Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis

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ABSTRACT

Peritoneal carcinomatosis (PC) is a common presentation of several gastrointestinal and gynecological malignancies. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) is a treatment regimen recently introduced in Pakistan for PC. The goal of cytoreductive surgery is complete removal of macroscopic disease. HIPEC is administered following surgery, with the aim of eliminating disease at a microscopic level. In this study, 11 patients, who underwent CRS+HIPEC at the Shifa International Hospital, Islamabad, Pakistan, were selected. Disease severity was classified using PCI score. There were 54.5% women and 45.5% men with mean age of 48.5 ± 12.5 years. The mean PCI score was 20.3 ± 3.4. The mean time from diagnosis was 12.7 ± 11.6 months. A complete tumor resection (CC-0) was achieved in 10 (90.9%) patients, while the rest were CC-1. The duration of HIPEC circulation was 90 minutes in every patient. Postoperative morbidity was observed in 2 (18.2%) patients. No 30-day perioperative mortality was seen. It was concluded that with effective patient selection, surgical skills and center experience, CRS+HIPEC can have low perioperative morbidity and mortality, and complete cytoreduction leads to prolonged overall survival.

Key Words: *Peritoneal carcinomatosis, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy.*

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Various gynecological and gastrointestinal malignancies present with peritoneal carcinomatosis (PC). PC is a Stage 4 disease, for which only palliative treatment was given traditionally. Once diagnosed, survival is generally less than six months.[1] In 1980s, the idea of treating PC as a locally advanced disease and to manage it with aggressive intervention was suggested. Since then, the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has gained popularity as a treatment regimen with curative intent and prolonged survival. The goal of cytoreductive surgery is complete removal of macroscopic disease. HIPEC is administered following the surgery, with the aim of eliminating disease at a microscopic level. Therapeutic levels of chemotherapy can be achieved with much lower doses compared to the intravenous chemotherapeutic regimen, avoiding major systemic side effects. Hyperthermia (40-42°C) further enhances effectiveness of the chemotherapy by direct cytotoxicity, improving tissue permeability, and increasing peritoneal blood flow.

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Complete cytoreduction in patients with extensive peritoneal disease requires major surgery with high morbidity and mortality. Yet, recent literature shows that curative approach to PC using CRS and HIPEC may prolong survival. In colorectal cancer, the median overall survival (OS) can be significantly increased with CRS + HIPEC to up to 21-63 months with 5-year OS of up to more than 40%.[2] For appendiceal neoplasms, CRS + HIPEC can improve median survival up to 100 months, with a 5-year OS of up to 71%.[3] Similarly, the OS in patients with ovarian cancer has also been significantly improved with CRS + HIPEC.[4] Despite these results, very few centers in Pakistan perform this procedure. It is being performed in Shifa International Hospital (SIH) since 2019.

The aim of this study was to analyse the safety, effectiveness, peri and postoperative outcomes of CRS+HIPEC at a tertiary care centre in Pakistan.

This study was approved by Institutional Review Board of SIH, Islamabad, Pakistan. All data was analysed using SPSS 23.0.

This prospective observational study included eleven patients with peritoneal carcinomatosis originating from the appendix, ovaries, and colon. Candidate patients were selected based on multiple factors including age, cardiopulmonary function, performance status, and peritoneal cancer index (PCI score). Preoperative staging was done using CT scans and tumor markers (CEA, CA 125). Candidate selection and indications for treatment were established in multi-disciplinary tumor board. Written informed consents were obtained from all patients. The

extent of peritoneal disease was evaluated using the PCI score, an index used to assess the extent of peritoneal cancer based on 13 well-defined abdominal regions (Figure 1). This score was calculated directly after explorative laparotomy and before CRS procedures, and was simultaneously recorded and calculated by an assistant.

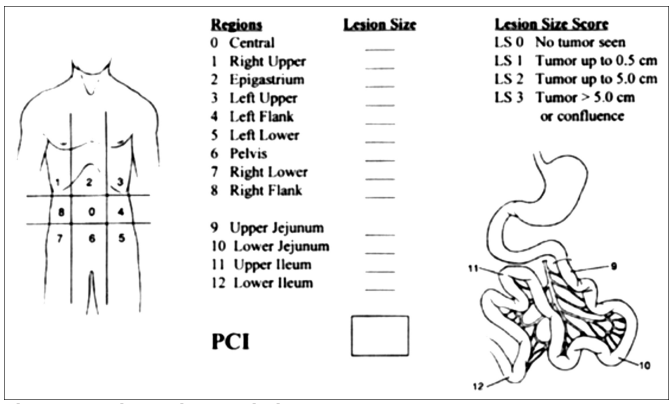

Figure 1: Peritoneal cancer index.

Table I: Completeness of cytoreduction score.

Score	Definition
CC-0	No peritoneal nodule was seen
CC-1	Tumor nodules persisting after cytoreduction are less than 2.5 mm in diameter
CC-2	Tumor nodules persisting after cytoreduction are between 2.5 mm and 2.5 cm in diameter
CC-3	Tumor nodules persisting after cytoreduction are greater than 2.5 cm in diameter

Aggressive CRS was carried out with the primary objective of achieving complete cytoreduction, using procedures including but not limited to exploratory laparotomy, abdominal wall resection, bowel resection, lymphadenectomy, enterolysis, ureterolysis, peritonectomy, and omentectomy. Completeness of cytoreduction score (CC score) was used to determine success of CRS (Table I). Following the cytoreduction, HIPEC was administered. The chemotherapeutic regimen varied for different tumor entities. Pre-heated (40-42°C) HIPEC was then delivered for 90 minutes in a closed abdomen in each case, using Mytomycin at 25 mg/m^2 or Cisplatin at 30mg/m^2.

There were 54.5% women and 45.5% men with mean age of 48.5 ± 12.5 years. The mean PCI score was 20.3±3.4. The mean time from diagnosis was 12.7±11.6 months. ECOG performance score was 0 in seven (63.6%) patients, 1 in three (27.3%) patients, and 2 in one (9.1%) patient. Seven patients (63.6%) underwent neoadjuvant chemotherapy. The primary diagnosis was mucinous neoplasm of the appendix in seven (63.6%) patients, high-grade ovarian carcinoma in one (9%) patient, and colorectal cancer in three (27.3%) patients. A complete tumor resection (CC-0) was achieved in 10 (90.9%) patients, while the rest were CC-1. The duration of HIPEC circulation was 90 minutes in every patient. The mean temperature of the perfusion was 41 ± 0.5°C. The mean operative time (surgery and HIPEC) was 9.8 ± 0.8 hours. All patients were shifted to the SICU as per protocol. The mean length of hospital stay was 8.2 ± 0.8 days and ICU stay was 3.2 ± 0.8 days.

Postoperative morbidity was observed in 2 (18.2%) patients. One patient with appendiceal neoplasm developed abdominal pain and significant drop in hemoglobin on postoperative day one; and was shifted to the operating room. The bleeding was controlled during re-exploration, after which the patient had an uncomplicated hospital stay. Another patient with appendiceal neoplasm developed reversible cardiomyopathy (ejection fraction of 25%) postoperatively. Her ICU stay was prolonged by two days. Echocardiography was repeated on her 2-month follow-up, which showed an ejection fraction of 50%. No 30-day peri-operative mortality was seen.

The factors associated with perioperative morbidity in these patients include disease dissemination, extent of cytoreduction, the number of removed organs, age, and operative time.[5] Another major risk factor for morbidity is HIPEC-related toxicity. For this reason, a thorough preoperative evaluation including kidney function, and close early postoperative monitoring is necessary. Furthermore, surgeon and centre experience are also significant factors affecting morbidity and mortality. The learning curve is not only for the surgeons but also the institution, since this type of treatment requires decision making on a multidisciplinary level.

Among these factors, completeness of cytoreduction (CC score), PCI score, and histological grade have been shown to be the most significant prognostic factors for perioperative and long-term survival.[5] The PCI score is commonly used tool to quantify the extent of tumor growth based on the region and size of metastatic nodules. The CC-score is another important quantitative prognostic factor. A complete cytoreduction indicates that the surgeon successfully cleared all visible sites of disease (CC-0) or left behind only a few minute nodules (CC-1 = <2.5 cm) which are expected to be eradicated by HIPEC. Various studies including an analysis of a prospective database at a national peritoneal tumor center demonstrated significant association between a low CC score with higher OS.[6]

Patient selection for curative approach is extremely important and multifactorial. These factors are related to the patient and the tumor in combination. The tumor-related factors include tumor origin, histological grade, presence of metastatic disease, lymph node involvement, response to previous chemotherapies, and PCI score. Patient related factors include patient performance status, co-morbidities, and multidisciplinary tumor board decision. Imaging studies including CT scans are also mandatory for patient selection.

CRS+HIPEC is offered at a limited number of healthcare facilities in Pakistan, due to lack of expertise and economic burden. However, it is a highly effective treatment modality, which is being used worldwide for PC originating from gastrointestinal or gynecological cancers. With effective patient selection, the peri-

operative morbidity and mortality is low, and complete cytoreduction leads to a significantly prolonged overall survival.

PATIENTS' CONSENT:
Written informed consents were obtained from all patients.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HMK: Operated in all cases, drafted the design of the study, conducted literature review and drafted the manuscript.
HH: Collected data from medical records, conducted statistical analysis and drafted the manuscript.

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