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The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) as second-line debulking in advanced ovarian cancer patients. A meta-analysis

Abstract

Purpose: Ovarian cancer, as a type of gynecological cancer with one of the highest morbidity and recurrence rates, has been the burning issue for modern research. With new therapeutic methods coming to light, the focus on the promising Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has raised questions about its efficacy on patients' overall survival (OS) and post-surgical quality of life.

Methods: A meta-analysis was performed in order to estimate the role of HIPEC in advanced ovarian cancer, concentrating, among others, on the following quality of life.

After thorough research on the PubMed and Cochrane databases, using the terms 'HIPEC, ovarian cancer', as well as decoding the results on the last decade, a total of nine articles were selected for this purpose.

Results: Data decoding revealed a notorious improvement of OS of the cytoreductive surgery (CRS) plus HIPEC versus the CRS arm at 1, 3, 4 and 5 years respectively; (OR 1.10; 95% CI, 0.85-1.43), (OR 1.53; 95% CI, 1.12-2.10), (OR 1.70; 95% CI, 1.03-2.81), (OR 1.22; 95% CI, 0.77-1.95). At 2 years, the collected data depicted a small worsening in OS (OR 0.92; 95% CI, 0.70-1.19).

Conclusion: HIPEC, in spite of its recent innovative nature, has already given positive signs for ovarian cancer therapeutic mapping.

Objective of the conducted study focuses on investigating its reflection in advanced stages and recurrent ovarian cancer lesions, respectively.

Keywords: Hyperthermic Intraperitoneal Chemotherapy (HIPEC), Ovarian cancer (OC), peritoneal carcinomatosis, Cytoreductive Surgery (CRS), quality of life

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Introduction

Ovarian cancer represents worldwide a total of 239 000 cases annually, with death incidence estimated at about 152 000 deaths, depicting higher incidence rates in more developed areas.

It reflects the 5th most common cause of death among women, obtaining the 3rd most frequent type of gynecological malignancy after cervical and uterine cancer, despite its worst prognosis and highest mortality rate.[1,2]

Approximately 90% of ovarian cancers consist of carcinomas (malignant epithelial tumors),[3] which can be divided into following types, based on a plethora of molecular, cytological, histological, and clinic pathological factors:

i. High-grade serous carcinoma
ii. Endometrioid carcinoma
iii. Clear cell carcinoma
iv. Mucinous carcinoma
v. Low-grade serous carcinoma.[4]

Surgical and pathological staging of ovarian cancer follows the FIGO classification, last revised in 2014 (Table 1).[3]

Factors related to ovarian cancer occurrence can be categorized into predisposing and protective.

Predisposing risk factors can be divided into the following:

(i) Age
(ii) Menstrual-related factors
(iii) Family history
(iv) BRCA mutations.

On the contrary,

(i) Hormonal contraceptive methods, as well as
(ii) Lactation are associated with a protective role in developing ovarian cancer.[2]

More studies have proven the preventive role of either tubal ligation or salpingectomy, especially in women at average risk for developing ovarian malignancy, as abundant evidence suggests the fallopian tubes as the origin of high-grade ovarian cancer.[5]

Plenty of theories have attempted to shine a light on the pathogenesis of ovarian cancer. According to the suggested hypothesis (i) "incessant ovulation", repetitive ovulation causes small damage to the ovarian surface and the total of these recurrent lesions predisposes to malignant development. Factors associated with ovulation encompass inflammation, inclusion cyst formation, as well as steroid hormone effects in extremely high concentrations during each menstrual cycle.[5]

Table 1 Ovarian cancer classification (FIGO-Committee on Gynecologic Oncology)

Stage I	Tumor confined to ovaries or fallopian tube(s)	T1 N0 M0
	IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1a N0 M0
	IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tutor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1b N0 M0
	IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following: (1) surgical spill, (2) capsule rupture before surgery or tumor on ovarian or fallopian tube surface, (3) malignant cells in the ascites or peritoneal washings	T1c N0 M0
Stage II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	T2 N0 M0
	IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	T2a N0 M0
	IIB: Extension to other pelvic intraperitoneal tissues	T2b N0 M0
Stage III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T1/T2 N1 M0
	IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven): (i) metastasis up to 10mm in the greatest dimension, (ii) metastasis more than 10mm in the greatest dimension	T3a1 N0/N1 M0
	IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a2 N0/N1 M0
	IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b N0/N1 M0
	IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2cm in the greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	T3c N0/N1 M0
Stage IV	Distant metastasis excluding peritoneal metastases	Any T, any N, M1
	IVA: Pleural effusion with positive cytology	
	IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

Thus, other explanatory mechanisms are (ii) increased estrogen concentrations due to excess gonadotropin secretion, (iii) high androgen concentrations, and (iv) stromal hyperactivity.[6]

According to the recent bibliography, many conducted studies have attempted to establish a worldwide screening program in order to properly diagnose cases with potential ovarian cancer.

More precisely, possible combinations of cancer antigens such as Ca-125, accompanied by transvaginal ultrasound evaluation did not appear as expected, as the PLCO trial managed to achieve.[7]

Treatment algorithms could be divided into appropriate surgical and systemic approaches.

In cases of primary malignancy, optimal surgical intervention could be complete resection or achievable cytoreduction (less than 1 cm of residual disease), including total hysterectomy, bilateral salpingo-oophorectomy, total resection of the omentum, cytologic evaluation of the peritoneal cavity, pelvic and para-aortic lymph node resection. Such patients are scheduled to undergo primary debulking surgery.

On the contrary, in cases of advanced malignant lesions, optimal therapeutic mapping consists of neoadjuvant chemotherapy prior to surgery.

In case that interval debulking surgery is considered infeasible, platinum-based chemotherapy is indicated. Primary recurrences are stratified into being either platinum-sensitive or resistant.

In platinum-sensitive cases (platinum-free interval until relapse more than 6 months) a secondary cytoreductive surgery is considered in a fit for surgery patient, followed by platinum-based chemotherapy.

An alternative single-agent chemotherapy is administered in platinum-resistant recurrences (platinum-free interval until relapse less than 6 months). In secondary and further recurrences, among the possible options are tertiary cytoreductive surgery before chemotherapy with alternative regimens, participation in clinical trials, palliative systemic treatment, and best supportive care.[8]

A promising contemporary approach in the treatment of ovarian cancer, although not yet extensively practiced, appears to be Hyperthermic Intraperitoneal Chemotherapy or HIPEC.

It is defined as chemotherapy distributed intraperitoneal under conditions of elevated temperature. As a direct outcome of hyperthermia, maximized intracellular drug penetration and lowered resistance result from increased cytotoxicity of the used chemotherapeutic agents. Compared to intravenous administration of chemotherapy, its agent concentration is significantly higher during intraperitoneal delivery, by overcoming the peritoneal-plasma barrier.[9]

Detailed, hyperthermia promotes DNA repair impairment, induces apoptosis, inhibits angiogenesis, activates heat-shock proteins and promotes the denaturation of proteins.[10]

Optimal indications focusing on HIPEC treatment consist of cases with first recurrence, followed by treatment of second recurrence, consolidative treatment subsequent to treatment of primary disease or disease recurrence, as well as primary treatment.[9]

Contraindications include advanced patient age, aggravated comorbidities, malnutrition, associated extra-abdominal metastasis, and retroperitoneal bulk disease.[11] Postoperative outcomes of HIPEC include sepsis, anemia requiring transfusion, neutro- and thrombocytopenia, renal dysfunction, and wound infection.[9]

Material and methods

Search strategy

An assiduous analysis was performed throughout PubMed and Cochrane databases until March 2022, entering the terms

['Hyperthermic Intraperitoneal Chemotherapy' OR 'HIPEC'] AND [ovarian cancer].

The following search was restricted to the last decade and the language to English. A total of nine articles were selected (Table 2), based on the following inclusion criteria:

1) Patients with primary or recurrent ovarian cancer
2) Females who underwent CRS and HIPEC, with or without systemic chemotherapy
3) The compared arms were CRS plus HIPEC versus CRS, regardless of the administration of systemic chemotherapy.

Table 2 Objective and conclusions of the included studies

	Objective	Conclusion
Tsilimparis et al.[12]	Investigation of the course of health-related QOL over time in patients with peritoneal carcinomatosis after complete CRS and HIPEC.	Similar pre- and postoperative QOL, with most of the reduced elements recovering after 6-12 months.
Bakrin et al.[13]	Early and long-term survival assessment after CRP and HIPEC.	The combination of CRS and HIPEC should be considered in achieving long-term survival in patients with a severe prognosis disease.
Spiliotis et al.[14]	The use of HIPEC in addition to treatment of recurrent OC.	HIPEC addiction plays an important role in the patients' survival.
Baiocchi et al.[15]	Determining the prognostic value of the addition of HIPEC to secondary CRS in recurrent OC.	The addition of HIPEC does not improve survival.
Ba et al.[16]	Assessment of the efficacy of CRS and HIPEC for controlling malignant ascites from OC.	HIPEC is effective in controlling ascites in patients with OC.
van Driel et al.[10]	Investigation whether the addition of HIPEC to CRS would improve outcomes among patients who were receiving neoadjuvant chemotherapy for OC.	The addition of HIPEC to CRS resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.
Koole et al.[17]	Evaluating the impact of HIPEC on patients' health-related quality of life (HRQoL).	The addition of HIPEC to interval CRS does not negatively impact HRQoL.
Spiliotis et al.[18]	Evaluation of the perioperative outcomes and long-term survival of patients undergoing CRS and HIPEC.	The results indicate the feasibility of repeat CRS and HIPEC procedures in patients with significant morbidity, acceptable mortality, and long-term survival outcomes.
Marrelli et al.[19]	The efficacy of a new protocol with 6 cycles of neoadjuvant chemotherapy, CRS, and HIPEC.	A notable improvement in peritoneal carcinomatosis, limited postoperative morbidity risk and high survival rates in responders.

Exclusion criteria reflect patients with primary cancer types other than ovarian, patients not submitted to CRS, as well as women allergic to chemotherapeutic agents.

The aim of our study consists of depicting the overall survival of CRS and HIPEC compared to CRS alone.

Statistical analysis

Statistical analysis was performed using Graph Pad Prism 9 Software.

All statistical values were reported with 95% Confidence Intervals (CI), whereas statistically significant was interpreted as a p-value less than 0.05.

Further subgroup analyses were focused on parameters such as HIPEC regimen, temperature, duration and technique, cytoreduction completeness, primary or recurrent type of OC, median follow-up, as well as overall survival.

Results

Study selection and characteristics

Decoding all identified and assessed studies, nine were selected as suitable reflecting our objective.

Assiduous study characteristics are summarized in Table 3 followed by publication in the time frame between 2012 and 2021.

Table 3 Demographic characteristics of the included studies

Author	Tsilimparis et al.[12]	Bakrin et al.[13]	Spiliotis et al.[14]	Baiocchi et al.[15]	Ba et al.[16]	van Driel et al.[10]	Koole et al.[17]	Spiliotis et al.[18]	Marrelli et al.[19]
Year	2012	2013	2014	2015	2016	2018	2019	2020	2021
Country	Germany	France	Greece	Brazil	China	Netherlands, Belgium	Netherlands, Belgium	Greece	Italy
Duration (years)	5	11	8	14	5	9	9	15	7
Number of patients (HIPEC group/ non-HIPEC group)	90 (90/0)	566 (566/0)	120 (60/60)	79 (29/50)	53	245 (122/123)	245 (122/123)	48 (48/0)	56 (46/10)
Disease status (primary/recurrent)	NS	both (92/474)	recurrent	recurrent	both (38/15)	primary	NS	recurrent	primary
Stage according to FIGO	NS	NS	IIIc and IV	all stages	NS	III	III	NS	III
Mean age (years)	56	57.9	58.2	56.4	54.2	62	62	51	63

HIPEC, hyperthermic intraperitoneal chemotherapy; NS, not specified

Citation: Sofoudis C, Baltaga L, Delis S. The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) as second-line debulking in advanced ovarian cancer patients. A meta-analysis. *Obstet Gynecol Int J.* 2024;15(2):93–100. DOI: 10.15406/ogij.2024.15.00742

Mean studies duration was 9.2 years, patients' number was estimated to be about 166.9, following the mean number of patients per study that underwent HIPEC about 126.2 respectively.

Mean age of the studied population calculated about 57.9 years and follow-up was 48.6 months, respectively, not specified in the two studies.

Disease status, primary or recurrent, was not specified in two of the selected studies, two studies included only patients with primary disease, three studies only patients with recurrent disease, and two studies included patients of both disease statuses.

According to FIGO lesion staging was not specified in 4 studies, in four studies was classified as stage III or more advanced, while one study included patients of all stages.

Completeness of cytoreduction

Treatment arms included CRS in combination with HIPEC, versus only CRS. Adjuvant systemic chemotherapy in the HIPEC group was received by all of the patients in 5 studies, 51.2% and 28.3% in another two studies respectively, while 2 studies did not specify this information (Table 4).

Table 4 Clinical characteristics of Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Author	Tsilimparis et al.[12]	Bakrin et al.[13]	Spiliotis et al.[14]	Baiocchi et al.[15]	Ba et al.[16]	van Driel et al.[10]	Koole et al.[17]	Spiliotis et al.[18]	Marrelli et al.[19]
Treatment arms	CRS+HIPEC	CRS+HIPEC	CRS+HIPEC / CRS	CRS+HIPEC / CRS	CRS+HIPEC / HIPEC+dCRS	CRS+HIPEC / CRS	CRS+HIPEC / CRS	CRS+HIPEC	CRS+HIPEC
Adjuvant systemic chemotherapy (HIPEC group)	51.2% (n=46)	28.3% (n=160)	100% (n=120)	100% (n=79)	NS	100% (n=245)	100% (n=245)	NS	100% (n=56)
Cytoreduction completeness	82% (n=74)	74.9% (n=423)	60% (n=72)	77.9% (n=60)	88.7% (n=47)	55.5% (n=136)	68% (n=166)	72.9% (n=35)	51.8% (n=29)
HIPEC technique (open/ closed)	NS	68.4% (n=387) / 31.6% (n=179)	66.7% (n=40) / 33.3% (n=20)	closed	64.2% (n=34) / 35.8% (n=19)	open	open	closed	closed
HIPEC regimen	NS	Cis, Dox, Oxa, Mit, Cis+Mit, Cis+Dox	Cis+Pac, Dox+ (Pac/Mit)	Mit+Cis, Cis+Dox, Cis, Oxa	Doc+Cis	Cis	Car+Pac	Cis+Pac	Mit+Cis
HIPEC temperature °C	NS	42	42.5	41.5	42	40	NS	42.5	41.5
HIPEC duration (mins)	NS	90	60	90	90	120	120	60	60
Median follow-up (months)	36	40	NS	49.6	48	56.4	NS	38	72
Mean survival (months) (HIPEC group/ non-HIPEC group)	NS	40.6	26.7 / 13.4	58.3 / 59.3	33.8	45.7 / 33.9	NS	37	NS

HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; cCRS delayed cytoreductive surgery; NS, non specified; Car, Carboplatin; Cis, Cisplatin; Doc, Docetaxel; Dox, Doxorubicin; Mit, Mitomycin; Oxa, Oxaliplatin; Pac, Paclitaxel

Cytoreduction completeness in the current study was defined as no macroscopic residual disease. Mean cytoreduction completeness was achieved in 70.2% of the patients.

HIPEC regimens

HIPEC technique was exclusively open in two studies, exclusively closed in three studies, combined in three studies, and not specified in one.

That suggests that out of 1046 patients that received HIPEC in the studies specifying the technique, 67.4% (n=705) underwent an open and 32.6% (n=341) a closed one.

As far as the HIPEC regimens were concerned, most frequent reference was to the combination of Cisplatin Mitomycin (3 references), followed by Carboplatin Paclitaxel, Cisplatin, Cisplatin Doxorubicin, Cisplatin Paclitaxel, Oxaliplatin (2 references each), as well as Cisplatin Docetaxel, Doxorubicin, Doxorubicin (Paclitaxel/ Mitomycin), Mitomycin (1 reference each) (Figure 1).

Mean temperature estimated about 41.7°C, whereas not specified in two studies. Additionally, mean HIPEC duration was calculated about 86.3mins (not specified in one study).

Overall survival

Data decoding revealed a notorious improvement of OS of the CRS plus HIPEC versus the CRS arm at 1, 3, 4 and 5 years respectively; (OR 1.10; 95% CI, 0.85-1.43) (Figure 2), (OR 1.53; 95% CI, 1.12-2.10) (Figure 4), (OR 1.70; 95% CI, 1.03-2.81) (Figure 5), (OR 1.22; 95% CI, 0.77-1.95) (Figure 6). At 2 years, the collected data depicted a small worsening in OS (OR 0.92; 95% CI, 0.70-1.19) (Figure 3).

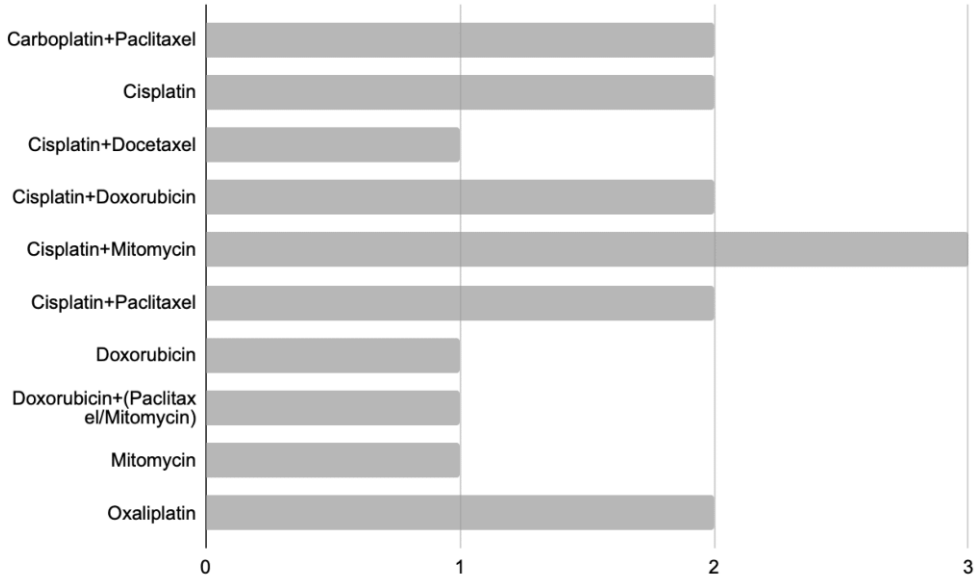

Figure 1 Number of references of HIPEC regimens.

	HIPEC		non-HIPEC				
Study	Events	Total	Events	Total	Odds Ratio	Upper 95%CI	Lower 95%CI
Tsilimparis et al. (2012)	79	90	0	0	NA	NA	NA
Bakrin et al. (2013)	487	566	0	0	NA	NA	NA
Spiliotis et al. (2014)	57	60	46	60	1.239130435	2.101348385	0.7306947507
Baiocchi et al. (2015)	25	29	43	50	1.002405774	1.963912697	0.511640531
Ba et al. (2016)	NS	53	0	0	NA	NA	NA
van Driel et al. (2018)	108	122	103	123	1.05713831	1.527739193	0.731500122
Koole et al. (2019)	NS	122	NS	123	NA	NA	NA
Spiliotis et al. (2020)	NS	48	0	0	NA	NA	NA
Marrelli et al. (2021)	42	46	7	10	1.304347826	3.73702678	0.455261188

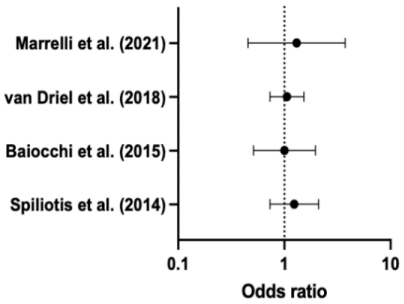

Figure 2 One-year OS forest plot.

NA: non-applicable.

	HIPEC		non-HIPEC				
Study	Events	Total	Events	Total	Odds Ratio	Upper 95%CI	Lower 95%CI
Tsilimparis et al. (2012)	70	90	0	0	NA	NA	NA
Bakrin et al.(2013)	NS	566	0	0	NA	NA	NA
Spiliotis et al. (2014)	54	60	42	60	1.285714286	2.204375045	0.7499001717
Baiocchi et al. (2015)	24	29	37	50	1.118359739	2.224994741	0.5621264998
Ba et al. (2016)	NS	53	0	0	NA	NA	NA
van Driel et al. (2018)	79	122	70	123	1.137822014	1.710571795	0.7568457162
Koole et al. (2019)	NS	122	NS	123	NA	NA	NA
Spiliotis et al. (2020)	NS	48	0	0	NA	NA	NA
Marrelli et al. (2021)	36	46	3	10	2.608695652	10.18385784	0.6682431268

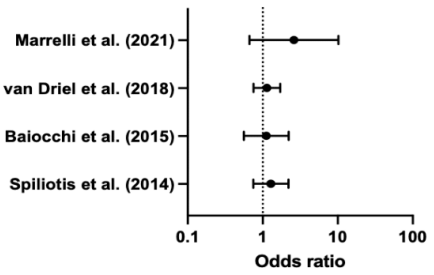

Figure 3 Two-year OS forest plot.

	HIPEC		non-HIPEC				
Study	Events	Total	Events	Total	Odds Ratio	Upper 95%CI	Lower 95%CI
Tsilimparis et al. (2012)	63	90	0	0	NA	NA	NA
Bakrin et al. (2013)	300	566	0	0	NA	NA	NA
Spiliotis et al. (2014)	45	60	11	60	4.090909091	8.661370214	1.932204348
Baiocchi et al. (2015)	23	29	35	50	1.133004926	2.275210931	0.5642114957
Ba et al. (2016)	NS	53	0	0	NA	NA	NA
van Driel et al. (2018)	56	122	44	123	1.283159463	2.048083306	0.8039215026
Koole et al. (2019)	NS	122	NS	123	NA	NA	NA
Spiliotis et al. (2020)	NS	48	0	0	NA	NA	NA
Marrelli et al. (2021)	25	46	2	10	2.717391304	13.38427346	0.5517083557

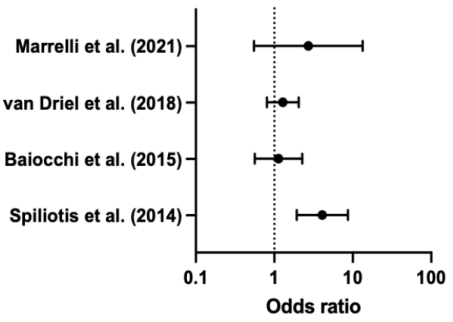

Figure 4 Three-year OS forest plot.

Citation: Sofoudis C, Baltaga L, Delis S. The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) as second-line debulking in advanced ovarian cancer patients. A meta-analysis. *Obstet Gynecol Int J.* 2024;15(2):93–100. DOI: 10.15406/ogij.2024.15.00742

	HIPEC		non-HIPEC				
Study	Events	Total	Events	Total	Odds Ratio	Upper 95%CI	Lower 95%CI
Tsilimparis et al. (2012)	NS	90	0	0	NA	NA	NA
Bakrin et al. (2013)	NS	566	0	0	NA	NA	NA
Spiliotis et al. (2014)	NS	60	NS	60	NA	NA	NA
Baiocchi et al. (2015)	NS	29	NS	50	NA	NA	NA
Ba et al. (2016)	NS	53	0	0	NA	NA	NA
van Driel et al. (2018)	37	122	27	123	1.381602914	2.408414645	0.7925656061
Koole et al. (2019)	NS	122	NS	123	NA	NA	NA
Spiliotis et al. (2020)	NS	48	0	0	NA	NA	NA
Marrelli et al. (2021)	23	46	1	10	5	41.47805667	0.6027283342

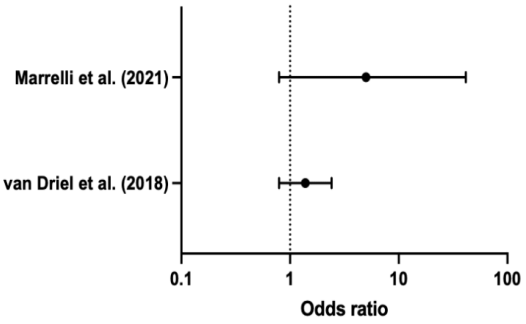

Figure 5 Four-year OS forest plot.

	HIPEC		non-HIPEC				
Study	Events	Total	Events	Total	Odds Ratio	Upper 95%CI	Lower 95%CI
Tsilimparis et al. (2012)	NS	90	0	0	NA	NA	NA
Bakrin et al. (2013)	153	566	0	0	NA	NA	NA
Spiliotis et al. (2014) [37]	42	60	0	60	NA	NA	NA
Baiocchi et al. (2015) [37]	14	29	25	50	0.9655172414	2.145258558	0.4345506699
Ba et al. (2016)	NS	53	0	0	NA	NA	NA
van Driel et al. (2018)	20	122	12	123	1.680327869	3.586702325	0.7872138503
Koole et al. (2019)	NS	122	NS	123	NA	NA	NA
Spiliotis et al. (2020)	NS	48	0	0	NA	NA	NA
Marrelli et al. (2021)	16	46	1	10	3.47826087	29.35486685	0.41213945

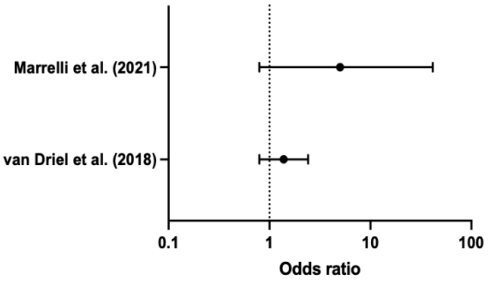

Figure 6 Five-year OS forest plot.

Discussion

There is no doubt that in the last decades HIPEC has emerged as a promising interventional tool in ovarian cancer management.

Thus, the current study has focused on HIPEC's efficacy regarding overall survival of affected patients, as well as their postoperative quality of life, based on nine recent studies with a statistically significant group population.

The performed analysis has shown that the addition of HIPEC to sole CRS leads to encouraging results regarding the clinical outcome, specifically the overall survival, without significant postoperative morbidity and mortality.

This outcome does not diminish the need of additional clinical data through new large-population trials, with the purpose of further extensive assessment of HIPEC's effectiveness along with its short- and long term side effects.

Furthermore, upcoming studies should be ideally designed to overcome limitations of the ones included in the current article, such as

(i) Wide heterogeneity in subgroup characteristics (malignancy stage, race, completeness of cytoreduction, type of HIPEC technique, initial physical state and performance, systemic chemotherapy drug),

(ii) Reduced number of studied population,

(iii) Diversity of included cancer types, apart from ovarian,

(iv) Different statistical baseline, perplexing data extraction and comparison.

Another imperative question requiring answers through further research is that of managing patients currently deemed unsuitable for undergoing HIPEC, such as those with extensive comorbidities, cardiovascular disease, severe respiratory impairment and renal failure, to state a few.

Similarly, patients with either severe allergic reaction to the chemotherapeutic agents or intolerability of their side effects require alternative treatment methods.

Finally, studies have shown that the incompleteness of surgical cytoreduction does not necessarily provide fertile ground for HIPEC implementation in terms of survival.[20]

Firstly, introduced to the academic world in 1980 thanks to Spratt's clinical research on animal models,[21] HIPEC has extensively evolved ever since.

There are currently 242 conducted studies including the term HIPEC, 59 of which refer specifically to ovarian cancer. A significant increase in the use of HIPEC for ovarian cancer has been documented in the US after the publication of the phase III study by van Driel et al. in 2018.[10,22]

Currently, Switzerland leads worldwide concerning the number of specialized HIPEC centers (1.792 per 1 million inhabitants), followed by Belgium (0.881) and Germany (0.726).[23]

According to the same medical database, Greece accounts for 0.186 HIPEC centers per 1 million inhabitants.[23]

A survey conducted in 2020 depicts the tendency of 467 oncologists in implementing HIPEC in ovarian cancer patients. Only 50% of the participant's view positively the use of HIPEC in interval debulking surgery, while the number rises to 68% as far as the utility of HIPEC in ovarian cancer recurrence is concerned.[24]

Confirming recent findings, there is increasing evidence that the overall survival in patients with ovarian cancer is positively affected following HIPEC administration.

Ziying et al. report a median OS by 15.8 months longer in the HIPEC subgroup, while the recurrence-free survival in the same group exceeded by 3.5 months.[25]

Le Brun et al. reveal a substantial difference in OS at 4 years in the HIPEC versus the non-HIPEC arm (75.6% vs 19.4%).[26]

Riggs et al. discloses a difference of 13.3 months in the OS (26.7 months in the HIPEC arm vs 13.4 months in the non-HIPEC arm). The same manuscript accentuates the importance of cytoreduction on OS (30.9 months after complete cytoreduction, with survival dropping to less than 12.1 months in remaining tumor deposits between 2.5mm and 1.2cm).[27] This data is in line with our results.

However, an assiduous depiction of current bibliography including 1450 patients revealed no apparent advantage of HIPEC in terms of survival outcomes.[28]

Quality of life, although substantially affected directly post-HIPEC, seems to be recovered after 6-12 months for most of the reduced elements.[29]

According to Steffens et al.[30] mental components score remains unchanged, while the physical one returns to baseline within 6 months.[30]

Hill et al.[31] depicted emotional improvement of well-being despite the short-term complications in the HIPEC subgroup.[31]

These findings are strongly suggestive of an acceptable correlation between HIPEC and quality of life mitigation.

Another point worth further research consists of the HIPEC response of ovarian cancer patients, according to their BRCA-mutation profile. The superiority of BRCA carriers regarding a more favorable outcome has been widely accepted, based on high quality data. However, this prognostic factor does not seem to be validated in cases of intraperitoneal chemotherapy.[32]

Since intraperitoneal chemotherapy effects are enhanced at temperatures above 40°C, a critical threshold for the overall and progression-free survival, it is crucial to maintain the average temperature above this limit for the whole duration of HIPEC.[33]

On the other hand, uncontrolled hyperthermia can cause harmful local and systemic effects.[34]

Moreover, newer pharmaceutical regimens are needed for a better nephroprotective effect, as currently mostly sodium thiosulphate is used to prevent nephrotoxicity caused by intraperitoneal chemotherapy agents.[10]

Likewise, more data needs to be provided on the difference on HIPEC effectiveness delivered either by the open or the closed method, as the latter provides a more aesthetically acceptable result, whose importance should not be omitted in the affected patients' population. All the above advocate for the need for future development of better HIPEC methods and technological means.

According to current bibliography, a vital and most controversial issue remains the correlation of fertility and childbirth in female patients undergoing HIPEC.

Spontaneous pregnancies and vaginal births have been reported in women after fertility preservation undergoing intraperitoneal chemotherapy.[35]

Unfortunately, limited data have been conducted concerning number of female patients undergoing fertility preservation methods after cytoreduction in combination with HIPEC.[36]

Thus, the need for an extended preoperative guidance concerning fertility options such as oocyte cryopreservation remains mandatory.[37]

Conclusion

Combination of cytoreductive surgery and HIPEC seems to be affecting substantially overall survival of ovarian cancer patients, without diminishing their long-term quality of life.

Per contra, extensive research and clinical data must be conducted in order to establish this innovative technique's limitations and replace them with better methodologies and outcomes.

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Author contribution

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Conflicts of interest

All authors declare any financial interest with respect to this manuscript.

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