Journal of Surgical Arts
ISSN NO: 1308-0709 Cerrahi Sanatlar Dergisi
Year 2018, Volume 11, Issue 2

Original study

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Initial experience in a low volume center

Sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi. Düşük sayılı bir merkezin ilk deneyimleri

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J Surg Arts (Cer San D), 2018;11(2):34-38.

ABSTRACT

Peritoneal carcinomatosis (PC) is defined as tumoral lesions located on peritoneal surface. In this study, we examined demographic findings, operational findings, early and late postoperative complications and survival times of our patients who underwent CRC + HIPEC due to PC.

Between January 2013 to September 2017 patients operated due to gynecological, gastrointestinal PC or primary peritoneal mesothelioma were studied retrospectively. CRS+HIPEC was performed for treatment of PC. Demographic characteristics of patients, preoperative and intraoperative findings, postoperative early and late complications, and survival times were evaluated. Statistical analysis was performed. Median follow-up and overall survival were calculated from the date of surgery until death, or last follow-up visit.

A total of 6 women (75%) and 2 men (25%) aged between 40-75 years (mean age 54.3 years) were operated due to PC secondary to ovarian cancer, gastric cancer, colon cancer, or due to primary mesothelioma. Two patients developed morbidity at the postoperative period including pleural effusion, intraabdominal abscess, sepsis, wound dehiscence. Two patients were died in early period due to recurrence.

This study presents outcomes of a very limited number of cases. CRC+HIPEC can be performed in a low volume center in selected patients with CC0 or CC1 resections.

Keywords: Peritoneal carcinomatosis, cytoreductive surgery, hipertermic intraabdominal chemotheraphy (HIPEC).

ÖZET

Peritoneal karsinomatoz (PK) periton yüzeyinde tümöral lezyonların olması şeklinde tanımlanır. Bu çalışmada sitoredüktif cerrahi (SRC) ve HİPEK uygulanan hastaların genel bilgileri, operasyonbulguları, erken ve geç dönem komplikasyonları ve sağkalım süreleri incelendi.

Ocak 2013 ile Eylül 2017 tarihleri arasında jinekolojik, gastrointestinal ve primer periton malignitesi tanıları ile opere edilen hastalar retrospektif olarak incelendi. Hastalara SRC ve HİPEK uygulandı. Genel hasta bilgileri, preoperatif ve intraoperatif bulgular, erken ve geç dönem komplikasyonlar, sağkalım süreleri incelendi ve istatiksel analiz yapıldı. Ortalama takip ve sağkalım süresi operasyon tarihinden ölüme ya da son hasta vizitine göre hesaplandı.

Toplam 6 (%75) kadın ve 2 (%25) erkek over mide, kolon tümörlerinin periton metastazları ya da primer mezotelioma nedeni ile opere edildi. Hastaların ortalama yaşı 54.3 olup 40-75 arası değişmekte idi. İki hastada morbiditeler gelişti. Bu komplikasyonlar; Plevral efüzyon, intraabdominal apse, sepsis ve yara ayrışması idi. İki hasta erken dönemlerde nüks nedeni ile kaybedildi.

Bu çalışmada kısıtlı sayıda hasta sonuçlarını bildirmektedir. SRC ve HİPEK uygulaması seçilmiş hastalarda düşük sayılı merkezlerde de planlanabilir.

Anahtar kelimeler: Peritoneal karsinomatoz, sitoredüktif cerrahi, hipertermik intraperitoneal kemoterapi (HİPEK).

INTRODUCTION

Peritoneal carcinomatosis (PC) refers to tumoral lesions located on peritoneal surface. PC may be primary as in the case of the peritoneal mesothelioma, or it may occur as secondary disease caused by metastasis of various tumors.

Secondary PC is much more common and may be caused by particularly gastrointestinal system malignancies, as well as gynecological and extraabdominal (e.g. breast cancer) tumors. For the majority of cases, PC is regarded as a terminal disease with no cure. Average survival is 3-6 months. (2). In recent years, there have been reports of favorable outcomes following resection of these diffuse tumoral lesions known as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (3). All procedure is difficult and ometimes exhausting. It also should be performed by an experienced surgical team.

HIPEC is based on the principle that the chemotherapeutic agent can be administered intraperitoneally at very high concentrations (up to 200 times of concentrations measured in bone marrow) without causing systemic toxicity due to blood-peritoneal barrier, showing direct effect on peritoneal lesions (4). However, since the chemotherapeutic agent acts on the metastatic lesions via simple diffusion, it is essential that the metastatic lesions are completely resected, or reduced to microscopic sizes below 2.5 mm (4,5). Administration of the chemotherapeutic agent intraperitoneally at high temperatures augments the tumoricidal effect.

In this study, we examined demographic findings, operational findings, and early and late postoperative complications and survival times of our patients who underwent CRC + HIPEC due to PC.

MATERIAL AND METHOD

We retrospectively reviewed the records of 8 patients who were operated between January 2013 to September 2017 due to gynecological, gastrointestinal PC or primary peritoneal mesothelioma. All patients were evaluated preoperatively in terms of appropriateness of CRC and HIPEC. Radiographic examination (CT scan of the chest and abdomen,) and tumor markers (CEA, CA19-9, and CA 125) were tested before surgery. CRC+HIPEC was planned if complete cytoreduction (CC) was seemed feasible by the operating team.

Complete cytoreduction was defined as residual tumor deposites less than 2.5 mm in size (CC=1) or the absence of any visible tumor deposites (CC=0) after surgical resection. PET-CT scan was routinely performed to rule out distant metastasis. Peritoneal carcinomatosis index was calculated after abdominal CT and during surgical exploration. Patients were informed about the procedure in detail, and all patients provided informed consent. The operations were performed by general surgeons, and in relevant cases, with gynecologists.

Electro-cautery was used particularly during peritonectomy. During CRC, total peritonectomy was performed in cases who had diffuse peritoneal involvement. Partial peritonectomy was performed in cases in which peritoneal involvement was restricted to the pelvic area. The main chemotherapeutic agents used in HIPEC was cisplatin (50 mg/m2), doxorubicin (15 mg/m2)and mitomycin-C (30 mg initially plus 10 mg added 30 minutes later). The duration of intraabdominal perfusion was 60-90 minutes using the closed HIPEC technique.

The mixed solution was given with 800-1000 mL/min with a HIPEC pump. The temperature of the solution was 42°C to 43°C. The temperatures of inflow and outflow of the HIPEC solution and the patient's body temperature, were monitored. All patients were followed-up in ICU in early postoperative period.

All patients were followed up postoperatively by oncology, gynecological oncology (relevant cases), and general surgery teams. Demographic characteristics of patients, preoperative and intraoperative findings, postoperative early and late complications, and survival times were evaluated. Statistical analysis was performed. Median follow-up and overall survival were calculated from the date of surgery until death, or last follow-up visit.

RESULTS

During the study period, 6 women (75%) and 2 men (25%) aged between 40-75 years (mean age 54.3 years) were operated due to PC secondary to ovarian cancer, gastric cancer, colon cancer, or due to primary mesothelioma. In two patients, PC secondary to gynecological malignancy was detected during exploration, and CRC + HIPEC was applied to these patients within the same session. Data regarding age, sex, primary tumor, chemotherapeutic agent, survival and mortality are presented in Table 1. Surgical resections were performed according to the extent of intraabdominal tumoral spread. Operative details are summarized in Table 2. None of the patients had intraoperative complications. Totally two patients developed morbidity at the postoperative period. Morbidities are shown in Table 3. Two patients died during the postoperative period due to early tumoral spread. One of these patients was operated due to PC secondary to colonic tumor, targeting to leave tumoral deposits below 2.5 mm; however, this was not possible.

Table 1: General characteristics of patients in serial (*MM:Mitomycin C, *Doxor:Doxorubicin)

Patient	Age/Gender	Diagnosis	Chemotheraphy	Survival
1	40y / Female	Ovary cancer	Cisplatin	46. month in follow up
2	50y / Female	Peritoneal mesotelioma	* MM/Cisplatin	18. month in follow up Recurrence (exitus)
3	75y/ Female	Peritoneal mesotelioma	MM/ Cisplatin	Recurrence in 4. month (exitus)
4	60 y / Female	Rec. endometrial cancer	Cisplatin	21. month in follow-up
5	41y / Male	Colon cancer	*Doxor/Cisplatin	Recurrence in 4.month (exitus)
6	68 y / Male	Gastric cancer	MM/Cisplatin	13. month in follow up
7	60y / Female	Ovarian cancer	Cisplatin	-
8	41y / Female	Ovarian cancer	Cisplatin	13. month in follow up

Table 2: Major complications in postoperative period (*VAC: Vacuum Assisted Closure).

Patient	Complication	Treatment	Follow-up
1	Intraabdominal abscess	Percutenous drainage	No problem
2	Pleural effusion	Drainage	No problem
	Postoperative sepsis (WBC:45.000 K/U, Prokalsitonin:56)	Antibiotherapy	No problem
	Partial evisceration	*VAC theraphy	Incisional hernia

Table 3: Operation details of all patients.
(*TAH+BSO: Total abdominal hysterectomy+Bilateral salphingo-oopherectomy)

Patient	Operation
1	Subtotal colectomy+ Omentectomy+total peritonectomy+splenectomy+cholecystectomy +(*TAH+BSO)
2	Total Peritonectomy+small bowel resection
3	Total peritonectomy
4	Pelvic peritonectomy+small bowel resection
5	Colectomy+total peritonectomy+omentectomy
6	Total gastrectomy+partial peritonectomy
7	Total peritonectomy+omentectomy+(TAH+BSO)
8	Subtotal colectomy+omentectomy+bilateral diaphram resection+splenectomy+ peritonectomy+ ileostomy+(TAH+BSO)

DISCUSSION

Peritoneal metastases are often observed at the advanced stages of intraabdominal cancers.Among all cancers, PC most commonly occurs secondary to ovarian cancer, with a rate reaching up to 60%. Peritoneal spread may be observed in 20% of gastric tumors, and 8-17% of colonic tumors (1,2). Classical therapy for patients with PC was surgical debulking followed by systemic chemotherapy; however, survival outcomes remain poor.

CRC and HIPEC was first applied in 1980 by Spratt et al. in a case with pseudomyxoma peritonei (3). In the following years, the studies of Dr. Sugarbaker helped CRC + HIPEC applications to gain popularity. Current literature shows that treatment of peritoneal mesothelioma with these methods resulted in increases in average survival from 12 months to 92 months, whereas survival in cases with ovarian cancer increased up to 54 months (4). In this series, the longest survival was observed in our first case who had ovarian cancer and diffuse intraabdominal involvement. This case received chemotherapy at the postoperative 24th month due to recurrence in the liver. She is still under follow-up at the 46th postoperative month without any recurrent tumor. CRC + HIPEC is known to yield successful results especially in peritoneal metastases secondary to ovarian cancer.

In patients with PC, preoperative evaluation, and selection of cases for CRC + HIPEC treatment is essential. Preoperatively, the abdomen is divided into 13 compartments, and the tumoral load is assessed by scoring between 0-3 points. This scoring system is known as peritoneal carcinomatosis index (PCI). Patients are given a score between 1-39 points. Many studies have identified the PCI score as a major prognostic factor (5-7). In addition to high PCI scores, advanced age and comorbid diseases can also present contraindications for CRS and HIPEC. CRS and HIPEC should not be performed if large portion of the

small bowel is affected by disease that resection would result in a short bowel syndrome.

For patients undergoing CRC, the main target is leaving no residual tumor after resection. However, it is acceptable to leave tumoral deposits below 2.5 mm in diameter. In our series, despite high PCI score in preoperative evaluation, one young adult case with colonic cancer underwent CRC + HIPEC. The tumoral deposits could not be reduced below 2.5 mm, and the patient showed early tumoral spread and mortality.

CRS + HIPEC is a complex procedure with high morbidity rate. Fujimura et al. reported a morbidity of 50% and a reoperation rate of 33.3% in their serial (8). Common major postoperative complications included neutropenia, anastomotic leakage, pneumonia, postoperative bleeding, intra-abdominal abscess, systemic sepsis, wound infection, pleural effusion, and renal insufficiency. In our study, 2 patients developed complications at the postoperative period. There was no mortality at the early postoperative period. Those patients who developed complications had multiple organ resections. In our series, CRC + HIPEC treatment was applied in 2 cases due to peritoneal mesothelioma, and in 2 patients due to local peritoneal spread. The reason why we had relatively low rates of general complications can be attributed to the fact that these patients did not undergo multiple organ resections. Many risk factors have been reported for morbidity following CRS and HIPEC including gender, age, colonic anastomosis, extend of peritonectomy procedures, number of visceral resections, incomplete cytoreduction, dose of chemotherapeutic agent and histopathologic grade (9-15).

In conclusion, this study presents outcomes of a very limited number of cases. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a feasible option with acceptable morbidity and mortality for selected patients with peritoneal carcinomatosis. It can be performed in a low volume center with CC0 or CC1 resections.

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