HIPEC for gynaecological malignancies: A last update (Review)

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Received November 22, 2022; Accepted April 24, 2023

DOI: 10.3892/mi.2023.85

Abstract. Advanced-stage gynaecological cancer represents a clinical entity with challenging surgical treatment in an effort to optimize prognosis. Hyperthermic intraperitoneal chemotherapy (HIPEC) following cytoreductive surgery (CRS) has been reported as a method potentially eligible to improve prognosis. However, no definitive conclusions have yet been made on which types of cancer and which context HIPEC may actually have a beneficial impact. The present review discusses the efficacy and safety of HIPEC as a treatment option for patients with primary/recurrent ovarian, endometrial and cervix cancer, as well as peritoneal sarcomatosis. A literature search was conducted using MeSH terms for each topic in the PubMed database and supplemented with a manual search to retrieve additional articles eligible for inclusion/fulfilling the inclusion criteria. The implementation of HIPEC appears to be beneficial in terms of survival in patients with epithelial ovarian carcinoma (EOC) following neoadjuvant chemotherapy, as well as in patients with recurrent EOC. Statistical superiority is not justified by current studies regarding other gynaecological malignancies with peritoneal dissemination. Furthermore, as regards safety, HIPEC following CRS does not appear to significantly increase the mortality and morbidity rates compared to the use of CRS alone. The rationale for using HIPEC and CRS in the treatment of ovarian cancer, particularly in the neoadjuvant setting, as well as for recurrences, is adequately evidenced, with acceptable safety and post-operative complication rate profiles. Its current place in the multimodal strategy for patients with peritoneal metastases remains uncertain, however. Randomized clinical trials are warranted to further examine the use of HIPEC and establish the optimal regimen and temperature settings. The role of optimal cytoreduction and no residual disease, as well as the proper patient selection remain basic parameters for maximizing survival parameters.

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Key words: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, ovarian cancer, endometrium cancer, cervix cancer, peritoneal sarcomatosis, gynaecological malignancies, update

Contents

1. Introduction

The possibility of developing peritoneal metastases (PM) is increased in patients with malignancies of the digestive system or gynaecological cancer. The treatment of PM has changed significantly over the past years; therefore, colorectal malignancies, appendicular malignancies, mesotheliomas and primary ovarian cancer are currently being managed with improved survival outcomes (1). Hyperthermic intraperitoneal chemotherapy (HIPEC) following cytoreductive surgery (CRS) has been a method gaining increasing interest in the context of the treatment of peritoneal malignancy over the past years. HIPEC involves the administration of anticancer drugs directly into the abdominal cavity for peritoneal lesions, as well as intraperitoneal administration, accompanied by heated chemotherapeutic agents that are administered immediately after cytoreduction. Based on some of the previously published evidence, HIPEC plus CRS is considered to offer a prognostic advantage for patients with primary peritoneal tumors or PM from colorectal, gastric and ovarian cancer (2-6). Nonetheless, HIPEC plus CRS has not yet been established as a standard of care. Furthermore,

in particular, as regards gynaecological malignancies, it remains a question whether HIPEC may be one of the novel therapeutic strategies for other gynaecological malignancies, such as endometrial and cervical cancer with peritoneal expansion, as well as peritoneal sarcomatosis. The lack of prospective studies and small sample sizes of already published articles have made it rather difficult to reach a definite consensus.

The present review summarizes the current evidence on the therapeutic role of HIPEC in various gynaecological malignancies, indicate those cancer types and settings in which HIPEC has an evidence-based beneficial impact. Furthermore, the present review highlights potential safety issues and concerns associated with the use of HIPEC, issues which remain to be answered by researchers.

2. Data collection methods

The present review presents a summary of the current literature, summarizing evidence retrieved from evidence dealing with the clinical impact of HIPEC regarding treatment of gynaecological malignancies, namely primary and recurrent ovarian cancer, endometrial cancer, cervical cancer and peritoneal sarcomatosis. A manual search was conducted using the PubMed and Scopus databases with the key phrases/key words, 'HIPEC AND ovarian cancer', 'HIPEC AND endometrial cancer', 'HIPEC AND cervical cancer', 'HIPEC AND peritoneal sarcomatosis'. Prospective randomized clinical trials (RCTs), prospective observational studies and meta-analyses written in the English language were set in the centre of interest for interpretation of their results. Retrospective studies, in the absence of higher-level evidence, were also considered for the purpose of the present review. Main survival outcomes set in the centre of interest were disease-free survival (DFS), overall survival (OS), overall recurrence and mortality. Furthermore, evidence of the safety of the methods was studied, specifically in the rate of complications, mainly 3 and 4, according to the Clavien-Dildo (CD) classification, as well as overall morbidity through the emergence of post-operative complications (POCs), in an effort to examine whether HIPEC significantly increases their incidence and thereafter evaluate their impact on overall survival parameters.

3. Primary ovarian cancer

Over the years, various trials have been conducted in an attempt to clarify the role of HIPEC in addition to CRS for the treatment of advanced ovarian cancer as regards both the primary and neoadjuvant setting. According to the current literature, HIPEC can be used at the time of first-line therapy, i.e., at the time of primary CRS (upfront CRS and HIPEC), or at the time of interval CRS, which is performed following neoadjuvant chemotherapy (interval CRS and HIPEC), but cannot be considered as a standard of care. Moreover, HIPEC can be used along with CRS performed as second-line therapy, in patients who have had suboptimal surgery followed by chemotherapy and therefore, have residual disease (secondary CRS and HIPEC), or in patients who have recurred after complete response to first line therapy (salvage CRS and HIPEC) (7,8). Deraco *et al* (9) were the first to provide evidence suggesting that HIPEC following CRS may have auspicious results (that are at least comparable) for primary advance-stage ovarian cancer in terms of OS and progression-free survival (PFS) when compared to control populations of previously published trials (10-13). Lim *et al* (14), monitoring 184 women with stage III or IV primary advanced ovarian cancer that underwent primary or interval cytoreductive surgery with or without the addition of HIPEC, indicated no significant improvement in the rate of PFS or OS between the two groups as regards the overall population of patients. However, when performing a sub-analysis separately for primary cytoreduction surgery and for interval debulking surgery, they indicated that in the neoadjuvant-treatment group, HIPEC + CRS led to a significant improvement in PFS compared with only CRS (14). Consistent with these data were the findings of van Driel *et al* (15) and Antonio *et al* (16), demonstrating that the addition of HIPEC to the interval CRS in patients with advanced ovarian cancer treated with neoadjuvant chemotherapy significantly improved DFS (by 3.5 and 6 months, respectively) and OS (by 11.8 and 7 months, respectively). Thereafter, even if the results for primary surgery are rather conflicting to support supremacy of HIPEC, there are still three RCTs firmly supporting the beneficial effects of HIPEC for patients with advanced-stage ovarian cancer (14-16).

As regards the safety of the method, HIPEC + CRS have been shown to be associated with a similar rate of grade 3 or 4 adverse events, along with lower disease recurrence or mortality rate compared to the surgery-only group, without negatively affecting the quality of life of patients and the incidence of POCs, while it was not identified as economically disadvantageous (17,18). Nonetheless, given the need for further research in this field, current clinical trials focus on assessing the potential superiority of this novel approach for epithelial ovarian carcinoma (EOC) in terms of efficacy, safety, treatment feasibility and quality of life (19).

It is evident that further research needs to be performed in this field. In this context, the study by Koole *et al* (20) attempted to determine the role of HIPEC by assigning 538 patients with FIGO stage III EOC to CRS with or without HIPEC. Likewise, the prospective multi-centre randomized trial, CHIPPI 1808 (19), which randomized 432 patients with stage III EOC, aimed to assess the potential superiority of the addition of HIPEC on the efficacy, safety, treatment feasibility, and patient quality of life.

However, based on the findings of already published trials, HIPEC plus CRS appears to have a beneficial effect on the survival outcomes of patients with advanced-stage ovarian cancer following neoadjuvant chemotherapy; however, the question remains regarding whether it is beneficial following primary cytoreduction surgery. Table I represents the main outcomes of studies dealing with the role of HIPEC in the treatment of primary ovarian cancer. A point worth mentioning, is that apart from the study by Deraco *et al* (9), which was a prospective study analysing the treatment of only one group of patients, the other three studies are similarly designed (14-16). They are prospective randomized trials comparing arms, where cisplatin is used and mainly NACH is followed by either CRS plus HIPEC or CRS alone.

4. Recurrent ovarian cancer

Recurrent ovarian cancer often represents a challenging clinical entity, where various treatment modalities need to be individualized in an effort to optimize patient survival outcomes. HIPEC

Table I. Main studies and the comparative outcomes of studies comparing the effects of HIPEC in the treatment of EOC.

Study	Deraco *et al* (9)	van Driel *et al* (15)	Lim *et al* (14)	Antonio *et al* (16)
Type of study	Prospective, multicenter phase 2 trial	Prospective, multicenter, randomized phase 3 trial	Prospective, multicenter, randomized trial	Prospective, single-center, randomized phase 3 trial
Publication year	2011	2018	2022	2022
Inclusion criteria	Patients with stage III/IV epithelial ovarian cancer (EOC) with advanced peritoneal involvement	Patients with International Federation of Gynecology and Obstetrics stage III ovarian, fallopian tube, or peritoneal cancer	Patients with International Federation of Gynecology and Obstetrics stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube cancer	Patients with a diagnosis of carcinomatosis from ovarian cancer treated with neoadjuvant systemic chemotherapy
No. of patients	26	245	184	71
HIPEC temperature	42.5˚C	40˚C	41.5˚C	42˚C
Method (open/closed)	Closed	Open	Closed	Open
Chemotherapeutic agents	Cisplatin (40 mg/l) + doxorubicin (15 mg/l) for 90 min	Cisplatin (100 mg/m^2, flow rate of 1 l/min)	Cisplatin (75 mg/m^2) for 60 min	Cisplatin (75 mg/m^2) for 60 min
Arms	1 arm (CRS + HIPEC)	CRS + HIPEC (122 patients) vs. CRS (123 patients)	CRS + HIPEC (92 patients) vs. CRS (92 patients)	CRS + HIPEC (35 patients) vs. CRS (36 patients)
Median DFS	30 months	14.2 vs. 10.7 months	17.4 vs. 15.4 months (P=0.04) (neoadjuvant setting) 23.9 vs. 29.7 months (primary cytoreductive surgery setting)	18 vs. 12 months
Median OS	Not reached	45.7 vs. 33.9 months	61.8 vs. 48.2 months (P=0.04) (neoadjuvant setting) 71.3 months control group (primary cytoreductive surgery setting)	52 vs. 45 months
Core outcomes				
3-year OS	NA	62% (95% CI, 54 to 72) vs. 48% (95% CI, 39 to 58)	-	-
5-year OS	60.7%	-	-	45 vs. 25%
3-year DFS	NA	17% (95% CI, 11 to 26) vs. 8% (95% CI, 4 to 16)	-	-
5-year DFS	15.2%	-	-	31 vs. 23%
Disease recurrence	-	81 vs. 89% (P=0.003)	77.2 vs. 80.4%	69% overall
Mortality	3%			47.9 % overall
Grade III and IV complications	15%	27 vs. 25% (P=0.76)	93.5 vs. 87%	27 vs. 27%
Quality of life	NA	No significant differences	-	No significant differences and stable during monitoring

HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; EOC, epithelial ovarian cancer; OS, overall survival; DFS, disease-free survival.

has also been proposed as an alternative modality of treatment combined with secondary CRS and followed by systematic chemotherapy. Spiliotis *et al* (21) presented the first phase 3 randomized controlled trial of 120 patients. The results indicated that both the mean OS (26.7 vs. 13.4 months, P=0.006) and 3-year OS (75 vs. 18%, P<0.01) were significantly improved following CRS and HIPEC vs. surgery alone. That study also highlighted that optimal cytoreduction appears to be an independent prognostic factor for OS. Furthermore, in the HIPEC group, a similar mean OS was achieved for both platinum-sensitive and platinum-resistant disease, which may lead to the conclusion that the addition of HIPEC rather eliminated the detrimental effect of platinum resistance (21). By contrast, a more recent randomized phase II trial by Zivanovic *et al* (22) did not demonstrate any comparative advantage of HIPEC plus CRS vs. CRS only as regards OS and DFS. Based on a 'pick-the-winner' design, an arm would be considered superior if at least 17 out of 49 patients were without progression at 24 months follow-up, which was accomplished in none of the arms.

Thereafter, as there are two prospective studies (21,22) with conflicting outcomes, no definitive conclusions may be deduced on the effects of HIPEC on recurrent ovarian cancer. The outcomes of aforementioned ongoing trials may also contribute to reaching conclusions in the field of research in recurrent ovarian cancer as well. HIPEC remains an experimental therapy with potential harm, and should only be offered in the context of well-designed, prospective RCTs, since the feasibility and the efficacy as a second-line treatment have yet to be established. Table II presents the main outcomes of studies comparing the effects of HIPEC in the treatment of recurrent EOC, as they arise from two prospective randomized studies, where different chemotherapeutic agent regimens are used and disparate arms in between are compared, since in one study in the treatment of all patients was included the systematic CH.

5. Endometrial cancer

Endometrial cancer is the most common female pelvic malignancies, with an incidence rate of 4% (23). Nonetheless, the survival outcomes of patients with endometrial cancer and PM warrant improvement. Tempfer *et al* (24), in a recent systematic review, identified 68 women from eight articles with EC-derived PM that underwent CRS and HIPEC as a therapeutic strategy, the majority of which (46/patients) also received post-operative systemic chemotherapy. At the time of the surgery, the peritoneal carcinomatosis index (PCI) was 16.7 and a macroscopically complete cytoreduction (CC)-0 was achieved in 44/63 (70%) of the patients. The analysis concluded that the median DFS and OS times ranged from 7 to 18 months and from 12 to 33 months, respectively. Of note, the percentage of treatment-associated mortality was 1% (1/63), while adverse events of grade 3 and 4 were observed in 18/63 (28%) patients (24). Despite the fact that these data are not comparative, they rather indicate that HIPEC may be a safe and effective option for advanced-stage endometrial cancer with PM; however, no evidence from prospective studies comparing CRS + HIPEC vs. only CRS is yet available to support beneficial impact of HIPEC in such patients.

Of note, another more recent multi-institutional study performed on 60 patients with peritoneal progression of EC reported no significant advantage from the combination of HIPEC plus CRS on the examined parameters of DFS and OS compared with CRS monotherapy (25). Nonetheless, that study was limited by its retrospective nature and by the fact that in the 'CRS plus HIPEC' group, 96.7% of women were treated for recurrence, whereas in the 'CRS only' group, 83.3% were treated for primary disease.

In conclusion, the combination of CRS and HIPEC for advanced-stage EC with PM has been proposed as having promising outcomes, constituting a safe and feasible approach with an acceptable morbidity and mortality rate. However, to date, there is no evidence supporting a beneficial effect of HIPEC addition to standard treatment; therefore, prospective comparative clinical trials are warranted to further explore this potential. Table III represents the main outcomes of studies dealing with the efficacy of HIPEC in the treatment of advanced-stage EC. The disparities between the two studies, need to be taken into consideration, with the one being a systematic review reporting only patients undergoing CRS plus HIPEC and in some cases accompanied by systematic chemotherapy, and the other being a retrospective non-randomized study comparing two different treatment strategies (24,25).

6. Peritoneal sarcomatosis

While the role of CRS plus HIPEC in peritoneal carcinomatosis has been well-documented, its utility in peritoneal sarcomatosis remains unproven. The applications of CRS and HIPEC were analysed by a recent meta-analysis by Wong *et al* (26), in which 16 studies with 320 women were included. The mean PCI was 11.8 and 79.3% out of 256 subjects who achieved CC-0 cytoreduction. Furthermore, that study reported that these techniques managed to significantly increase the median OS, compared to the conventional treatments, in which the prognosis is still reported to be poor (median survival ranging from 13 to 18 months) (27,28). According to that study (26), the overall pooled median OS was 29.3 months (95% CI, 23.8-34.8), with a 5-year OS of 35.3% (95% CI, 26.3-44.8), the median DFS was 12.0 months (95% CI, 8.0-16.0) and the 5-year DFS was 21.8% (95% CI, 13.2-31.7). Of note, the subgroup analysis resulted in a pooled median OS of 33.5 months for leiomyosarcomas and 39.1 months for liposarcomas, indicating the discrepant response between the various histological subtypes. In addition, patients with CC-0 cytoreduction had a higher median OS of 34.6 months (95% CI: 23.2-45.9), suggesting once more that the maximal cytoreduction is a favourable prognostic marker. The percentage of severe complications (grade ≥3) was 17.4% (95% CI: 9.8-26.3).

In summary, HIPEC appears to be an effective therapeutic alternative for selected patients with PS and a low tumour burden. However, a safe conclusion cannot be drawn, since the majority of the studies were retrospective single arm studies, while the rarity of the disease often led to compromised the sample size. Therefore, further studies involving a direct comparison between HIPEC, CRS and conventional treatments are required to comprehensively assess the effects of this method.

7. Cervical cancer

Cases of cervical cancer involving the recurrence of peritoneal carcinomatosis remain limited. Recently, the effects

Table II. Main studies and the comparative outcomes of studies comparing the effects of HIPEC in the treatment of recurrent EOC.

Study	Spiliotis *et al* (21)	Zivanovic *et al* (22)
Type of study	Prospective, multicenter, randomized phase 3 trial	Prospective, multicenter, randomized phase 2 trial
Publication year	2015	2022
Inclusion criteria	Patients with stage IIIc/IV EOC with disease recurrence after initial treatment with CRS or debulking surgery and systemic chemotherapy	Patients with first recurrence of high-grade epithelial ovarian cancer platinum-sensitive epithelial ovarian cancer undergoing secondary cytoreduction/first recurrence of high-grade epithelial ovarian cancer
No of patients	120	98
HIPEC temp	42.5˚C	41-43˚C
Method (open/closed)	40 Patients open 20 Patients closed	Closed
Chemotherapeutic agents	Cisplatin (100 mg/m^2) + paclitaxel (175 mg/m^2) for 60 min (platinum-sensitive disease, n=34) doxorubicin (35 mg/m^2) + paclitaxel (175 mg/m^2) or mitomycin (15 mg/m^2) for 60 min (platinum-resistant disease, n=26)	Carboplatin (800 mg/m^2) for 90 mins
Arms	CRS+HIPEC +CH (60 patients) vs. CRS +CH (60 patients)	CRS+HIPEC (49 patients) vs. CRS (50 patients)
Median DFS	-	12.3 vs. 15.7 months
Median OS	26.7 vs. 13.4 months (P=0.006)	52.5 vs. 59.7 months
Core outcomes	-	-
3-years OS	75 vs. 18% (P<0.01)	-
5-year OS	-	-
3-year DFS	-	-
5-year DFS	-	-
Disease recurrence	-	-
Mortality	-	38%
Grade III and IV complications	-	12 vs. 10% (P=0.81)
Quality of life	-	-

HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; CH, chemotherapy; EOC, epithelial ovarian cancer; OS, overall survival; DFS, disease-free survival.

of HIPEC plus CRS f or such patients were analysed by Duzgun and Kalin (29). They performed a retrospective analysis including 10 cases of women who underwent HIPEC plus CRS following the occurrence of intraabdominal metastases. The mean average of the PCI score was 12.3 (range, 7-36) and the mean average of completeness of cytoreduction score was 1 in 2 patients and 0 in 8 patients. During the first 30 days post-operatively no mortality was recorded, while grade 3 complications were reported in 5 cases (50%). In the early period of 3 years post-operatively, 4 patients succumbed at 2, 5, 6 and 12 months, respectively. Based on the findings of that study, no definite consensus can be made on whether there is any sign of benefit in advanced-stage cervical cancer with PM, both due to high complication rate and the short-expected OS in the early period in patients at this stage of the disease. Furthermore, Lantsman *et al* (30) published their results on 2 cases of recurrent cervical cancer with peritoneal carcinomatosis, in which HIPEC was implemented during debulking surgery. Notably, patients displayed a substantial DFS time of 15 and 24 months, respectively. In conclusion, there is no sufficient evidence regarding HIPEC implementation in cervical cancer patients with peritoneal recurrence. The published literature is rather limited and may offer inadequate evidence in terms of efficacy and safety. The

Table III. Main studies and the comparative outcomes of studies comparing the effects of HIPEC in the treatment of endometrial cancer.

Study	Tempfer *et al* (24)	Gomes David *et al* (25)
Type of study	Systematic review of literature	Retrospective, multi-center, non-randomized study
Publication year	2019	2021
Inclusion criteria	Patients with EC-derived PM undergoing CRS and HIPEC	Patients with peritoneal evolution of endomtrial cancer
No of patients	68 (8 Publications)	60
HIPEC temp		41-43˚C
Method (open/closed)	Closed (55/68 patients) Open (13/68 patients)	-
Chemotherapeutic agents	Cisplatin (39/68 patients) cisplatin + doxorubicin/paclitaxel/mitomycin (29/68 patients)	Cisplatin or doxorubicin or mitomycin (2 l/m^2) for 60 to 90 min
Arms	1 arm (CRS + HIPEC, 8 publications)	CRS+HIPEC (30 patients) vs. CRS (30 patients)
Median DFS	7-18 months	10.7 vs. 13.1 months (P=0.606)
Median OS	12-33 months	19.2 vs. 29.7 months (P 0.511)
Core outcomes		
3-years OS	-	-
5-year OS	-	-
3-year DFS	-	-
5-year DFS	-	-
Disease recurrence	-	-
Mortality	1%	No post-operative mortality
Grade III and IV complications	29%	20.7 vs. 20.7% (P=0.739)
Quality of life	-	-
Primary endpoint	Therapeutic efficacy of CRS in these patients	Benefit of CRS + HIPEC for the treatment of endometrial peritoneal carcinomatosis compared to CRS alone
PCI (P=0.702)	16.7	9.9 (7.5;12.2) vs. 10.0 (5.6;14.4)
CC-0	Was achieved in 44/63 (70%) patients	73.3% overall

HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; PCI, peritoneal carcinomatosis index; CC, complete cytoreduction; OS, overall survival; DFS, disease-free survival

only relevant evidence includes publications, both presenting retrospectively the implementation of HIPEC plus CRS in a very limited number of patients. However, HIPEC may be considered as an alternative for symptomatic patients with peritoneal recurrence when alternative treatment options are considered of poor effectiveness on an individualized basis.

8. HIPEC complications

A special concern about HIPEC implementation is considered to be the safety and risk for intraoperative and mostly POCs. Although the majority of the complications according to the CD classification may be attributed to CRS itself, the possibility that HIPEC increases the morbidity cannot be ruled out. In the study by van Driel *et al* (15), it was reported that in each group, >95% of the patients had a minimum of one adverse event of any grade until the last cycle of chemotherapy, although no significant difference was observed between the two groups. Additionally, as regards the incidence of grade 3 or 4 adverse events, both the control and intervention group presented comparable numbers (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P=0.76). Although the most common adverse events were abdominal pain, infection and ileus, an increased rate of infection, thromboembolic, pulmonary and electrolyte disturbance events were noted particularly in the HIPEC group. As for the rates of completion

of all three cycles of chemotherapy after surgery and the median total length of hospital admission, both values were also similar between the groups (15). In summary, according to recent literature, the addition of HIPEC is not associated with significantly higher rates of complications (24,25).

Interesting observations of POCs with HIPEC may be derived from the results published by US HIPEC Collaborative, even though this did not concern gynaecological malignancies, but HIPEC for appendiceal/colorectal disease (31). Gamboa *et al* (31) reported POCs of patients who underwent CCR0/1 surgery with CRS and HIPEC for appendiceal/colorectal cancer. As their analysis was stratified by non-invasive vs. invasive disease, they highlighted that complications were associated with a decreased OS and RFS for invasive histology, which was not the case for non-invasive neoplasms. Specifically, their study manifested that the presence of any POC was connected with a decreased 3-year OS (59 vs. 74%; P<0.001) and RFS (32 vs. 42%; P<0.001) for invasive appendiceal neoplasms. Of all types of adverse events, a substantially higher proportion was regarded as infectious complications in both types, which can further induce inflammatory responses that prolong the aforementioned pro-metastatic processes.

In conclusion, the combination of HIPEC plus CRS, when compared to traditional methods, does not have a significant effect on the incidence of POCs, type of grade 3 or 4 adverse events, safety and health-related quality-of-life outcomes. However, since POCs are associated with a decreased OS and RFS in certain groups of patients, further research is required targeting the optimal practices and standardized prevention strategies, alongside with proper patient selection.

9. Conclusions and future perspectives

Over the past few years, the use of HIPEC following CRS for the treatment of peritoneal malignancies has exhibited an increasing trend. HIPEC entails the intraperitoneal delivery of heated chemotherapeutic agents straight into the abdominal cavity for peritoneal lesions following cytoreduction. The heating of the abdominal cavity, in particular by maintaining the temperature at 41 to 43˚C, can itself have a direct antitumor effect, and it can enhance the antitumor effect and tissue migration of certain anticancer agents, such as cisplatin, mitomycin C and oxaliplatin. The team can choose to administer treatment for 60 to 90 min, either by open or close method one or a combination of the following agents: Cisplatin (40-100 mg/m^2), doxorubicin (35 mg/m^2), paclitaxel (175 mg/m^2), carboplatin (800 mg/m^2) or mitomycin (15 mg/m^2). To the best of our knowledge, HIPEC has been studied mainly as a first-line treatment for gynaecological malignancies and only for recurrent ovarian cancer as a second line-treatment in a wider range. This novel method has not been proven to be beneficial in appropriately designed prospective studies, with only a few case reports or case series reporting encouraging results regarding its role as a consolidation therapy, following the completion of first-line therapy of ovarian cancer, along with second-look surgery (consolidation CRS and HIPEC) or as a second-line treatment of gynaecological cancer and peritoneal carcinomatosis from gynaecological malignancies (8,30,32,33). In summary, there is sufficient evidence from three prospective RCTs that HIPEC has a beneficial effect in patients with advanced-stage ovarian cancer after neoadjuvant chemotherapy (14-16). Specifically, when compared with CRS alone, HIPEC provides an advantage in terms of OS and DFS, while rates of adverse events are comparable. There is also level-I evidence supporting the beneficial effect of HIPEC also for recurrence of ovarian cancer. However, as it is only one RCT supporting therapeutic supremacy and results are disputed by those of another prospective phase II trial, no definitive conclusion may be made and still research need to be performed. Existing evidence does not support the benefit of HIPEC addition to primary surgery for EOC. Furthermore, as regards peritoneal sarcomatosis, endometrial and cervical cancer, studies are not sufficient to support the benefit of this approach, even if results still appear promising. The addition of HIPEC is not significantly associated with higher rates of POCs. Cisplatin appears to be the chemotherapeutic agent of choice. Finally, of note, as is indicated by the publications on HIPEC, CC with no residual disease remains the main and mostly determining prognostic factor, particularly for patients with ovarian cancer. Thus, the key message may be that the addition of HIPEC to CRS may not be considered as a substitute of non-optimal surgery, but as a beneficial addition to optimize results following CC. Moreover, of paramount importance is the evaluation of a multidisciplinary approach regarding these types of malignancies. Over the course of the years, several studies have attempted to indicate the beneficial role of the multidisciplinary tumour boards (MTBs) (34). In a recent systematic literature review regarding multidisciplinary approach in cancer patients, the adherence to clinical guidelines and the improvement in patient outcomes was indicated, although it was often associated with an increase in expenditure costs and not always with a significant impact on the prognosis of patients (35). There are studies which have highlighted that the patient-cantered care approach improved the management and decision-making process, particularly in multifactorial malignancy types, such as ovarian cancer (36,37). When allocating the optimal treatment, the crucial factor becomes the selection criteria for each strategy, and to determine which group would be benefit from each treatment by individualizing the approach. In order for this to be accomplished, the multimodal tumour board consists of experts, who evaluate patients' characteristics and tumour behaviour. Defining the clinical criteria for different strategies and applying a structured algorithm may help maximize the overall outcome and minimize the overall treatment-related morbidity and mortality, particularly when patients are treated in specialized structures where multidisciplinary teams operate (36,37). Moreover, in the concept of personalized treatment, the most effect strategy to minimize heterogeneity is by an expert consensus that aims to identify and define a limited number of regimens for each indication and primary site. At this point, selections of the regimen can then be tailored to the patient profile and its expected toxicity and the methodology according regional factors (38). The analysis of the BRCA mutational status has allowed the first step into individualized strategies for the management of patients with ovarian cancer. A large number of BRCA1/2 mutations have been described over the years, and several of these are reliably known to increase cancer susceptibility (39). BRCA mutations confer various properties, including increased response to DNA-damaging agents such as platinum-based chemotherapy and poly-ADP-ribose polymerase (PARP) inhibitor. The treatment armamentarium

has recently been expanded by the addition of targeted therapies, including bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) and PARP inhibitors. These have recently been approved for the treatment of ovarian cancer, based on the findings of RCTs that demonstrated significant benefits in terms of progression-free survival, with acceptable tolerability and no negative effects on the quality of life. Olaparib, the first PARP inhibitor approved, is currently used as maintenance monotherapy in patients with ovarian cancer who have relapsed disease and a mutated BRCA gene, and have achieved a complete or partial response to platinum-based chemotherapy. As a result, determining the BRCA mutation status has become critical for therapeutic decisions (40,41). It would of interest if the efficacy of HIPEC could also be demonstrated in a large scale of selective patient groups stratified by the BRCA1/2 positive status. Although it is not extensively studied, there is some retrospective evidence that suggests a possible increase in efficacy in this population (42,43). As regards the addition of the anti-VEGF monoclonal antibody, bevacizumab, to the carboplatin-paclitaxel regimen, as reported in the ICON7 and GOG-0218 phase 3 studies, it remains the only treatment that has prolonged PFS (44,45). An innovative technique that is used to treat primary peritoneal malignancies, as well as carcinomatosis originating from various tumours is bidirectional intraoperative chemotherapy. It involves the intraoperative simultaneous administration of intravenous chemotherapy and HIPEC, immediately after CRS. This technique in combination with bevacizumab has been studied by Walker *et al* (46), comparing intravenous vs. intraperitoneal chemotherapy plus bevacizumab in advanced ovarian carcinoma; however, no statistically significant increase was reported in the duration of PFS with either regimen. Large multicentre well-designed RCTs are still required to explore all the spectrum of potential therapeutic usage of HIPEC to treat advanced-stage gynaecological cancer.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

CMS was a major contributor to the writing of the manuscript. CMS, AA, KD and SP were responsible for the collection of the relevant literature for inclusion in the review. AP, ASL, GM and FG revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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