

ORIGINAL ARTICLE

Is there a role of repeat cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with relapse from peritoneal metastatic disease? A survival analysis

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Summary

Purpose: We aimed to evaluate the role of repeat cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of patients with recurrent peritoneal metastatic disease (PM) with special consideration to perioperative outcomes and long-term survival outcomes.

Methods: Patients with recurrent PM who underwent CRS and HIPEC for the management of the disease for an interval of 15 years were retrospectively analyzed. Primary tumor location, peritoneal cancer index, completeness of cytoreduction (CC), morbidity, mortality, overall survival (OS), and progression-free survival (PFS) after the 1st and 2nd HIPEC were assessed.

Results: A total of 48 patients who underwent repeat CRS

and HIPEC for the management of disease relapse were included in this study. The median OS from initial diagnosis was 37 months (range: 12-128) while the PFS after the second CRS and HIPEC was 12 months (range: 0-36). A total of 30 complications were recorded among which 18.8% were classified as major. CC-0 resection was a significant indicator of survival either on univariate or on multivariate analysis.

Conclusions: The outcomes of the present study indicate the feasibility of repeat CRS and HIPEC procedures in patients with recurrent peritoneal metastasis with significant morbidity, acceptable mortality and long-term survival outcomes which were highly associated with CC status.

Key words: peritoneal metastasis, cytoreduction, CRS, HIPEC, repeat

Introduction

Dissemination of malignant tumors to the peritoneal cavity has been associated with adverse survival outcomes [1]. Malignancies of the gastrointestinal and the gynecological tract are the most prevalent primary locations of peritoneal metastasis (PM). The incidence of detection of synchronous peritoneal dissemination due to colorectal cancer ranges from 4 to 18%, whereas in a proportion of 40% of patients with gastric cancer

greater than stage II, a peritoneal spread is recognized during laparotomy [1,2]. Patients with PM were previously considered end-stage and received only palliative treatment. However, during the last decades the advances in chemotherapeutic regimens and in surgical techniques, have resulted in a more aggressive management of patients with PM [3,4]. To that end, PM in patients without distant metastasis is considered a locoregional disease and

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cytoreductive surgery (CRS) and intraperitoneal hyperthermic chemotherapy (HIPEC) with additional systemic chemotherapy and more recently targeted therapy, have been suggested as modalities which can improve the survival outcomes of those patients [5]. The final goal of the aforementioned procedures should be completeness of cytoreduction which has been considered the most critical independent factor to enhance survival and improve the prognosis. A meticulous evaluation of patients with PM is required in order to designate the most appropriate candidates for CRS and HIPEC. Thus peritoneal carcinomatosis index (PCI) and completeness of cytoreduction (CC) score have been proposed as the most significant prognostic factors for the selection of patients who will benefit from those extensive procedures which have been related with considerable morbidity [6].

However, a significant proportion of patients with PM of any primary origin who underwent CRS and HIPEC will be diagnosed with recurrent disease [7,8]. The management of recurrences is challenging and the effect of a repeated CRS and HIPEC in the perioperative outcomes and survival rates as well as the specific indications of performing the technique is still limited [9].

The aim of the present study was to evaluate the role of repeat HIPEC in the management of patients with recurrent peritoneal metastatic disease with special consideration to perioperative outcomes and long-term survival outcomes.

Methods

A retrospective analysis of a prospectively maintained database was performed for patients with recurrent peritoneal metastasis who underwent cytoreductive procedures and HIPEC for the management of their disease between January 2005 and October 2019 at the General Hospital of Mesologgi (2005-2009), Metaxa Cancer Memorial Hospital (2009-2017) and Athens Medical Centre (2017-2019). The institutional Review Board of the institutions approved the study. All patients were individually presented and discussed on each center's multidisciplinary team meeting (MDT) and inclusion/exclusion criteria were decided. Inclusion criteria were as follows: age \geq 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; confirmation of peritoneal metastasis through histology or cytology of peritoneal fluid or high clinical suspicion of recurrent disease in preoperative laboratory (i.e. elevated tumor markers) or radiological examination; patients who had a previous CRS and HIPEC for resectable peritoneal disease of any primary origin. Patients with extraperitoneal disease or parenchymal liver lesions as well as those with unresectable disease according to preoperative radiological evaluation were not included. Accordingly, those who were initially evaluated as candidates for CRS

and HIPEC but they finally underwent palliative surgery without HIPEC were excluded.

The completeness of cytoreduction and R0 resection was the primary target of the surgeon. All the procedures were performed by three different teams with the same chief surgeon (JS). All patients underwent peritonectomies and further organ resections (e.g. gallbladder, spleen, colon, small bowel) as evaluated by the surgeon and indicated in order to achieve completeness of cytoreduction of the recurrent macroscopic lesions. A peritoneal cancer index (PCI) was intraoperatively assessed for each patient to record the extent of the disease [10]. After maximal cytoreduction of the macroscopic residual disease, the degree of cytoreduction (CC-score) was determined [11]. According to this score, CC-0 was indicative of no residual macroscopic disease, CC-1 as no lesions >2.5 mm, CC-2 identified tumors sized from 2.5mm to 2.5cm and in CC-3 residual tumor was >2.5 cm. Following CRS all patients received HIPEC with cisplatin $100\text{mg}/\text{m}^2$ and paclitaxel $175\text{mg}/\text{m}^2$ for 60 min delivered at 42.5°C with a closed technique. The patients received the same agents during the 1st and 2nd HIPEC. Postoperative surgical complications and morbidity were evaluated according to the Dindo-Clavien classification [12]. Patient demographics included age, gender and ECOG performance status, while disease-related and operated characteristics were also recorded and included primary tumor location, interval between 1st and 2nd HIPEC, PCI and CC scores. Final outcomes included morbidity/complications, 30-d postoperative mortality, cancer-related deaths, OS from the initial diagnosis and PFS after the 1st and 2nd HIPEC.

Statistics

Data was expressed as frequencies and proportions for categorical variables whereas mean/median and standard deviation/range was utilized for measurement of continuous variables. PFS and OS were estimated from the surgical operation date, using Kaplan-Meier analysis and log-rank test was used to assess survival differences between two groups. Univariate and multivariate analyses were also performed. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23.0 (IBM corporation).

Results

From a total of 608 patients who had CRS procedures and HIPEC during the study period, a total of 48 (7.9%) were referred for repeat CRS and HIPEC due to recurrent disease. A total of 48 CRS and HIPEC procedures were performed.

The mean patient age was 51 years ($\text{SD} \pm 9.4$). There were 16 males and 32 females. The location of the primary tumor was as follows: 23 patients (47.9%) were diagnosed with primary epithelial ovarian cancer, 11 (22.9%) had colorectal cancer, 1 (2.1%) primary gastric cancer, 9 patients (18.75%) suffered from pseudomyxoma, 3 (6.25%) had peritoneal mesothelioma while sarcoma was the pri-

primary diagnosis in one patient (2.1%). Table 1 depicts the main patient and tumor characteristics as well as survival outcomes according to the type of the primary tumor.

The median interval between the 1st CRS and HIPEC and detection of recurrent peritoneal disease was 18 months (range: 6-44). The median PCI score at the 1st CRS and HIPEC was 20 (range: 7-35), while a CC-0 resection was achieved in 24 patients during this procedure, a CC-1 in 21 patients and a CC-2 in the remaining 3 patients. During the 2nd CRS and HIPEC, the median PCI was 8 (range: 2-18) and 35 patients had CC-0 resection, 12 excisions were CC-1 and 1 was CC-2. Of the 24 patients who had CC-0 resection during the first procedure, 22 had also CC-0 resection of their residual disease during the 2nd CRS and HIPEC. Additionally, for the

24 patients with CC-1 or CC-2 disease during the 1st surgery, 13 (54.2%) had CC-0 disease during the second procedure. Patients who had CC-0 resection had significantly improved OS compared to those with CC-1 and CC-2 after second CRS and HIPEC ($p < 0.0001$).

The median follow-up was 38 months (range: 24-106). A total of 30 complications (62.5%) were recorded. Among them, 21/30 (70%) were classified as Dindo-Clavien grade I-II and 9/30 (30%) were grade III-IV. The main major postoperative complications included digestive fistulas ($n=4$), pancreatic fistulas ($n=2$), catheter sepsis ($n=1$), pneumonia ($n=1$) and intra-abdominal abscess ($n=1$). The 30-d postoperative mortality was 2.1% (1/48 patients). Cancer-related death rates were 48% ($n=23/48$). Median OS was 37 months (range: 12-128) for

Table 1. Patient, tumor characteristics and survival outcomes according to tumor type

	Ovarian cancer	Colorectal cancer	Pseudomyxoma	Mesothelioma	Gastric cancer	Sarcoma
Patient No (N)	23	11	9	3	1	1
Age (years)	51±9.8 ^a	52±9.3 ^a	50±8.13 ^a	49±8.99 ^a	58	63
Gender (M/F)	0/23	7/4	6/3	2/3	1/0	0/1
Time to 1 st HIPEC (months)	18 (6-31) ^b	14 (8-20) ^b	26 (8-44) ^b	22 (10-38) ^b	36	30
PCI (1 st /2 nd)	18 (7-30) ^b /8 (3-18) ^b	24 (10-30) ^b /9 (2-14) ^b	20 (12-35) ^b /6 (4-16) ^b	28 (16-30) ^b /10 (10-14) ^b	28	7
CC-0 (1 st /2 nd)	14/19	4/7	4/7	1/1	0/0	1/1
CC≥1 (1 st /2 nd)	9/4	7/4	5/2	2/2	1/1	0/0
Complications DC≥III	3	5	2	1	0	1
PFS (1 st /2 nd) (months)	6 (0-33) ^b /18 (0-33) ^b	0 (0-40) ^b /10 (0-24) ^b	0 (0-32) ^b /12 (0-36) ^b	0 (0-20) ^b /0 (0-26) ^b	0/0	12/10
OS (months)	18 (0-33) ^b	26 (14-106) ^b	50 (21=90) ^b	16 (12-100) ^b	52	54
Survival status (D/A)	8/15	7/4	4/5	2/1	1/0	1/0

^a Mean±SD, ^b Median (range), HIPEC: Hyperthermic Intraperitoneal Chemotherapy, PCI: Peritoneal Carcinomatosis Index, CC: Complete cytoreduction, DC: Dindo-Clavien, PFS: Progression free survival, OS: Overall survival, D: Dead, A: Alive, Mean±SD

Table 2. Uni- and multivariate analysis of overall survival

Parameter	Univariate analysis p value	Multivariate analysis p value
Age (years)		
Age < 55	0.290	0.453
Age ≥ 55		
CC status at 1 st HIPEC		
CC-0	<0.001	0.02
CC≥1		
CC status at 2 nd HIPEC		
CC-0	<0.001	0.002
CC≥1		
Type of tumor		
Ovarian /Colorectal/ Pseudomyxoma/ Mesothelioma/Sarcoma	0.410	NS

CC: Complete cytoreduction, HIPEC: Hyperthermic Intraperitoneal chemotherapy, NS: Non-significant

the 48 patients. Median PFS from the 1st CRS and HIPEC was 3.5 months (range: 0-40), whereas the respective interval after the 2nd CRS and HIPEC procedures was 12 months (range: 0-36). On multivariate analysis, CC-0 status during the first and second CRS and HIPEC were the only significant indicators of improved survival (HR 0.727, 95% CI 1.342 to 23.158, $p=0.02$ and HR 0.545, 95% CI 1.904 to 16.138, $p=0.002$, respectively) (Table 2). Lack of statistical significance was detected in multivariate analysis with regards to age and type of tumor (Table 2).

Discussion

The present study presented the outcomes of a proportion of 8% of patients with peritoneal metastasis who were evaluated in three institutions during an interval of 15 years and managed with repeat CRS and HIPEC. Approximately half of the patients were primarily diagnosed with ovarian cancer. The median OS from the initial diagnosis was 37 months while the PFS after the second CRS and HIPEC was 12 months. Two thirds of the patients presented with any kind of postoperative complications and 30% of them were classified as major. According to the findings of the present study, CC-0 resection was a significant indicator of survival either on univariate or on multivariate analysis.

The management of patients presenting with residual or recurrent disease due to peritoneal metastasis after primary CRS and HIPEC is controversial. Despite the fact that the addition of HIPEC in cytoreductive surgical procedures in primary management of peritoneal metastasis has shown significant improvement in survival and has been extensively studied, the survival benefit of repeat CRS and HIPEC in recurrences after the first CRS and HIPEC is still limited [13,14]. The currently available evidence on the role of repeat CRS and HIPEC is encouraging providing evidence that this modality can prolong patients' OS- and PFS. More specifically, median OS ranged from 20.7 to 140 months among the studies which evaluated outcomes after repeat CRS and HIPEC in patients with various primary malignancies which is in accordance to our findings [15-23]. Accordingly, our morbidity rates were as high as those reported by previous studies in the field ranging from 30 to 80%, while major complications classified as Dindo-Clavien grade III-IV ranged from 2.3 to 40% in the literature [16,17,24]. The majority of those studies reported comparable morbidity rates among first and second CRS and HIPEC procedures [15,17,19,25].

Peritoneal carcinomatosis index (PCI) scores and CC status during the first surgery were both considered as potential indicators of the postoperative course of patients who had secondary CRS and HIPEC [15,19]. Patients with CC-0 resection were more likely to have favorable survival outcomes after repeat CRS and HIPEC.

In that setting, as shown in the present study, from the 24 patients who had CC-0 resection during the first surgery, a significant proportion of 92% also had CC-0 resection during the second CRS and HIPEC procedure. However, interestingly, we observed that in patients with CC-1 and CC-2 resection during the first surgery, approximately 50% had a CC-0 resection at the second CRS and HIPEC. This could be attributed to the potential effect of postoperative chemotherapy after the first CRS and HIPEC on the regression of the residual disease resulting in a significant reduction in the extent of the disease which rendered it resectable. This is of critical clinical importance considering the fact that the decision of performing a second surgical procedure after an incomplete cytoreductive surgery will potentially improve the OS. The potential beneficial effect of HIPEC on survival of patients with residual disease is also reflected in the study by Spiliotis et al, demonstrating about 14 months longer OS in ovarian cancer patients when compared to the OS of patients who received only CRS for the secondary management of residual disease [26]. Furthermore, patients who had CC-0 resection during the second procedure had lower median PCI scores compared to PCI of those who had CC-1 or CC-2 (6 vs 14). Despite the fact that lower PCI scores have been related to improved survival outcomes, PCI score over a proper value could not be considered a contraindication for CRS and HIPEC as supported by El Halabi et al who found no difference in survival for patients with appendiceal cancer and PCI over and under 20 and CC-0 or CC-1 [19,27]. Furthermore, the expertise of the surgeon should be taken into account when evaluating the degree of completeness of cytoreduction in those challenging surgical procedures.

The identification of patients who will benefit from secondary cytoreductive procedures and HIPEC was also discussed in the study by Choudry et al who highlighted the critical role of tumor biology as a criterion to decide on proceeding to second CRS and HIPEC [19]. In that setting, the authors observed a survival benefit after second CRS and HIPEC in patients with G2/G3 appendiceal cancer and those with moderately differentiated colorectal tumors [23]. Interestingly, for patients with G1 appendiceal cancer who had CC-2 or CC-3 resection during the first CRS and HIPEC, an improved

overall survival was demonstrated in those who received second CRS and HIPEC [23]. On the contrary, for patients with poorly differentiated colorectal cancer and intermediate or high grade peritoneal mesothelioma which were all considered aggressive tumors, no benefit was recorded [23]. Despite the fact that no guidelines are available it can be assumed that based on the currently available evidence, a meticulous preoperative evaluation could designate the patients who will benefit from repeated procedures for the management of their recurrence.

The OS in patients with peritoneal metastasis who presented with recurrence and did not receive repeat CRS and HIPEC has been reported to be poorer compared to the the respective rates after repeat CRS and HIPEC for various primary malignancies. More specifically, for patients with recurrent peritoneal metastasis of appendiceal origin, the 5-year OS reported in the literature for those who had re-operation for the management of the recurrence ranged from 79 to 83% compared to 64.5 to 20%, respectively, for those without surgery [19,28]. Nonetheless, R0 resection was considered the most significant indicator of improved survival.

Before reaching to firm results, there are some limitations of the study that need to be addressed. First of all, the retrospective nature of the study and the small number of the recruited patients consist significant limitations. Our study is subjected to significant bias concerning the selection of the patients included and more specifically, the selection criteria of the patients that are suitable candidates for second CRS and HIPEC procedures. Furthermore, despite the fact that the type of primary

tumor was not a significant indicator of survival in multivariate analysis, each type of cancer has its own progress and biological behavior which consists a further limitation of the study. Additionally, the heterogeneous population came from different surgical units but under the surveillance of the three different teams by the same chief surgeon. The selection of patients who were eligible for a second CRS and HIPEC was not based on certain guidelines and recommendations but on the experience of the multidisciplinary team of the hospital.

Conclusions

The outcomes of the present study indicate the feasibility of repeat CRS and HIPEC procedures in patients with recurrent PM. Additionally, the procedures were related to significant morbidity but acceptable mortality and long-term survival outcomes which were highly associated with the CC status. Further studies are warranted in order to designate the selection criteria and to elucidate the malignancies as well as the group of patients that will have a survival benefit after second CRS and HIPEC procedures.

Authors' declaration

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved its submission.

Conflict of interests

The authors declare no conflict of interests.

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