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Review

A Clinician's perspective on the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer management

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ABSTRACT

The prevention of intraperitoneal spread is of utmost importance in the management of advanced ovarian cancer (OC), thus demanding the exploration of innovative treatment techniques. The propensity of OC to spread to the peritoneum has highlighted the potential of local therapy as a promising approach. Among the proposed treatments thus far are several local intraperitoneal therapies, with hyperthermic intraperitoneal chemotherapy (HIPEC) being one of them. The application of HIPEC may potentially enhance the survival rates of patients with OC, as indicated by a recent publication of high-quality prospective data. The incorporation of HIPEC in conjunction with primary cytoreductive surgery (CRS) does not have a significant impact on either overall survival (OS) or disease-free survival (DFS). However, the incorporation of HIPEC alongside interval CRS, followed by systemic chemotherapy (CTH), markedly enhances both OS and DFS. The most recent data also substantiates the effectiveness of HIPEC in recurrent ovarian cancer (ROC), resulting in an improvement of survival outcomes.

Additional research will contribute to the improvement of the HIPEC regimen and technique, as well as the precise identification of patients who will gain the most advantage from this treatment approach. It is recommended to discuss and update (inter)national clinical guidelines for managing patients with advanced OC and peritoneal involvement.

1. Introduction

The mortality rate of ovarian cancer (OC) surpasses that of all other gynecologic malignancies [1]. Based on Globocan's 2020 projections, there will be a notable surge of nearly 42 % in the number of OC cases diagnosed globally, reaching 445,721 by 2040. The estimated annual increase in the number of women diagnosed with OC is expected to reach 313,617, indicating a growth of more than 50 % compared to the previous year. The global significance of OC necessitates intensified efforts towards comprehensive measures to address this disease [2].

Appropriate surgical staging and debulking surgery are typically the initial treatment modalities for OC, followed by systemic chemotherapy (CTH) in the majority of patients (though exceptions do exist) [3–5]. However, surgery alone (followed by observation) may be adequate as the primary treatment for certain patients with early-stage disease. Furthermore, for specific histologic subtypes, the inclusion of hormonal agents as adjuvant therapy can be considered. The consideration of neoadjuvant chemotherapy (NAC) with interval debulking surgery (IDS) is recommended for patients with advanced-stage OC who are deemed unsuitable for upfront primary debulking surgery (PDS) due to factors such as advanced age, frailty, poor performance status, comorbidities, or suboptimal cytoreduction prognosis [6,7].

The dissemination of OC seldom adheres to an invasion-metastasis cascade, wherein individual cells or groups of cells breach the basal lamina, infiltrate adjacent tissues, and intravasate into the vasculature [8,9]. OC has the ability to develop loosely attached outgrowths that extend beyond the apical boundary of the tissue mucosa [10]. Outgrowths can undergo complete detachment from the mucosa, travel through the peritoneal fluids, and subsequently adhere to new sites [11]. This uncommon route of dissemination is connected to tumor heterogeneity, the progression of treatment-resistant illnesses, and the obstruction of abdominal organs, leading to increased patient morbidity

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and mortality [12–14]. Each phase of OC dissemination is characterized by a specific molecular mechanism and cellular phenotype. Comprehensive knowledge of the molecular and cellular factors influencing outgrowth formation and interaction with the microenvironment is imperative in the pursuit of novel therapeutic approaches for addressing peritoneal dissemination. Given the particular manner in which OC spreads, relying solely on surgery and CTH seems inadequate as a therapeutic strategy. The application of systemic CTH and cytoreductive surgery (CRS) in conjunction shows minimal effectiveness in the treatment of peritoneal metastases, primarily attributed to the resistance exhibited by these metastases to low intraperitoneal concentrations and the inherent safety limitations in achieving sufficient concentrations using this approach [15,16].

The prevention of intraperitoneal spread is a paramount objective in the management of advanced OC, necessitating the development of new treatment techniques. The propensity of OC to spread to the peritoneum has highlighted the potential of local therapy as a promising approach. To date, several local intraperitoneal therapies have been proposed. Among these treatments is hyperthermic intraperitoneal chemotherapy (HIPEC), which is administered in the operating room after the surgical procedure. In order to enhance local-regional control, the introduction of normothermic intraperitoneal chemotherapy (NIPEC) delivered via an intraperitoneal port for long-term use has been implemented [17]. The technique known as pressurized intraperitoneal aerosol chemotherapy (PIPAC) involves delivering normothermic chemotherapy into the abdominal cavity as an aerosol under pressure. This method has documented positive outcomes by addressing the elevated tumoral interstitial fluid pressure and improving drug penetration and distribution [18].

This paper seeks to provide a clinician's viewpoint on the critical role of HIPEC in the treatment of OC.

2. The rationale behind hyperthermia and a practical overview of HIPEC

The phenomenon of hyperthermia exhibits a diverse impact on cancer cells. Firstly, hyperthermia exerts a direct cytotoxic effect on cancer cells by inducing the production of lysosomes. Moreover, it has been determined that the application of hyperthermia improves CTH penetration and can synergistically enhance the effectiveness of certain anti-mitotic agents, including cisplatin, paclitaxel, oxaliplatin, and mitomycin [19–21]. Hyperthermia application contributes to the reduction of resistance to cisplatin by specifically targeting cellular resistance mechanisms [22]. It also contributes to immunomodulation and boosts the immune response against tumor cells by inducing heat shock proteins (HSPs) (specifically Hsp70 and Hsp90), activating antigen-presenting cells, and facilitating lymphocyte migration [23,24]. Regardless of the potential risks entailed in an increase in body temperature, several techniques have been devised to selectively raise the intraperitoneal cavity temperature while minimizing the effects on the rest of the body [25].

The technique known as HIPEC entails the administration of a heated solution containing a CTH agent throughout the peritoneal cavity. The objective is to directly target the residual disease on the peritoneal surface following the CRS [26]. Moreover, the blood peritoneal barrier serves the purpose of constraining the systemic absorption of the CTH agent, thereby decreasing its side effects and toxicity. Temperatures exceeding 41 °C induce a direct anti-tumour effect through the enhancement of cytotoxicity of certain CTH agents and improved penetration depth into tumour nodules [16]. In the procedure of HIPEC, local heat application is employed while maintaining control over the body's core temperature. Additionally, there are automated pumps available that have been specifically created for the purpose of temperature-regulated continuous drug delivery and monitoring of the infusion process [27].

CRS refers to the comprehensive surgical excision of all visible peritoneal diseases and includes five specific procedures, such as visceral or parietal peritonectomy. The techniques employed in CRS have been outlined by Sugarbaker [28]. The most significant prognostic factor, according to the clinical data analyzed extensively using both univariate and multivariate approaches, is the CRS of nodules smaller than 2.5 mm [29]. It is important to remember that this procedure is intricate and carries comparable morbidity rates to major surgical procedures. Multiple strategies have been explored in an effort to anticipate the extent of CRS, which has a direct impact on surgical outcomes and patient survival. The peritoneal cancer index (PCI) is considered one of the most valuable tools. It quantitatively assesses the extent of intraperitoneal disease by combining the size of cancer implants with tumor distribution across 13 abdominopelvic regions. The PCI yields a maximum score of 39 [30].

According to Kusamura, there are eight parameters that have an impact on pharmacokinetics and the efficacy of HIPEC, and these parameters can be modified during HIPEC. The factors to consider include the type of drugs, drug concentration, drug combination, carrier solution, perfusate volume, temperature, duration, and the technique of either open or closed abdominal cavity [31].

2.1. HIPEC chemotherapy protocols

Within the realm of primary OC, cisplatin is widely acknowledged as the most frequently employed chemotherapeutic drug for HIPEC in gynecological malignancies, as recommended by the NCCN guidelines [32,33]. Among other drugs frequently employed in HIPEC are paclitaxel and liposomal doxorubicin, either individually or in different combinations [34]. The optimal drug regimen for CTH in patients undergoing HIPEC for recurrent ovarian cancer (ROC) remains a subject of ongoing debate, lacking a definitive consensus. Fagotti described the application of oxaliplatin, whereas Bakrin et al. employed cisplatin either alone or in combination with mitomycin C or doxorubicin [35,36]. Spiliotis et al. conducted a study wherein platinum-sensitive patients were administered cisplatin and paclitaxel, while platinum-resistant patients were given doxorubicin and paclitaxel or mitomycin C [37]. In the future, it is imperative to conduct large-scale randomized controlled trials to address this issue. Table 1 presents most common CTH agents employed in HIPEC.

2.2. Temperature and duration of HIPEC

The synergistic impact of hyperthermia and intraperitoneal CTH becomes apparent once the temperature reaches 39 °C, and subsequently exhibits a linear progression. Despite this, the upper threshold for intraperitoneal heat administration is governed by the tolerance of bowel tissue to temperature. According to retrospective studies, the likelihood of complications increases when the intra-abdominal temperature surpasses 42 °C [38]. Based on these data, there is a general

Table 1
CTH agents employed in HIPEC along with their average peritoneal activity peaks [25].

Drug	Dosage	Mean peak peritoneal cavity: plasma concentration ratio
Carboplatin	AUC 5-6	18
Cisplatin	50–75 mg/m2	20
5FU	600 mg/m2	298
Paclitaxel	60–175 mg/m2	1000
Doxorubicin	30–75 mg/m2	494
Liposomal doxorubicin	20–50 mg/m2	600–1000
Gemcitabine	1000 mg/m2	500–800

AUC: area under the curve.

consensus among surgeons that the optimal level of intra-abdominal hyperthermia lies within the range of 41 °C–43 °C. The cytotoxicity in malignant cells is effectively induced by this optimal temperature range, which impairs DNA repair, denatures proteins, and inhibits oxidative metabolism in their microenvironment. Consequently, this leads to increased acidity, activation of lysosomes, heightened apoptotic cell death, and inhibition of angiogenesis [39].

The duration of the HIPEC procedure can vary from 30 to 120 min, depending on institutional protocols and factors such as the pharmacokinetics of the CTH drug, the patients' cell count, and renal function [40,41].

2.3. Comparison of HIPEC techniques

There are multiple perfusion systems available that can generate hyperthermia. The systems are comprised of closed-circuit pumps that distribute heated CTH drugs through inflow catheters and aid in drainage through outflow catheters. There are two available techniques for implementing HIPEC, specifically the open or coliseum technique and the closed technique [25]. Table 2 displays the comparison of those techniques.

2.4. The impact of hyperthermia on genome instability

The hallmarks of cancer include genome instability and mutation. The application of heat leads to damage in DNA and protein, hindering the progression of the cell cycle and ultimately initiating apoptosis [42]. Impaired DNA damage repair mechanisms have been found to be associated with heightened chemosensitivity. The induction of DNA damage is observed solely with CTH, but its combination with heat impedes homologous recombination (HR), thus ultimately stimulating cancer cell death. It has been proposed that hyperthermia causes the inactivation of the HR repair mechanism, necessitating cells to resort to alternative repair mechanisms, such as Poly(ADP-ribose) polymerase-mediated DNA repair [43].

The family of proteins called Poly(ADP-ribose) polymerase (PARP) plays a crucial role in DNA repair. The suppression of these proteins leads to an enhancement of CTH cytotoxicity [44]. The detection of single-stranded DNA breaks is carried out by PARP enzymes, which then proceed to bind to the DNA-binding domain [45]. Given its role in the repair of single-stranded DNA breaks, PARP1 has garnered attention in the field of cancer therapy, specifically as a focal point for PARP1 inhibitors. The BRCA gene, known for its role as a mediator in HR, is found to be mutated in OC. The presence of a mutation in BRCA impedes the release of proteins that suppress tumor growth. Application of hyperthermia on tumor cells resulted in the degradation of BRCA and the inhibition of HR [43]. The potential augmentation of HIPEC advantage for BRCA-positive patients can be ascribed to the synergistic impact of hyperthermia and CTH, resulting in the inhibition of PARP-1-dependent DNA replication [46]. Tumor cells with BRCA mutation exhibit heightened sensitivity to PARP-1 inhibitors [43]. The studies indicate that hyperthermia can induce a greater susceptibility to PARP-1 inhibitors in HR-proficient tumors, and this susceptibility is further augmented by HSPs inhibition [43]. The simultaneous suppression of Hsp90 and PARP-1 via hyperthermia might potentially heighten the susceptibility of tumors to HR inactivation, thereby hindering the repair mechanisms of tumor cells and demonstrating promise as a potential therapeutic strategy for OC treatment. HIPEC mechanism of action is presented in Fig. 1.

Table 2
Comparison of HIPEC techniques [25].

	Open (coliseum) technique	Closed technique
Heat loss	Accelerated heat loss	Minimal heat loss
Distribution of CTH	Even distribution of heated CTH throughout the abdominal cavity	Unequal intra-abdominal distribution of CTH drugs The theoretical benefit of improved drug penetration
Risk of spillage and exposure	High risk of spillage and exposure to CTH drugs	Reduced chance of spillage and exposure to chemotherapy drugs
Consumption of time	Time-consuming	Less time-consuming
Intraperitoneal temperature	Achievement of intraperitoneal goal temperature is more problematic	Easy achievement of intraperitoneal goal temperature
CTH concentration in the blood	Lower concentration of drug in the blood	Higher concentration of drug in the blood, leading to myelosuppression

CTH- chemotherapy.

3. Insights into the use of HIPEC in primary OC

POC presents a difficult disease to manage due to its aggressive nature and rapid dissemination to other organs. HIPEC has been suggested as a potential therapeutic approach for POC. Implementing HIPEC in the management of POC signifies a groundbreaking step in oncological treatment. This approach, combining CRS and HIPEC, is evidenced by significant studies demonstrating its effectiveness.

The effectiveness of HIPEC in the cohort of patients who underwent NAC followed by interval CRS was established in three randomized controlled trials. The research conducted by van Driel et al. (OVIPEC-1) played a crucial role in advancing this area of study. The study involved a total of 245 patients who had achieved stable disease after completing 3 cycles of NAC. These patients were randomly assigned to receive either CRS alone or CRS combined with HIPEC. The initial outcomes were first published in 2018 after a follow-up duration of 4.7 years [32]. The study demonstrated that the inclusion of HIPEC with cisplatin (100mg/m2 for 90 min) during interval CRS in patients diagnosed with stage III OC resulted in a 3.5-month improvement in recurrence-free survival (RFS) ($p = 0.003$) and 11.8 months in overall survival (OS) ($p = 0.02$). The incidence of grade 3-4 adverse events was similar in both treatment groups (25 % versus 27 %), indicating a similar safety profile. Following a decade of follow-up, the ultimate survival results of this trial were presented in June 2023 at the latest ASCO Annual Meeting in Chicago and subsequently promptly published. A comparison between the surgery group and the surgery-plus-HIPEC group revealed a median RFS of 10.7 months and 14.3 months, respectively ($p < 0,001$). The study findings reveal a notable contrast in median OS, with values of 33.3 months and 44.9 months ($p = 0,011$) respectively. The median RFS improvement was 3.6 months, and the median OS improvement was 11.6 months. An interesting discovery emerged from the post-hoc analysis: patients without pathogenic BRCA1/2 mutations but with HRD tumors might experience greater benefits from HIPEC than patients with BRCA1/2 tumors. The findings underscore the potential of HIPEC in enhancing survival outcomes in advanced POC. This study presents the initial comprehensive analysis of HIPEC in OC, highlighting its importance in enhancing patient outcomes [47].

Diaz-Montes et al.'s provides additional support for these findings, as their phase II trial revealed a notable response rate to HIPEC as an initial treatment, indicating its potential efficacy early in the treatment regimen [47].

Furthermore, Lim et al. found compelling evidence to support the notion that the incorporation of HIPEC with interval CRS yielded a substantial increase in PFS [48]. The collective findings of these studies indicate a paradigm shift in the treatment of POC, positioning HIPEC not only as a treatment method with immediate advantages but also as a vital element in improving long-term patient survival and QoL. The research involved two distinct patient groups to study the utilization of HIPEC in POC. The first group consisted of 92 patients with potentially resectable tumor load who underwent primary CRS followed by cisplatin-based HIPEC (75mg/m2 for 90 min) and systemic CTH. The second group composed of 92 patients with a low likelihood of achieving

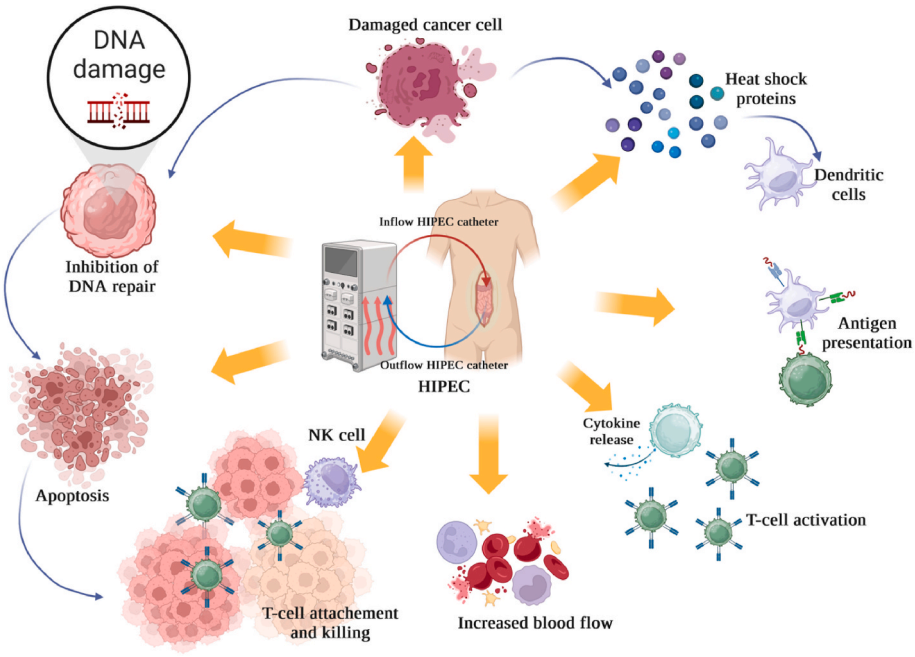

Fig. 1. The multidimensional mechanism of action of HIPEC. HIPEC induces immunogenic cell death by damaging cancer cells, which release heat shock proteins. These proteins are recognized by dendritic cells, leading to the activation of cytotoxic T cells and Natural Killer cells, which attack the cancer cells. Additionally, HIPEC enhances the effectiveness of chemotherapeutic by increasing its cellular uptake and improving DNA crosslinking. This synergy inhibits DNA repair and promotes apoptosis, combining direct cytotoxic effects with robust immune activation for comprehensive cancer treatment.

complete primary CRS and were therefore more suited for NAC followed by interval CRS and systemic CTH [48]. In the general cohort of primary CRS did not result in significant improvements in PFS and OS. However, a significant increase in PFS (median 15.4 months vs. 17.4 months) was observed in the subgroup of patients receiving interval CRS after NAC. These findings were substantiated by the OVIPEC-1 study, which employed the same drug as HIPEC but administered it in a different dosing regimen [48].

The RCT that studied HIPEC in interval setting was conducted by Cascales Campos et al., 71 patients were randomized to receive interval CRS alone or with the addition of cisplatin-based HIPEC (75mg/m2 for 60 min). The median PFS was observed as follows: 12 months in the surgery group and 18 months in the surgery-plus-HIPEC group ($p = 0.12$). Unfortunately, the trial patient recruitment ended prematurely due to lack of funding and the refusal of patients to participate after the results of OVHIPEC-1 became known [49,50].

Systematic review by Filis et al. consolidated data from RCTs, consistently highlights HIPEC's efficacy in not only addressing POC but also its recurrence. Meta-analysis by Filis et al. revealed that adding HIPEC immediately after primary CRS had no significant impact on OS and disease-free survival (DFS) at any time point of the analyzed periods (5 years). The study revealed that in POC, combining HIPEC with interval CRS and NAC, the use of HIPEC significantly improved the 5-year DFS ($p = 0{,}008$) and OS ($p = 0{,}001$) with a durable long-term (at 5 years) reduction of 23 % in the risk of death when compared with treatment without HIPEC indicating a substantial improvement compared with standard treatment [51].

Llueca et al. conducted a meta-analysis with the objective of evaluating the impact HIPEC on OS and DFS for patients with POC who underwent NAC. Six studies were utilized, incorporating a total of 674 patients. The combined meta-analysis of all studies, including both observational studies and RCT, did not demonstrate significant findings. Despite the separate analysis of OS ($p = 0.03$) and DFS ($p < 0.01$) in the RCT, there was a clear suggestion of an impact on survival. The subgroup analysis revealed that studies that employed higher temperatures ($\geq$42 °C) for shorter durations ($\leq$60 min), as well as using cisplatin as the CTH agent in HIPEC, achieved better outcomes for both OS and DFS. Additionally, the utilization of HIPEC did not result in an increase in high-grade complications [52].

These trials indicate that HIPEC, particularly when combined with interval CRS and NAC, can offer significant benefits in primary OC treatment, though its role in front-line treatment and in combination with primary CRS requires further investigation.

Despite the progress, as of now, there are still no published trials on the impact of HIPEC in front-line treatment of OC for primary CRS. A projected completion date of 2023 was established for ongoing trials in this area, indicating the forthcoming availability of additional data.

4. Insights into the use of HIPEC in recurrent ovarian cancer

The management of ROC presents a formidable obstacle in oncology, compelling the exploration of innovative approaches. One particular approach that has gained attention in recent years is HIPEC. Multiple studies have demonstrated the potential benefits of HIPEC in the management of ROC.

While CRS and systemic CTH are the current standard of care for OC, there is ongoing research into HIPEC as an alternative treatment modality for ROC [49]. A meta-analysis was conducted to assess the effectiveness of HIPEC for ROC, wherein seven studies were selected for analysis [53,54]. The meta-analysis findings indicate that HIPEC demonstrates effectiveness solely in individuals who have had recent CTH, rather than in CTH-naïve OC patients [37]. The maximization of the effect of HIPEC after NAC is observed in POC [37]. Moreover, HIPEC has been linked to improved clinical prognosis for patients with POC [55]. However, HIPEC only resulted in improved OS and did not demonstrate a significant impact on PFS in cases of ROC [55].

The exact role of HIPEC in the treatment of OC is yet to be determined, although HIPEC has shown encouraging outcomes in OC [56]. The effectiveness of HIPEC for ROC may be increased by administering higher doses of carboplatin. Additionally, HIPEC with an alternative agent, like cisplatin, could potentially also be effective for ROC [7]. The main advantage of HIPEC in cases of ROC lies in its capacity to enhance

both survival rates and QoL. Achieving optimal outcomes necessitates meticulous patient selection and a multidisciplinary approach. Furthermore, it is crucial to conduct additional research to assess the long-term benefits and potential complications.

Regarding the utilization of HIPEC in ROC, there is accessible data from three randomized controlled trials, and the outcomes they present are conflicting. The results of a prospective randomized phase III trial conducted by Spiliotis et al. (2015) highlight the effectiveness of HIPEC in the treatment of ROC. The Greek study evaluated the efficacy of HIPEC applied at first recurrence in platinum-sensitive and platinum-resistant patients. Sixty participants were randomly assigned to each group: one receiving CRS plus systemic CTH, and the other receiving CRS with an additional HIPEC followed by systemic CTH. Platinum-sensitive patients received a combination of cisplatin and paclitaxel, whereas platinum-resistant patients undergoing HIPEC were treated with either doxorubicin and paclitaxel or mitomycin. In the HIPEC group, the mean OS was 26.7 months, while it was 13.4 months in the control group ($p < 0.01$). The OS showed similarities in both subgroups, with 26.8 months in the platinum-sensitive group and 26.6 months in the platinum-resistant group. However, a significant difference in OS was observed in the control arm, with 15.2 months in the platinum-sensitive subgroup and 10.2 months in the platinum-resistant subgroup ($p < 0.01$) [37]. While the study's results uphold the application of HIPEC in recurrent cases, it received criticism concerning its methodology, including the randomization process, and the documentation of statistical analysis, such as the unclear definition of the primary outcome and the calculation of sample size [49].

The study conducted by Zivanovic et al. (2021) focused on the application of carboplatin in secondary CRS and HIPEC for platinum-sensitive ROC, offering valuable insights into the effectiveness of HIPEC in specific groups of patients. Zivanovic et al. conducted a phase 2 RCT to compare the effectiveness of HIPEC based on carboplatin followed by five cycles of CTH with CRS alone, followed by five cycles of CTH in patients with ROC. In opposition to the outcomes reported by Spiliotis et al. this study did not reveal a survival advantage associated with the combination of secondary CRS and HIPEC in patients with ROC. The randomized data analysis of this trial revealed a statistically significant 18 % increase in the risk of disease progression or death among the patients receiving HIPEC [53].

In June 2023, the CHIPOR phase 3 RCT results were presented at the latest ASCO meeting in Chicago, providing additional knowledge in the theme. This multicentric trial, conducted over a span of 10 years and involving 31 institutions, aimed to enroll patients who had experienced their initial platinum-sensitive ROC. The patients received 6 cycles of platinum and taxane-based CTH, either with or without bevacizumab. Those who were eligible for complete CRS after CTH were enrolled and randomly allocated to receive HIPEC (cisplatin 75mg/m2 for 60 min) or not. The trial conclusions indicate HIPEC had a substantial impact on both OS (54.3 vs. 45.8 months) and peritoneal PFS (13.1 vs. 12.2 months). The observed improvement in global PFS was 10.2 vs. 9.8 months, respectively [54].

The aforementioned studies' findings are mirrored in the guidelines concerning the usage of HIPEC. Although the current guidelines of worldwide societies/organizations do not endorse the combination of HIPEC with primary or secondary CRS, their stance on HIPEC in association with interval CRS ranges from advocacy to exclusion or consensus (Table 3) [55,56].

Study, such as those conducted by Classe et al., in 2023, along with the findings presented at the 13th PSOGI International Congress, contribute to an understanding of the significance of HIPEC in the treatment of OC [55,57]. The ongoing research primarily centers on the improvement of HIPEC protocols, the comprehension of its long-term outcomes, and the identification of patient populations that would be most suitable for this treatment.

Table 3
Guidelines on HIPEC combined with interval CRS – current status worldwide [56].

Organization	Guidelines
National Comprehensive Cancer Network (**NCCN**)	Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease (Version 3.2022, 07/25/22) [58].
European Society for Medical Oncology (**ESMO**)/European Society of Gynaecological Oncology (**ESGO**)	No consensus [63]. Such statement actually reflects change of sentiment - there was negative statement in 2018.
Peritoneal Surface Oncology Group International (**PSOGI**)	Strong positive recommendation for HIPEC in addition to interval CRS in patients with epithelial ovarian cancer meriting inclusion in routine care. The recommended HIPEC regimen: cisplatin for a minimum of 60 min with a recommended minimum intraabdominal temperature of 41 °C [55].
The Program in Evidence-Based Care with the Surgical Oncology Program at Ontario Health (Cancer Care Ontario)	For patients with newly diagnosed stage III primary epithelial ovarian or fallopian tube carcinoma, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease after neoadjuvant chemotherapy at the time that interval CRS (if complete) or optimal cytoreduction is achieved [60].
Chicago Consensus Working Group on peritoneal surface malignancies	HIPEC indicated following NACT and complete/optimal interval CRS [61].
French organizations (FRANCOGYN, Collège National des Gynécologues et Obstétriciens Français (CNGOF), Société Française d'Onco Gynécologie (SFOG), GINECO-ARCAGY)	HIPEC may be proposed for FIGO stage III ovarian, fallopian tube or primary peritoneal carcinosis at the time of interval surgery with a residue <10 mm, conducted after 3 cycles of intravenous chemotherapy, for patients with initially non-resectable disease [62].
Multisociety International Consensus on Peritoneal Surface Malignancies (PSM): Ovarian Cancer – presented in the 13th PSOGI International Congress on PSM, 4–6th October 2023, Venice. Societies involved in working out the consensus: Peritoneal Surface Oncology Group International (**PSOGI**), Society of Surgical Oncology (**SSO**), International Society for the Study of Pleura and Peritoneum (**ISSPP**), European Society of Surgical Oncology (**ESSO**), International Gynecologic Cancer Society (**IGCS**) [64]	Strong recommendation for CRS + HIPEC + 3 cycles adjuvant chemotherapy in selected patients who received 3 cycles neoadjuvant chemotherapy for stage III high-grade serous ovarian cancer.

5. Consensus guidelines

The guidelines pertaining to the implementation of HIPEC have been formulated based on the evidence and research findings presented in the aforementioned studies. The existing guidelines set by global societies/organizations do not support the use of HIPEC with primary or secondary CRS. However, their position on HIPEC in combination with interval CRS varies, with some endorsing it and others excluding it or lacking consensus (Table 3) [55,56].

The NCCN guidelines recommend using cisplatin at a dose of 100 mg/m^2 for HIPEC in OC, based on the OVHIPEC-1 trial. Currently, there is a deficiency in determining an optimal combination of perioperative CTH regimens with the HIPEC agent. The NCCN Guidelines do not impose any specific restrictions on the HIPEC recommendation in relation to the selected NAC or postoperative CTH regimen [58]. According to the European Society for Medical Oncology (ESMO)/European Society of Gynaecological Oncology (ESGO), intraperitoneal CTH is not supported as a standard first-line therapeutic intervention. This conclusion is based on a substantial consensus of 95 % among experts.

Similarly, HIPEC is not recognized as a standard first-line treatment modality, also reflected in a 95 % consensus within the scientific community [59]. In the consensus process conducted by the Peritoneal Surface Oncology Group International (PSOGI), 73 experts (67.5 %) responded in the initial round, with 68 (62.9 %) participating in the subsequent round. The resolution of 94.7 % of the questions, or 34 out of 38, was achieved through consensus. Only 6 questions (15.7 %) received a strong positive consensus for incorporation into routine care. One of the recommendations provided a strong endorsement for the routine clinical practice of combining HIPEC with interval CRS. Cisplatin has been confirmed as the only agent recommended for routine application, with the OVHIPEC-1 regimen being the most favored. The expert panel has put forward a recommendation stating that a minimum HIPEC duration of 60 min and a minimum intraabdominal temperature of 41 °C should be followed. Additionally, they suggested the application of sodium thiosulfate for nephroprotection during cisplatin-based HIPEC [55]. The Program in Evidence-Based Care and the Surgical Oncology Program at Ontario Health (Cancer Care Ontario) have reached a consensus after conducting a thorough systematic review of relevant literature, consulting with patients and caregivers, and conducting internal and external assessments. HIPEC should be considered for patients diagnosed with stage III primary epithelial ovarian or fallopian tube carcinoma, or primary peritoneal carcinoma, who demonstrate stable disease after NAC, especially after achieving complete interval CRS or optimal cytoreduction. The current evidence is lacking in its ability to substantiate the suggestion of incorporating HIPEC during primary CRS for patients with newly diagnosed advanced forms of these cancers, unless as part of a clinical trial. The use of HIPEC with CRS for ROC outside of a clinical trial context cannot be recommended due to insufficient evidence [60]. The Chicago Consensus Working Group provides multidisciplinary guidelines for the management of peritoneal surface malignancies, including OC. The development of these guidelines necessitated the collective expertise of professionals from different domains, encompassing surgical oncology, medical oncology, gynecologic oncology, pathology, radiology, palliative care, and pharmacy. The principles of intraperitoneal CTH have been thoroughly examined, leading to the establishment of dosing regimens for normothermic and hyperthermic CTH [61]. In accordance with the French guidelines established by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY, and endorsed by INCa, the proposal of HIPEC as a therapeutic measure is permissible for patients diagnosed with FIGO stage III ovarian, fallopian tube, or primary peritoneal carcinomatosis. This recommendation is relevant for patients with initially non-resectable disease who have undergone 3 cycles of intravenous CTH, and have a residue measuring less than 10 mm during interval surgery [62].

6. Future considerations

The ongoing trials primarily involve patients who have been diagnosed with primary OC. The main drug administered for HIPEC in these trials is cisplatin, closely followed by paclitaxel. The objective of the HIPECOV trial is to assess the efficacy of HIPEC with lobaplatin after CRS in patients with primary and ROC, and the current enrollment is ongoing [65]. There are currently two significant trials, HORSE and CHIPOR, in progress, which seek to recruit patients with ROC. In both trials, patients in the treatment arm underwent platinum-based NAC, interval debulking surgery, and subsequent HIPEC [66–68].

PIPAC is a newly developed technique that ensures the direct delivery of CTH drugs in aerosol form into the abdominal cavity, while maintaining high pressure. The aerosol form enables the uniform distribution of the drug across the peritoneal surface, while the applied pressure promotes greater drug penetration. During laparoscopy, the CTH drug is administered into the abdominal cavity by means of a high-pressure injector and a micropump. After a duration of 30 min, the drug-aerosol is removed using a suction system [69]. Current research is investigating the role of PIPAC in ROC and peritoneal metastasis. In the context of this particular group, the application of intraperitoneal CTH with PIPAC, in the absence of CRS, has been deemed safe and well-tolerated [70]. Tempfer et al. conducted a systematic review, which revealed an objective tumor response rate of 69 % and a mean OS duration of 13.7 months. The study's findings suggest that PIPAC is a safe and effective treatment for OC and peritoneal carcinomatosis, while also maintaining the patients' QoL [71]. The safety of administering PIPAC with dose-escalating cisplatin and doxorubicin in patients with ROC was confirmed in a single-arm phase 1 study [72]. It is of utmost importance to conduct large randomized control trials in order to obtain more conclusive evidence for this novel technique, as the current studies have been limited to single-armed designs. The current clinical trials are presented in Tables 4–6.

Ascites is frequently documented in cases of OC. The utilization of hyperthermia treatment and localized CTH through laparoscopic administration in continuous hyperthermic intraperitoneal perfusion chemotherapy (CHIPC) is regarded as advantageous in the treatment of peritoneal metastases, in comparison to HIPEC [73]. The study assessed the effectiveness of CHIPC in the presence of malignant ascites, involving a total of 36 patients, of which 12 had primary ovarian cancer (POC) [73]. The findings demonstrate that the CHIPC led to complete resolution of ascites in a majority of the patients. It was reported that there were no significant adverse effects, and the management of ascites was found to be associated with an improvement in QoL. CHIPC involves the administration of significantly lower doses of CTH compared to systemic treatment [73].

The cGAS-STING pathway is an essential element of the innate immune system [79]. It has been established that the activation of the cGAS-STING pathway in macrophage-like cells is promoted by hyperthermia [74]. The protein-coding gene known as Cyclic GMP-AMP synthase (cGAS) is responsible for detecting cytosolic DNA. Upon detection, it activates the Stimulator of Interferon Genes (STING) pathway, ultimately leading to the activation of cytokines [75]. The cGAS-STING pathway has been assigned a crucial role in the detection of DNA in response to immune defense mechanisms [76]. In order to optimize the effectiveness of HIPEC, the incorporation of hyperthermic activation of the cGAS-STING pathway in forthcoming therapeutic approaches is imperative, given its apparent significance. The augmentation of cGAS-STING expression would enhance the activation of inflammatory genes, leading to an intensified immune response and the targeted elimination of the tumor.

7. Summary

The primary cause for criticism directed at HIPEC is the absence of convincing outcomes from RCTs that endorse its application in OC patients with peritoneal dissemination. Presently, there are no established guidelines regarding the optimal patient population and histology of ovarian tumors that would maximize the advantages of HIPEC. The absence of standardized CTH drug regimens and treatment guidelines regarding duration and temperature poses a challenge in the implementation of HIPEC. The ongoing trials may potentially provide answers to these questions, and there is a high level of anticipation surrounding their results. Moreover, it is worth contemplating whether the outcomes of these trials will impact everyday clinical practice is unknown. Five years after the publication of the OVIPEC-1 study results, a national survey was conducted by the Spanish group of peritoneal surgical oncology (Grupo Español de Cirugía Oncológica Peritoneal, GECOP) in order to evaluate the influence of these findings on clinical practice. In 85 % of the 33 participating groups, the findings of the Dutch trial did not bring out any modifications in the clinical practice. Notwithstanding the results of this RCT, the predominant viewpoint among most groups is that additional RCTs are necessary and that HIPEC may potentially achieve the status of standard of care in the future [77].

Several other controversial matters are intertwined with HIPEC. This includes assessing its effectiveness when used in conjunction with

Table 4
Ongoing randomized trials evaluating HIPEC in primary ovarian cancer.

NCT Number	Study Title	Acronym	Phase	Study Status	Drug and dose	Subtype	Primary Outcome Measures	Enrollment	Start Date
NCT01628380	Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer (CHORINE)	CHORINE	3	Publication pending	Cisplatin (100 mg/m^2) + Paclitaxel (175 mg/m^2)	Epithelial	DFS	94	2012–06
NCT02124421	HIPEC in Ovarian Cancer as Initial Treatment (CRS/HIPEC)	HOT	2	Recruiting	Carboplatin (AUC 6)	Epithelial	Compare complication rates between the two study arms: CRS with HIPEC and CRS alone.	32	2014–04
NCT03180177	Efficacy of HIPEC as NACT and Postoperative Chemotherapy in the Treatment of Advanced-Stage Epithelial Ovarian Cancer (EHNPCTASEOC)	EHNPCTASEOC (HIPEC-03)	3	Unknown	Paclitaxel (175 mg/m^2) succeeded by Cisplatin (75 mg/m^2)	Epithelial	DFS, PR/SD rate, CC rate	263	2018–03
NCT03275194	HIPEC in Ovarian Carcinoma Clinical Stage IIIC and IV During Interval Laparotomy	–	2	Recruiting	Cisplatin, doxorubicin (dose unknown)	HGSOC, low-grade endometrioid	Mortality, morbidity, QoL	100	2017–09
NCT03373058	Efficacy of HIPEC in the Treatment of Advanced-Stage Epithelial Ovarian Cancer After Cytoreductive Surgery (EHTASEOCCS)	EHTASEOCCS (HIPEC-4)	3	Unknown	Docetaxel (75 mg/m^2) succeeded by Cisplatin (75 mg/m^2)	Epithelial	RFS	310	2019–10
NCT03772028	Primary Cytoreductive Surgery with or without Hyperthermic Intraperitoneal Chemotherapy (HIPEC)	OVHIPEC-2	3	Recruiting	Cisplatin (100 mg/m^2)	Epithelial	OS	538	2020–01
NCT03842982	Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer (CHIPPI)	CHIPPI	3	Recruiting	Cisplatin (100 mg/m^2)	Epithelial	DFS	362	2019–04
NCT04280185	HIPEC in the Treatment of Stage IIc-IV Epithelial Ovarian Cancer After CRS (HIPECOC)	HIPECOC	3	Recruiting	Paclitaxel (60 mg/m^2) succeeded by Carboplatin (AUC 5–6)	Epithelial	PFS	202	2020–06
NCT04815408	PD-1 Antibody Combined Neoadjuvant Chemotherapy for Ovarian Cancer	Z2HOC-01	2	Recruiting	Albumin-bound Paclitaxel 260 mg/^{m2}, Carboplatin (AUC 5), Tislelizumab (BGB-A317)	Non-mucinous adenocarcinoma	PFS	40	2021–04

(*continued on next page*)

Table 4 (*continued*)

NCT Number	Study Title	Acronym	Phase	Study Status	Drug and dose	Subtype	Primary Outcome Measures	Enrollment	Start Date
NCT05246020	Efficacy of Neoadjuvant Hyperthermic Intraperitoneal Chemotherapy in Advanced High-grade Serous Ovarian Cancer (the NHIPEC Trial)	NHIPEC	2	Recruiting	Docetaxel (60–75 mg/m^2) succeeded by Cisplatin (75 mg/m^2)	HGSOC	Chemotherapy response score	80	2020–12
NCT05406674	Body Surface Area-based vs Concentration-based Dosing of Cisplatin for Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Women with Advanced Ovarian Cancer	CisCon	2	Recruiting	Cisplatin (100 mg/m^2 versus 40 mg/L)	HGSOC	Intratumoral platinum concentration at the end of perfusion	40	2022–06
ACTRN12621000269831p	Hyperthermic and Normothermic intraperitoneal chemotherapy following interval cytoreductive surgery for stage III epithelial OVArian, fallopian tube and primary peritoneal cancer	HyNOVA	2	Recruiting	Cisplatin (100 mg/m^2)	Epithelial	Proportion of AEs $\geq$ grade 3	80	2022–02
NCT03188432	Hyperthermic Intraperitoneal Chemotherapy Trial Comparing Quality of Life in Patients With Stage IIIC-IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	–	2	Recruiting	Carboplatin (dose unknown)	Epithelial	QoL	40	2017–10
NCT03275194	HIPEC in Ovarian Carcinoma Clinical Stage IIIC and IV During Interval Laparotomy	–	2	Recruiting	Cisplatin and doxorubicin (dose unknown)	Epithelial	Mortality	100	2017–09
NCT05827523	Interval Cytoreductive Surgery With or Without HIPEC for Ovarian Cancer (KOV-HIPEC-04)	KOV-HIPC-04	3	Recruiting	Cisplatin (75 mg/m^2)	Epithelial	OS	520	2023–05
NCT05659381	Heated Intraperitoneal Chemotherapy Followed by Niraparib for Ovarian, Primary Peritoneal and Fallopian Tube Cancer	HOTT	3	Not yet recruiting	Cisplatin (100 mg/m^2)	Epithelial	PFS	230	2023–09

Note: Information retrieved from clinicaltrials.gov (3 December 2023).

Abbreviations: AEs-adverse events, CC-completeness of cytoreduction, CRS-cytoreductive surgery, DFS-disease-free survival, HGSOC-high grade serous ovarian cancer, NACT-neoadjuvant chemotherapy, OS- overall survival, PFI- progression-free interval, PFS-progression-free survival, PR-partial response, QoL-quality of life, RFS-recurrence-free survival, SD-stable disease.

Table 5
Ongoing randomized trials evaluating HIPEC in ROC.

NCT Number	Study Title	Acronym	Phase	Study Status	Drug and dose	Subtype	Primary Outcome Measures	Enrollment	Start Date
NCT01376752	Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment	CHIPOR	3	Active, not recruiting	Cisplatin (75 mg/m^2)	Epithelial	OS	415	2011–04
NCT01539785	Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence (HORSE)	HORSE	3	Publication pending	Cisplatin (75 mg/m^2)	Epithelial	PFI	158	2012–09
NCT03220932	Cytoreductive Surgery and HIPEC in First or Secondary Platinum-resistant Recurrent Ovarian Epithelial Cancer (HIPOVA-01)	HIPOVA-01	3	Recruiting	Cisplatin (70 mg/m^2)	Epithelial	PFS	132	2019–11
NCT05316181	HIPEC for Platinum-Resistant Recurrent Ovarian Cancer	KOV-HIPEC-02	3	Recruiting	Doxorubicin (35 mg/m^2), Mitomycin (15 mg/m^2)	Epithelial	PFS	140	2022–04

Note: Information retrieved from clinicaltrials.gov (3 December 2023).
Abbreviations: OS- overall survival, PFI- progression-free interval, PFS-progression-free survival.

Table 6
Ongoing randomized trials evaluating HIPEC in both primary and recurrent OC.

NCT Number	Study Title	Acronym	Phase	Study Status	Drug and dose	Subtype	Primary Outcome Measures	Enrollment	Start Date
NCT02567253	Intraoperative Intraperitoneal Chemoperfusion to Treat Peritoneal Minimal Residual Disease in Stage III Ovarian Cancer	OvIP1	2	Completed	Cisplatin (100 versus 75 mg/m^2)	Epithelial	Tissue penetration distance of cisplatin	56	2016–03
NCT02681432	Hyperthermic Intraperitoneal Chemotherapy with Paclitaxel in Advanced Ovarian Cancer (hipecova)	HIPECOVA	3	Publication pending	Paclitaxel (175 mg/m^2)	Epithelial	OS	60	2012–01
NCT03371693	Cytoreductive Surgery (CRS) Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) With Lobaplatin in Advanced and Recurrent Epithelial Ovarian Cancer (HIPECOV)	HIPECOV	3	Active, not recruiting	Lobaplatin (30 mg/m^2)	Epithelial	OS	112	2017–09
NCT04473339	A Randomized Prospective Trail of HIPEC in Recurrent Ovarian Cancer Patients with HRR Mutation	–	3	Recruiting	Lobaplatin (30 mg/m^2)	Epithelial	PFS	280	2020–08

Note: Information retrieved from clinicaltrials.gov (3 Decemmber 2023).
Abbreviations: OS- overall survival, PFS-progression-free survival.

upfront surgery and post-surgical treatment for recurrent diseases, comparing its efficacy to adjuvant intraperitoneal CTH, examining the potential adverse effects of hyperthermia on the body, determining the ideal healthcare setting required for HIPEC procedures, and exploring the utilization of biomarkers to identify suitable patients who would benefit from HIPEC. Future research endeavors should place priority on examining mechanisms and identifying therapeutic strategies with the objective of extending efficacy, potentially through the targeting of immune surveillance. The effectiveness of HIPEC appears to be primarily impacted by the engagement of the immune system. A research study designed to examine the role of the immune system in HIPEC would serve as a preliminary measure in comprehending the mechanistic benefits of HIPEC, thereby promoting its translation into clinical practice.

High-quality prospective data that have been recently published suggest that the application of HIPEC may benefit survival of patients with OC, although the efficacy may depend on the specific setting. The introduction of HIPEC in conjunction with primary CRS have no significant influence on either OS or DFS. However, the incorporation of HIPEC alongside interval CRS, followed by systemic CTH, markedly enhances both OS and DFS. The most recent data also substantiates effectiveness of HIPEC in ROC, resulting in an improvement of survival outcomes.

To conclude, there is unquestionably a place for HIPEC in the management of patients with POC and ROC. Further research will aid in refining the HIPEC regimen and technique, as well as in accurately identifying the patients who will derive the maximum benefit from this treatment approach. It would be desirable to discuss and update (inter) national clinical recommendations for the treatment of patients with advanced OC with peritoneal involvement.

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Tomasz Ostrowski: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jakub Litwiński:** Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Katarzyna Gęca:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Izabela Świetlicka:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. **Wojciech P. Polkowski:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Magdalena Skórzewska:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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