Surgical and survival outcomes of cytoreductive surgery alone or with perioperative intraperitoneal chemotherapy in high peritoneal cancer index

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ABSTRACT

Objective: The aim of this study was to examine the early surgical and long-term survival outcomes of cytoreductive surgery (CRS) alone and CRS plus perioperative intraperitoneal chemotherapy (IPC) in patients with peritoneal metastases (PM).

Material and Methods: CRS alone or CRS plus IPC was performed on 122 patients for various intraabdominal PMs. Patients were divided into two groups as PCI ≤19 and PCI >19 to compare early surgical outcomes.

Results: Among PM patients 70 (57.4%) were of non-ovarian and 52 (42.6%) were of ovarian origin. Of the patients 74 (60.7%) were in the peritoneal cancer index (PCI) ≤19 group and 48 (39.3%) were in the PCI >19 group. The complication ratio of PCI >19 group was higher than that of the PCI ≤19 group and median overall survival (OS) of PCI >19 group was lower than that of the PCI ≤19 group. Complete or nearly complete (CCR-0/CCR-1) resections rates were similar in both groups (95.9% in the PCI ≤19 group and 93.8% in the PCI >19 group). However, CCR-0 resection rate was found to be lower in the PCI >19 group compared to the PCI ≤19 group (60.8% vs. 39.6%) (p< 0.001).

Conclusion: CCR-0/CCR-1 resections can be achieved with CRS in most patients with PCI >19 score. It would be appropriate to consider CRS or CRS plus perioperative IPC for palliative purposes in selected patients with PCI >19 score.

Keywords: Peritoneal metastases, peritoneal cancer index, cytoreductive surgery, early post-operative intraperitoneal chemotherapy, hyperthermic intraperitoneal chemotherapy

INTRODUCTION

Peritoneal metastases (PM) is a disease characterized by the distribution of avascular tumor nodules in different diameters and numbers on peritoneal surfaces, and its prognosis is poor, especially in non-gynecological cancers (1). In recent years, cytoreductive surgery (CRS) plus perioperative, intraperitoneal chemotherapy (IPC) methods in PM of gastrointestinal and ovarian cancers have provided positive oncological results.

The most critical factors in selecting patients treated with CRS are the type of primary tumor, the volume and distribution of peritoneal disease, and the patient's performance status (2). As it is known, the parameters to be considered in the application of curative perioperative chemotherapy are the peritoneal cancer index (PCI) and the complete cytoreduction (CCR), which indicates the completion of cytoreduction. Some authors suggest prognostic cut-offs for PCI as <17 for colorectal PM, <7 for gastric PM, and <15 for ovarian PM (3-6). On the other hand, there is no specific PCI cut-off value for patients with pseudomyxoma peritonei (PMP) and long-term survival is not affected by the extent of the disease (7). Regardless of the origin of PM, the most important prognostic factor for survival is the removal of all visible tumor tissues with complete cytoreduction. The HIPEC or EPIC is eligible for patients undergoing complete (CCR-0) or nearly complete (CCR-1) resection (8,9).

In the literature, it is emphasized that high PCI is associated with suboptimal cytoreduction, while the complication rates due to CRS are higher and survival outcomes are worse in patients. A study of colorectal cancer has shown that PCI >19 correlated with suboptimal cytoreduction and is associated with increased major morbidity and worse survival (10). Similarly, PCI ≥21 has been shown to be an independent predictor of high-grade complications after ovarian cancer surgery (11).

Additionally, since systemic chemotherapy cannot be started in cases of intestinal obstruction, surgical treatment is usually preferred. Averbach and Sugarbaker evaluated early post-operative IPC with CRS in patients with bowel obstruction due to recurrent intraabdominal cancer (12). The authors demonstrated that with aggressive treatment, favorable oncologic outcomes (three-year survival 32.7%) can be achieved with acceptable morbidity and mortality rates (55% and 7.14%, respectively).

In the light of these studies, we wanted to question the rationality of the treatment methods by revealing the early surgical and long-term survival results of CRS or CRS plus perioperative IPC in our patients with PMs with a high PCI (PCI >19).

MATERIAL and METHODS

Patients

Between 2011 and 2019, CRS alone or CRS plus IPC was performed on 122 patients for various intraabdominal PMs. The patients whose data were regularly recorded were analyzed retrospectively and were divided into two groups as PCI ≤19 and PCI >19.

Patient characteristics of the groups (origin of PMs, age, sex, BMI, clinical and radiological features), CCR-R resections (CCR-0, CCR-1, CCR-2), treatment modalities (CRS alone and SRC plus perioperative IPC), operative time, hospital stay, surgical procedures (organ resections and peritonectomies), early post-operative complications, and hospital mortality were compared. In the survival analysis, patients were categorized into two groups as non-ovarian and ovarian. Survival analysis was performed according to PCI scores [≤9, (10-19) and >19], CCR resections, and treatment modalities (CRS alone, CRS plus HIPEC, and CRS plus EPIC) in groups.

Peritoneal cancer index and complete cytoreduction scores

PCI scoring defined by Sugerbaker was used (15). Resections (completeness of cytoreduction) were classified as CCR-0, CCR-1, CCR-2. CCR-0 was defined as the absence of visible tumor tissue in the abdomen, CCR-1 residual tumor ≤2.5 mm, and CCR-2 residual tumor between 2.5 mm and 2.5 cm.

Patient selection criteria

All patients were discussed in detail in the multidisciplinary oncology council before the surgery and evaluated in terms of treatment planning. Imaging methods such as ultrasonography, computerized tomography, magnetic resonance imaging, and positron emission tomography were used to evaluate the extent of the disease in the pre-operative period. The selection criteria of the patients to be admitted to the CRS are listed below.

1- Performance status must be EGOG ≤2

2- Age >18

3- Absence serious medical histories (for example; severe cardiac or chronic obstructive pulmonary disease)

4- Nutritional status (albumine >2.5 ng/dL)

5- Absence of signs of extra-abdominal metastases

6- Absence of signs of biliary obstruction

7- No bulky involvement in the mesenteric root

8- Absence of bilateral hydroureteronephrosis

Surgical procedures

Laparotomy was performed with a median incision extending from the xiphoid to the pubis. Incision scars due to previous surgeries were removed and intraabdominal adhesions were separated by dissection. Except for PMP, only peritoneal areas infiltrated with tumor were removed in the dissection of the peritoneum. Routinely, after the resections, the abdomen was irrigated with a mixture of povidone-iodine and oxygenated water for one minute and then with 0.9% isotonic NaCl. HIPEC was not performed in patients who developed excessive blood loss and severe acidosis during the operation. After the HIPEC procedure was completed, the abdomen was re-opened and anastomoses were performed.

Organ resections and peritonectomy procedures were based on Paul H. Sugarbaker's procedures (13).

Perioperative intraperitoneal chemotherapy

In HIPEC for colorectal PM and PMP we used mitomycin C (15 mg/m^2, with 1.5% dextrose dialysis solution at 42 °C for 90 minutes) or oxaliplatin (360 mg/m^2, with 5% dextrose solution at 43 °C for 30-45 minutes). In HIPEC for gastric PM, PMP and ovarian PM we used cisplatin (50 mg/m^2, 1.5% dextrose dialysis solution at 42 °C for 90 minutes). In non-ovarian PM, 5-fluorouracil was used for EPIC (400-600 mg/m^2 with 50 meq $NaHCO_3$ and 1 liter of 5% dextrose). In ovarian PM, paclitaxel or cisplatin was used for EPIC. In EPIC, the drains were clamped for 23 hours after the chemotherapeutic agent was administered intraperitoneally. Then, the drains were opened for one hour and the chemotherapeutic agent was drained out of the abdomen. The EPIC procedure was reapplied in patients with good tolerance in the follow-up.

Post-operative approach

All patients were followed in the the intensive care unit after the operation. Post-operative bleeding was defined as more than 200 cc of blood coming from the drains. Post-operative mortality

was defined as mortality within the first month. Patients with CRS alone were transferred to medical oncology after recovery and were allowed to receive adjuvant chemotherapy regimens in the early period.

Statistical Analysis

Statistical analysis was achieved using the SPSS 21.0 software version. The variables were investigated using analytical methods (Kolmogorov-Smirnov test) to determine distribution. Descriptive analyses were introduced using means and standard deviations if the variables were normally distributed; medians and interquartile ranges were used if the variables were non-normally distributed. Categorical variables are specified as numbers and percentages. Pearson Chi-square test was used to compare categorical variables, and student's t test was used for pairwise comparison of normally distributed continuous variables.

The survival analysis of cancers according to treatment status, CC score, and PCI score was performed using the log-rank test. Chi-square test was used to compare categorical variables, and Mann-Whitney U test was used to compare non-normally distributed variables.

RESULTS

Among the PM patients 70 (57.4%) were of non-ovarian and 52 (42.6%) were of ovarian origin. Of the patients 74 (60.7%) were in the PCI ≤19 group and 48 (39.3%) were in the PCI >19 group. Male sex ratio was higher in the PCI >19 group than in the PCI ≤19 group. The origin of PMs with high PCI was colorectal cancer in the first place and ovarian cancer in the second place. A adverse clinical findings were found at a higher rate in the PCI >19 group. Especially bowel obstruction and hydroureteronephrosis were detected at a significantly higher rate in the PCI >19 group (p= 0.001, p= 0.041) (Table 1).

Table 1. Pre-operative patient characteristics			
	PCI ≤19 (n= 74)	**PCI >19 (n= 48)**	**p**
Sex			
Female	58 (78.4%)	26 (54.2%)	**0.005**
Male	16 (21.6%)	22 (45.8%)	
Age (years), mean ± SD	54.18 ± 11.5	52.4 ± 13.7	0.431
BMI, mean ± SD	26.1 ± 5.5	25.4 ± 6.3	0.584
Origin of PM			
Colorectal	24 (32.4%)	23 (47.9%)	0.086
Appendiceal	3 (4.1%)	4 (8.3%)	0.321
Gastric	3 (4.1%)	4 (8.3%)	0.321
Mesothelioma	3 (4.1%)	2 (4.2%)	0.976
Pancreas	0	1 (2.1%)	0.212
GIST	1 (1.4%)	2 (4.2%)	0.327
Ovarian	40 (54.1%)	12 (25%)	**0.002**
Primary	37 (50%)	21 (43.7%)	0.596
Secondary*	37 (50%)	27 (56.3%)	0.499
Clinical and radiological findings			
Bowel obstruction	7 (9.5%)	16 (33.3%)	**0.001**
Ascites	30 (40.5%)	25 (52.1%)	0.211
Liver metastasis and/or			
Glisson capsule involvement	14 (18.9%)	16 (33.3%)	0.071
Mesenteric root involvement	1 (1.4%)	3 (6.3%)	0.550
Hydroureteronephrosis	7 (9.5%)	11 (22.9%)	**0.041**
5 cm >intraabdominal mass	34 (45.9%)	27 (56.2%)	0.266
BMI: Body mass index, PCI: Peritoneal cancer index, PM: Peritoneal metastasis, GIST: Gastrointestinal stromal tumor.			
*Secondary: Peritoneal metastasis was detected after primary tumor surgery.			

Table 2. Comparison of post-operative variables in PCI groups

	PCI ≤19 (n= 74)	PCI >19 (n= 48)	p
CCR score			
CCR-0	45 (60.8%)	19 (39.6%)	**<0.001**
CCR-1	26 (35.1%)	26 (54.2%)	**<0.001**
CCR-2	3 (4.1%)	3 (6.2%)	0.456
Treatment modalities			
CRS alone	37 (50.0%)	15 (31.2%)	0.060
IPC (HIPEC or EPIC)	37 (50.0%)	33 (68.8%)	0.058
Duration of surgery (minute), mean ± SD	391.9 ± 127.3	523.0 ± 159.9	**<0.001**
Duration of hospital stay (day), mean ± SD	16.9 ± 11.6	31.4 ± 24.1	**<0.001**
Follow up (mounth), mean ± SD	26.5 ± 15.1	12.8 ± 13.6	**<0.001**

PCI: Peritoneal cancer index, CCR: Complete cytoreduction, CRS: Cytoreductive surgery, EPIC: Early post-operative intraperitoneal chemotherapy, HIPEC: Hyperthermic intraperitoneal chemotherapy, SD: Standard deviation.

Seven appendicial tumors and two ovarian tumors were mucinous ascites, the others were non-mucinous. Primary surgery rate was (number of patients without previous abdominal surgery for cancer) 58 (47.5%), Recurrence rate was 64 (52.5%) (patients who had previously undergone abdominal surgery for cancer). All patients with recurrence had previously received different neoadjuvant and adjuvant chemotherapy regimens. All patients with primary recurrence underwent emergency surgery for obstruction and bleeding. In principle, neoadjuvant chemotherapy was administered except in cases where it was not needed. Adjuvant treatment is given between 4-6 months and neoadjuvant treatment between 8-12 months depending on the origin of the primary tumor. We use Folfox or Folfiri in colon cancer, Folfox or Folfiri in ovarian cancer Carboplatin and Flot combinations in gastric cancer as adjuvant and neoadjuvant chemotherapy regimens.

Complete or nearly complete (CCR-0/CCR-1) resections rates were similar in both groups (95.9% in the PCI ≤19 group and 93.8% in the PCI >19 group). However, the CCR-0 resection rate was found to be lower in the PCI >19 group compared to the PCI ≤19 group (60.8% vs. 39.6%) (p< 0.001). The rate of IPC was higher in the PCI >19 group (50% vs. 68.8%) (p= 0.058).

Mean duration of surgery time and the mean duration of hospital was significantly longer in the PCI >19 group than in the PCI >19 group (p< 0.001) (Table 2).

Comparison of complications

Surgical complications rates were very high in the PCI >19 group compared to the PCI ≤19 group (Table 3). The rates of reoperation (16.7% vs. 5.4%) and percutaneous intraabdominal abscess drainage (14.6% vs. 4.1%) were also significantly higher in the PCI >19 group than in the PCI ≤19 group (p= 0.042 and p= 0.038, respectively). Reasons for reoperation were bowel leakage in six patients, intraabdominal bleeding in four patients, and bladder/ureteral leakage in two patients. While hospital mortality rate was 12.5% in the PCI >19 group, there was no mortality in the PCI ≤19 group (p= 0.003).

Hospital mortality occurred in six patients. The causes of death

Table 3. Comparison of early post-operative complications and mortality in PCI groups

Complications	PCI ≤19 (n= 74) n (%)	PCI >19 (n= 48) n (%)	p n (%)
*Elevated AST-ALT levels	18 (24.3)	22 (45.8)	**0.014**
Acute renal failure	1 (1.4)	11 (22.9)	**<0.001**
Leukopenia	1 (1.4)	5 (10.4)	**0.037**
Wound site (seroma, dehiscence, infection)	20 (27.0)	27 (56.2)	**0.001**
Pulmonary (effusion, atelectasis, pneumonia)	13 (17.6)	20 (41.7)	**0.003**
Sepsis	4 (5.4)	16 (33.3)	**<0.001**
Intraabdominal bleeding	10 (13.5)	15 (31.2)	0.018
Intraabdominal fluid collection	7 (9.5)	14 (29.2)	**0.005**

Table 3. Comparison of early post-operative complications and mortality in PCI groups (continue)

Complications	PCI ≤19 (n= 74) n (%)	PCI >19 (n= 48) n (%)	p n (%)
Ileus	4 (5.4)	6 (12.5)	0.190
Bowel leakage	1 (1.4)	7 (14.6)	**0.006**
Urine leakage	1 (1.4)	6 (12.5)	**0.015**
Pancreatic leakage	0	5 (10.4)	**0.008**
Interventions for complications			
Re-operation	4 (5.4)	8 (16.7)	**0.042**
Percutaneous intraabdominal abscess drainage	3 (4.1)	7 (14.6)	**0.038**
Percutenous nephrostomy catheterization	2 (2.7)	3 (6.3)	0.346
Hospital mortality	0	6 (12.5)	**0.003**
ALT: Alanin aminotransferase, AST: Aspartat aminotransferase, PCI: Peritoneal cancer index.			

of the patients were sepsis and pneumonia due to surgical complications.

Survival analysis

The follow-up period was 14.3 ± 9.5 months in the non-ovarian group and 20.5 ± 16.1 months in the ovarian group (p= 0.059). The survival distribution of non-ovarian and ovarian patients according to PCI score, CCR resections and treatment modalities is shown in Table 4. Median survival time of the patients with PC >19 in the non-ovarian and ovarian groups was similarly low (Table 4). Median survival time of patients with CCR-0 resection of non-ovarian and ovarian PMs was almost twice that of patients with CCR-1 resection (Table 4).

Although not statistically significant in either group, the best survival outcomes were achieved in patients who underwent CRS plus EPIC (Table 4).

DISCUSSION

CRS is an extensive surgical procedure that allows complete resection of all visible macroscopic peritoneal metastatic disease and treatment of residual microscopic peritoneal disease with perioperative IPC modalities. Most peritoneal surface malignancy treatment centers use HIPEC only, some use EPIC only, and others use both in turn.

The method of application of IPC may also vary according to cost conditions. We generally prefer to apply HIPEC, but due to perioperative instability, we may have to apply EPIC or alone CRS to some of our patients.

Patients to whom CRS plus IPC is applied are at risk of serious morbidity due to the possible side effects of both the complex surgical procedure and the drugs administered intraperitoneally (14). In this respect, identifying patients who will benefit from CRS plus IPC is extremely important from a prognostic point of view. Therefore, the authors proposed prognostic PCI score cut-

off values for PMs of various origins (4-6,15-17). PCI ≥20 score, perihepatic region involvement and diffuse small bowel involvement were determined as risk factors in radiological prognostic evaluation in colorectal PM (18). Yan et al. have reported that the probability of suboptimal cytoreduction is 100% in the presence of a tumor >5 cm in the epigastric region and small intestine involvement and the probability of CCR is 94% in the absence of these findings, in the peritoneal mesothelioma study (19). Massive small bowel and mesenteric involvement and the presence of extensive hepatobiliary disease are negative predictive factors for cytoreduction, as emphasized in large-centered studies. However, it is not possible to exclude patients with bowel obstruction from cytoreduction, especially since they do not receive chemotherapy. In our study, approximately 40% of all patients had high PCI score. All negative clinical findings, especially bowel obstruction, liver metastasis and hydroureteronephrosis were found to be significantly higher in the PCI >19 group. As can be seen from these findings, a significant number of our patients were candidates for suboptimal cytoreduction. Despite this, in our study, complete or nearly CCR could be obtained with multiple organ resections and peritonectomy procedures in most (93.8%) patients with PCI >19. However, despite these extensive surgical procedures, the CCR-0 resection rate was significantly lower in the PCI >19 group than in the PCI ≤19 group (39.6% and 60.8%, respectively). Similarly, Yonemura et al. have reported in patients with colon cancer that, the rate of CCR decreased as the PCI score increased (20).

In a systematic review of morbidity and mortality of SRC plus HIPEC, mean mortality rate has reported as 2.9% (range 0-17%), and primary morbidity rate as 28.8% (0-52%). A multi-institutional study has reported a, reoperation rate of 14%, mortality rate due to SRC plus IPC as be 4.1% and the morbidity rate as 33.6% in non-ovarian peritoneal carcinomatosis (21).

Table 4. Distribution of the survival of non-ovarian and ovarian groups according to PCI scores, CCR resections and treatment modalities

	Number of patients (n)	Mortality (n)	Overall survival (%)	Overall survival rates (%)			Overall survival time (months)			
				6 months	1 year	3 years	Median ± Standard error	95% Confidence interval	Log-rank Chi-square/df	p
Non-ovarian	**70**	**33**	**52.9**	**75.3**	**59.4**	**41.8**	**24.0 ± 6.6**	**10.9 - 37.0**		
PCI (≤9)	16	2	87.5	100.0	90.9	81.8	31.6 ± 2.8	26.1 - 37.1		
PCI (10-19)	18	9	50.0	88.9	76.9	41.1	26.8 ± 4.1	18.8 - 34.9	13.697/2	**0.001**
PCI (>19)	36	22	38.9	58.0	36.7	24.1	13.4 ± 2.0	9.3 - 17.5		
CCR-0	35	10	71.4	96.9	83.4	60.8	32.5 ± 3.4	25.8 - 39.2		
CCR-1	29	17	41.4	82.8	71.3	24.1	18.8 ± 3.7	11.6 - 26.1	10.505/2	**0.005**
CCR-2	6	6	0	83.3	16.7	16.7	12.6 ± 5.0	2.7 - 25.5		
CRS alone	17	8	52.9	58.8	58.8	51.5	20.2 ± 3.8	12.7 - 27.7		
HIPEC	36	18	50.0	77.7	56.0	30.8	19.8 ± 2.7	14.5 - 25.2	0.990/2	0.610
EPIC	17	7	58.8	87.4	65.7	46.0	27.7 ± 4.9	18.0 - 37.3		
Ovarian	**52**	**16**	**69.2**	**82.1**	**74.8**	**60.4**	**38.4 ± 3.3**	**31.8 - 45.0**		
PCI (≤9)	17	2	88.2	100.0	86.5	50.0	50.1 ± 3.1	44.0 - 56.2		
PCI (10-19)	23	5	78.3	100.0	80.4	33.3	35.8 ± 3.4	28.9 - 42.6	20.210/2	**<0.001**
PCI (>19)	12	9	25.0	80.8	68.9	25.0	14.2 ± 4.9	4.6 - 23.8		
CCR-0	29	6	79.3	92.9	89.0	70.0	44.9 ± 3.6	37.8 - 51.9		
CCR-1	22	9	59.1	86.4	60.0	54.0	25.9 ± 4.2	17.6 - 34.3	10.456/2	**0.005**
CCR-2	1	1	0	0	0	0	2.0 ± 0	2.0 - 2.0		
CRS alone	36	9	75.0	79.8	76.2	69.8	32.7 ± 2.9	27.0 - 38.5		
HIPEC	4	4	0	50.0	50.0	0	17.0 ± 8.7	0 - 34.1	8.685/2	**0.013**
EPIC	12	3	75.0	100.0	77.8	64.8	39.3 ± 7.3	24.9 - 53.7		

PCI: Peritoneal cancer index, CCR: complete cytoreduction, CRS: Cytoreductive surgery, EPIC: Early post-operative intraperitoneal chemotherapy, HIPEC: Hyperthermic intraperitoneal chemotherapy.
The median OS of non-ovarian group with PCI <9 and PCI (10-19) score is higher than PCI score >19 (p= 0.001). The median OS of ovarian group with PCI <9 and PCI (10-19) score is higher than PCI score >19 (p< 0.001). The median OS in the non-ovarian and ovarian groups with a CCR-0 resection was much higher than the CCR-1 and CCR-2 resections (p= 0.005). The significant difference in overall survival on the treatment of ovarian PM is due to the fact that alone SRC and SRC plus EPIC procedures have more prolonged median OS than SRC plus HIPEC procedures (p= 0.001).

As demonstrated in the studies above, CRS plus perioperative IPC method is generally accepted as a surgical procedure with morbidity and mortality rates similar to those seen in any major abdominal surgery. Studies have shown that especially the increase in PCI is correlated with major morbidity. In a study on ovarian cancer, it has been found that high PCI (>24) caused an increase in complication rates (22). In another study, PCI ≥21 has been found to be an independent predictor of high-grade complications after ovarian cancer surgery (11). A study on colorectal cancer has confirmed that longer operative time (>540 minutes) and PCI >19 are independent risk factors for major morbidity (10). In our study, the mean duration of surgery time was significantly longer in the PCI >19 group (523 minutes vs. 391.9 minutes). We found that the morbidity and mortality rates after CRS were very high in the PCI >19 group compared to the PCI ≤19 group. Especially, intraabdominal bleeding, intraabdominal fluid collection bowel leakage, urine leakage, and pancreatic leakage were found to be quite high in the PCI >19 group. On the other hand, our results show that the incidence of post-operative complications in patients with PCI ≤19 is not significantly different from that seen in any major intraabdominal surgery.

Intestinal fistulase have been reported as the most important cause of morbidity in SRC plus perioperative IPC (22-24). In a study, the authors have reported that a high PCI score was the only independent risk factor for gastrointestinal complications in patients undergoing CRS plus IPC in multivariate analysis. In the study, it has been reported that the frequency of gastrointestinal complications was highly correlated with a PCI >30 score (25). In our study, we found a high rate of bowel leakage (8.6%) like the literature. However, one of these patients was in the PC ≤19 group and seven of them were in the PCI >19 group. In addition to intestinal fistulaes, urinary anastomotic leaks are complications that are difficult to manage. In the literature, it is stated that urological procedures increase the risk of major complications in CRS (26,27).

In our study, the hospital mortality rate was 12.5% in the PCI >19 group, while there was no mortality in the PCI ≤19 group. The causes of mortality of the patients were sepsis and pneumonia due to surgical complications. The rates of sepsis and pulmonary complications were found to be quite high, especially in the PCI >19 group (18.7 % and 41.7 %). Similarly, it is stated that the leading cause of death after CRS/HIPEC is sepsis and related respiratory complications (8,22).

In this study, the distribution of patients in the PCI groups (54% ovarian PM in PCI ≤19 and 48% colorectal PM in PCI >19) was not homogeneous. Therefore, it was thought that it would be more appropriate to perform survival analyzes in two separate groups (non-ovarian and ovarian) based on tumor origins. Analysis of survival in the groups was performed separately according to PCI scores [≤9, (10-19) and >19], CCR resections, and treatment modalities (CRS alone, CRS plus HIPEC, and CRS plus EPIC).

In our series, median survival time of the non-ovarian group was 31.6 months in the PCI ≤9 group, 26.8 months in the PCI (10-19) group and 13.4 months in the PCI >19 group. In colorectal carcinoma, Leonardo et al. have indicated that patients with high PCI (PCI >6) and significant nodal involvement (N2) may not benefit from the SRC plus HIPEC procedure (28). Weber et al. have reported that the median survival in patients with colon cancer was 33.2 months in patients with PCI ≤10, 12.1 months in patients with PCI (11-19) and the two-year overall survival was 89% with PCI ≤10 (29). Da silva and Sugarbaker have reported that patients with PCI of <20 had a median survival of 41 months compared with 16 months for patients with PCI >20 (17). The authors state that when PCI is greater than 20 in colorectal cancer, five-year survival rate is less than 10%, and that widespread disease becomes a relative contraindication for this combined therapy (6). In our series, non-ovarian PMs were heterogeneous, but the majority (approximately 2/3) were colorectal PMs. Therefore, it is seen that similar survival results have been obtained. In our series the

median survival time of ovarian group was 50.1 months in the PCI <9 group, 35.8 months in the PCI (10-19) and 14.2 months in the PCI >19 group. In a study for ovarian cancer, PCI >10 in primary advanced ovarian cancer was positively associated with poor prognosis (6). A recent prospective study concluded that the PCI score is a reliable tool to help assess disease extent in patients with advanced epithelial ovarian cancer and may help predict complete surgical cytoreduction, but not as a predictor of death. In this study, the cut off value for over PC is PCI >13 (30). In our series, the survival of ovarian PM patients with PCI >19 was quite low. In fact, the median survival time of patients with PC >19 in the non-ovarian and ovarian groups was nearly identical.

In our study, one of the best prognostic factors for median OS was a CCR score as well as a low PCI score. Median survival time of the non-ovarian group was 32.5 months in CCR-0, 18.8 in months CCR-1 and 12.6 months in CCR-2. Three-year survival rates of the non-ovarian group was 60.8% in CCR-0, 24.1% in CCR-1 and 16.7% in CCR-2 (p= 0.005). Median survival time of non-ovarian PM patients with CCR-0 resection was almost twice that of patients with CCR-1 resection. We found that in non-ovarian PMs, the CCR-1 resection did not provide a significant long-term (three-years) survival advantage over the CCR-2 resection. Yonemura et al. have also reported the median survival time as 25.9 months and five-years overall survival 20% in patients who underwent CCR-0 resection and in 8.0 months and 9.9%, respectively with CCR-1 resection (20). In their study, CCR-0 resection and PCI ≤10 have been reported as independent favorable prognostic factors in multivariate analysis (20). Elias et al. have achieved a median survival of 33 months with CCR in 84% of patients with colorectal carcinoma. In multivariate analysis showed that CCR was one of the independent prognostic factors (8).

Median survival time in the ovarian group was 44.9 months in CCR-0, 25.9 months in CCR-1 and 2.0 months in CCR-2 (p= 0.005). Likewise, studies with ovarian cancer have emphasized that the survival benefit of R1 resection is low. Arjona-Sanchez A. have reported the mean PCI score of the patients as 15.8 and performed a CCR-0 score of 95% in their study (31). In the study, R1 cytoreduction was detected as a risk factor in multivariate analysis (31). Robella et al. have reported that the most important prognostic factor for survival was the completeness of cytoreduction (32). In their study, overall survival with CCR was 48 months. Similarly, CCR-0 resection was one of the most important prognostic factors affecting survival in our patients with ovarian PM. As with non-ovarian PMs, median survival time of ovarian PM patients with CCR-0 resection was almost twice that of patients with CCR-1 resection.

In the literature for PM due to gastric cancer, Yang et al. in a prospective randomized Phase III study, have reported median

survival as 6.5 months in the CRS group and 11 months in the CRS plus HIPEC group (33). In a recent phase three study for ovarian cancer, adding HIPEC to interval CRS in patients with stage III epithelial ovarian cancer resulted in longer recurrence-free survival and overall survival compared to surgery alone without increased side effects (34). A recent study has investigated the specific benefit of adding HIPEC to CRS in colorectal PM. The authors have reported overall survival of 41.7 months in the CRS plus HIPEC group and 41.2 months in the CRS alone group. The authors have underlined that adding HIPEC to CRS had no overall survival benefit (35). We performed CRS plus perioperative IPC (HIPEC or EPIC) in 50% of our patients with PCI ≤19 and 68.8% of our patients with PCI >19. CRS alone was applied to a significant proportion of patients in both groups. Overall in our study, it was observed that adding HIPEC to CRS in non-ovarian PMs did not provide a survival advantage over other treatment modalities. This may be due to the fact that most of the non-ovarian patients were of colorectal origin. On the other hand, the survival results of our patients who underwent CRS plus HIPEC for the ovarian PM group were poor. The reason for this may be the low number of patients who underwent CRS plus HIPEC in this group, as well as the fact that some of the patients died in the early post-operative period due to complications. In addition, it is clear in this series that alone CRS provided a remarkable survival in both groups.

The superiority of HIPEC and EPIC methods over each other is controversial in the literature. In the study on the method of IPC, Elias et al. have compared CRS and HIPEC/EPIC methods for complications and therapeutic outcomes in colorectal cancer (36). They have reported that HIPEC was better tolerated, had less morbidity and mortality, and provided a more prolonged survival. The same author, in a later study for colon PM, has shown that the use of HIPEC or EPIC did not have a statistically significant prognostic effect (8). Glehen et al. have shown that no significant difference in survival was observed between patients treated with intraperitoneal chemohyperthermia (IPCH) alone and EPIC alone or both, but survival outcomes were better with the combination (9).

The present study has some limitations. It is heterogeneous in terms of histopathological features and treatment modalities.

CONCLUSION

This study showed that a high rate of CCR-0/CCR-1 resections can be achieved with extensive CRS in patients with PCI >19.

However, this result was obtained with extensive surgery results in high post-operative morbidity and mortality. In both non-ovarian and ovarian groups, the CCR-1 resection provides approximately half the survival time of the CCR-0 resection. In the PCI >19 group, low CCR-0 resection rate and high CCR-1 resection rate also negatively affect long-term survival

outcomes. In general, the best survival results are obtained in patients with a PCI ≤9 score and a CCR-0 resection. The survival time of patients who underwent EPIC in non-ovarian and ovarian PMs was relatively longer, but this was not statistically significant.

The results of this study showed that the application of CRS or CRS plus IPC treatment methods should be considered for palliative purposes in selected patients with PCI >19 score.

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Yüksek periton kanseri indeksinde tek başına veya perioperatif intraperitoneal kemoterapi ile birlikte sitoredüktif cerrahi ve sağkalım sonuçları

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, peritoneal metastazlı (PM) hastalarda tek başına sitoredüktif cerrahi (CRS) ve CRS artı perioperatif intraperitoneal kemoterapinin (IPC) erken cerrahi ve uzun dönem sağkalım sonuçlarını incelemektir.

Gereç ve Yöntem: Çeşitli intraabdominal PM'ler için 122 hastaya tek başına CRS veya CRS + IPC uygulandı. Erken cerrahi sonuçları karşılaştırmak için hastalar peritoneal kanser endeksi (PCI) ≤19 ve PCI >19 olmak üzere iki gruba ayrıldı.

Bulgular: Peritoenal metastazlı hastalarının 70 (%57,4)'i non-ovaryan ve 52 (%42,6)'si over kökenliydi. Hastaların 74 (%60,7)'ü PCI ≤19 grubunda ve 48 (%39,3)'i PCI >19 grubundaydı. PCI >19 grubunun komplikasyon oranı PCI ≤19 grubundan daha yüksektir ve PCI >19 grubunun medyan genel sağkalımı (GS) PCI ≤19 grubundan daha düşüktü. Tam veya tama yakın (CCR-0/CCR-1) rezeksiyon oranları her iki grupta da benzerdi (PCI ≤19 grubunda %95,9 ve PCI >19 grubunda %93,8). Ancak CCR-0 rezeksiyon oranı PCI >19 grubunda PCI ≤19 grubuna kıyasla daha düşük bulunmuştur (%60,8'e karşı %39,6) (p< 0,001).

Sonuç: PCI >19 skoru olan hastaların çoğunda CRS ile CCR-0/CCR-1 rezeksiyonları elde edilebilir. PCI >19 skoru olan seçilmiş hastalarda palyatif amaçlar için CRS veya CRS + perioperatif IPC'yi düşünmek uygun olacaktır.

Anahtar Kelimeler: Peritoneal metastazlar, peritoneal kanser endeksi, sitoredüktif cerrahi, erken postoperatif intraperitoneal kemoterapi, hipertermik intraperitoneal kemoterapi

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