HIPEC in Ovarian Cancer: When and to Whom?

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ABSTRACT

Objective: To evaluate the optimal candidates for hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer.

Study Design: Descriptive study.

Place and Duration of the Study: Health Sciences University, Dr. Abdurrahman Yurtasian Ankara Oncology Training and Research Hospital, Ankara, Turkey, between 2013 and 2021.

Methodology: Ovarian cancer patients who underwent HIPEC and CRS for peritoneal involvement were included in this study. Thermosolutions were prepared as a closed system by using HT 2000 hyperthermic perfusion device. Then, cisplatin was applied at 100 mg/m^2 at 42-42.5 °C for 60 minutes after CRS.

Results: A total of 47 patients were enrolled. The median age was 54 years (27-80) at the time of diagnosis. Forty (85.1%) patients had high grade serous carcinoma and 22 (46.7%) patients had clinical stage 3C disease. The median peritoneal cancer index (PCI) was 13 (3-24) in the whole population. HIPEC was applied as first-line treatment in 25 (51%) patients. Eleven (23.4%) patients had HIPEC in the post-neoadjuvant interval whereas 10 (21.3%) patients had it in platinum sensitive relapse. Median progression free survival (PFS) was 31(95% CI:11-50), 33 (95% CI:1-67), and 18 (95% CI:8-27) months in the primary, post-neoadjuvant interval, and platinum-sensitive relapse HIPEC groups, respectively. The patients with lower PCI (PCI<13) had significantly better OS than others with higher PCI (PCI≥13, 145 months *versus* 42 months, p=0.034).

Conclusion: HIPEC with CRS should be considered in selected serous carcinoma patients with peritoneal involvement, especially for the patients with primary ovarian cancer with lower PCI (PCI<13).

Key Words: *Ovarian cancer, HIPEC, Peritoneal cancer index.*

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INTRODUCTION

Ovarian cancer is the second most common gynaecological malignancy all around the world.[1] Due to insidious growth and the late symptomatic nature of ovarian cancers, 60% of patients have advanced disease at diagnosis.[2] Peritoneal carcinomatosis is present in approximately 75% of patients with advanced stage ovarian cancer. It has the highest mortality rate among all gynaecological cancer types. Despite all treatment modalities, 5-year overall survival is below 30%.[1] The most significant prognostic factor is residual disease. Neoadjuvant treatment modalities may contribute to a decrease in the risk of residual disease, to have better survival outcomes in Stage 3 and 4 disease.

Despite advances in systemic therapy in advanced stage ovarian cancer, the relapse rate is around 70%. Peritoneum is the most common site for relapse.

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Intraperitoneal chemotherapy increases the medicine delivery at the peritoneal surface and eliminates possible residual peritoneal micrometastases more effectively than systemic chemotherapy. Albert *et al.* compared intraperitoneal and intravenous chemotherapy.[3] A total of 654 patients were randomised to either IV cisplatin or IP cisplatin arms with 6 cycles of IV cyclophosphamide after optimal surgery. Median OS was higher in the IP arm (49 months *vs.* 41 months; p=0.02, HR=0.76). A survival benefit was reported in three randomised trials and a meta-analysis.[4] However, the recurrence rate was 65% and DFS was only five months. In addition, the patient compliance was suboptimal due to the high rate of toxicity and the need for catheters.[5]

Hyperthermic intraperitoneal chemotherapy (HIPEC) aims to destroy the remaining microscopic residual tumour during optimal cytoreductive surgery.[6,7] Hyperthermia is directly cytotoxic *via* disruption of the cells' microtubule system and protein structure, and it works synergistically with commonly used chemotherapy agents, such as cisplatin, paclitaxel, oxaliplatin, doxorubicin, and mitomycin C.[8] In addition, hyperthermia has been shown to overcome platinum resistance mechanisms.[9] It increases the penetration of chemotherapy to the peritoneal surface, impairs DNA repair by increasing chemosensitivity, induces apoptosis, and activates heat shock proteins that act as

receptors for NK cells, inhibits angiogenesis, and exerts a direct cytotoxic effect by promoting denaturation of proteins.[10] The blood peritoneal barrier limits the systemic absorption of the chemotherapy agent, thus causing less side effects when compared to the systemic chemotherapy.

Peritoneal cancer index (PCI) is an indicator of disease extent, and it is used as a prognostic and predictive tool for the efficacy of CRS and HIPEC. The Sugar Baker Score Index is more commonly used.[11] In this scoring index, the abdomen is divided into 9 regions and the small intestines into 4 regions. These regions are scored according to the implantation load (0-3 points). The residual disease is defined by complete cytoreduction (CC), scored as CC-0 (no residue), CC-1 (residue <2.5mm), CC-2 (residue 2.5 mm - 2.5 cm) and CC-3 (residue >2.5 cm). The aim of this study was to evaluate optimal candidates for HIPEC and CRS in ovarian cancer.

METHODOLOGY

Patients diagnosed with Stage 3-4 ovarian cancer and who followed up in Oncology Training and Research Hospital were retrospectively reviewed. Patients with peritoneal involvement and older than 18 years of age, who underwent CRS and HIPEC, were included. Patients with diffuse metastatis were excluded. The study had an approval from the ethics committe (2020-12/911). A total of 47 patients were included in the study between 2013-21. Thermo-Solutions were prepared as a closed system by using HT 2000 hyperthermic perfusion device. Then, cisplatin (100 mg/m^2) was applied at 42-42.5 C for 60 minutes after CRS. Most (n=39) of the patients had cisplatin (100 mg/m^2) monotherapy, others were administered combination chemotherapy during HIPEC. Four patients had cisplatin (100 mg/m^2) and paclitaxel (175 mg/m^2), and the remaining patients (n=4) had cisplatin (100 mg/m^2) and mitomycin (15 mg/m^2), respectively.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 25, SPSS, Inc, Chicago, IL). The standard descriptive statistics were used to characterise the sample data set. Numerical data that did not conform to the normal distribution were expressed as the median and interquartile range of values. Progression free survival (PFS), and overall survival (OS) of the groups were calculated by the Kaplan–Meier method, and the log-rank test was used to compare survival rates. A p-value <0.05 was accepted as statistically significant.

RESULTS

The median age was 54 (27-80) years. While 36 (76.6%) patients had primary ovarian cancer, 11(23.4%) patients originated from the primary serous surfaces (Table I). Forty (85.1%) patients had high-grade serous carcinoma and 22 (46.7%) were diagnosed with stage 3C disease. A significant percentage of patients (72.3%) were high-graded. In total, 19 (40.4%) patients received neoadjuvant chemotherapy. Median PCI was 13 (3-24). The rate of patients with CC-0 was 59%.

Table I: Patients and tumour characteristics.

	Ovarian cancer
N	47
Median age at diagnosis	54 (27-80)
Diagnosis FIGO stage	
Evre3a	13 (27.7%)
Evre3b	4 (8.5%)
Evre3c	22 (46.7%)
Evre4a	1 (2.1%)
Evre4b	1 (2.1%)
Tumour Location	
Ovarian	36 (76.6%)
Primary serous surfaces	11 (23.4%)
Neoadjuvant chemotherapy	
Yes	19 (40.4%)
No	27 (57.4%)
Pathology	
High-grade serous	40 (85.1%)
Low-grade serous	1 (2.1%)
Endometroid	2 (4.3%)
Mucinous	1 (2.1%)
Clear cell	1 (2.1%)
Undifferenced carcinoma	1 (2.1%)
Unknown	1 (2.1%)
PCI	13 (3-24)
HIPEC	
Primer CRS and HİPEC	25 (51%)
Post neoadjuvant interval	11 (23.4%)
Platinum sensitive recurrence	10 (21.3%)
Platinum resistant recurrence	1 (2.1%)
Neoadjuvant chemotherapy cure	
2 cycles	1 (2.1%)
3 cycles	13 (27.7%)
4 cycles	3 (6.4%)
6 cycles	3 (6.4%)
Complete cytoreduction (CC score-%)	
CC 0	59.6 (n:28)
CC 1	17 (8)
CC 2	14.9

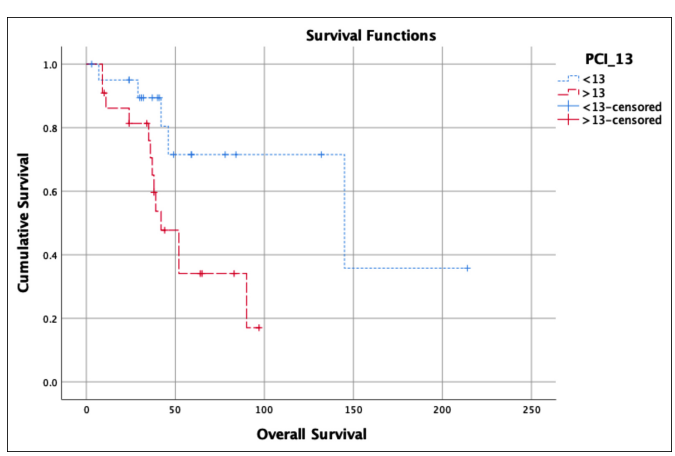

Figure 1: Survival curve according to PCI 13.

HIPEC was applied after primary CRS in 25 (51%) patients, while it was applied in the post-neoadjuvant interval (*i.e.* between neoadjuvant and adjuvant chemotherapy) in 11 (23.4%) patients. HIPEC rate was 21.3% (n=10) in platinum sensitive relapse and 1 patient in platinum resistant relapse. Table II shows the patient characteristics according to the HIPEC groups. All patients received additional systemic chemotherapy after HIPEC.

Table II: Patient characteristics by HIPEC groups.

	HIPEC; After primary CRS (n=25)	HIPEC; Post-neoadjuvant interval (n=11)	HIPEC; Platinum sensitive recurrence (n=10)	HIPEC; Platinum resistant recurrence (n=1)
Pathology				
High-grade serous	20 (80%)	11 (100%)	9 (90%)	1 (100%)
Mucinous	1 (4%)		1 (10%)	
Endometroid	2 (8%)			
Low-grade serous	1 (4%)			
Undifferenced carcinoma	1 (4%)			
Figo stage				
Stage 3a	7 (28%)	5 (45.%)	1 (10%)	
Stage 3b	2 (8%)	1 (9%)	1 (10%)	
Stage 3c	13 (52%)	4 (36%)	5 (50%)	1 (100%)
Stage 4a	1 (4%)	1 (9%)		
Tumour origin				
Ovarian	22 (88%)	6 (55%)	8 (80%)	1 (100%)
Primary serous surfaces	3 (12%)	5 (45%)	2 (20%)	
Complete cytoreduction (CC score-%)				
CC-0	14 (56%)	10 (91%)	4 (40%)	
CC-1	5 (20%)	1 (9%)	1(10%)	
CC-2	4 (16%)		3 (30%)	1 (100%)
Median PCI	12(4-24)	12 (3-21)	18 (5-20)	

Table III: Toxicity of CRS and HIPEC.

	HIPEC; After primary CRS (n=25)	HIPEC; Post-neoadjuvant interval (n=11)	HIPEC; Platinum sensitive recurrence (n=10)	HIPEC; Platinum resistant recurrence (n=1)
Acute renal failure				
Grade 1-2	%24(6)	-	-	-
Grade 3-4	%4(1)			
Hepatic liver function increase				
Grade 1-2	%16(4)	-	%10 (1)	-
Grade 3-4	%12 (3)	%9(1)	-	
Leukocytosis				
Grade1-2	%48(12)	%45(5)	%20(2)	-
Grade 3-4	-	-	-	
Anaemia				
Grade1-2	%52(13)	%72(8)	%30(3)	-
Grade 3-4	%24(6)	%9(1)	-	
Thrombocytopenia				
Grade 1-2	%4(1)	%18(2)	-	-
Grade 3-4	-	-		
Hypoalbuminaemia				
Grade 1-2	%68(17)	%72(8)	%40(4)	-
Grade 3-4	%16(4)	%9(1)	-	
CK increase	%12 (3)	-	%20(2)	-
Hypokalaemia	%16 (4)	%36(4)	-	-

All patients with platinum-sensitive or platinum-resistant relapse had almost systemic chemotherapy after HIPEC. Median PFS was 29 (95% CI 14-43) months. In subgroup analysis, median PFS was 33 months for the patients with lower PCI (<13) and 26 months for others with higher PCI (≥13, p=0.281). Median OS was 90 (95% CI 34-144) months for the whole population. While it was 145 months in lower PCI (<13) subgroup, it was 42 months in higher PCI (≥13) subgroup, as well (p = 0.023, Figure 1). In addition, median PFS of the patients who underwent primary CRS & HIPEC were as 31 (95% CI 11-50) months. Median OS was estimated 52 months in the primary HIPEC group. Platinum-sensitive relapsed ones had median PFS and OS as 18 (95% CI 8-27) months and 42 (95% CI:6-77) months, respectively. While the median PFS was 33 (95% CI 15-50.9) months in those who underwent interval HIPEC. Median OS could not have been estimated because of the immature data. There was no significant difference for OS between CRS and HIPEC administration as *'primary'* or *'at platinum sensitive relapse'* (52 months *versus* 42 months, p = 0.705). Table III shows side effect patterns according to the timing of CRS and HIPEC. The most common side effects were nephrotoxicity (*i.e.* acute renal failure, electrolyte imbalance), hepatotoxicity (*i.e.* increased transaminases), haematological toxicity (*i.e.* anaemia, thrombocytopenia).

DISCUSSION

Cytoreductive surgery and HIPEC administration in ovarian cancer is still controversial. First, trials evaluated the efficacy of CRS and HIPEC in both platinum-sensitive and platinum-refractory relapsed ovarian cancer patients. Then, interval HIPEC administration trials were reported in the literature. Currently, the role of HIPEC after *'primary'* CRS is being investigated in ongoing trials. In the present study, a major decrease in the progression risk was achieved by *'interval'* HIPEC administration. Additionally, median OS could not have been reached in this subgroup, while it was 52 months in the *'primary'* CRS and HIPEC group. In a prospective randomised phase 3 study by Spiliotis *et al*., 120 patients with stage 3C-4 platinum-sensitive and platinum-resistant relapsed ovarian cancer were randomised to two arms as CRS and CRS with HIPEC.[12] After CRS in one arm, HIPEC was applied to the other arm with CRS. Half of the patients had PCI >10. Cisplatin 100 mg/m^2-paclitaxel 175 mg/m^2 combination was administered as HIPEC in the platinum-sensitive relapsed subgroup, and paclitaxel 175 mg/m^2-mitomycin 15 mg/m^2 combination in the platinum-resistant relapsed subgroup. An addition of HIPEC to CRS increased OS significantly (p<0.01). Median OS was 26.7 *vs.* 13.4 months, favouring the arm with HIPEC. It was almost significantly higher for platinum-sensitive relapsed ones. Median OS was 26.8 months in CRS and HIPEC arms, while it was 15.2 months in only CRS arm (p=0.035).[13] However, there was no significant OS difference for platinum-resistant ones (26.6 months *vs.* 26.8 months). The present survival data is in parallel to the literature, especially for platinum-sensitive relapsed ones by supporting these similar outcomes. Bakrin *et al*. evaluated the role of HIPEC (open or closed method) in recurrent ovarian cancer.[13] In this multicentric trial, most of the patients were administered cisplatin alone or in combination with doxorubicin or mitomycin C at 44-46°C for 90 minutes. In this study, HIPEC was applied with the closed method. Most patients received cisplatin 100 mg/m^2 as HIPEC. Median OS was 90 months for all patients in this study. Survival outcomes of the patients were comparable, almost better than the reported ones in the literature. Bakrin *et al.* reported median OS as 48.9 months in the whole population. Platinum-sensitive relapsed subgroup had numerically longer OS, as expected. It was 52 months for platinum-sensitive relapsed and 48 months for the platinum-resistant subgroups, 1-year, 3-year, and 5-year OS rates were reported as 86%, 60%, and 35%, respectively. Baiocchi *et al.* reported similar OS rates for both platinum-sensitive and platinum-resistant relapsed ovarian cancer patients with HIPEC.[6] HIPEC did not also differ for PFS.

In a Korean study by Lim *et al*., HIPEC was applied with a lower dose of cisplatin (75 mg/m^2 for 90 minutes at 41.5 degrees) to stage 3-4 recurrent ovarian cancer patients after '*primary*' or '*interval*' CRS. Despite the lower dose, there was no difference for relapse-free survival or OS.[14] HIPEC arm had more toxicity rates, especially for anaemia and creatinine increase. Acute renal failure and transaminase elevation were among common side effects in the study, and cisplatin dose was 100 mg/m^2.

Cascales-Campos *et al*. performed HIPEC with paclitaxel 60 mg/m^2 in stage 3-4 ovarian cancer. Fifty-six percent of the patients had '*interval*' HIPEC with a median OS as 52 months.[15] In the presented study, median OS could not have been calculated for interval HIPEC subgroup yet. The median PFS was 33 months for these patients.

In another study, interval CRS and HIPEC was performed in stage 3 ovarian cancer patients who responded to neoadjuvant chemotherapy.[16] In this study, patients were administered cisplatin at 100 mg/m2 at 40°C for 90 minutes during HIPEC. There was 4 months of PFS and OS benefit of HIPEC. Median values for PFS and OS were as 14.2 months *versus* 10.7 months (p=0.003, HR=0.66) and 45.7 months *versus* 33.9 months (p=0.02, HR=0.67).

The major limitations of this study are heterogenous patient population with smaller number of patients in subgroups besides its retrospective design and nonuniform chemotherapy applications (*i.e*. regimen, dose) during HIPEC. In conclusion, an early administration of CRS and HIPEC is encouraging. However, it may increase morbidity, in terms of relatively higher but manageable side effects and prolongation of postoperative recovery period leading to delays in starting the standard treatment. Therefore, CRS and HIPEC should not be considered as first-line treatment approach.

CONCLUSION

HIPEC with CRS should be considered in the selected serous carcinoma patients with peritoneal involvement, especially for the patients with primary ovarian cancer with lower PCI (PCI <13).

ETHICAL APPROVAL:
An ethical approval was obtained from the Health Sciences University, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital's Ethical Committee with decision No. 2019-03/240.

PATIENTS' CONSENT:
Patients' consent was waived as this study was conducted retrospectively.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
BA, MHA, IO, CY, MD: Conception and design of the research,

analysis and interpretation of data, and drafting of the manuscript.
OA: Performed the statistical analysis and participated in data acquisition.
All authors have approved the final version of the manuscript to be published.

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