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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Surface Malignancy: Initial Report from Shiraz Surgical Oncology Group

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Abstract

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used to treat peritoneal carcinomatosis (PC). The objective was to evaluate the outcomes of cytoreductive surgery (CRS) and HIPEC in our center.

Method: In this retrospective study, data were collected from 43 patients with PC who underwent CRS-HIPEC in 2016 at Faghihi Hospital of Shiraz University of Medical Sciences. Outcomes were collected and analyzed. Analyses were conducted through SPSS 23. *P*-value < 0.05 was considered to be statistically significant.

Results: The mean age of the patients was 52.23 ± 11.82 years. The participants in the study analysis consisted of 36 female (83.7%) and seven male patients (16.3%). The most common primary tumor was ovarian cancer (62.8%). Completeness of the cytoreduction score of CC0/CC1 was obtained in 87.7% of the patients. The 1- and 3-year overall survivals were 88% and 60%, respectively.

Conclusion: Our study supports that employing CRS and HIPEC for PC is feasible with acceptable morbidity in our center.

Keywords: Peritoneal malignancy, Drug therapy, Cytoreductive surgical procedures

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Introduction

Peritoneal surface metastases occur from a majority of the pelvis or abdomen malignancies. Once peritoneal carcinomatosis (PC) is diagnosed, a decision regarding palliative or aggressive cytoreductive surgery (CRS) and hyperthermic perioperative intraperitoneal chemotherapy (HIPEC) should be

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made.[1] PC has been associated with poor prognosis and low quality of life and is considered an end-stage condition with few effective treatments.[2]

In the last decade, CRS and HIPEC have been applied as hopeful treatments for several patients with PC of different originating cancers, such as appendiceal cancer, malignant peritoneal mesothelioma, colon cancer, and ovarian cancer.[3-6] Aggressive CRS/HIPEC are the treatments of choice for selected cancer patients with PC.

At the Surgical Oncology Department of Faghihi hospital affiliated with Shiraz University of Medical Sciences, CRS and HIPEC have been used to treat PC since 2016.

Our center is one of the first centers in the Middle East and an approved cancer surgery center in Iran employing CRS and HIPEC to treat peritoneal surface metastasis. In recent years, the management of PC has changed around the world. CRS and HIPEC became the standard treatment for PC secondary to ovarian cancer and colorectal cancer. Prior to HIPEC, patients did not have several choices except for palliative support and waiting during the few months they were told to have. Meanwhile, the survival period will increase to years, and outcomes will improve when using CRS and HIPEC treatment.

This study aimed to report these treatment approach outcomes in terms of survival, morbidity, and mortality rate and identify clinical and pathologic prognostic factors for survival in our center.

Materials and Methods

This single-center retrospective study evaluated the outcomes of CRS and HIPEC in 43 PC patients at Shiraz University of Medical Sciences in Faghihi hospital with a HIPEC machine in 2016. To the best of our knowledge, this is the second published report of patients with PC treated using CRS and HIPEC in Iran. The ethics committee of Shiraz University of Medical Sciences approved the study protocl. The ethcs committee reference number was IR.SUMS.MED. REC. 1398.1061. Written informed consent was obtained from all study participants.

In this retrospective cross-sectional study, the data were collected from a total of 43 patients with peritoneal surface malignancy (PSM) originating from colorectal, appendiceal, mesothelioma, stomach, and gynecological origins who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy via HIPEC machine since 2016 at the Surgical Oncology Department of Faghihi hospital affiliated with Shiraz University of Medical Sciences. We included data from all the patients, including a peritoneal cancer index (PCI)[7] less than 20/39 and fewer than three contiguous segments of liver metastasis according to the Coinaud definition[8] and without extensive small bowel involvement. Moreover, 1- and 3-year survival rates and post-operation mortality and morbidity rates were reported.

We gathered the patients' characteristics and primary cancer characteristics and histopathology grade, PCI9 for PC, intraoperative and postoperative data[10] including CRS completeness (CC0-3) data, duration of HIPEC, and kind of the drug used, post-operative morbidities, major morbidity (Clavien-Dindo 3 and 4),[11] overall and 60 days postoperative mortality, and overall survival (OS), disease-free survival (DFS), recurrence rate, and 1- to 3-year survival. Cytoreductive surgery and HIPEC procedure at laparotomy, via a long midline incision, abdominal exploration and evaluation of the resectability of the lesions were carried out. Careful dissection were performed with the purpose of eliminating all the visible tumor nodules. The extent of PC was examined utilizing PCI. CRS's success was evaluated with the completeness of CRS score (CSS), as previously described.

The aim of CRS was the removal of all gross tumors and involved tissues, peritoneum, and supracolic omentum in all the patients. All HIPEC procedures were carried out with an open abdomen using a HIPEC device immediately after completing CRS. Temperature probes were placed on the inflow and outflow tubing and were monitored continuously. A perfusion circulation was recognized with about 3 L of Ringer's lactate. Flow rates of about 1.2 L/min were continued

Table 1. Patient demographic, operative, and survival data (continued)

Characteristics		Overall patients (n = 43), (%)
Age		52.23 ± 11.82
Weight (Kg)		64.37 ± 12.46
Height (cm)		161.60 ± 5.74
BMI (Kg/cm^2)		24.26 ± 4.09
Sex		
Male		7 (16.3)
Female		36 (83.7)
Comorbidity disease		
DM		5 (11.6)
CVA		5 (11.6)
Smoking		3 (7)
Pulmonary disease		2 (4.7)
Primary tumor site		
Colorectal (%)		8 (18.6)
Appendix (%)		3 (7)
Ovarian cancer (%)		27 (62.8)
Gastric cancer (%)		3 (7)
Mesothelioma (%)		1 (2.3)
Uterus		1 (2.3)
Previous chemotherapy (during prior treatment)		
Yes		35 (81.4)
No		8 (18.6)
Neo-adjuvant chemotherapy (before CRS/HIPEC)		
Yes		32 (74.4)
No		11 (25.6)
Adjuvant chemotherapy		
Yes		40 (90.7)
No		4 (9.3)
Histopathology	**Ovary**	
	Papillary serous cystadenocarcinoma of ovary	16 (37.20)
	Mucinous	10 (23.25)
	Clear cell	1 (2.32)
	Appendix	
	Adenocarcinoma	2 (4.65)
	Mucinous neoplasm	1 (2.32)
	Colon	
	Adenocarcinoma	8 (18.60)
	Stomach	
	Poorly differentiated Adenocarcinoma	3 (7)
	Other	
	Primary peritoneal carcinoma	1 (2.32)
	Mesothelioma	1 (2.32)
Previous surgery		
USO		5 (11.62)
TAH-BSO ± Debulking Surgery		18 (41.9)
Abdominal exploration		3 (7)
Distal gastrectomy		1 (2.3)
Hemi colectomy		3 (7)
Left hemicolectomy and splenectomy		1 (2.3)
Colostomy		1 (2.3)
Without surgery		9 (20.9)
Duration of procedure (minutes)		368.79 ± 95.88
PCI score		8.79 ± 5.83

Table 1. Patient demographic, operative, and survival data (continued)

Characteristics	Overall patients (n = 43), (%)
Bleeding mL	528.84 ± 564.64
ICU stay, median day (range)	2 (0-32)
Hospital stay, median day (range)	7 (2-48)
HIPEC drug	
Cisplatin	32(74.4)
Mitomycine	11 (25.6)
HIPEC type	
Open	42 (97.7)
Close	1 (2.3)
Ileostomy	
Yes	3
No	40
Colostomy	
Yes	3
No	40
Anastomosis	
SB-SB	4 (8.16)
SB-Colon	5 (10.20)
Colon-Colon	6 (12.24)
Colon-Rectum	2 (4.08)
Esophago-SB	3 (6.12)
None	29 (59.18)
Peritonectomy site	
Upper abdomen	6 (14.63)
Parietal	9 (21.95)
Pelvic	24 (58.53)
Total	2 (4.87)
Peritonectomy	
Yes	31 (72.09)
No	12 (27.9)
CC Score	
0	32 (74.4)
1	6 (13.9)
2	4 (9.3)
3	1 (2.3)
Mortality at 60 days, No. (%)	3 (7)
Mortality, No. (%)	12 (27.9)
Overall survival, No. (%)	31 (72.1)
Surgical morbidity, No. (%)	
No complication	35 (81.4)
Wound infection	1 (2.3)
Intra-abdominal abscess/collection	2 (4.7)
Ileus or DGE >7 days (delayed gastric emptying)	4 (9.3)
Leak/fistula	1 (2.3)
Minor and major complications, Clavien-Dindo classification	
2	32 (74.41)
3	5 (11.62)
4	3 (6.97)
5	3 (6.97)
Reoperation	
Yes	3 (7)
No	40 (93)
Reoperation cause	
Anastomosis leak	1 (33.3)

Table 1. Patient demographic, operative, and survival data (continued)

Characteristics	Overall patients (n = 43), (%)
Collection	1 (33.3)
Colostomy necrosis	1 (33.3)
Readmission	
Yes	2 (4.7)
No	41 (95.3)
Reoperation cause	
Obstruction	1 (50)
Wound infection	1 (50)

CCS: Completeness cytoreductive surgery; PCI: Peritoneal cancer index; HIPEC: Hyperthermic intraperitoneal chemotherapy; SD: Standard deviation; BMI: Body mass index; DM: Diabetes mellitus; CVA: Cardiovascular accident; TAH-BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy; USO: Unilateral salpingo-oophorectomy; DGE: Delayed gastric emptying; SB: Small Bowel

with a HIPEC device. The total planned perfusion time following the initial addition of chemotherapy was typically 90-110 minutes, and the planned outflow temperature was 42 ºC. In heated intraperitoneal chemotherapy through HIPEC device, Mitomycin C 30 mg and 10 mg, respectively at 0 and 45 minutes, were entered into the abdomen and circulated for 90 minutes for colorectal, appendiceal, and PseudoMyxoma Peritonei (PMP).

CDDP Cisplatin 50 mg/m^2 at time 0 and Doxorubicin 15mg/m^2 at time 0 were entered into the abdomen and circulated for 90 minutes for primary peritoneal carcinomatosis. CDDP Cisplatin 75 mg/m^2 at time 0 was entered into the abdomen and circulated for 90 minutes for ovarian cancer PC. The statistical analyses were carried out through statistical package for the social sciences (version 23; IBM SPSS Inc. Chicago, IL, USA). All the data were collected retrospectively. Descriptive statistics were generated for all measures, including means, median, ranges, and standard deviations for continuous measures and frequencies and proportions for categorical data. Time-events values were given in median and a 95% confidence interval (CI). Overall survival (OS) rates were estimated with Kaplan-Meier product-

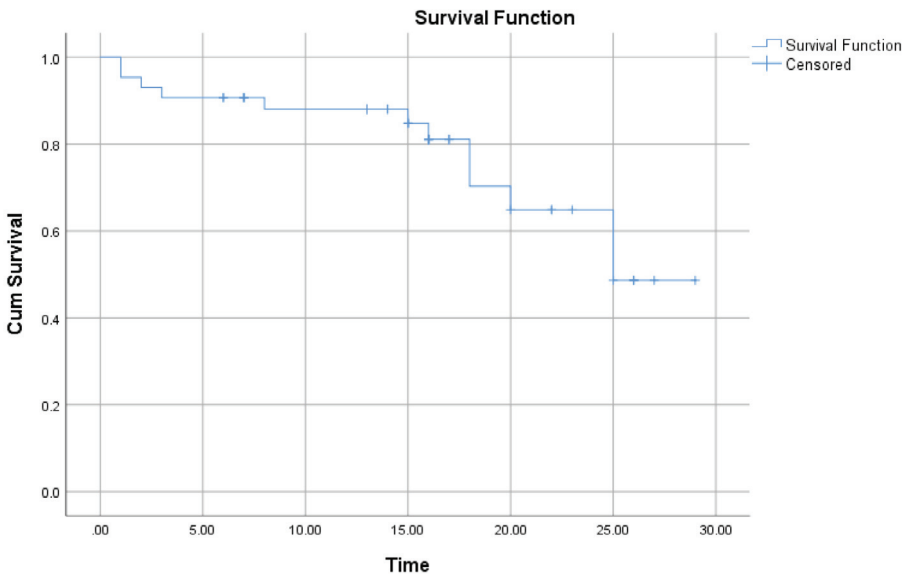

Figure 1. This figure portrays the overall survival (month) of the patients undergoing CRS and HIPEC (Kaplan-Meier curve).

CRS: Cytoreductive surgery; HIPEC: Hyperthermic perioperative intraperitoneal chemotherapy; Cum: Cumulative

limit method and reported with a 95% CI. Survival was calculated from the time of first complete cytoreduction to death or the present time.

Results

The mean age of the patients was 52.23 ± 11.82 years. The participants in the study analysis consisted of 36 females (83.7%) and seven (16.3%) males. The most common primary tumor location was in the ovary (62.8%). The second most prevalent primary tumor was colon cancer (18.6%). A completeness of cytoreduction (CC) score of CC0/CC1 was obtained in 87.7% of the patients (73.7% and 14%).

The 60-day postoperative mortality rate was 6.97%, and 11.62% of the patients developed a postoperative complication, such as leakage and collection. Wound infection and post-operation obstruction were reported in two patients. Pulmonary thromboembolism and deep vein thrombosis, pancreatitis, and fistula were not found in the patients. Three patients were re-operated due to anastomosis leakage, collection formation, and colostomy necrosis. In addition, 18.59% of the patients developed grades 3 and 4 of the Dindo-Clavien classification for post-operation complications. The mean PCI was 8.79 ± 5.83. (Range: 1-20). The mean of hospital and ICU stay respectively were 9.16 ± 8.86 and 3.6 ± 7.02 days. The mean surgery duration was 368.79 ± 95.88 minutes (range: 249-670). The mean intraoperative bleeding was 528.84 ± 564.64 cc (range: 20-2500). The mortality rate was 27.9%. The 60-day postoperative mortality rate was 6.97%. Demographic, procedure, and survival data are presented in table 1. The follow-up period of the study was 30 months. The 1- and 3-year OS were 88% and 60%, respectively (Figure 1).

Discussion

During the short period of our work, the mean PCI was 8.79 ± 5.83 (Range: 1-20). CC0-CC1 cytoreductive was accomplished in 87.7% of the patients. The 60-day postoperative and mortality rates were 6.97% and 27.95, respectively. The 1- and 3-year OS rates were 88% and 60%, respectively. Recent studies have shed light on the positive effect of HIPEC on OS when CC0 and CC1 cytoreduction are achieved. CRS and HIPEC, most commonly with a platinum and Taxane combination, have become the standard treatment for PC of ovarian cancer.

Munoz-Casares et al. showed that the 5-year OS in patients with R0 cytoreduction for primary ovarian cancer was 63%. They recommended that CRS plus HIPEC is an excellent surgical approach to achieve high rates of complete cytoreduction and improve survival in patients with PC from ovarian cancer.[12]

Nikeghbalian et al.[2] in their study on 30 patients with different origin PCs via cardiac pump machine using the close method from 2008 to 2016 in Iran revealed the 80% CC0/CC1, and a mortality rate of 20%. The 1- and 4-year OS rates were 89% and 54%, respectively. In a multi-institutional study, 10- and 15-year survival rates of 63% and 59% were reported for 2298 patients with pseudomyxoma peritonei from appendiceal origins treated with CRS and HIPEC.[13] Helm and colleagues' systematic review study showed that complete CRS was achieved in 67% of the cases of malignant peritoneal mesothelioma, and 3- and 5-year OS rates were 59% and 42%, respectively.[14]

A study by Glehen et al. on 150 patients with CRS and HIPEC for PC of gastric origin demonstrated a 5-year survival rate of 13%.[15]

HIPEC is the standard for metastatic appendiceal cancer and peritoneal mesothelioma in the United States and metastatic colon cancer in Europe in well-selected patients.[16]

The 5-year survival rate varies from 12%-66% for ovarian cancer PC.[17-19]

Primary ovarian cancer was the most prevalent cause of PC (62.8%) in our center. The major morbidity (grades 3 and 4) occurred in eight patients (18.6%). Minor postoperative morbidities, such as ileus or delayed gastric emptying, wound infection, anastomosis leakage/fistula formation, and intra-abdominal abscess/collection were 9.3%, 2.3%, 2.3%, and 4.7%, respectively. The 60-day postoperative mortality rate was 7%. Post-operative major morbidity has been reported in

36% of PC cases in the literature.[20] Low mortality rate (2.3%) and acceptable morbidity have also been reported in a recent study.[21]

This work experienced numerous limitations, including a small population and being cross-sectional and retrospective. Other confounding factors related to the different PC origins and the role of systemic therapy on the performance of isolated peritoneal disease.

Conclusion

Our study supports that using CRS and HIPEC for PC is feasible with acceptable morbidity in our center. It should be noted that our results cannot be applied to every case with PC of all cancer origins. However, we believe that this treatment is practicable and safe for carefully selected patients.

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Conflict of Interest

None declared.

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