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Cytoreductive Surgery and Hyperthermic Intraoperative Chemotherapy for Management of Peritoneal Carcinomatosis

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Abstract

Background: Treatment of peritoneal metastases has gained interest among oncologic communities around the world. Cytoreductive surgery (CRS) and hyperthermic intraoperative chemotherapy (HIPEC) have come to be the treatment of choice for selected patients with peritoneal carcinomatosis (PC) in recent years. Prior to HIPEC, patients were treated with palliative support and only guaranteed a few months to live. We reviewed our first 30 patients who underwent CRS and HIPEC. The aim of the study was assessment of the patients' survival, morbidity, and mortality rate and identifying prognostic factors of patients treated with CRS and HIPEC.

Methods: In this cross-sectional study, data were retrospectively collected from 45 patients (15 men and 30 women) who underwent CRS and HIPEC between December 2008 and October 2016, at Nemaazi educational hospital and Shiraz central hospital of Shiraz University of Medical Sciences. Peri-operative and regular follow-up data on survival and complications were gathered and analyzed to identify their prognostic value for survival.

Results: The mean age of the patients was 49.7±16.46 years. The participants in this study consisted of 19 females (63.3%) and 11 males (36.7%). The most common primary tumor was ovarian cancer (30.1%). A completeness of cytoreduction score of CC0/CC1 was obtained in 80% of patients operated on with curative intent. The overall mortality rate was 20%. The 1- and 4-year overall survival (OS) were 89% and 54%, respectively.

Conclusion: CRS and HIPEC are most successful in treatment of selected patients. Development of complete resection with CRS in these 8 years and good OS in our patients encourage us to continue the procedure with all its difficulties and cost.

Keywords: Cytoreductive surgery, HIPEC, Peritoneal carcinomatosis

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Introduction

Peritoneal carcinomatosis (PC) is the result of the peritoneal metastatic cascade and is a common sign of advanced tumor stage and has been overall considered as end-stage malignancy only responsive to palliative care.[1,2] PC epitomizes progressive malignant and recurrent disease, has usually been associated with poor prognosis and low quality of life, and often has low overall survival (OS); it is of major alarm in cancer treatment.[3] In the recent years, cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) have been used as treatment for carefully chosen patients with PC from ovary, colorectal, and gastric cancers, mesothelioma, and pseudomyxoma peritonei (PMP).[4]

Several studies report low mean OS without treatment in cases of PC due to different primary malignancies such as ovarian, gastric, colorectal, appendix and PMP: between 5–9 months.[5–7] Advances in procedure and intraoperative agent led to an increase in OS and quality of life in the last decade.[8] CRS and HIPEC have come to be the treatment of choice for selected patients with PC.

At the Transplant and Hepatobiliary Surgery Center of Nemaazi hospital and Shiraz central hospital, aggressive CRS and HIPEC are used as the treatment of PC since 2008. The aim of this study is to evaluate this treatment approach in terms of survival, morbidity and mortality rate and to identify clinical and pathologic prognostic factors for survival.

Materials and Methods

Patient and Method

In this cross-sectional study, data were retrospectively collected on a total of 45 patients (15 men and 30 women) who had PC due to primary peritoneal surface malignancy (PSM), PMP, colorectal peritoneal metastasis, ovarian cancer, gastric cancer, appendiceal cancer and pancreatic cancer who underwent CRS and HIPEC with

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cardiopulmonary bypass machine between December 2008 and October 2016, at Nemaazi educational hospital and Shiraz central hospital of Shiraz University of Medical Sciences. All 45 patients were identified and enrolled in this study.

We included data from 30 patients who had good ECOG (Eastern Cooperative Oncology Group) performance status (<2),[9] peritoneal cancer index (PCI) less than 20/39 (since 2009, Figure 1), fewer than 3 contiguous segments liver metastasis according to the Coinaud[11] definition that did not demand major liver resection and without extensive small bowel, gastrohepatic involvement. The other 15 patients who did not meet the above criteria were excluded from final analysis.

The most important events in our study were 1- and 5-year survival rate, postoperation mortality and surgery morbidity. The present study had variable follow-up time according to CRS time.

After fully informed consent was obtained from the patients, we collected the patient's characteristics and primary cancer characteristics and histopathology grade, PCI[12] for PC, duration of surgery, intraoperative bleeding, kind of operation[13] including complete CRS (CC0), residual less than 2.5 mm (CC1), residual between 2.5 mm to 2.5 cm (CC2) and residual more than 2.5 Cm (CC3) data, 1 or 2 stage surgery, duration of HIPEC and kind of the drug used, morbidity such as early postoperative complication such as bleeding, need reoperation and anastomosis leakage, ileus, wound infection and pulmonary thromboembolism, major morbidity (Clavien-Dindo 3 and 4),[14] overall and 30 days postoperative mortality, and OS and 1- to 4-year survival.

Cytoreductive and HIPEC Procedure

At laparotomy via a long midline incision, an abdominal exploration and evaluation of the resectability of the lesions was done. Careful dissection was performed with the aim of eliminating all visible tumor nodules; the extent of PC was evaluated using the PCI and the success of CRS was evaluated with the completeness of CRS score (CSS), as previously described. The aim of CRS was elimination of all gross tumor and involved tissue, peritoneum and supracolic omentum in all patients.

All HIPEC procedures were carried out with closed abdomen, using cardiopulmonary bypass machine immediately after the completion of CRS, three 34F, 2 in the right and left lower quadrant for outflow and 1 in the right upper quadrant for inflow catheters placed percutaneously into the abdominal cavity (Figure 2).

Temperature probes were placed on the inflow and outflow tubing and continuously monitored. The abdominal wall and skin incision were closed temporarily with a running fascia and separated skin suture to prevent leakage of peritoneal perfused. A perfusion circulation was recognized with about 3 L Ringer's lactate. Flow rates of about 1.2 L/min were continued using a cardiac-pulmonary bypass pump managed by a Pumpist. Total planned perfusion time after the initial addition of chemotherapy was typically 90–110 minutes and the planned outflow temperature was 40°C. One HIPEC treatment was used. The peritoneal cavity was perfused with 3 L/m^2 of circulating physiological Ringer's lactate containing Mitomycin-C (MMC) at a dose of 30 mg/m^2 and at 60 minutes; an additional 10 mg MMC was added to keep MMC perfused concentrations >5 mg/mL for 90 to 110 minutes, totally. At the end of the procedure, the inflow catheter was removed and one outflow catheter was left in the abdominal cavity and then removed 24 hours later in the ward.

Statistical Analysis

The statistical analyses were carried out using Statistical

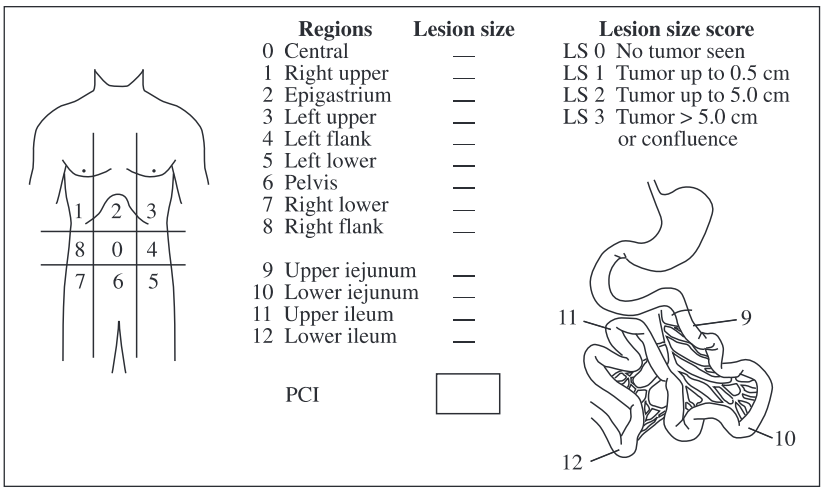

Figure 1. Peritoneal Carcinomatosis Index (PCI) Staging System. Reprinted by permission from Springer Nature, © 2018.[10]

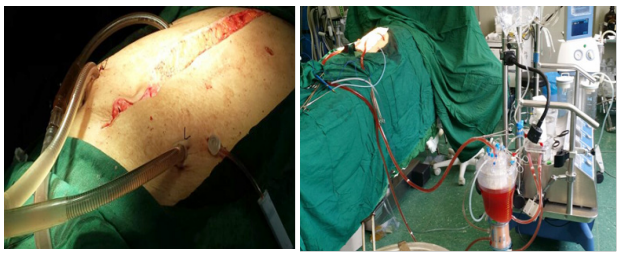

Figure 2. HIPEC With Cardiopulmonary Bypass Machine.

Package for the Social Sciences (version 21; IBM SPSS Inc. Chicago, IL, USA). All 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 95% CI. OS rates were estimated with Kaplan-Meier product-limit method and reported with their confidence interval (95% CI). Survival was calculated from time of first complete cytoreduction to death or present time.

Results

The patients' characteristics are presented in Table 1. The mean age of the patients was 49.07 ± 16.46 years. The participants in the study analysis consisted of 19 females (63.3%) and 11 (36.7%) males. The most common primary tumor was ovarian cancer (30.1%). The second most common primary tumor was PMP (20%). The majority of tumors were low-grade (63.3%) and the others were intermediate- and high-grade (26.7% and 10%, respectively). A completeness of cytoreduction score of CC0/CC1 was obtained in 80% of patients operated on with curative intent. There were 3 patients with 30-day postoperative mortality; also, 26.6% of patients developed a postoperative complication such as ileus, wound infection and pulmonary thromboembolism. 16.7% of patients developed grade 3 and 4 of Dindo-Clavien classification for postoperation complication. The overall mortality rate was 20%. Procedure and survival data are presented in Table 2. The median of surgery duration was 6 hours (95% CI: 6.24–8.55). The mean intraoperative bleeding was 613.33 ± 255.94 cc. Also, the median HIPEC duration was 110 minutes (95% CI: 107.80–139.52). Some patients had 2 stage CRS and twice HIPEC. The mean intraoperative temperature was 40.76 ± 0.43. The overall postoperation 30 days' mortality rate was 10%. The 1- and 4-year OS were 89% and 53%, respectively (Figure 3).

The 1- and 4-year OS rate in patients with CC0/CC1

Table 1. Patient Characteristics

Population Characteristics	Overall Patients (n = 45)	Selected Patients (n = 30)
Age*	46.17 (14–80)	49.07 (14–80)
Sex		
Male (%)	15 (33.3)	11 (36.7)
Female (%)	30 (66.6)	19 (63.3)
ECOG performance status [0-4]		
≤2 (%)	39 (86.66)	15 (50)
		9 (30)
		6 (20)
		0
> 2 (%)	6 (13.33)	0
Primary tumor diagnosis		
Primary PSM (%)	4 (8.8)	1 (3.3)
PMP (%)	10 (22.2)	6 (20)
Colorectal (%)	7 (15.5)	5 (16.7)
Ovarian cancer (%)	10 (22.2)	9 (30.1)
Gastric cancer (%)	6 (13.3)	4 (13.3)
Mesothelioma (%)	2 (4.4)	2 (6.7)
Others (%)	6 (13.3)	3 (10)
Histological subtype		
Low (%)	28 (62.2)	19 (63.3)
Intermediate (%)	11 (24.4)	8 (26.7)
High (%)	6 (13.3)	3 (10)

Abbreviations: ECOG, eastern cooperative oncology group; PSM, pritoneal surface malignancy; PMP, pseudomyxoma peritonei.
*Mean (range).

Table 2. Operative and Postoperative Outcomes of Selected Patients

Operation stage, No. (%)	
One stage	19 (63.3)
Two stage	11 (36.7)
Time of operation, No. (%)	
2008–2010	2 (6.7)
2011–2013	5 (16.7)
2014–2016	23 (76.7)
CCS, No. (%)	
CC0	18 (60)
CC1	6 (20)
CC2	2 (6.7)
CC3	4 (13.3)
PCI, median (range)	14 (1–17)
Duration of procedure, median hours (95% CI)	6 (6.24–8.55)
HIPEC duration, median min (95% CI)	110 (107.80–139.52)
Blood transfusion, mean mL (SD)	613.33 (255.94)
ICU stay, median day (range)	4 (3–7)
Hospital stay, mean day (range)	8 (5–38)
Mortality at 30 days, No. (%)	3 (10)
Overall mortality, No. (%)	6 (20)
Overall survival, No. (%)	24 (80)
Major morbidity, grade 3 and 4, No. (%)	5 (16.7)
Surgical morbidity, No. (%)	
No complication	22 (73.3)
Ileus	3 (10)
Wound infection	4 (13.3)
Pulmonary thrombo-embolism	1 (3.3)

Abbreviations: CCS, completeness cytoreductive surgery; PCI, peritoneal cancer index; HIPEC, hyperthermic intraperitoneal chemotherapy; SD, standard deviation.

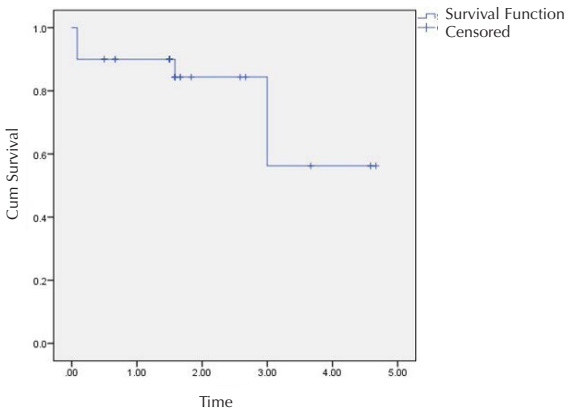

Figure 3. Overall survival (year) of patients who underwent CRS and HIPEC (Kaplan-Meier curve).

Table 3. Cumulative proportion surviving of patients who underwent CC0 and CC1 (Complete re-section) and overall CRS and HIPEC at the end of the study

Year	CC0 +CC1 Survival	OS
0	91%	89%
1	91%	83%
2	91%	83%
3	65%	53%
4	65%	53%

Abbreviations: CC, complete cytoreductive resection; OS, overall survival.

resection was 91% and 65%, respectively (Table 3).

Discussion

This single center study evaluated the outcomes of CRS and HIPEC in 30 selected PC patients at Shiraz University of Medical Sciences in Nemaazi educational and Shiraz central hospitals from 2008 to 2016. In the past decade, the treatment of peritoneal metastases has gained interest among oncologic communities around the world. During the 1990s, the first pioneering centers began treating patients with HIPEC.[15–20] Prior to HIPEC, patients were treated with palliative support and only assured a few months to live. Today, if a patient with peritoneal metastases is provided with appropriate treatment, the survival increases to an average of several years and improved outcomes are reported every day. To the best of our knowledge, this represents the first published series of patients with PC treated using CRS and HIPEC in a single center in IR Iran. The clinical characteristics of PC make it predominantly suitable for this treatment. Furthermore, some retrospective studies and a recent randomized clinical trial have shown the positive effect of HIPEC on OS when R0, R1-cytoreduction is accomplished.[21–25]

In our experience, the patients with PC who underwent CRS and HIPEC manifested a suitable R0-R1 cytoreductive survival at 3 and 4 years (91% and 65%, respectively). These data are consistent with other reported series such as primary ovarian cancer (5-year OS 63%).[25]

In a retrospective multi-institutional registry of 2298 patients with PMP and treated with CRS and HIPEC, 10- and 15-year survival rates of 63% and 59% were reported, respectively.[26] Complete CRS was achieved in 67% of cases of malignant peritoneal mesothelioma and collective estimations of survival yielded 3- and 5-year OS rates of 59% and 42%, respectively.[27] The combined experience of 15 Western centers on 150 patients with CRS and HIPEC for PC of gastric origin has shown a 5-year survival rate of 13%.[28]

The efficacy of CRS and HIPEC for colorectal PC reported a median survival of 22.3 months in CRS and HIPEC (P = 0.032) after a median follow-up of 21.6 months.[29] HIPEC is most successful in the treatment of selected patients. HIPEC is now the standard of care for metastatic appendiceal cancer and peritoneal mesothelioma in the United States[30] whereas HIPEC is accepted as standard of care for metastatic colon cancer in Europe.

In our center, the most common patient with PC who underwent CRS and HIPEC had primary ovarian cancer (30.1%). Five-year survival rate varies from 12% to 66% in PC due to ovarian cancer.[31–38] All these studies demonstrate that the procedure is feasible and well-accepted by the patients.

The major morbidity (grades 3 and 4) occurred in 5 patients (16.7%). Minor postoperative morbidities such as ileus and wound infection were 10% and 13.3%, respectively. The mortality at 30-day postoperation was 10%. Pulmonary thrombo-embolism occurred in one patient. CRS and HIPEC are associated with high morbidity and low mortality rate. Major complications occurred in approximately 23% of the patients.[28]

The degree of PC significantly increases the risk of major complications.[39,40] In correctly selected patients, the mortality rate is not high.[31,32] The rate of postoperative complications does not usually exceed 30%–35%, except one study which reported a morbidity rate of 54%.[34] However, if the patients are not correctly selected, the mortality rate rises intensely.[33]

We know that this survey has numerous limitations; it has a small patient population and it is cross-sectional retrospective. PCI was introduced in 2009. Hence, one of the limitations of our study was the inaccessible data of one of the patients who underwent CRC and HIPEC procedure in 2008 (prior to the PCI definition). Other confounding factors relate to the different PC origin and the role of the systemic therapy on the performance of isolated peritoneal disease. We do not claim that our results can be applied to every patient with PC of

all types of cancer origin. However, we do believe that this treatment is practicable and safe for carefully high-selected patients. Development of complete resection by CRS in these years and OS in our patients encourage us to continue the procedure with all its difficulties and cost.

Authors' Contribution

MYK and SN designed the study, carried out the implementation, analysed the data, and wrote the manuscript; MYK and HN verified the analytical methods and helped in interpreting the results and revised the manuscript; SN, HN, and MYK and RH performed Surgical procedures and HIPEC; SN supervised the work and processed the clinical data; All authors discussed the results and contributed to the final manuscript.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study was approved by the ethical committee of Shiraz University of Medical Sciences.

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