JBUON 2015; 20(1): 244-247
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Clinical history of patients with peritoneal carcinomatosis exluded from cytoreductive surgery & HIPEC

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Summary

Purpose: *The aim of this study was to explore the natural course of peritoneal carcinomatosis (PC) in patients who are not fit to undergo cytoreductive (CRS) surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).*

Methods: *Over an 8-year period (2006-2013) 320 patients were excluded from CRS and HIPEC at our center. Exclusion criteria were: (a) age >75 years; (b) ASA score ≥ 3; (c) extraperitoneal disease; (d) massive disease involvement of the small bowel; (e) disease involvement of the hepatic pedicle or the pancreas; (f) invasion of retroperitoneal space; (g) more than two stenoses of the small bowel. Another 130 patients underwent CRS and HIPEC.*

Results: *In the HIPEC group (N=130), the mean overall survival was 26.2±11.7 months, while from the non-HIPEC group (N=320), 200 patients underwent palliative surgery, with a mean overall survival of 11.7±8.3 months. Only 120 patients received palliative chemotherapy with a mean overall survival of 7.2±4.3 months.*

Conclusion: *Our study suggests that, in patients unfit to undergo CRS & HIPEC, an exploratory laparotomy and palliative surgery should be performed, offering a survival benefit and improved quality of life.*

Key words: *cytoreductive surgery, HIPEC, peritoneal carcinomatosis*

Introduction

The prognosis of patients with PC is poor, and represents the spread of malignancies to parietal and visceral peritoneum. With CRS and HIPEC in appropriately selected patients long term survival is achievable [1,2].

CRS aims to remove all visible tumor tissue (<2.5mm). The HIPEC procedure is based on the principle that a high concentration of chemotherapeutic drugs can eradicate the non visible malignant cells in the peritoneal cavity. The outcome of CRS and HIPEC depends on the tumor extent and the completeness of cytoreduction [3].

Patient selection is a very significant task to identify which patients will benefit more from the application of CRS and HIPEC. On the other hand it is important to identify the natural course of PC, when the therapeutic possibilities are limited.

Methods

Over the past 8 years two groups of surgeons from two different hospitals under the same peritoneal surface malignancy program initiated by the same person (JS) have recruited patients with PC and potential need for CRS & HIPEC and have prospectively registered and studied these cases from January 2006 to December 2013.

The departments are national referral centers for CRS & HIPEC.

Inclusion criteria

Patients eligible for CRS & HIPEC were those with PC from colorectal cancer, pseudomyxoma peritonei, malignant peritoneal mesothelioma and gynecologic carcinomas.

Exclusion criteria

Exclusion criteria were: (a) age > 75 years; (b) ASA

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Received: 20/08/2014; Accepted: 05/09/2014

score ≥ 3; (c) extraperitoneal disease; (d) massive disease involvement of the small bowel; (e) disease involvement of the hepatic pedicle or the pancreas; (f) invasion of retroperitoneal space; (g) more than two stenoses of the small bowel.

Preoperative assessment included CT/PET-CT, magnetic enteroclysis, gastroscopy and colonoscopy and decisions were finalized in multidisciplinary team meetings.

From January 2006 to December 2013, 450 patients were introduced in the program and 320 patients (71%) were excluded perioperatively from CRS & HIPEC.

In cases of intraoperative exclusion, standard palliative surgery was performed at the surgeon's discretion, including tumor resection or bypass and after recovery patients were transferred to the Medical Oncology department for palliative chemotherapy.

Statistics

Overall survival was estimated using the Kaplan – Meier method with log rank test, and chi-square test was used to estimate the significance between two medians. A p value <0.05 was considered statistically significant.

Results

Four hundred and fifty patients were assessed for possible inclusion in the study.

Of them, 130 (29%) patients were included in the HIPEC group and their mean overall survival was 26.2±11.7 months (group A).

The remaining 320 (74%) patients were excluded from the CRS & HIPEC group. Palliative surgery was performed in 200 (44.5%) patients with a mean overall survival of 11.7±8.3 months (group B).

Only 120 (26.5%) patients received palliative chemotherapy with a mean overall survival of 7.2±4.3 months (group A vs group B, p=0.032 ; Table 1).

The main reasons for exclusion included presence of more than 10 peritoneal regions on peritoneal cancer index (PCI) nomenclature or a PCI of more than 30 in colorectal patients, more than 35 in pseudomyxoma peritonei or ovarian tumors, more than 15 in malignant mesothelioma or more than 10 in gastric carcinoma.

In 240 patients, PC had spread in the mesenterium axis, in 110 in the hepatic pedicle and 95 had invasive growth in the retroperitoneal space (Table 2).

Postoperative morbidity and mortality were as follows: in the HIPEC group, 30% morbidity and 3.8% mortality; in the palliative surgery group, 24% morbidity and 5.2% mortality; and in

Table 1. Treatment procedures and mean survival rates in the 3 groups

Groups	*N (%)*	*Mean survival (months)**
Group A CRS & HIPEC	130 (29)	26.2 ± 11.7
Group B Palliative surgery & systemic chemotherapy	200 (44.5)	11.7 ± 8.3
Group C Exploratory laparotomy (open – close) & systemic chemotherapy	120 (26.5)	7.2 ± 4.3

*p values: A vs B= 0.032, A vs C= 0.09, B vs C= 0.04

Table 2. Criteria for perioperative exclusion in 320 patients

Criteria	*N (%)*
Involvement of hepatic pedicle	110 (34.3)
Involvement of >10 regions in PCI	46 (14.3)
Stenosis of ureters	37 (11.5)
Involvement of mesenterium axis	240 (75.0)
Retroperitoneal involvement	95 (29.6)
> 2 bowel stenoses	40 (12.5)
More than 4 liver metastases	67 (20.9)
Involvement of pancreas	25 (7.8)

Table 3. Morbidity and mortality data

	*Morbidity (%)**	*Mortality (%)**
Group A (CRS & HIPEC)	30	3.8
Group B (Palliative surgery & systemic chemotherapy)	24	5.2
Group C (Exploratory laparotomy (open-close) & systemic chemotherapy)	35	1.9

*p values: A vs B= 0.078, A vs C= 0.094, B vs C= 0.133

Table 4. Palliative procedures performed in 200 group B patients

Procedures	*N*	*%*
Gastrectomy	14	7
Colon resection	42	21
Splenectomy	5	2.5
Small bowel resection	63	31.5
Bypass procedures	117	58.5
Rectal resections	28	14
Ileostomy	94	47
Colostomy	62	31
Gynecologic procedures	17	8.5

the palliative chemotherapy group morbidity due to toxicity was observed in 35% of patients (Table 3).

Palliative procedures performed during exploratory laparotomy are presented in Table 4.

Discussion

Patients not meeting the inclusion criteria for CRS & HIPEC represent a group with advanced PC. Most of these patients have a rapid, fatal clinical course. Our results showed a mean survival in the CRS group of 11.7±8.3 months. These findings are comparable to results found by Rodt et al. who reported a median survival of 12.7 months [4].

Concerning the patients treated with palliative chemotherapy in our study, the mean survival was 7.2±4.3 months. This result is comparable to the results found by Hompes et al. who found a median survival of 9.3 months for patients with PC who received systemic chemotherapy [5].

Our study demonstrated a 30-day mortality rate of 3.8% for the HIPEC group and 5.2% for the palliative surgery group ($p>0.05$).

With the implementation of this new treatment strategy, our group decided to apply very strict criteria to include patients with PC in the CRS & HIPEC procedures, concerning the tumor location, grade, PCI and the completeness of cytoreduction (CC) score together with the ASA score and the performance status of each patient rather than biological age [6,7].

The prognostic relevance of the CC score and the PCI was evaluated by Elias et al. in 523 patients [8]. In multivariate analysis, they found that CC and PCI strongly correlated with overall survival.

In our study patients who were excluded from the HIPEC group represented a group with a very high PCI index (27.5±6.8 in the palliative surgery group and 31.8±5.2 in the palliative chemotherapy group), which was statistically significantly different from the PCI in the HIPEC group (15.2±7.1, $p<0.05$).

The most important information from this study is that patients in whom a rapid fatal clinical course was expected, the results demonstrated >9 months survival in the palliative surgery group and >6 months in the palliative chemotherapy group.

On the other hand, in the HIPEC group of patients, the overall survival rose up to 26.2 months, because the potential candidates for CRS & HIPEC had lower PCI, meaning no massive PC and fitness for major surgery.

A prospective trial [9] found an overall survival of 12.6 months for 50 patients with PC, randomized to standard treatment with simple chemotherapeutic regimens and not modern combination regimens with targeted therapies.

Our study suggests that patients with PC must be evaluated by a multidisciplinary team in order to assess with objective criteria the candidates for CRS and HIPEC.

Exploratory laparotomy and palliative surgery are not associated with considerable morbidity and mortality for patients excluded from CRS & HIPEC and offer a survival benefit with better quality of life.

Conclusion

CRS and HIPEC have proven to be a safe treatment modality in PC in well selected patients. Our study suggests that patients unfit to undergo CRS & HIPEC an exploratory laparotomy and palliative surgery should be performed, offering survival benefit and improved quality of life.

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