

A Retrospective Clinical Analysis of Hyperthermic Intraperitoneal Chemotherapy in Gynecological Cancers: Technical Details, Tolerability, and Efficacy

Jinekolojik Kanserlerde Hipertermik İntraperitoneal Kemoterapinin Retrospektif Olarak Değerlendirilmesi: Teknik Detay, Tolerabilitesi ve Etkinliği

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ABSTRACT

Objective: The aim of this study was to reveal the results of hyperthermic intraperitoneal chemotherapy (HIPEC procedure) performed during cytoreductive surgery (CRS) in patients with endometrial cancer and epithelial ovarian cancer which included mainly platinum-resistant patients.

Method: Patients who underwent CRS+HIPEC between May 2015 and January 2020 were evaluated retrospectively. Surgical complications were graded according to the Clavien-Dindo classification.

Results: A total of 33 CRS+HIPEC procedures were performed in 32 patients, two of whom had recurrent endometrial cancer. Of the 30 patients with epithelial ovarian cancer (EOC), five underwent interval CRS+HIPEC, and remaining 25 patients underwent secondary CRS+HIPEC treatment due to relapsed disease. Eighteen of the patients with relapsed disease were platinum-resistant. The overall operative mortality and severe morbidity rates were %3 and 12%, respectively. For 30 patients with EOC, during a median follow-up period of 15 months, Kaplan-Meier survival analysis revealed a 1-year OS and PFS rates of 69.7% and 30.3%, respectively. Moreover, in the subgroup analysis of the platinum-resistant cohort, median OS and PFS were 14 and five months, respectively.

Conclusion: CRS+HIPEC procedures had acceptable severe morbidity and mortality rates. In addition, patients with recurrent EOC and without a visible residual disease at the end of cytoreductive surgery had, though not statistically significant, longer OS. HIPEC administration during CRS was not associated with adverse outcomes in the platinum-resistant EOC cohort. The short-term results of the current study are promising.

Keywords: Cytoreductive surgery, endometrial cancer, hyperthermic intraperitoneal chemotherapy, ovarian cancer

ÖZ

Amaç: Bu çalışmanın amacı, ağırlıklı olarak platine dirençli hastalardan oluşan epitelyal over kanserli ve endometriyal kanserli hastalarda sitoredüktif cerrahi (SRC) esnasında yapılan HIPEK işleminin sonuçlarını ortaya koymaktır.

Yöntem: Mayıs 2015-Ocak 2020 arasında SRC sonrası HIPEK uygulanan hastaların bilgileri retrospektif olarak değerlendirildi. Cerrahi komplikasyonlar, Clavien-Dindo sınıflamasına göre sınıflandırıldı.

Bulgular: 32 hastaya SRC+HIPEK uygulandı. Tedavinin uygulandığı hastalardan 2 tanesi endometriyum kanseriydi. Epitelyal over kanseri olan 30 hastanın 5 tanesine interval SRC+HIPEK yapıldı. Nüks epitelyal over kanseri olan 25 hastaya ise sekonder SRC+HIPEK uygulandı. Nüks epitelyal over kanserli 18 hasta platine dirençliydi. Retrospektif olarak operasyona bağlı mortalite %3 ve ciddi morbidite %12 olarak saptandı Epitelyal over kanseri olan 30 hastanın ortalama takip süresi 15 ay idi. Kaplan-Meier sağkalım 1 istatistik testine göre 1 yıllık toplam sağkalım %69 ve hastaliksız sağkalım %30.3 olarak hesaplandı.

Sonuç: SRC+HIPEK prosedürünün kabul edilebilir ciddi morbidite ve mortalite oranları vardır. Öte yandan, tam sitoredüktif cerrahi geçiren nüks epitelyal over kanserli hastaların genel sağkalımlarının sayısal olarak daha uzun olduğu ancak bunun istatistiksel olarak anlamlı olmadığı görülmüştür. SRC esnasında HIPEK uygulaması, platine dirençli epitelyal over kanseri kohortunda olumsuz sonuçlarla ilişkili bulunmamıştır. Mevcut çalışmanın kısa dönem sonuçları umut vericidir.

Anahtar kelimeler: Sitoredüktif cerrahi, endometriyal kanser, hipertermik intraperitoneal kemoterapi, over kanseri

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal type of gynecological cancer and accounts for approximately 50% of the related deaths. Serous adenocarcinoma is the most common histological subtype. Approximately 90% of the patients are diagnosed with the disease spread outside the ovaries (Stage II-IV) with a poor prognosis. In advanced stage EOC, tumor spreads from the lower pelvis to the upper abdomen by invading the peritoneal surfaces. Majority of advanced stage EOC patients die within three years after establishment of diagnosis due to disease progression that causes diffuse tumoral mass occupying the abdominopelvic cavity¹. On the other hand, endometrial cancer is the most common gynecological cancer in the developed countries. The most common histopathological type in endometrial cancer is the endometrioid subtype, followed by the serous subtype. Although serous endometrial cancer is the histological type which constitutes approximately 10% of endometrial cancer, it has the worst prognosis, similar to those with serous histology of ovarian origin. Furthermore, two-thirds of the patients with serous histological subtype have a cancer spread outside the uterus at the time of diagnosis. Accordingly, the natural course of the serous endometrial cancer is also similar to EOC.

The standard treatment approach in both EOC and endometrial cancer patients with serous histology is the surgical removal of all visible lesions in the abdominopelvic cavity followed by the administration of systemic chemotherapy. The term 'Cytoreductive Surgery' (CRS), first described by Sugarbaker, includes a series of organ resection and peritonectomy procedures. It aims to remove organs and peritoneal surfaces infiltrated with tumoral tissue without leaving any visible lesions in the abdominopelvic cavity². Thus, via systemic platinum-based chemotherapy, it is aimed to achieve the 'microscopic cytoreduction of the remaining tumor. However, 80% of women with ad-

vanced disease EOC will recur despite the appropriate treatment approach mentioned above^{3,4}.

Platinum resistance in EOC is a well-defined clinical entity with worse survival defined as the development of relapse within the first six months after the end of systemic platinum-based chemotherapy⁵. Overall survival (OS) in the presence of platinum-resistant disease is approximately 12 months, and progression-free survival (PFS) is three months⁶. In the case of recurrence after first-line therapy, response to platinum is seen in less than 10% of platinum-resistant patients and second-line chemotherapeutic agents are preferred⁷. There is no benefit for the secondary CRS in platinum-resistant patients and surgery is often performed for palliative purposes in recurrent cases. Few clinical studies and case reports have been published about the treatment of recurrent platinum-resistant cases. While these articles cannot go further than the experimental stage; therapeutic strategies including targeted agents such as bevacizumab, olaparib, cediranib, immunotherapeutic agents such as atesolizumab, and hyperthermic procedures have drawn attention⁸⁻¹¹.

Intraperitoneal administration of chemotherapeutic agents heated to 41-43°C during surgery is termed as hyperthermic intraperitoneal chemotherapy (HIPEC). Hyperthermia triggers the cascade that causes activation of heat shock proteins and folding of intracellular proteins, ultimately inducing apoptosis. In addition, hyperthermia enhances the penetration of chemotherapeutics into the peritoneal surface. On the other side, via intraperitoneal administration, both possibility of reaching all peritoneal surfaces and high drug concentrations are achieved in the peritoneal cavity with low plasma drug concentrations, thus reducing the risk of systemic toxicity. Consequently, intraperitoneal administration of hyperthermic chemotherapy has some advantages and synergistic effects but there is limited data on use of HIPEC in gynecological cancers¹².

The aim of our study was to reveal the results of CRS+HIPEC treatment in recurrent endometrial cancer and EOC which included mainly platinum-resistant patients.

MATERIAL and METHODS

Thirty-two patients who were hospitalized in the Gynecological Oncology Clinic of Istanbul University Faculty of Medicine, between May 2015 and January 2020 were included in the study. The study design was based on retrospective data analysis, all cases were diagnosed with a cancer of gynecologic origin and CRS with HIPEC was administrated to all patients. Peritonectomy was performed according to the technique described by Sugarbaker². HIPEC treatment was approved by the ethics committee of Istanbul University Faculty of Medicine (EC number:280 date:203/2020), informed and signed consents were obtained from the patients after detailed explanation of possible postoperative complications of CRS and HIPEC procedures. Peritoneal Cancer Index (PCI) scoring system was used to quantify the extent of disease at the beginning of the surgery¹³. At the end of CRS, completeness of cytoreduction score (CCS) was recorded according to the Sugarbaker's classification¹⁴. In addition, result of the surgery was considered as complete CRS when all visible disease was completely resected, and also presence of maximal residual disease with less than 10 mm in diameter was considered as optimal CRS. HIPEC was administrated immediately after CRS using a heat exchange perfusion machine with closed technique and the procedure was initiated after abdominal closure. Mitomycin C (13 mg/m²) and cisplatin (75 mg/m²) were administered as chemotherapeutic agents through four separate surgical drains at a rate of 1000 cc/min. The procedure was started after intraperitoneal temperature measured by the abdominal sensor reached 42°C and the intraperitoneal temperature was maintained at 42°C - 43°C for 60 minutes. Complications were recorded according to the Clavien-Dindo classification (grade 1: mild through

grade 5: death), and surgical mortality was defined as death of any cause within 30 days after surgery¹⁵. All operations were performed by the experienced gynecological oncology team in our clinic. Between May 2015 and December 2017, HIPEC was only administered to recurrent cases of endometrial cancer and EOC. Since January 2018, patients with the primary EOC who received neoadjuvant systemic chemotherapy (NACT) underwent interval cytoreductive surgery with the administration of HIPEC according to the consensus of the multi-disciplinary oncology council and the patient's approval. Clinical examination, measurement of CA125 level and radiological imaging (CT scan or MRI if needed) were performed every three months for two years, then every six months. The diagnosis of recurrence was made according to the radiographic findings or tissue biopsy. Patients diagnosed with relapse were evaluated by the council. As a rule, the decision of the administration of HIPEC was made based on the consensus of the council before surgery. The primary endpoint of the study was the rate of severe morbidity and mortality, and the secondary one was OS which was defined as the time from the date of diagnosis to death of any cause and PFS which was calculated from the date of diagnosis to the date of progression, recurrence or death.

Statistical analysis was performed using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). Categorical data were given in numbers (n) and percentages (%). Quantitative data were given as median and range. Survival analysis and curves were established according to the Kaplan-Meier method and compared with using the log-rank test. Multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model, and p values less than or equal to 0.05 were considered as significant. Post-hoc power calculation was also carried out.

RESULTS

Thirty-two patients who underwent CRS+HIPEC in our clinic were evaluated. The median age was 59 (range: 33-74) years, and 79% of the patients were 50 years or older. Our cohort consisted of 30 patients with EOC and two patients with en-

dometrial cancer. Five of the patients who had been newly diagnosed with EOC underwent interval cytoreductive surgery+HIPEC after NACT. The remaining 25 patients underwent secondary CRS+HIPEC treatment due to relapse, and 18 of them were platinum-resistant (Figure 1). Both endometrial cancer patients in the study were re-

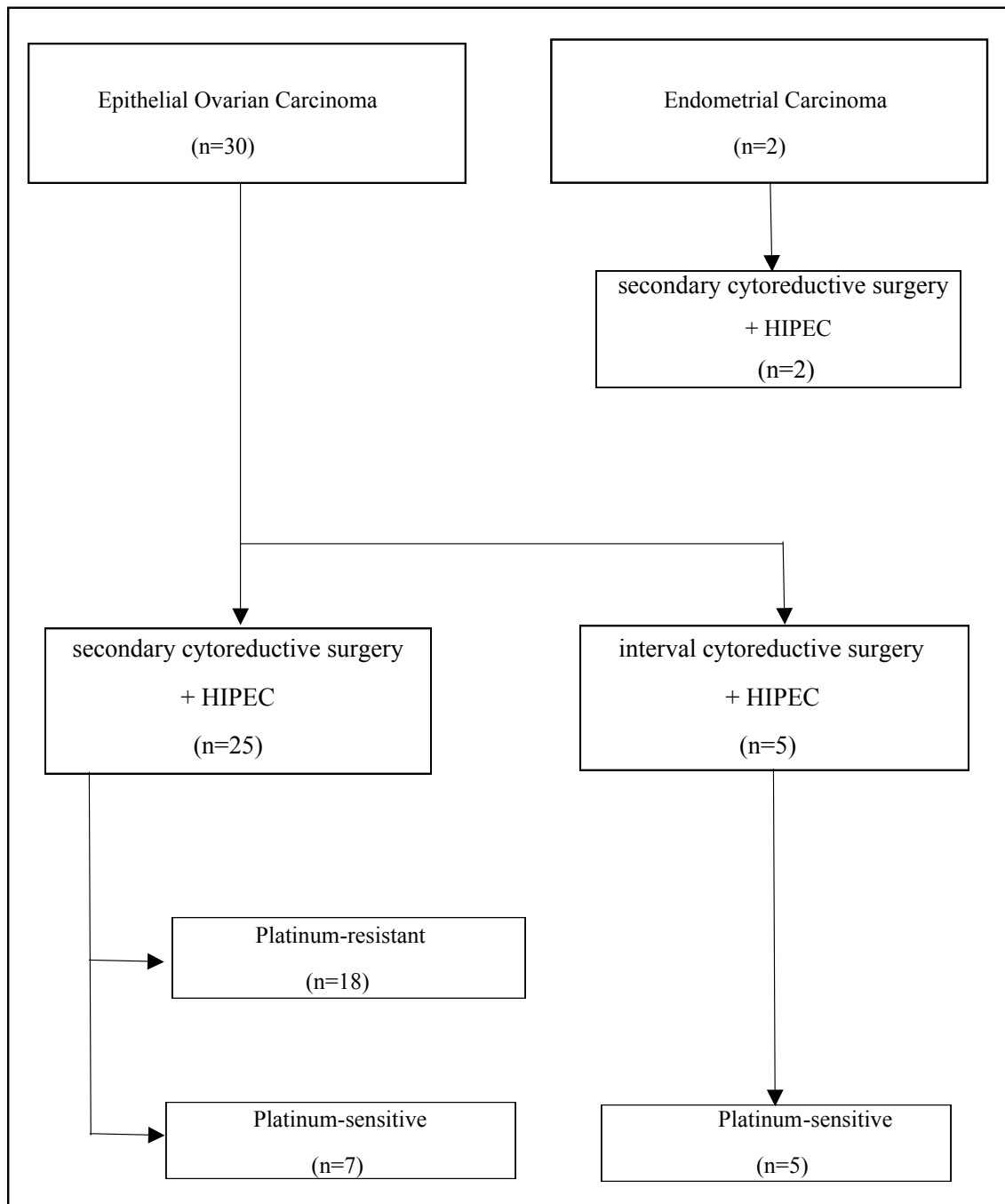


Figure 1. Distribution of the Groups.

Table 1. Demographic features and surgical details.

Variables		All patient groups	PR subgroup
Number of patients who underwent CRS+HIPEC	(n)	32	18
The mean surgery time (except HIPEC)	(minutes)	210 (90-550)	270 (150-550)
Median CA 125 level before surgery	(IU/L)	144 (13-25.000)	175 (10-1078)
The median length of hospital stay	(days)	8 (4-31)	9 (6-31)
Epithelial Ovarian Carcinoma		30	18
Patient who underwent CRS+HIPEC after NACT		5	-
Serous histology		5	-
High grade		5	-
Patient who underwent CRS+HIPEC after relapse		25	18
Serous histology		23	16
High grade		20	16
low grade		1	-
Mucinous histology (high grade)		2	2
Platinum resistant relapsed EOC		18	18
Platinum sensitive relapsed EOC		7	-
Endometrial Carcinoma (recurrent)		2	-
Serous histology (high grade)		1	-
Endometrioid histology (high grade)		1	-
Disease left after surgery			
CCS 0 (no visible tumor - complete resection)		11	1
CCS 1 (residual tumor diameter <0.25 cm - optimal resection)		9	5
CCS 2 (0.25 cm < residual tumor diameter < 1cm - optimal resection)		11 γ	11 γ
CCS 2 (1 cm < residual tumor diameter < 2.5 cm - suboptimal resection)		2 γ	2 γ
CCS 3 (2.5 cm < residual tumor diameter - suboptimal resection)		-	-
Complications	n		
Grade 5		1 (%3.1)	1 (%5.6)
Grade 4		1 (%3.1)	-
Grade 3		2 (%6.3)	1 (%11.1)

γ A patient in the platinum-resistant group underwent CRS+HIPEC twice with an interval of twenty-three months, while the first surgery achieved optimal cytoreduction, the second surgery remained suboptimal.

PR=Platinum-resistant, CRS=Cytoreductive surgery, NACT=Neoadjuvant chemotherapy, EOC=Epithelial ovarian carcinoma, CCS=Completeness of cytoreduction score, HIPEC=Hyperthermic intraperitoneal chemotherapy

current cases, one with serous and the other one with high-grade endometrioid histopathology. Demographic features and surgical details of the patients are described in Table 1. The median duration of surgery (except HIPEC) was 210 (range: 90-550) minutes. Various levels of peritonectomy procedure were performed for all except eight patients. Eight patients underwent upper abdominal surgery procedure and three patients underwent bowel resection and anastomosis. No patient had a permanent stoma. The median length of hospital stay was eight (range: 4-31) days and the median preoperative CA 125 level was 144 (range: 10-25,000) IU/L. One of the patients died after total colectomy and ileorectal anastomosis at the end of the first postoperative month due to anastomosis leakage that led to sepsis and multiple organ failure. In a patient who had type-2

diabetes mellitus for 30 years, and underwent CRS+HIPEC for relapsed endometrial cancer, anastomosis leakage developed after ileal resection and anastomosis, therefore relaparotomy together with a temporary stoma was performed. In addition, chronic renal failure occurred following acute kidney injury immediately after relaparotomy (Grade 4). Another patient developed an abscess in the paracolic region and the last patient who developed complication was found to have a hematoma in the pelvis. Both of the patients underwent percutaneous drainage via radiological intervention (Grade 3). The overall operative mortality rate was 3.1% and severe morbidity rate (grade 3 & 4) was 9.4%. Post hoc power calculation was performed; due to the small number of our patients, power of overall operative mortality and severe morbidity rates were found to be

Table 2. Results of recent studies on CRS and HIPEC.

Author, Country, Publication Year	Study design	Patient number (n)	Mean age (year)	PFS (month)	Overall survival (month)	Severe morbidity (%)	Mortality (%)
Königsrainer, Germany, 2011	Retrospective, single-center	31	60	35	N/A	42 ^β	0
Fagotti, Italy, 2012	Retrospective multi-center	30 [^]	51	26	N/A	35	0
Bakrin, France, 2013	Retrospective, multi-center	92	60	12	35	N/A	N/A
Spiliotis, Greece, 2014	Retrospective, single-center	60 [^]	58	27	N/A	N/A	N/A
Coccolini, multi-national, 2015	Prospective, multi-center	30	55	13	22	35	6
Escales-Campos, Spain, 2016	Retrospective, single-center	111	61	30	N/A	12.5	1.8
D'Hondt, Belgium, 2016	Prospective, multi-center	16	59	33	N/A	31.3	0
Di Giorgio, Italy, 2017	Retrospective, multi-center	226	60	20	54	14,2	N/A
Van Driel, Holland, 2018	Prospective, multi-center	122	61	14	46	27	0
Mikkelsen, Denmark, 2019	Prospective, single-center	25	54	N/A	N/A	44 [≈]	0
Minareci, Turkey, 2020	Retrospective, single-center	32	59	6 ^Δ	19 ^Δ	9.4	3.1

PFS=Progression-free survival, CRS=Cytoreductive surgery, HIPEC=Hyperthermic intraperitoneal chemotherapy, N/A=Not available

[≈] only grade 3 morbidity

^β mild and severe morbidity is given together

[^] only the number of patients in the HIPEC group was taken into account

^Δ including only the epithelial ovarian cancer patients who underwent CRS+HIPEC

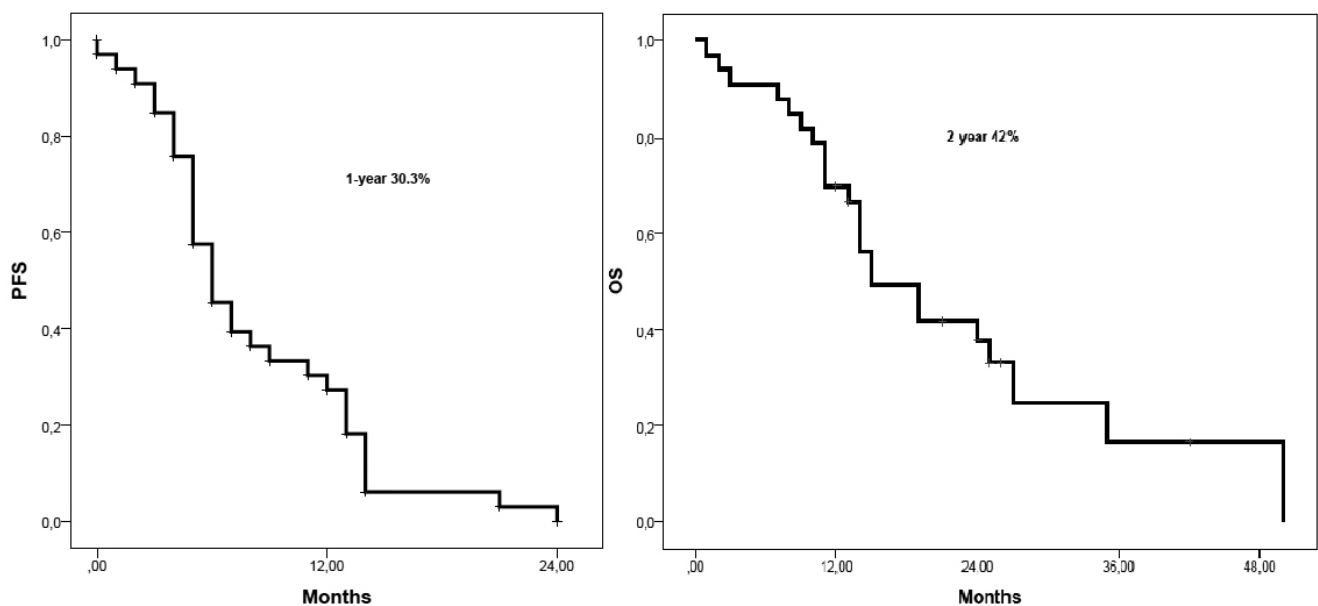


Figure 2. Kaplan-meier survival analysis of all patients.

0.792 and 0.692, respectively. At the beginning of laparotomy, the median PCI score was eight (range 0-24). Thirty-three CRS+HIPEC procedures included in our study were evaluated in terms of cytoreduction rate. As a result, complete cytoreduction was achieved in ten cases (30%) and optimal cytoreduction in 21 cases (64%). However, in two of 33 cases (6%), the residual tumor diameter was larger than one cm. Consequently, opti-

mal cytoreduction could not be achieved in these two cases. One patient had undergone secondary CRS+HIPEC in 2015 with the diagnosis of relapsed EOC, due to second relapse of the disease after 23 months, tertiary CRS+HIPEC was administered in 2017 (reHIPEC). For all patient populations, 1-year OS and PFS rates were 69.7% and 30.3%, respectively. For 30 patients with EOC, during a median follow-up period of 15 months (95% CI

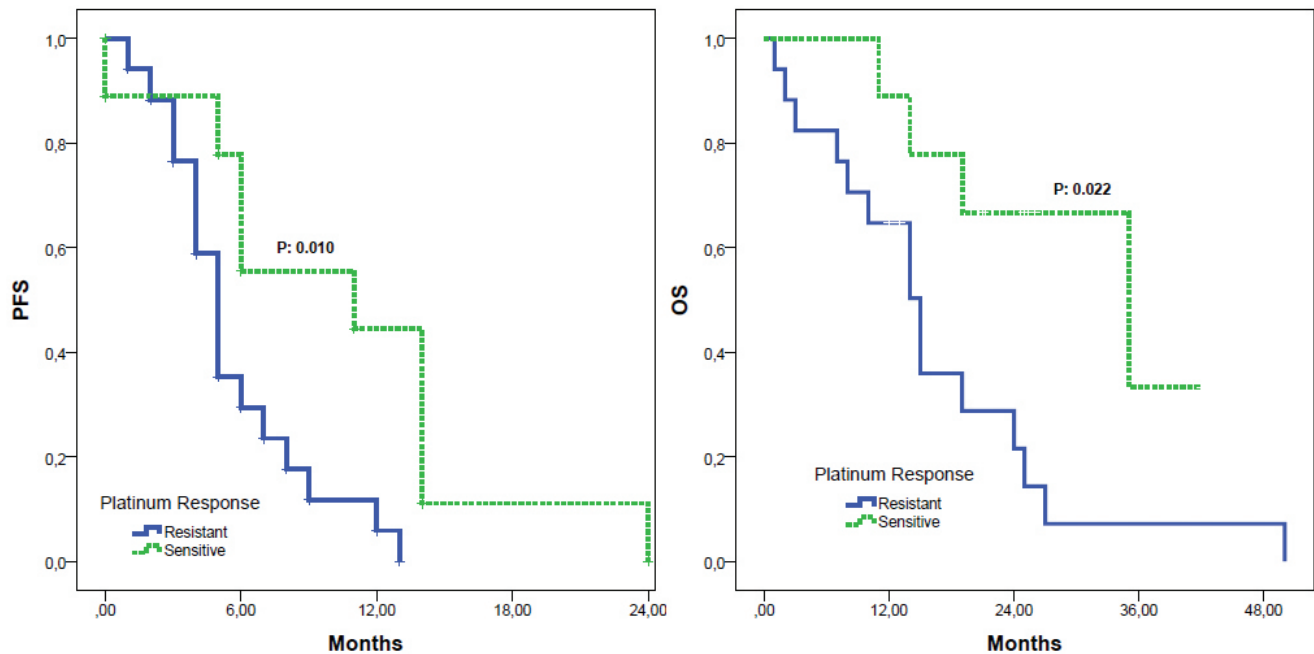


Figure 3. Kaplan-Meier survival analysis of platinum-resistant and platinum-sensitive patients.

8.7-21.4), Kaplan-Meier survival analysis showed 1-year OS and PFS rates of 76.7% and 33.3%, respectively. Importantly, all patients experienced recurrence at the end of the second year, and also 2-year OS rate was 42.0% (Fig. 2). In the subgroup analysis of 18 patients with platinum-resistant EOC, the median OS and PFS were 14 months and five months, with the rates of 1-year OS and PFS were 64.7% and 15.9%, respectively (Fig. 3). The univariate analysis revealed that the previous response of the disease to platinum was a statistically significant factor affecting survival, ($p=0.022$ for OS, $p=0.010$ for DFS). In addition, if complete cytoreduction was achieved, patients had, though not statistically significant, longer OS, (2-year OS 77.8% vs. 24.9%, $p=0.068$) (Figure 3). The multivariate analysis with confounding factors which include age, PCI score, response to platinum, and the rate of cytoreduction showed that only response to platinum had a significant effect on OS ($p=0.012$).

DISCUSSION

EOC is the leading cause of death in women with gynecological cancers, and the annual mortal-

ity rate ranges from three to nine per 100.000 women. In many cases with widespread peritoneal disease, searches have been sought for alternative ways to increase the effectiveness of chemotherapy because of the development of intraperitoneal recurrence despite complete CRS and adjuvant chemotherapy¹⁶. The administration of chemotherapy directly into the abdominal cavity provides a higher drug concentration on the peritoneal surface, thereby enhancing the cytotoxic effect of chemotherapy. Moreover, hyperthermia itself has been described to boost the effect of chemotherapy with a direct cytotoxic effect on tumor cells¹⁷. The philosophy of HIPEC is based on these two basic ideas. Since chemotherapeutics have a tissue penetration depth of one to two mm, it is accepted that cases without residual macroscopic tumor at the end of cytoreductive surgery will be more likely to benefit from this strategy¹⁸. In ovarian cancer, HIPEC may be administered in many different time periods; e.g. at the time of primary staging surgery, after the primary surgery+completion of adjuvant chemotherapy as consolidation therapy, at the time of interval cytoreductive surgery performed after neoadjuvant chemotherapy, as salvage therapy or

at the time of secondary/tertiary CRS¹⁹. The most preferred period of HIPEC administration is during CRS for recurrent disease. In addition, administration of HIPEC at the time of interval cytoreductive surgery has recently come to the fore.

There is a limited number of randomized prospective studies on HIPEC in gynecological cancers. In a multicenter prospective observational study performed between 2007 and 2013, patients (n=54) who had undergone surgery+HIPEC at various periods (during primary staging surgery, interval cytoreductive surgery, and secondary CRS for recurrent disease) were evaluated by Coccolini et al. Grade 3 and 4 complications were reported in 35% and grade 5 complication in 6% (n=3) of patients²⁰. In a recent meta-analysis of 37 studies conducted by Huo et al.²¹ grade 3 and 4 morbidity rates after CRS+HIPEC in patients with recurrent EOC have been reported as 26.2% (1.8-55.6) and mortality rate as 1.8% (0-13.6). In our cohort, mortality rate was 3.1% and severe morbidity rate was 9.4%. Thus, our findings were consistent with the literature.

The first randomized prospective study on HIPEC in gynecological cancers was published in 2015 by Spiliotis et al²². In this study, women with advanced stage EOC (n=120) were randomized in an eight-year period between 2006 and 2013, after primary staging surgery+adjuvant systemic chemotherapy. Patients divided into two groups: CRS+adjuvant chemotherapy was applied to group A and CRS+HIPEC+adjuvant chemotherapy to group B. When the results were analyzed, the mean survival in group B was found to be significantly increased compared to group A. (26.7 vs. 13.4 months, $p < 0.006$). In addition, when the patients in group B were subdivided into platinum-resistant and platinum-sensitive disease groups, survival had no statistical difference between the groups (26.6 vs. 26.8 months). The study also revealed that complete cytoreduction was associated with longer survival in parallel with many other studies. The main criticisms have focused on the

selection of primary and secondary targets, lack of PFS data, methodological and scientific errors in statistical analysis and randomization, as well as the absence of postoperative complication data²³. Recently, a prospective study has been published by van Driel et al.²⁴ Patients with advanced stage ovarian cancer (n=245) were divided into two groups after receiving neoadjuvant chemotherapy. The first group of the patients (n=123) were treated with CRS+adjuvant chemotherapy and the second group (n=122) with CRS+HIPEC+adjuvant chemotherapy. When the results were evaluated, PFS in the first group was 10.7 months and in the second group it was 14.2 months ($p=0.003$). Moreover, OS was 33.9 and 45.7 months, respectively ($p=0.01$). In addition, the rates of severe morbidity in both groups (25% vs. 27%, respectively) were similar. This study has been the subject of many criticisms. Many authors stated that methodological errors were made in the selection of the study plan (e.g. the institution giving the most patients to the study, having the least effect on the results) and serious postoperative complications were also neglected. In addition, the authors noted that smaller number of patients with histological subtypes with poor prognosis in the second group caused inequality against the first group, and they also stated the underreported renal toxicity due to HIPEC²⁵⁻²⁸. In our study, patients with recurrent EOC who had no visible residual disease at the end of cytoreductive surgery had-though not statistically significant-longer OS. Additionally, mortality and severe morbidity rates were within acceptable limits.

Nonetheless, there are few case reports that evaluate the effect of CRS+HIPEC on platinum-resistant patients. Most often, platinum-resistant patients were not included in clinical trials due to their poor prognosis and short survival. Furthermore, there are insufficient randomized data to establish HIPEC as the standard of care for neither recurrent EOC nor platinum-resistant cases. In the present study, platinum-resistant group who comprised approximately three quarters of

our cohort (n=18) were evaluated within themselves, and the findings were in parallel with the publications detailed above (Table 2). Based on the present study, HIPEC might be considered as an option in the management strategy of patients with platinum-resistant EOC, given the acceptable serious morbidity and mortality rates. Finally, although there was only one reHIPEC case in our study, repetition of HIPEC might be kept in mind as a feasible treatment option at the time of CRS in selected cases of recurrent EOC. In future research, HIPEC may be administered more effectively in the treatment of platinum-resistant patients. In addition, administration of new targeted therapeutic agents intraperitoneally together with conventional chemotherapeutics at the beginning or the end of HIPEC for synergistic effects should also be considered.

However, the main limitations of the present study were its retrospective design, the small number of the patient cohort, and relatively short follow-up period. On the other hand, strengths of the study were that it consisted mainly of platinum-resistant EOC patients and conducted in one center. In fact, conducting the study in a single center has been an advantage due to the establishment of the standard HIPEC protocol for each case.

In conclusion, CRS+HIPEC might be administered in gynecological cancers with peritoneal spread, particularly in EOC. However, available data suggest that it is still early to consider HIPEC as an additional therapy to cytoreductive surgery in patients with EOC. In addition, the group of patients who will benefit the most through this treatment is still undefined. The present study was notable as it suggested that HIPEC administration during CRS was not associated with adverse outcomes in the platinum-resistant EOC cohort. In addition, patients with recurrent EOC who had no visible residual disease at the end of cytoreductive surgery, though not statistically significant, had longer OS. Finally, CRS+HIPEC procedures had acceptable severe morbidity and mortality rates. In

this context, it is clear that large-scale randomized prospective studies are needed on the subject of HIPEC. The results of large-scale randomized phase III Italian HORSE (NCT01376752) and French CHIPOR (NCT01376752) studies evaluating HIPEC in patients with EOC are expected to be announced.

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