% CI 0.84-34.72, p=0.076) and lower DFS (HR 3.76, 95% CI 0.92-15.30) compared to younger patients (Table 3). This emphasizes the importance of early detection of PM in particular for older patients, although more studies with a longer follow up duration would be required to prove a significant correlation between age and oncological outcomes in PM.

This study bears several other limitations. Firstly, data collected on pre-hospital symptoms relies on patient-reported duration and severity of symptoms which may bear an inherent recall bias at the time of consult. Secondly, median follow up time was relatively short (12.4 months) with a small sample size of 58, which also did not include any patients previously treated with neoadjuvant chemotherapy or patients with PSM secondary to previously treated primary tumors, thus limiting the analytic power of this study as well as generalizability of results to a small subset of patients with primary PSM who received upfront CRS-HIPEC. Thirdly, this study does not account for the impact of adjuvant treatment regimens on the overall outcomes of patients undergoing CRS-HIPEC. With greater amounts of data obtained from further follow up, further studies can be conducted on the individual treatment outcomes tailored to peritoneal malignancies of each subtype with further subgroup analyses being performed these cases.

5 Conclusion

Treatment delays are predominantly contributed by healthcare-provider related factors which can be further optimized by streamlined referral processes and wider awareness towards evaluation and management of peritoneal malignancies among healthcare workers. Delayed presentation of >60 days appears to be associated with poorer disease free survival in index-presentation peritoneal surface malignancies receiving upfront CRS-HIPEC. Further studies evaluating the effects of treatment delays on survival outcomes in peritoneal malignancies would be useful in improving treatment protocols and optimizing outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Centralized Institutional Review Board (CIRB) of Singapore Health Services, CIRB reference number 2018/2638. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JKT, JSM and CSC contributed to conception and design of the study. JKT, JCO and JSM organized the database. JKT and CL performed the statistical analysis. JKT and JSM wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Descriptive review of current practices and prognostic factors in patients with ovarian cancer treated by pressurized intraperitoneal aerosol chemotherapy (PIPAC): a multicentric, retrospective, cohort of 234 patients

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Introduction: Ovarian cancer (OC) is the primary cause of mortality in women diagnosed with gynecological cancer. Our study assessed pressurized intraperitoneal aerosol chemotherapy (PIPAC) as treatment for peritoneal surface metastases (PSM) from recurrent or progressive OC and conducted survival analyses to identify prognostic factors.

Material and methods: This retrospective cohort study, conducted across 18 international centers, analyzed the clinical practices of patients receiving palliative treatment for PSM from OC who underwent PIPAC. All patients were initially treated appropriately outside any clinical trial setting. Feasibility, safety, and morbidity were evaluated along with objective endpoints of oncological response. Multivariate analysis identified prognostic factors for OS and PFS.

Results: From 2015-2020, 234 consecutive patients were studied, from which 192 patients were included and stratified by platinum sensitivity for analysis. Patients with early recurrence, within one postoperative month, were excluded. Baseline characteristics were similar between the groups regarding platinum sensitivity (platinum sensitive (PS) and resistant (PR)), but chemotherapy frequency differed, as did PCI before PIPAC. Median PCI decreased in both groups after three cycles of PIPAC (PS 16 vs. 12, $p < 0.001$; PR 24 vs. 20, $p = 0.009$). Overall morbidity was 22%, with few severe complications (4-8%) or mortality (0-3%). Higher pathological response and longer OS (22 vs. 11m, $p = 0.012$) and PFS (12 vs. 7m, $p = 0.033$) were observed in the PS group. Multivariate analysis (OS/PFS) identified ascites (HR 4.02, $p < 0.001$/5.22, $p < 0.001$), positive cytology at first PIPAC (HR 3.91, $p = 0.002$/1.96, $p = 0.035$), and $\geq$ 3 PIPACs (HR 0.30, $p = 0.002$/0.48, $p = 0.017$) as independent prognostic factors of overall survival/progression-free survival.

Conclusions: With low morbidity and mortality rates, PIPAC is a safe option for palliative treatment of advanced ovarian cancer. Promising results were observed after 3 PIPAC, which did improve the peritoneal burden. However, further research is needed to evaluate the potential role of PIPAC as an independent prognostic factor.

KEYWORDS

peritoneal metastases, ovarian cancer, PIPAC, prognostic factors, platinum sensitivity

1 Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer, affecting more than 300,000 new cases annually worldwide. Despite its rare incidence, it is burdened with a high mortality rate of more than 200,000 deaths in 2020 (1, 2). Despite a high initial response rate after first-line chemotherapy, only 40-60% result in a complete response (3). The 60-70% of diagnoses occur at the stage of peritoneal carcinosis and the natural course includes sequential relapses, which leads to an ever-increasing probability of platinum resistance relapse (4–7). In addition, several studies have shown the feasibility, safety, and good tolerance of PIPAC (8–10). In the palliative setting after first-line chemotherapy, pressurized intraperitoneal aerosol chemotherapy (PIPAC) with a cisplatin-doxorubicin protocol is currently a safe option. The oncological efficacy has yet to be evaluated [Bakrin et al. (11); Tempfer et al. (12)]. The present study aimed to provide a descriptive report of the current practices in the management of PSM in recurrent or first-line progressive EOC treated with PIPAC in a palliative setting. This study aimed to outline prognostic factors for survival and progression.

2 Materials and methods

2.1 Patient's selection

This multicenter international retrospective analysis from 18 centers included 234 patients diagnosed with PSM from EOC, irrespective of the histologic subtype, between July 2015 and March 2020. Eligibility criteria were as follows: adult patients having palliative treatment with PIPAC, recurrent EOC, tumor board approval for PIPAC, and signed surgical informed consent. Patients with extraperitoneal metastases were excluded from this study. Recurrence was defined according to the timing of recurrence. Patients were described as "platinum-sensitive" (PS) if recurrence occurred more than 6 months after the completion of the initial treatment. Early recurrence before 6 months was considered "platinum-resistant" (PR) (13).

2.2 Morphological and pathological responses evaluation

Treatment strategies were defined and regularly reassessed during multidisciplinary team (MDT) meetings. Following 3 or at least 2 PIPAC, the morphological and pathological responses were confirmed during the MDT meeting, based on expert radiologists' and pathologists' reviews. Morphological response was described according standard and objective radiological response criteria described using the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (14). The types of response described were: complete response, partial response, progressive disease, and stable disease. Pathological response was described according the peritoneal regression grading score (PRGS); no residual cancer cells in all specimens (PRGS 1: complete response), 1 to 49% residual cancer cells (PRGS 2:

major response), ≥ 50% (PRGS 3: minor response) and finally no response (PRGS 4) (15).

2.3 Surgery

Eligibility for PIPAC was confirmed after a systematic exploratory laparoscopy done with a peritoneal cancer index (PCI); a sample of ascitis or peritoneal washing for cytology; peritoneal biopsies for histopathological examination; and the sufficient work space for aerosolization of the intraperitoneal chemotherapy. All PIPAC procedures were performed by expert surgeons dedicated to peritoneal metastases management. Every surgeon was specifically trained in PIPAC procedures following published standard practice and safety protocols (8, 16–18). Drugs administered during early experience were cisplatin at 7.5 mg/m2 dosage and doxorubicin at 1.5 mg/m2. Furtherly those dosages were upgraded to respectively 10.5 and 2.1 mg/m2 with supporting safety and encouraging data (12) Postoperative morbidity and mortality were recorded according to Dindo-Clavien classification (19).

2.4 Statistical analysis

Student's t-test was used for continuous variables, as a parametric test, and the McNemar test for categorical variables, as a non-parametric test. Fisher's exact test was used for comparisons between the groups. The Mann-Whitney U test was used as a non-parametric test for comparisons between independent variables without a Gaussian distribution and the equality of variance assumption. Univariate and multivariate survival analyses were conducted using Cox model regression. Missing data was handled without imputation. Survival endpoints were defined as the time between the PSM diagnosis date and first PIPAC until death from any cause for overall survival (OS), and disease progression (PFS) expressed by radiological recurrence, symptomatic disease progression or death. The potential impact of PIPAC on OS is further supported by the fact that our study focused on patients with previously controlled disease through systemic chemotherapy, without the presence of extraperitoneal disease. By selecting patients with controlled disease, we aimed to evaluate the additional benefits of PIPAC in a specific subset where the peritoneal cavity remained a significant site of disease burden. The assumption underlying our study is that by targeting and controlling the spread of cancer within the peritoneal cavity, PIPAC may further contribute to improved survival outcomes in this particular context. The hazard ratios (HR) for PIPAC, clinical symptoms, and PCI before PIPAC, and the confounding factors were estimated with 95% confidence interval (95% CI) through the Cox regression multivariate model. The assumption of hazard proportionality over time was confirmed in the selected model. The best regression model was chosen with the literature based known prognostic factors, with the "stats" R package. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Analysis was performed using RStudio Software (RStudio: Integrated Development for R. PBC, Boston, MA, 2020). Statistical significance was set at a two-sided p-value of < 0.05.

2.5 Compliance with ethical standards

This study was conducted in compliance with international standards for research practice and reporting. Written informed consent was obtained from all included patients. All data were de-identified and anonymized prior to analysis. A retrospective analysis was approved by the local institutional review board of each participating center and was conducted in compliance with the STROBE criteria (www.strobe-statement.org).

3 Results

3.1 Baseline characteristics

A total of 234 consecutive patients were treated with palliative intent for OC. Patients without sufficient data were excluded (n = 20, 9%). After excluding early recurrence, 192 patients (82%) had recurrence after receiving initial treatment, including chemotherapy ± surgery, and 22 patients (9%) were treated frontline after initial chemotherapy and unrespectability. A flow chart of the included patients is shown in Figure S1 (Supplementary Materials). Baseline patient characteristics are shown in a comparative cross-table by platinum sensitivity group, with the majority of patients in the platinum-sensitive group (116 patients, 60%). Patients were comparable in terms of comorbidities, performance status, and delay of management between PSM diagnosis and 1st PIPAC cycle. The patients differed in age and primary tumor subtype. Patients in the PS group were older (median 64 vs. 60 years, p = 0.024) and more heterogeneous regarding histologic subtypes compared to the PR group. Further details are provided in Table 1.

3.2 Past chemotherapy history

Regarding the number of previous chemotherapy lines or maintenance treatments (bevacizumab) received, PR group (n=28/48, 58%) had more bidirectional treatment in combination with PIPAC cycles compared to PS group (n=27/79, 34%, p = 0.008). About 2/3 and 1/3 of patients had undergone prior PIPAC initiation respectively 3 and 2 lines of chemotherapy. Further details are presented in Table 2.

3.3 Surgical data

Past surgical history analysis showed differences among groups, with a history of CRS greater in the PR group (80% vs. 67%, p = 0.047); however, the PS group showed more cases with a history of HIPEC (12% vs. 1.3%, p = 0.007). The peritoneal burden in the PR group was higher during the PCI evaluation at 1st PIPAC, with a higher median PCI value (16 vs. 24, $p < 0.001$). The PS group had

TABLE 1 Baseline characteristics.

Characteristic	N	Platinum sensitive N = 116 (60%)[1]	Platinum resistant N = 76 (40%)[1]	p-value[2]
Age	192	64 (57, 70)	60 (53, 67)	0.024
BMI	162	23.5 (20.7, 26.8)	23.8 (20.6, 27.3)	0.39
Missing		20	10	
ASA	179			0.34
1		15 (14%)	9 (13%)	
2		61 (55%)	33 (49%)	
3		35 (32%)	24 (35%)	
4		0 (0%)	2 (2.9%)	
Missing		5	8	
ECOG	172			0.65
0		57 (56%)	34 (48%)	
1		32 (32%)	26 (37%)	
2		10 (9.9%)	9 (13%)	
3		1 (1.0%)	2 (2.8%)	
4		1 (1.0%)	0 (0%)	
Missing		15	5	
Primary tumor subtype	174			0.038
Serous adenocarcinoma		91 (92%)	71 (95%)	
Mucinous		6 (6.1%)	0 (0%)	
Other		2 (2.0%)	4 (5.3%)	
Missing		17	1	
Delay between PSM-PIPAC*	178	22 (9, 40)	16 (8, 32)	0.23
Missing		12	2	

[1] Median (IQR); n (%).
[2] Wilcoxon rank sum test; Fisher's exact test.
*Delay since peritoneal metastases (PSM) diagnostic and 1st PIPAC.
ASA, American Society of Anesthesiology classification; ECOG, European Eastern Cooperative Oncology Group for performance status scale; BMI, body mass index (kg/m^2).

TABLE 2 Past chemotherapy history.

Characteristic	N	Platinum sensitive N = 116 (60%)[1]	Platinum resistant N = 76 (40%)[1]	p-value[2]
1st line	190	115	75	>0.99
Missing		1	1	
1st line (type)	186			0.30
Platinum based		100 (88%)	61 (84%)	
Bevacizumab + CT		11 (9.7%)	12 (16%)	
Other		2 (1.8%)	0 (0%)	
Missing		3	3	
2nd line	187	94 (82%)	65 (89%)	0.22

(Continued)

TABLE 2 Continued

Characteristic	N	Platinum sensitive N = 116 (60%)[1]	Platinum resistant N = 76 (40%)[1]	p-value[2]
Missing		2	3	
2nd line (type)	182			0.009
Platinum based		43 (38%)	17 (24%)	
Bevacizumab + CT		37 (33%)	27 (39%)	
Other		12 (11%)	19 (27%)	
No CT		20 (18%)	7 (10%)	
Missing		4	6	
3rd line	180	60 (55%)	42 (60%)	0.47
Missing		6	6	
3rd line (type)	178			0.23
Platinum based		16 (15%)	9 (13%)	
Bevacizumab + CT		11 (10%)	6 (8.6%)	
Other		26 (24%)	27 (39%)	
No CT		55 (51%)	28 (40%)	
Missing		8	6	
Systemic chemotherapy (cycles)	123	14 (8, 20)	13 (10, 18)	0.70
Missing		46	23	
PARPi (before PIPAC)	159	10 (11%)	5 (7.8%)	0.57
Missing		21	12	
Bidirectional chemotherapy (IV-IP)	127	27 (34%)	28 (58%)	0.008
Missing		37	28	

[1] n (%); Median (IQR).
[2] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test.
CT, platinum based or other chemotherapy; PARPi, poly ADP ribose polymerase inhibitor.

significantly more PIPAC cycles (median, 3 vs. 2 cycles; p = 0.016). Follow-up after the 3rd PIPAC showed a significant decrease in initial PCI in both groups, with a median of 16 vs. 24 at 1st PIPAC (p < 0.001), and 12 vs. 20 after 3rd PIPAC (p = 0.009), respectively, for the PS vs. PR groups. The results detailed in Table 3 also showed overall surgical morbidity of 19 vs. 28% (p = 0.16), with low open laparoscopy-related morbidity (0.92% vs. 2.7%, p = 0.56), low severe postoperative complications (4.3 vs. 7.9%, p = 0.35), and in-hospital mortality (2.6 vs. 0%, p = 0.28), respectively, for the PS and PR groups. Renal parameters were closely monitored throughout the treatment course, and no instances of renal failure related to cisplatin use were observed for this cohort.

3.4 Oncological response

In terms of objective assessment, the morphological evaluation at the end of PIPAC cycles showed only a tendency for more complete responses in the PS group and more stable responses in the PR group (p = 0.16) with a substantial amount of missing data (49.5%). The pathological evaluation showed a significant difference with a higher rate of complete or major response in the PS group (26% and 38% versus 8 and 32% in the PR group, respectively; p = 0.016). The details of the data are presented in Table 4.

3.5 Follow-up

The median follow-up was 8 months (IQR 3-17) vs. 6 months (IQR 2-14) for the PS and PR groups, respectively. The overall population follow-up rate was 86.5%. The reasons for the termination of PIPAC are listed in Table S2. A small proportion of patients (7-8%) had to withdraw due to surgical access difficulties (multivisceral adhesions). Approximately 38% of the patients with PS and 24% of those with PR completed the planned PIPAC cycles. Between 9% and 10% of patients were eligible for CRS. Roughly 30% of patients received supportive or palliative care. The remaining 2/3 of the patients resumed systemic chemotherapy. Progression at follow-up was documented for 67% of the PS group and 81% of the PR group (see Table S2 in Supplementary Materials).

TABLE 3 Surgical data.

Characteristic	N	Platinum sensitive N = 116 (60%)[1]	Platinum resistant N = 76 (40%)[1]	p-value[2]
History of HIPEC	191			0.007
None		102 (88%)	74 (99%)	
Yes		14 (12%)	1 (1.3%)	
Missing		0	1	
History of CRS	185			0.047
None		36 (33%)	15 (20%)	
Yes		73 (67%)	61 (80%)	
Missing		7	0	
PCI (at 1st PIPAC)	183	16 (9, 24)	24 (17, 30)	<0.001
Missing		9	0	
PCI (at 2nd or 3rd PIPAC)	128	12 (6, 19)	20 (6, 28)	0.009
Missing		36	28	
Cytology (at 1st PIPAC)	115			0.76
positive		36 (63%)	35 (60%)	
Missing		59	18	
N PIPAC (by patient)	192	3 (1, 3)	2 (1, 3)	0.016
PIPAC (2 cycles)*	192	20 (17%)	18 (24%)	0.27
PIPAC (3 cycles)*	192	66 (57%)	30 (39%)	0.018
Overall complications	192	22 (19%)	21 (28%)	0.16
Severe complications (Clavien ≥3)[#]	192	5 (4.3%)	6 (7.9%)	0.35
Open laparoscopy related[¶]	184	1 (0.9%)	2 (2.7%)	0.56
Missing		5	3	
Mortality at 30-days	191	3 (2.6%)	0 (0%)	0.28
Missing		1	0	

[1] n (%); Median (IQR).
[2] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test; Mann-Whitney U test.
* Patients who completed at least 2 or 3 PIPAC cycles. 1 cycle = 1 PIPAC procedure.
[#] Clavien-Dindo classification, greater or equal than grade 3.
[¶] Complications related to surgical access issue (e.g., small bowel perforation during open-laparoscopy).

3.6 Survival analysis

Overall survival (OS) Overall survival analysis showed a median of 16 months (95%CI, 12-22). Subgroup OS analysis showed a median of 22 vs. 11 months (PS vs. PR, p = 0.012). The survival rates at 12, 24, and 36 months were 65% vs. 47%, 47% vs. 30%, and 36% vs. 19% for the PS and PR groups, respectively. OS analysis adjusted for the number of PIPACs performed revealed difference in platinum sensitivity, with a greater delta in the PR group (p = 0.002) (Figure S2). In the subgroup analysis, patients with three or more PIPACs showed a longer OS in the PS vs. PR group (median 30 vs. 18 months, p = 0.31). Subgroup with fewer than three PIPACs had longer OS in the PS group (median 17 vs. 5 months, p = 0.051) (Figure 1A).

3.7 Progression-free survival

The overall population PFS analysis showed a median of 10 months (95%CI, 9-13). Subgroup PFS analysis showed median of 12 vs. 7 months (PS vs. PR, p = 0.033). Survival rates at 12, 24, and 36 months were 49% vs. 35%, 22% vs. 20%, and 16% vs. 6% for the PS vs. PR groups, respectively. Comparison of PFS between groups adjusted for the number of PIPACs performed showed a significant difference in platinum sensitivity (p = 0.007) (Figure S3). Subgroup analysis with less than 3 PIPACs had median PFS 12 vs. 4 months (p = 0.12), in PS vs. PR-group, respectively. The subgroups with three or more PIPACs were comparable, regardless of platinum sensitivity (median 16 vs. 13 months, p = 0.47) (Figure 1B).

TABLE 4 Oncological response.

Characteristic	N	Platinum sensitive N = 116 (60%)[1]	Platinum resistant N = 76 (40%)[1]	p-value[2]
Morphologic response (RECIST 1.1)*	100			0.16
Complete		12 (20%)	4 (9.8%)	
Partial		14 (24%)	8 (20%)	
Stable		13 (22%)	17 (41%)	
Progression		20 (34%)	12 (29%)	
Missing		57	35	
PRGS#	96			0.016
PRGS 1		15 (26%)	3 (7.9%)	
PRGS 2		22 (38%)	12 (32%)	
PRGS 3		19 (33%)	16 (42%)	
PRGS 4		2 (3.4%)	7 (18%)	
Missing		58	38	
Positive cytology*	64	29 (78%)	19 (70%)	0.46
Missing		79	49	

[1] n (%).
[2] Fisher's exact test; Pearson's Chi-squared test.
* Morphological response according RECIST 1.1 criteria, after 3 PIPAC or at least 2 PIPAC.
# PRGS: Pathological Regression Grading Score; 1= complete response; 2= major response (>50% fibrosis); 3=partial response (<50% fibrosis); 4=no response.

3.8 Multivariate survival analysis: Cox model

The multivariate overall survival analysis is summarized in Figure 2A. The OS forest plot shows the predictive factors adjusted for the key prognostic factors for survival, including platinum sensitivity. The presence of ascitis (HR = 4.02, 95% CI 1.84-8.81, p < 0.001) with positive cytology (HR = 3.91, 1.67-9.14, p = 0.002) at the 1st PIPAC was an independent OS prognostic factor. Performing three or more PIPACs treatments (HR = 0.3, 0.14-0.63, p = 0.002) showed to be an independent OS prognostic factor. The adjusted analysis of the predictive factors of PFS showed the same trends as OS (Figure 2B). The presence of ascitis (HR = 5.22, 2.56-10.62, p < 0.001), PCI > 15 (HR = 2.5, 1.2-5.2, p = 0.014), and cytology (HR = 1.960, 1.05-3.67, p = 0.035) were found to be independent unfavorable predictive factors for PFS. The completion of at least three PIPACs (HR = 0.48, 0.27-0.88, p = 0.017) was an independent factor for good prognosis regarding PFS. Detailed univariate and multivariate Cox regression analyses are depicted in Tables S3A, B (Supplementary Material).

4 Discussion

Treatment of patients with recurrent or unresectable OC remains a therapeutic challenge. An increasing number of subsequent lines of chemotherapy is associated with decreased benefits for patients. Hanker et al. showed a very diminished survival benefit of successive chemotherapy lines after the 4th recurrence (4). Moreover, the prognostic becomes poorer with PR recurrence regardless the adjunct of bevacizumab to chemotherapy as in described in the AURELIA trial, which is currently the best available treatment (PFS 6.7 months from start of 2nd line chemotherapy), or PARP inhibitor (20, 21). Intraperitoneal route for chemotherapy is a valid option largely described since Armstrong et al. work in 2006 (22, 23). PIPAC represents currently a safe and effective technique and vector of IP chemotherapy for palliative OC after failure of multiple lines of chemotherapy and targeted therapies (anti-VEGF, PARPi) (24–27).

The present study reports descriptive terms for the current practices of 12 centers around the world. The detailed analysis of postoperative morbidity and mortality found the same conclusions in the literature in terms of safety, even in patients with a history of extensive cytoreduction (8, 25). The theoretical goal of PIPAC is to stabilize intra-abdominal disease, improve QoL in case of symptoms and delay a new line of IV chemotherapy, in a palliative management setting. In our study, objective radiological and pathological evaluations were difficult to document exhaustively. This is likely due to the inconsistent availability of targets for radiological evaluations. Accessibility to specialized pathological reading expertise was also a limiting factor in cases of PR recurrence where the prognosis was poor, with a median overall survival of 12 months. In this setting, the primary goal of treatment is to maintain or improve QoL without impeding the OS (20, 28).

There is a lack of literature yet proposing a decision algorithm for PIPAC management for patients with OC (29). The additional analyses allowed us to highlight some trends of longer OS and

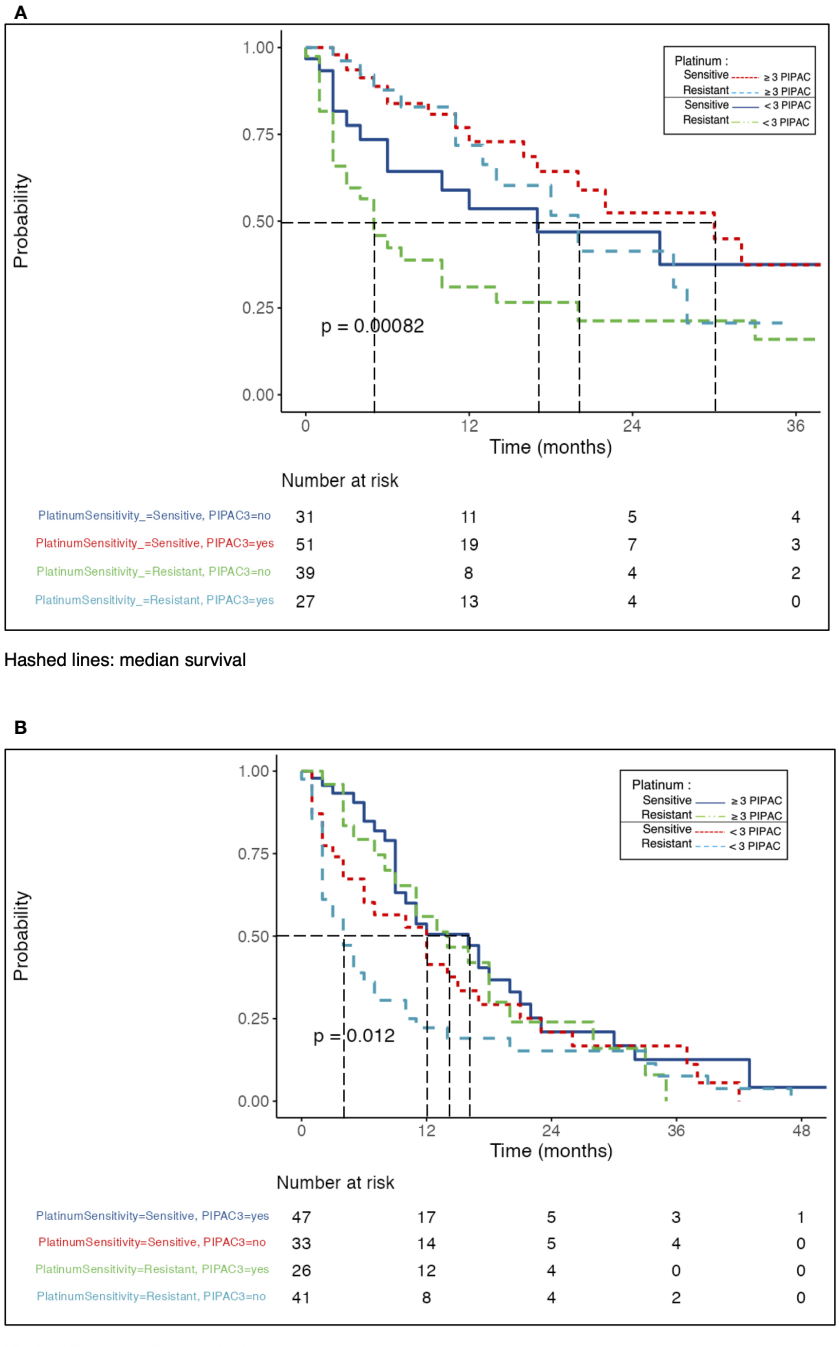

FIGURE 1
(A) Overall survival after PIPAC adjusted to platinum sensitivity. **(B)** Progression-free survival after PIPAC adjusted to platinum sensitivity.

PFS, in favor of the subgroup having performed three or more PIPACs. The multivariate analysis, although on a retrospective cohort, seemed to emphasize, the presence of ascites, the PCI and the number of PIPACs performed as prognostic factors for OS and PFS. As for the number of pipac, we can assume that only patients with a better performance status can complete their three pipac course.

The emergence of PARPi drugs has profoundly changed the prognosis of patients with platinum-sensitive recurrence regardless of their BRCA or HRD mutation status. In our cohort, we did not have the number of platinum-sensitive recurrences or situations where chemotherapy was contraindicated due to toxicity or patient refusal. To date, PIPAC has no place in the treatment armamentarium for PS OC, given the large and effective therapeutic options available for this subgroup. In our cohort, 9–10% of patients with initially unresectable tumors were eligible for CRS. OC with peritoneal involvement remains a complex site to target with less bioavailability to systemic chemotherapy and less distribution throughout peritoneal metastases (23). Vergote et al. showed in their randomized trial that 45% of patients remained

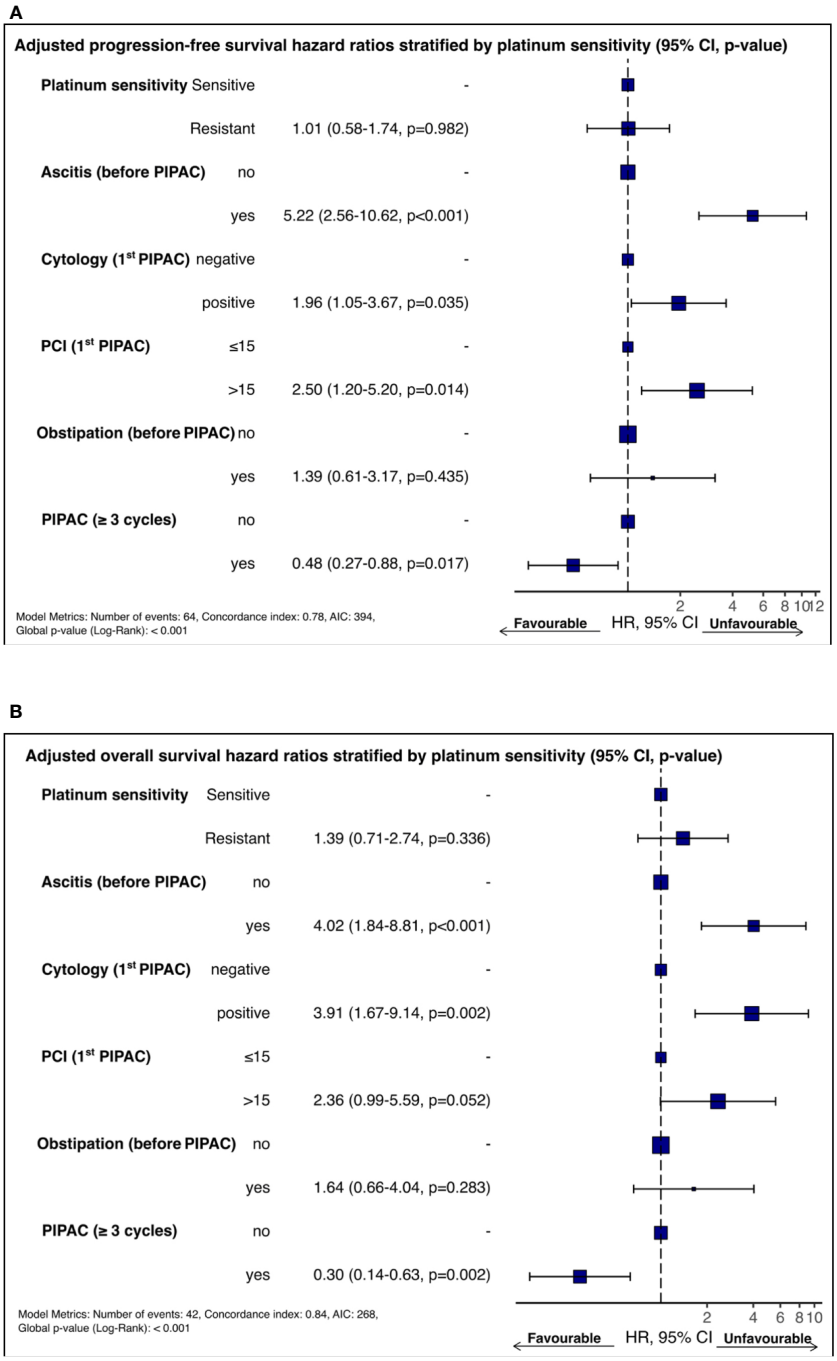

FIGURE 2
(A) Forest plot of adjusted OS predictors stratified by platinum sensitivity. **(B)** Forest plot of adjusted PFS predictors stratified by platinum sensitivity.

unresectable after completing three cycles of carboplatin-paclitaxel as neoadjuvant chemotherapy (30). Combined with systemic chemotherapy, PIPAC could be an option to overcome the risk of peritoneal disease. PIPACOVA is a French phase I dose escalation clinical trial (NCT04811703) with a secondary endpoint of assessing the success rate of conversion to surgery in initially unresectable patients treated with bidirectional chemotherapy if deemed unresectable after three courses. The trial is currently in the recruitment stage. There is currently an Indian phase 3 trial ongoing evaluating the role of PIPAC for recurrent OC PSM, with RECIST morphological assessment as the primary endpoint (31). Interim analysis showed PIPAC with better objective response rates and improved quality of life when compared to chemotherapy arm with acceptable morbidity, which supports our findings (32).

The limitations of our study are its retrospective design, the wide heterogeneity of systemic chemotherapy regimens across centers, and the relatively high rate of missing data for radiological and pathological endpoints. However, it provides a snapshot of the use of PIPAC in patients treated palliatively for ovarian cancer, alone or in combination with systemic chemotherapy.

The administration of PIPAC for patients with PSM from recurrent OC has been confirmed to be safe and associated with low perioperative morbidity and mortality. Future trials will have to determine the place of PIPAC in the therapeutic armamentarium of patients with ovarian cancer and non-met needs, such as unresectable disease, high recurrence number, or platinum-resistant relapse.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRB, Hospices Civils de Lyon, France IRB, CHUV, Lausanne, Switzerland IRB, Zydus Hospital, Ahmedabad, India IRB, Clinica del Pilar, Barcelona, Spain IRB, P.A. Herzen, Thoracoabdominal, Moscow, Russia IRB, University Hospital Tübingen, Tübingen, Germany IRB, University Hospital of Leipzig, Leipzig, Germany IRB, Cancer Institute Montpellier (ICM), Montpellier, France IRB, Ghent University Hospital, Ghent, Belgium IRB, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy IRB, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The authors AK, NB, OG, MH contributed to the conception and design of the study, analysis and interpretation of the data, and drafting and critical revision of the manuscript. AK and NB contributed to data collection and statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1204886/full#supplementary-material

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