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The short-term results of cytoreduction+hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with grade IIIC and IV ovarian cancer

Evre IIIC ve IV over kanserli hastalarda kısa dönem sitoredüksiyon + hipertermik intraperitoneal kemoterapi (HIPEC) sonuçlarımız

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Aim: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to prolong survival in patients with advanced-stage ovarian cancer. This study aimed to determine present the short-term outcomes of CRS +HIPEC in patients with primary and recurrent advanced-stage ovarian cance.
Methods: A retrospective study was performed in 18 patients with advanced stage ovarian cancer who received CRS+HIPEC at a single center between May 2019 and March 2020. The demographic data, CA-125 values, peritoneal carcinomatosis index (PCI), completeness of cytoreduction score (CC), surgical procedures, complications, disease-free survival (DFS) and overall survial (OS) data of each patient were recorded.
Results: In the group with PCI ≥10, DFS was 18 months, and OS was 19 months, and the group with PCI ≤9, the DFS and OS were 20 months. No significant difference was observed in the DFS and OS between the two groups in respect of DFS and OS (p = 1.000). In patients with CC0, DFS and OS were calculated as 20 months; in those with CC1+CC2, DFS was 12 months and OS was 13.2 months. A statistically significant difference was observed in the DFS and OS (p = 0.039) between the two groups.
Conclusion: Our results showed that optimal CRS with HIPEC prolonged the survival in patients with advanced-stage ovarian cancer.

Key Words: cytoreduction, HIPEC, hyperthermia, ovarian cancer, survival.

Öz
Amaç: İleri evre over kanserinde sitoredüktif cerrahi (SRC) ile birlikte yapılan Hipertermik İntraperitoneal Kemoterapi (HİPEK)'nin sağkalımı artırdığı gösterilmiştir. Bu çalışmada; tek merkezde primer ve rekürren ileri evre over kanseri tanısı ile SRC+HİPEK yapılan hastaların erken dönem sonuçlarını sunmayı amaçladık.
Yöntemler: Mayıs 2019- Mart 2020 tarihleri arasında tek merkezde ileri evre over kanseri tanısı ile SRC+HİPEK yapılan hastaların sonuçları retrospektif olarak incelendi. Hastaların; demografik verileri, preopereatif CA-125 değerleri, peritoneal karsinomatozis indexi (PKİ), sitoredüksiyon skoru (SS), cerrahi işlemler ve komplikasyonları, postoperatif takip süreleri, hastalıksız sağkalım HSK ve genel sağ kalım (GSK) süreleri kayıt altına alındı.
Bulgular: PKİ ≥ 10 olan grupta HSK 18 ay, OS 19 ay iken, PKİ ≤ 9 olan grupta HSK ve GSK 20 ay olarak bulunmuştur. İki grup arasında HSK ve GSK'de anlamlı fark yoktur (p=1.000). SS0 olanlarda HSK ve GSK 20 ay, SS1+SS2'de ise HSK 12 ay, GSK 13,2 ay olarak hesaplanmıştır. İki grup arasında HSK ve GSK'de istatistiksel anlamlı fark mevcuttur (p=0,039).
Sonuç: Sonuçlarımız; over kanserlerinde optimal SRC ile yapılan HİPEK'in sağkalımı uzattığını göstermiştir.

Anahtar Kelimeler: sitoredüksiyon, HİPEK, hipertermi, over kanseri, sağ kalım.

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Introduction

According to the 2018 data of the Global Cancer Observatory (GLOBOCAN), approximately 295,000 patients are diagnosed with ovarian cancer per year worldwide, and ovarian cancer has a mortality rate of 185,000 [1]. Epithelial carcinoma is the most frequently observed type of ovarian cancer with an incidence of 95% [2]. Unfortunately, ovarian cancer patients are generally diagnosed at an advanced stage, and at least 75% of these patients have widespread peritoneal involvement and findings of obstruction [3].

Debulking surgery and chemotherapy regimens have shown good clinical outcomes in patients with advanced-stage ovarian cancer. To date, however none of the treatments have shown an improvement success rate of more than 30% in the 5-year survival rates [4]. Epithelial ovarian cancer (EOC) metastasizes via local, systemic or lymphatic routes. The most significant feature of EOC is peritoneal carcinomatosis (PC) that is caused by spread through implantation to the peritoneum. Sugarbaker recommended cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for the first time for the treatment of PC and showed promising results [5]. The advantages of HIPEC are as follows: it exerts at direct effect on cancer cells, increases the cytotoxic effect of chemotherapy with an increase in temperature, and inhibits angiogenesis [6]. This study was aimed to investigate the short-term clinical outcomes of patients with a diagnosis of primary and recurrent ovarian cancer (International Federation of Gynecology and Obstetrics-FIGO IIIC, IV) receiving CRS+HIPEC.

Material and methods

Ethical approval

Approval for the study was granted by the Non-interventional Clinical Research Ethics Committee of Mustafa Kemal University (decision no: 10, session no:10, dated: 03/09/2020).

Patient selection

The results of patients with advanced stage ovarian cancer (IIIC and IV) confirmed histologically who received CRS+HIPEC at Hatay Training and Research Hospital between May 2019 and March 2020 were retrospectively reviewed. For patients with primary EOC, six cycles of paclitaxel (175 mg/m2) and carboplatin (AUC 5-6) were administered after optimal CRS+HIPEC, and patients who underwent interval debulking surgery received three cycles of neoadjuvant chemotherapy (NACT) preoperatively. Patients with low performance and not suitable for optimal CRS with imaging methods were accepted as contra indicated for NACT. Patients showing recurrence were followed up with second-generation platin-based chemotherapy following CRS+HIPEC. Thoracic and abdominopelvic computed tomography (CT) images of all patients were acquired perioperatively. A diagnosis of recurrence was confirmed in patients with an increase in CA-125 levels or, when necessary, by peritoneal sampling (laparoscopic or Tru-cut biopsy). CRS+HIPEC was performed in all the patients by the same surgical team. Peritonectomy and diaphragm stripping was performed in all patients. When there was invasion of the diaphragm, resection was preferred to stripping. Resections were performed in solid organs (liver metastasectomy and splenectomy) and the gastrointestinal tract (gastrectomy, small intestine resection, colectomy) showing tumor invasion, and lymph node dissections (pelvic, para-aortic, hepatoduodenal) were performed in lymph node-positive patients. Immediately after the termination of the operation, a catheter was placed in the four quadrants of the abdomen and HIPEC was using with the closed method [7] using a perfusion pump (Stockert S5®, Germany, 2018) with a single agent at 41.5°C for 90 min. For patients sensitive to platin, 100 mg/m2 cisplatin [8] was administered, and for patients resistant to platin, 175 mg/m2 paclitaxel was administered [9].

Inclusion and exclusion criteria

The patients included in the study were aged 18-70 years, had ovarian cancer (FIGO grade IIIC, IV), Eastern cooperative oncology group performance status (ECOG PS) of 0-2, and sufficient bone marrow function for performing HIPEC (neutrophil count ≥1000 mm3, platelet count ≥100,000/ mm3, hemoglobin level ≥8.5 g/dL, international normalized ratio (INR) ≤1.5, creatinine and bilirubin levels ≤1.5 fold of the upper limit, and alanine aminotransferase and aspartate aminotransferase levels ≤3-fold of the upper limit). Patients with an ECOG PS of ≥3, a history of cancer other than ovarian cancer, with >3 intestinal obstructions, unresectable liver metastasis, or involvement of the mesenteric root of the small intestine were excluded from the study.

Data collection

The demographic information, CA-125 levels, the presence of ascites, ECOG PS, surgical procedures, operative time, bleeding amount, length of stay, pathology results, and surgical complications were recorded. The surgical complications were classified according to the National Cancer Institute, Common Terminology Criteria for Adverse Events version 3 (NCI, CTCAEv3). The criteria were defined as follows: G1, mild; G2, moderate; G3, severe; and G4, life-threatening [10]. The peritoneal cancer index (PCI), which reflects the intra-abdominal cancer burden and distribution, was calculated perioperatively for each patient. For calculating the PCI, the abdomen was separated into 13 anatomic regions. Each region was scored scoring according to the largest tumor diameter (TD) as follows: TD-0, no tumor; TD-1, ≤0.5 cm; TD-2, 0.5–5 cm; and TD-3, ≥ 5cm, with a maximum possible score of 39 [11]. Residual disease was classified according to the completeness of cytoreduction (CC) scoring system defined by Sugarbaker et al. [12] According to this system, CC0, no macroscopic tumor; CC1, the largest macroscopic tumor is ≤2.5 mm; CC2, ≥2.5 to ≤2.5 cm; and CC-3, ≥2.5 cm. The patients were separated into subgroups as those with PCI ≤9 and ≥10 and those with CC0 and CC1+CC2.

Disease-free survival and overall survival

The follow-up period was accepted as the period from the date of the operation to the last date on which information was taken from the patient. Disease-free survival (DFS) was recorded as the time from the operation to recurrence, and overall survival (OS) was the time from the operation to death or the final follow-up examination.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS version. 27.0 software (Chicago, IL, USA). Descriptive statistics were stated as mean ± standard deviation (SD), median, minimum, and maximum values, number (n), and percentage (%). Conformity of the variables to normal distribution was tested using the Kolmogorov–Smirnov test. The Mann Whitney U-test was used in the analysis of independent quantitative data. The independent qualitative data were analyzed using the chi-square test or the Fisher test, where appropriate. Survival analysis was applied in a 95% confidence interval using

the Kaplan–Meier (log-rank) method. A value of $p < 0.05$ was accepted as statistically significant.

Results

Clinical and pathological characteristics

Between May 2019 and March 2020, 23 consecutive patients underwent an operation for advanced-stage (FIGO IIIC and IV) ovarian cancer. Five patients did not meet the inclusion criteria; therefore, 18 patients were included in the evaluation. Cisplatin was administered to 17 patients (94.4%), and paclitaxel was administered to 1 patient (5.6%) because of platin resistance. The median age of the patients was 51.5 years (range, 22–69 years), and the median operating time was 350 mins (range, 250.0–590.0 mins). Primary cytoreduction (PC) was performed in 7 patients (38.9%), interval debulking cytoreduction (IDC) in 3 patients (16.7%), and secondary cytoreduction (SC) in 8 patients (44.4%) with recurrence. The CC evaluations were CC0 in 9 patients (50%), CC1 in 7 patients (38.9%), and CC2 in 2 patients (11.1%). The most common diagnosis was serous carcinoma in 13 patients (72.2%). Ten patients (55.6%) patients were classified as FIGO IIIC and 8 patients (44.4%) as grade IV. The demographic data, surgical data, and pathological results of all the patients are shown in Table 1. PCI was calculated as median 10 (range, 2–22); 7 patients with PCI ≤9 and 11 patients with PCI ≥10. Comparison according to the PCI showed that the operating time (CRS+HIPEC) was significantly longer in the PCI ≥10 group than in the PCI ≤9 group ($p = 0.006$). The ECOG PS was higher in the PCI ≥10 group ($p = 0.043$). No significant difference was observed in other results ($p > 0.05$, Table 2). The operating time was longer, the perioperative bleeding was higher, and the rate of splenectomy were statistically significantly higher in the CC1+CC2 patients than in the CC0 patients ($p = 0.042$, $p = 0.049$, and $p = 0.016$, respectively). The mortality rate was higher in the CC1+CC2 group ($p = 0.09$, Table 3).

Survival

The median follow-up period of the patients was 13.5 months (range, 1–22 months), the median DFS was 18.8 months (95%CI: 15.69–21.97), and the median OS was 20 months (95% CI: 16.84-21.97). Five patients (27.8%) died during this period. In the group with PCI ≥10, the DFS was 18 months, and OS was 19 months, and in the group with PCI ≤9, the DFS and OS were 20 months. No significant difference was observed in the DFS and OS ($p = 1.000$) between the two groups (Figure 1). The DFS and OS in the CC0 group were 20 months, and in the CC1+CC2 group, the DFS was 12 months and the OS was 13.2 months. A statistically significant difference was observed between in the DFS and OS ($p = 0.039$) between the two groups (Figure 2).

Table 1. Characteristics of patients (n = 18).

	Min - Max	Median	Mean ± SD
Age (years)	22.0-69.0	51.5	51.7±12.7
CA-125	8.7-6742.1	274.0	985.0±1661.9
PCI	2.0-22.0	10.0	10.9±5.2
Number of positive LN	0.0-32.0	2.0	9.3±11.5
Total LN	10.0-74.0	32.5	36.1±18.9
Duration of CRS+HIPEC (min)	250.0-590.0	350.0	351.7±86.0
Bleeding (mL)	1000.0-3000.0	1875.0	1861.1±601.6
ICU (day)	2.0-9.0	3.5	3.9±1.7
Hospitalization (day)	10.0-35.0	19.0	20.4±7.5
	n	%	n
Ascites (+)	11	61.1%	
ECOG PS			
0	3	16.7%	
I	10	55.6%	
II	5	27.8%	
TAH-BSO	10	55.5%	
PEL-PA LND	17	94.4%	
Vaginal cuff resection	1	5.6%	
Hemicolectomy	1	5.6%	
Subtotal colectomy	2	11.1%	
Total colectomy	5	27.8%	
LAR	8	44.4%	
Small bowel resection	3	16.7%	
Appendectomy	18	100.0%	
Omentectomy	18	100.0%	
Peritonectomy	18	100.0%	
DS/DR			
DS	15	83.3%	
DR	3	16.7%	
Liver metastasectomy	3	16.7%	
Splenectomy	7	38.9%	
Cholecystectomy	3	16.7%	
Gastrectomy	4	22.2%	
Hepatoduodenal LND	2	11.1%	
Histologic type			
Serous	13	72.2%	
Mucinous	3	16.7%	
Mixed epithelial carcinoma	1	5.6%	
Carcinosarcoma	1	5.6%	
FIGO			
IIIC	10	55.6%	
IV	8	44.4%	
Cisplatin	17	94.4%	
Paclitaxel	1	5.6%	
CC0	9	50.0%	
CC1	7	38.9%	
CC2	2	11.1%	
PC	7	38.8%	
IDC	3	16.7%	
SC	8	44.4%	
Complications*			
Anastomotic leak[2]	1	14.3%	
Intestinal fistula[3]	2	28.6%	
Wound infection[2]	1	28.6%	
Rectovesical fistula[4]	1	14.3%	
Ureteral injury[1]	1	14.3%	
Re-operation	1	5.6%	
Exitus	5	27.8%	

PCI = peritoneal carcinomatosis index, LN = lymph node, CRS+HIPEC = cytoreductive surgery+hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, ECOG PS = Eastern cooperative oncology group performance status, TAH+BSO = total abdominal hysterectomy bilateral salpingo-ooferectomy, PEL-PA LND = pelvic-paraaortic lymph node dissection, LAR = low anterior resection, DS = diaphragm stripping, DR = diaphragm resection, FIGO = International federation of gynecology and obstetrics, CC = completeness of cytoreduction PC = primary cytoreduction IDC = interval debulking cytoreduction, SC = secondary cytoreduction, *CTCAE = common terminology criteria for adverse events grade (1: mild, 2: moderate, 3: severe, G4: life-threatening), sd, standard deviation

Discussion

EOC is the most frequently observed ovarian malignancy and is the leading cause of death among gynecological malignancies [2,3]. Recurrence develops within 3 years of treatment in approximately 60% of patients [13]. Although no consensus has been reached regarding the extent of CRS+HIPEC, the timing of administering this treatment, the chemotherapeutic agent to be administered, the doses, and the methods of administration of intraperitoneal chemotherapy in the treatment of advanced stage ovarian cancer, the results obtained in the last 20 years have been encouraging [14].

In a multicenter study during which CRS+HIPEC was performed at different times, the OS was 52.4 months and the DFS was 16.6 months. The patients were divided into eight subgroups, and the OS and DFS were longer in patients with PC than in those who received recurrent cytoreduction. The shortest survival among patients with PC was reported to be in those who did not respond after NACT. CC score and PCI were shown to be independent markers [15]. The results of another study comparing primary cytoreduction with and without HIPEC showed no difference between the 2 groups in OS (33.8 months vs. 33.6 months), and the DFS was significantly longer in the group receiving HIPEC (25.6 months vs. 20 months) [16]. In a prospective study by Spiliotis et al. [17] patients with recurrent grade IIIC and IV ovarian cancer were followed-up and those receiving CRS+HIPEC were compared with those receiving CRS alone. OS was significantly longer in patients sensitive to platin and receiving HIPEC (26.7 months vs. 13.4 months). Results of a previous study investigating the role of HIPEC in improving the survival in patients with recurrent

Table 2. Comparison of PCI ≤9 and PCI ≥10.

	PCI ≤9 (n = 7)		PCI ≥10 (n = 11)		
	Mean ± SD	Median	Mean ± SD	Median	p¥
Age (years)	52.3±15.0	57.0	51.4±11.9	50.0	0.683
CA-125	624.6±701.7	408.8	1214. 3±2062	139.2	0.892
PCI	6.1±2.4	7.0	14.0±4.1	14.0	0.004
Number of LN metastases	7.1±10.2	2.0	10.6±12.6	2.0	0.782
Number of total LN	34.1±20.2	29.0	37.3±18.8	36.0	0.650
Duration of CRS+HIPEC (min)	291.4±35.3	300.0	390.0±87.5	390.0	0.006
Bleeding (mL)	1535.7±548.3	1500.0	2068.2±560.0	2000.0	0.067
ICU (day)	3.9±1.2	3.0	3.9±2.0	4.0	0.780
Hospitalization (day)	19.3±7.1	16.0	21.2±8.1	21.5	0.591
	n	%	n	%	
Ascites	4	57.1%	7	63.6%	1.000
ECOG PS					
0	3	42.9%	0	0.0%	
I	1	14.3%	9	81.8%	0.043
II	3	42.9%	2	18.2%	
TAH-BSO	4	57.1%	6	54.5%	0.119
PEL-PA LND	7	100.0%	10	90.9%	1.000
Vaginal cuff resection	0	0.0%	1	9.1%	1.000
Hemicolectomy	1	14.3%	0	0.0%	0.389
Subtotal colectomy	0	0.0%	2	18.2%	0.497
Total colectomy	0	0.0%	5	45.5%	0.101
LAR	4	57.1%	4	36.4%	0.630
Small bowel resection	0	0.0%	3	27.3%	0.245
Appendectomy	7	100.0%	11	100.0%	1.000
Omentectomy	7	100.0%	11	100.0%	1.000
Peritonectomy	7	100.0%	11	100.0%	1.000
DS/DR					
DS	7	100.0%	8	72.8%	0.131
DR	0	0.0%	3	27.2%	
Liver metastasectomy	1	14.3%	2	18.2%	1.000
Splenectomy	2	28.6%	5	45.5%	1.000
Cholecystectomy	0	0.0%	3	27.3%	0.245
Gastrectomy	0	0.0%	4	36.4%	0.119
Hepatoduodenal LND	0	0.0%	2	18.2%	0.497
Histologic type					
Serous	7	100.0%	6	54.5%	0.101
Mucinous	0	0.0%	3	27.3%	0.245
Mixed epithelial carcinoma	0	0.0%	1	9.1%	1.000
Carcinosarcoma	0	0.0%	1	9.1%	1.000
FIGO					
IIIC	6	85.7%	4	36.4%	0.311
IV	1	14.3%	7	63.6%	
Cisplatin	7	100.0%	10	90.9%	1.000
Paclitaxel	0	0.0%	1	9.1%	
PC	3	42.9%	4	36.4%	
IDC	2	28.6%	1	9.1%	0.367
SC	2	28.6%	6	54.5%	
Complications					
+	5	71.4%	6	54.5%	0.637
-	2	28.6%	5	45.5%	
Re-Operation	0	0.0%	1	9.1%	1.000
Exitus	2	28.6%	3	27.3%	1.000
CC0	5	33.3%	4	44.4%	
CC1	1	22.2%	6	11.1%	0.146
CC2	1	44.4%	1	44.4%	

¥Mann–Whitney U test and chi- square test (Fischer) were used for calculations. PCI = peritoneal carcinomatosis index, LN = lymph node, CRS+HIPEC = cytoreductive surgery+hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, ECOG PS = Eastern cooperative oncology group performance status, TAH+BSO = total abdominal hysterectomy bilateral Salpingo-ooferectomy, PEL-PA LND = pelvic-paraaortic lymph node dissection, LAR = low anterior resection, DS = diaphragm stripping, DR = diaphragm resection, FIGO = International federation of gynecology and obstetrics, CC = completeness of cytoreduction, PC = primary cytoreduction IDC = interval debulking cytoreduction, SC = secondary cytoreduction, sd, standard deviation

ovarian cancer showed an OS of 59.3 months and a DFS of 15.8 months. Compared with the control group, the group receiving CRS+HIPEC showed no improvement in survival [18]. Our results showed that the DFS was 18.8 months, which is consistent with findings reported previously. However, our study had a short follow-up period, we evaluated patients with primary and recurrent tumors together, and included only patients with grade IIIC and IV tumors, which may attribute to the shorter OS than that reported in previous studies.

Table 3. Comparison of CC0 and CC1+CC2.

	CC0 (n = 9)		CC1 +CC2 (n = 9)		
	Mean ± s.d	Median	Mean ± s.d	Median	p¥
Age (years)	49.6±14.6	49.0	53.9±11.1	57.0	0.536
CA-125	943.2±1011.4	826.9	1026.7±2200.6	136.2	0.354
PCI	9.3±5.6	9.0	12.6±4.6	11.0	0.132
Number of LN metastases	9.6±11.2	4.0	9.0±12.6	2.0	0.446
Number of total LN	36.9±21.9	31.0	35.2±16.5	34.0	0.965
Duration of CRS+HIPEC (min)	313.3±45.8	310.0	390.0±101.5	390.0	0.042
Bleeding (mL)	1583.3±484.1	1500.0	2138.9±600.9	2250.0	0.049
ICU (day)	4.0±2.1	3.0	3.8±1.4	4.0	0.892
Hospitalization (day)	20.2±8.5	16.0	20.6±6.9	20.5	0.772
	n	%	n	%	
Ascites	6	66.7%	5	55.6%	0.629
ECOG PS					
0	3	33.3%	0	0.0%	
I	5	55.6%	5	55.6%	0.206
II	1	11.1%	4	44.4%	
TAH-BSO	5	55.5%	5	55.5%	1.000
PEL-PA LND	9	100.0%	8	88.9%	1.000
Vaginal cuff resection	0	0.0%	1	11.1%	1.000
Hemicolectomy	1	11.1%	0	0.0%	1.000
Subtotal colectomy	0	0.0%	2	22.2%	1.000
Total colectomy	2	22.2%	3	33.3%	0.599
LAR	4	44.4%	3	33.3%	0.343
Small bowel resection	1	11.1%	2	22.2%	1.000
Appendectomy	9	100.0%	9	100.0%	1.000
Omentectomy	9	100.0%	9	100.0%	1.000
Peritonectomy	9	100.0%	9	100.0%	1.000
DS/DR					
DS	9	100.0%	6	66.7%	0.206
DR	0	0.0%	3	33.3%	
Liver metastasectomy	2	22.2%	1	11.1%	1.000
Splenectomy	1	11.1%	6	66.7%	0.016
Cholecystectomy	1	11.1%	2	22.2%	1.000
Gastrectomy	1	11.1%	3	33.3%	0.257
Hepatoduodenal LND	0	0.0%	2	22.2%	0.471
Histologic type					
Serous	8	88.9%	5	55.6%	0.114
Mucinous	0	0.0%	3	33.3%	0.206
Mixed epithelial carcinoma	1	11.1%	0	0.0%	1.000
Carcinosarcoma	0	0.0%	1	11.1%	1.000
FIGO					
IIIC	5	55.6%	5	55.6%	1.000
IV	4	44.4%	4	44.4%	
Cisplatin	8	88.9%	9	100.0%	1.000
Paclitaxel	1	11.1%	0	0.0%	
PC					
IDC	4	44.4%	3	33.3%	
SC	3	33.3%	0	0.0%	0.153
	2	22.2%	6	66.7%	
Complications					
+	6	66.7%	5	55.6%	0.629
-	3	33.3%	4	44.4%	
Re-Operation	0	0.0%	1	11.1%	1.000
Exitus	0	0.0%	5	55.6%	0.009

¥Mann–Whitney *U* test and chi- square test (Fischer) were used for calculations, PCI = peritoneal carcinomatosis index, LN = lymph node, CRS+HIPEC = cytoreductive surgery+hyperthermic intraperitoneal chemotherapy, ICU = intensive care unit, ECOG PS = Eastern cooperative oncology group performance status, TAH+BSO = total abdominal hysterectomy bilateral Salpingo-ooferectomy, PEL-PA LND = pelvic-paraaortic lymph node dissection, LAR = low anterior resection, DS = diaphragm stripping, DR = diaphragm resection, FIGO = International federation of gynecology and obstetrics, CC = completeness of cytoreduction, PC = primary cytoreduction, IDC = interval debulking cytoreduction, SC = secondary cytoreduction, sd, standard deviation

Multiple organ resection may be necessary for effective CRS, and this can increase the morbidity and mortality rates associated with the operation. Previous studies have reported morbidity rates of 14%–55%, 30-day mortality rate of 0%–4.9%, and a mortality rate of 0%–20% in the subsequent period [19,20]. Consistent with the results reported previously, results of our study showed that the rate of complications causing morbidity was 38.9%. While there was no perioperative mortality was observed during this study, the mortality rate in the subsequent period was 27%. The higher rate of mortality observed in this study than that in previous studies may be because CRS+HIPEC

was performed only in patients with grade IIIC and IV disease, and therefore, there was a higher rate of multiorgan resection

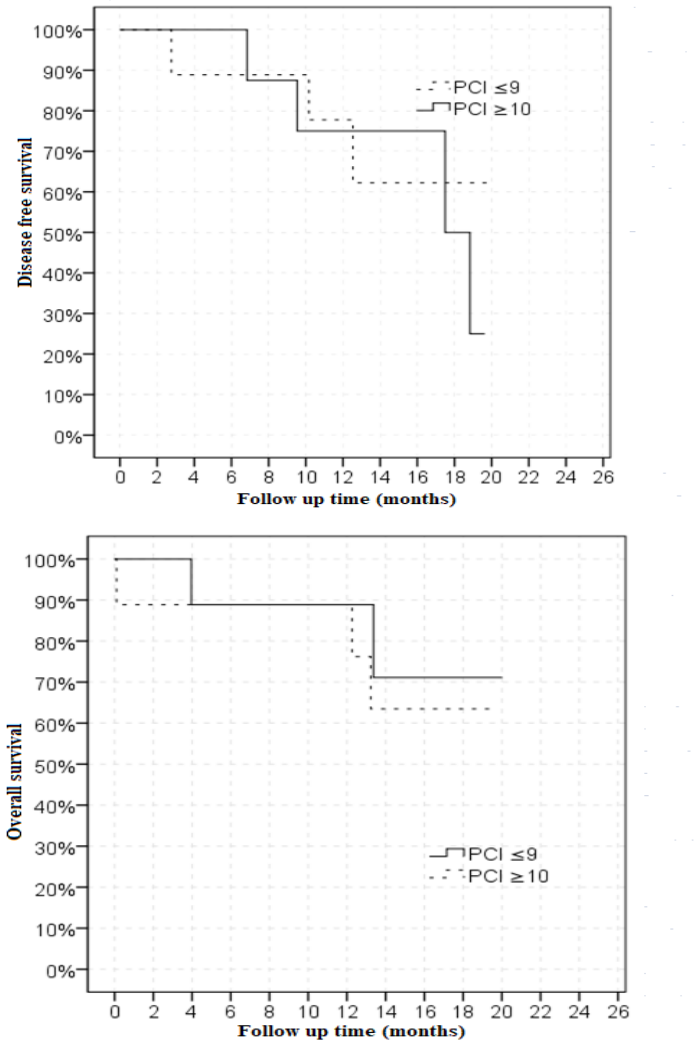

Figure 1 a. Kaplan–Meier curves of disease-free survival for patients with peritoneal carcinomatosis index (PCI) ≤9 and PCI ≥10, **b.** Kaplan–Meier curves of overall survival for patients with PCI ≤9 and PCI ≥10

Previous studies showed that a residual tumor <1 cm was sufficient for optimal cytoreduction. Recent studies indicate that optimal cytoreduction is evaluated using the CC score [12]. Optimal cytoreduction (CC0 and CC1) is directly related to positive results of the surgery and is a strong marker of survival [21]. A previous study showed that the survival in patients with CC0, CC1, and CC2 was 30.9, 23.9, 12.1 months, respectively [17]. Patients with CC0 had longer survival and a greater need for perioperative blood transfusion than those with CC >0 [15]. Unlike the results reported previously, our results showed that the amount of bleeding, operating time, and rates of splenectomy were significantly lower in patients with CC0, and the mortality rate was significantly higher in the CC1+CC2 group. The number of patients with CC1 were higher than those with CC2 in our study. Higher bleeding and longer operating time were attributed to the greater efforts made to ensure CC1 during the operation. Survival analysis showed that the OS and DFS were significantly longer in the CC0 than in the CC1+CC2 group, which was consistent with the results reported previously. No significant difference was determined between the groups in respect of morbidity, and all patients who died were in the CC1+CC2 group. Absence of mortality in the CC0 group during the follow-up period shows the importance of optimal cytoreduction. PCI, showing the tumor distribution within the

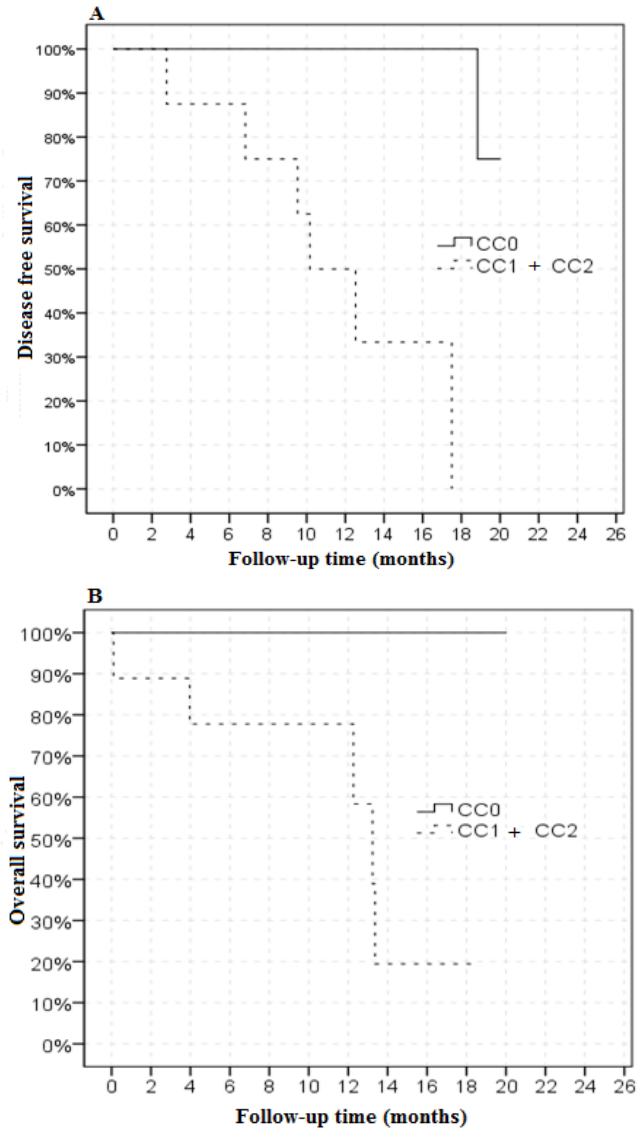

Figure 2 a. Kaplan–Meier curves of disease-free survival for patients with completeness of cytoreduction score 0 (CC0) and CC1+CC2 **b.** Kaplan–Meier curves of overall survival for patients with CC0 and CC1+CC2

abdomen, is a scoring system providing information of the applicability of optimal cytoreduction, and is calculated while making perioperative exploration [11]. The median PCI value in our study was 10. A previous study showed that the mean PCI was 12.7, and the mean survival was longer in those with PCI ≥12.7 [15]. A previous study in patients with secondary cytoreduction showed that patients with PCI >6 had a worse survival than those with PCI ≤6 [18]. The results of a retrospective study investigating the predictive value of PCI in patients with primary cytoreduction showed that high PCI values had a negative effect on OS and DFS. Additionally, operating time was significantly longer in patients with high PCI values [22]. Total colectomy, small intestine resection, liver metastasectomy, gastrectomy, and hepatoduodenal lymph node dissection were performed a greater number of patients with PCI ≥10, but the difference was not statistically significant. Similar to the results reported previously, our results showed an increase in operating time with an increase in PCI. However, unlike the results reported previously, PCI did not have an effect on OS and DFS. HIPEC can be performed using two different techniques, namely, open (coliseum) or closed. In the coliseum technique,

the heated chemotherapeutic agent is administered within the abdomen with catheters without closing the abdominal wall after the CRS. The most important advantage of this technique is that the heated chemotherapeutic agent can be homogenously distributed within the abdomen. The disadvantage of the open technique is that the chemotherapeutic agent may form an aerosol because of the high heat, and thus, may increase the exposure of the surgical personnel to the chemotherapeutic agent. The closed technique is performed by closing the abdominal wall, placing drains in the four quadrants and then administering the heated chemotherapy into the abdomen. Although homogenous distribution of the drug is more difficult using this technique than with the open technique, the most important advantage of the closed technique is less dissipation of heat [7, 23]. We used the closed technique in this study to maintain high intra-abdominal temperature and to reduce the exposure of the surgical personnel to chemotherapy.

This study had low number of patients, lacked a control group, and had a short follow-up period. Thus, additional, prospective, randomized, and comprehensive studies on this topic should be performed in the future. For many years, CRS+HIPEC has been performed in patients with primary and recurrent grade IIIC and IV ovarian cancer. Although a consensus has not been established thus far, HIPEC is believed to play a role in improving the survival, irrespective of the time when it is performed. In conclusion; we report the short-term results of CRS+HIPEC performed by the same team at a single center to a specific patient group. HIPEC alone is not sufficient and should be performed with optimal CRS.

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