World J Surg (2015) 39:1578–1583
DOI 10.1007/s00268-015-2986-8

ORIGINAL SCIENTIFIC REPORT

Repeat Cytoreductive Surgery and HIPEC for Peritoneal Surface Malignancy and Peritoneal Carcinomatosis

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Published online: 5 February 2015

Abstract

Background Peritoneal-based malignancy (PBM), especially peritoneal carcinomatosis from gastrointestinal malignancies traditionally carries a poor prognosis. Cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) have been shown to attain long median survival of 34–92 months and 5 year survival of 29–59 % in patients with favorable histopathological subtypes. Recurrence after CRS and HIPEC poses a management dilemma. This paper evaluates our institution's experience with repeat CRS and HIPEC, its associated morbidity and outcomes.

Methods One-hundred and thirty underwent CRS and HIPEC for PBM from April 2001 to June 2013. 49 had peritoneal recurrences, of which 24 had peritoneal only recurrence. 7 out of the 24 underwent a second CRS and HIPEC.

Results Five females and two males with median age of 51 (37–63), underwent a second CRS and HIPEC. The primary malignancies were: 1 peritoneal mesothelioma, 3 appendiceal, 2 ovarian, and 1 colorectal cancers. Median peritoneal cancer indices for the initial and second CRS were 19 and 12, respectively. Completeness of cytoreduction score of 0 was achieved for all patients. Median hospitalization after second CRS and HIPEC was 12 days (7–60). 1 out of 7 (14 %) experienced grade 3 or 4 post-operative complications. There was no 30-day or inpatient mortality. Median follow-up was 13 months (1–97). Median disease-free interval between the first CRS and HIPEC to peritoneal recurrence was 20 months (14–87). Median disease-free survival of 6 months (1–97) was achieved after the second CRS and HIPEC. Six patients remained alive without disease and one passed away with disease. Two had recurrences at 12 and 71 months after second CRS and HIPEC, 1 died and the other, still alive, went on to have a third CRS.

Conclusion Repeat CRS and HIPEC can achieve prolonged survival in selected patients with peritoneal-based malignancies, and can be performed with acceptable morbidity and mortality.

Introduction

Cancer dissemination to peritoneal surfaces has traditionally resulted in a poor prognosis with fatal disease progression. Even with treatment by systemic chemotherapy, median survival of patients with peritoneal carcinomatosis, of only 6–12 months [1, 2] is expected.

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Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have proven effective for selected patients with peritoneal carcinomatosis [3–12].

With the progression of surgical technologies and techniques, the morbidity and mortality of such treatment approaches have also decreased accordingly with a corresponding increase in the overall survival. Long-term median survival of 34–92 months [3] and 5 year survival of 29–59 % [4] can be expected from this selected group of patients. Major morbidity (grade III/IV) and mortality rates in high volume centers (>100 cases) are typically 0–52 and 0.9–5.8 %, respectively [13]. The management dilemma arises when patients who have undergone CRS and HIPEC recur in the peritoneal cavity alone. The options of palliative chemotherapy and a potentially curative redo-CRS and HIPEC became possible considerations.

The objective of this study is to perform a retrospective analysis of the patients at our institution who underwent a second CRS and intraperitoneal chemotherapy for treatment of recurrent peritoneal carcinomatosis after primary CRS and HIPEC. Evaluation of the rationale, feasibility, and outcomes of CRS + HIPEC are discussed.

Materials and methods

This study was approved by the Centralized Institutional Review Board of the Singapore Health Services. We performed a retrospective review of a prospectively maintained database of all patients who suffered recurrent disease after primary CRS and HIPEC at the National Cancer Center of Singapore (NCCS) between the study period of April 2001 and June 2013. Only patients who underwent a second CRS and HIPEC were included in the study.

Patients were seen 3 monthly for the first year after their first CRS and HIPEC and 6 monthly thereafter. CT scans of the thorax, abdomen and pelvis, and tumor markers were obtained at 6 monthly intervals. Patients with recurrent disease confined to the peritoneum were discussed at the multidisciplinary tumor board for consideration of a second CRS and HIPEC.

Exclusion criteria included extraperitoneal metastases or liver parenchymal disease. The radiological images were reviewed and evaluation of the likelihood of complete cytoreduction was also undertaken. Other prognostic factors such as disease-free interval (DFI), ECOG status, comorbidities, and primary tumor histology were also taken into consideration at the tumor board discussion. Patients with a DFI of <12 months, multiple medical morbidities, or poor ECOG were generally not recommended a repeat CRS and HIPEC.

Method of CRS and HIPEC

CRS was performed as described by Sugarbaker et al. [14] which consists of six peritonectomy procedures and resection of all macroscopic peritoneal disease. The aim of CRS is to attain a complete R0 cytoreduction, with no visible residual disease. The objective of the repeat CRS and HIPEC remained similar. All surgeries were performed by either one of two specialist surgical oncologists from NCCS (KC Soo and M Teo).

After completion of CRS, 60 min of HIPEC was administered using the closed method via the inflow and outflow catheters placed during the operation. Chemotherapeutic agent was infused at 42 °C using the Belmont hyperthermia pump. Mitomycin C was the drug of choice for PC from primary colorectal and appendiceal carcinoma and cisplatin was the drug used when the primary was ovarian carcinoma or primary peritoneal. The same agent was used in the first and second CRS and HIPEC procedures for the respective patients.

PCI and CC scores

To determine the extent of peritoneal disease, the peritoneal cancer index (PCI) score was used. Scoring was done intra-operatively by dividing the peritoneal space into 13 abdomino-pelvic regions and assigning score of 0–3 to each region according to the size of the nodule found [14, 15]. Completeness of cytoreduction score (CC-score) measures the amount of disease left behind after CRS and was graded from a score of 0–3. A score of 0 denotes no residual tumor and 1–3 denotes macroscopic tumor measuring <0.25, 0.25–2.5, >2.5 cm, respectively [14, 15].

Outcome measures

DFI was defined as duration from date of initial CRS and HIPEC to the date of peritoneal recurrence.

The cases were analysed and evaluated based on primary endpoints of disease-free survival (DFS) and overall survival (OS). DFS was calculated from second CRS and HIPEC to the time of local, peritoneal or distant recurrence, and death or time of analysis (June 2013). OS was calculated from primary CRS and HIPEC to the same endpoint events or time of analysis.

Results

Between April 2001 and June 2013, 130 patients underwent CRS and HIPEC at the National Cancer Centre Singapore. 62 patients developed recurrences after CRS and HIPEC, of which 48 had peritoneal disease as one of their

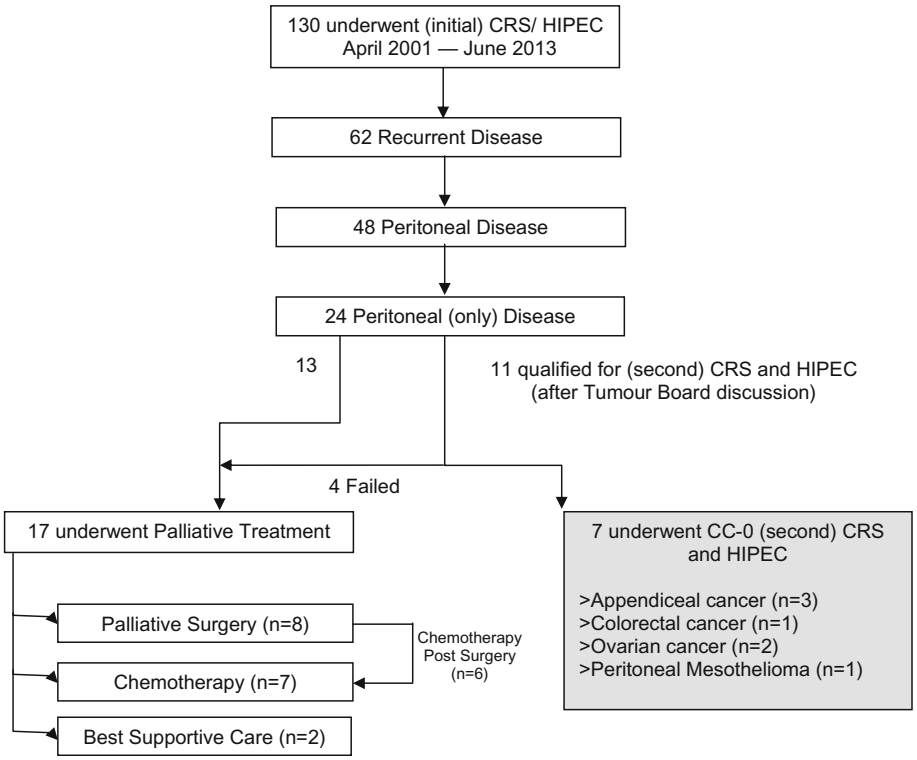

Fig. 1 Schematic diagram of patient distribution

sites of recurrence. 24 patients had recurrences confined to the peritoneal cavity only and these patients were considered for a repeat CRS and HIPEC.

Eleven patients were recommended for a second CRS and HIPEC based on the inclusion criteria. They underwent exploratory laparotomies with the plan for a second CRS and HIPEC. 7 patients successfully underwent a second CRS and HIPEC and the remaining 4 patients were deemed unresectable due to extensive small bowel involvement.

The primary tumor biologies in the 7 patients who underwent second CRS and HIPEC were as follows: primary appendiceal cancer ($n = 3$), primary colorectal cancer ($n = 1$), primary ovarian cancer ($n = 2$), and primary peritoneal mesothelioma ($n = 1$). There were five females and two male patients (see Fig. 1).

For the 17 patients with peritoneal only recurrence who were not recommended a second CRS and HIPEC, 8 underwent palliative surgery, 7 were referred for palliative chemotherapy, 2 refused further treatment, and were offered best supportive care. The patients were deemed not suitable for second CRS and HIPEC if they were unfit for the aggressive treatment or if their DFI was short (<12 months). In this group of 7, recurrent disease was seen within a median DFI of 6 months (4–10 months) after the initial CRS and HIPEC.

Out of the 8 patients who underwent palliative surgery, 7 underwent bowel resection for prevention of or for diagnosed intestinal obstruction and 1 had surgery for a symptomatic enlarging anterior abdominal wall metastasis. 6 of the 8 patients, who underwent palliative surgery, subsequently received palliative chemotherapy post-operatively, while the remaining two patients were deemed unfit for palliative chemotherapy.

The median follow-up period of patients who underwent a second CRS and HIPEC, was 13 months (1–97 months). The median DFI since the initial CRS and HIPEC was 20 months (14–87 months) before disease recurrence was detected radiologically. All patients in this study cohort had a disease-free duration of at least 1 year before disease recurrence was detected. The median OS of at least 26 months (11–131 months) was achieved by all 7 patients who underwent a second CRS with HIPEC since the initial one. This is significantly better than the median OS of 20 months (2–70 months) seen in the 17 patients with peritoneal only recurrence who did not undergo CRS and HIPEC (see Fig. 2).

The median PCI score during the first CRS and HIPEC was 19 (range 4–31) and complete cytoreduction was achieved for all seven patients with a final cytoreduction score of 0 (CC-0) in the initial operation. During the second CRS, the median PCI score was 12 (range 3–39) and CC-0 cytoreduction was again achieved in all patients.

The median hospitalization after the second CRS and HIPEC was 12 days (range 7–60). 2 of 7 patients suffered post-operative morbidities of renal impairment ($n = 1$) and anastomotic leakage ($n = 1$). In the former, there was

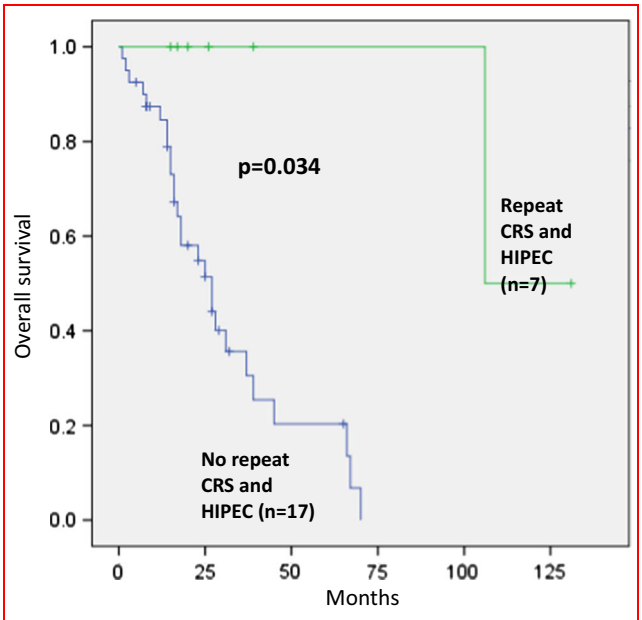

Fig. 2 Kaplan–Meier survival analysis of patients with peritoneal only recurrences who underwent repeat CRS and HIPEC versus debulking surgery with or without chemotherapy

resolution with conservative management. The latter patient required a laparotomy and resection of the anastomosis but was discharged well after a prolonged hospitalization. Hence the morbidity of major complications requiring invasive intervention, was 14 % ($n = 1$) in our cohort. There was no 30-day or inpatient mortality.

One patient with appendiceal carcinoma went on to have a third CRS with no intra-operative HIPEC approximately 6 years after the second CRS with HIPEC. In her third CRS, her intraoperative PCI score was 5 and a score of CC-0 was achieved. In view of the dense adhesion, HIPEC was not performed during this surgery. She was hospitalized for a total of 10 days and her post-operative recovery was uneventful.

To date, 5 patients are still alive with no evidence of disease recurrence, 2 patients recurred after 71 and 8 months, respectively. Of those who recurred, 1 patient went on to have a third CRS and remains disease-free to the time of review, 26 months after her third CRS and HIPEC.

One patient passed away from his disease 20 months after the second CRS + HIPEC. This patient had been lost to follow-up for a period of 4 years after the initial CRS and HIPEC. When he represented again and underwent the second CRS and HIPEC, he was found to have a PCI score of 30. Although we were able to achieve complete cytoreduction, disease recurred in the liver after a short DFS of 12 months.

The details of all seven patients are summarised in Table 1.

Discussion

Recurrence post primary CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) presents as a management dilemma to the clinician. Currently, there is no clear evidence to dictate what treatment modality is indicated for recurrent peritoneal carcinomatosis after primary CRS and HIPEC. However, patients who were previously treated with CRS and HIPEC for peritoneal-based malignancy (PBM), and survived with good physical and functional status, may benefit from a redo-CRS and HIPEC for their peritoneal recurrence [1, 2, 4].

In patients with disease biology characterized by slow and indolent natural history like that of pseudomyxoma peritonei (PMP), CRS, and HIPEC can be offered as repeat treatment to improve survival. There has been evidence that selected patient who undergo repeated debulking and peri-operative intraperitoneal chemotherapy for PMP, may expect median survival of beyond 5 years [16], with survival of 20 years being reported [17–19], especially if complete cytoreduction has been attained.

Patient selection is important in the consideration of any treatment options, especially for an aggressive treatment like CRS and HIPEC. Specialized centers are able to overcome the learning curve and can perform this aggressive modality of treatment repeatedly with acceptable morbidity rates and without compromising post treatment quality of life [20]. The current indications for combined treatment using CRS and perioperative intraperitoneal chemotherapy include peritoneal disease confined intra-abdominally with the absence of extra-abdominal metastases and liver parenchymal metastases, taking into consideration patient's performance status [21]. These various criteria and patient factors must be evaluated by the multidisciplinary tumor board before a decision is made for this aggressive local-regional treatment strategy that might offer prolonged survival or cure [22].

When evaluating the benefits of repeated CRS and HIPEC, distribution and volume of PC as defined by the peritoneal cancer index (PCI) and the completion of cytoreduction as indicated by the CC score are important in predicting and prognosticating outcomes. It has been shown that complete cytoreduction confers significant survival benefit over incomplete cytoreduction [23]. PCI may predict likelihood of complete cytoreduction but a high PCI may not necessarily indicate an inability to attain CC-0 resection, especially in the case of PMP [24].

PCI and CC scores from the initial CRS can help identify patients for a repeat procedure and that from the repeat CRS can help prognosticate the outcome [25]. Patients in whom complete cytoreduction in the initial CRS and HIPEC was not achieved, are unlikely to benefit from a repeat CRS and HIPEC when the disease progresses since

Table 1 Summary table of treatment and outcomes

Patient	1	2	3	4	5	6	7
Primary malignancy	Appendiceal	Appendiceal	Peritoneal	Ovarian	Ovarian	Colorectal	Appendiceal
Gender	F	M	F	F	F	F	M
Age (at first CRS + HIPEC) years	28	56	51	56	63	51	36
First CRS and HIPEC							
PCI score	26	12	13	4	31	24	19
CC score	0	0	0	0	0	0	0
Disease free interval (DFI) months	34	87	24	20	16	14	16
Second CRS and HIPEC							
PCI score	7	39	3	12	5	13	16
CC score	0	0	0	0	0	0	0
Disease free survival (DFS) months	71	12	15	6	5	1	1
Overall survival (OS) (since second CRS) months	97	20	15	6	5	1	1
Overall survival (OS) (since initial CRS) months	131	107	39	26	21	11	17
Total number of CRS (since initial CRS)	2[a]	1	1	1	1	1	1
Current status	Alive, NED	Died with disease	Alive, NED	Alive, NED	Alive, NED	Alive, NED	Alive, NED

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI score* peritoneal carcinomatosis index score, *CC* completeness of cytoreductive score, *NED* no evidence of disease

[a] 71 months after the second CRS + HIPEC, patient 1 had disease recurrence and underwent her third CRS with no HIPEC

the likelihood of a CC-0 resection in the repeat procedure is low.

All seven patients who underwent a second CRS and HIPEC managed to achieve median OS of at least 26 months (11–131 months) since the initial CRS with HIPEC. For patients with peritoneal recurrence only who were not suited for a second CRS and HIPEC, the median OS was only 16 months (2–70 months). We recognised that there is a selection bias but this study shows that with careful selection, some patients may benefit from a second CRS and HIPEC. Despite the limitations of a small patient population in this series, we recognised that if patients were selected appropriately to undergo repeated CRS and HIPEC as treatment for recurrent locoregional disease, we can expect potentially good outcomes of prolonged OS and DFS, with minimum morbidity and mortality. Similar survivals have been reported in patients with favorable histology by other centers [20, 26].

Of the 7 patients who underwent a second CRS and HIPEC, only one patient recurred without an avenue for further treatment. This was as a result of late detection of his recurrence, resulting in extensive peritoneal disease, likely due to the gap in his follow-up. Patients should be surveyed with the appropriate imaging at regular intervals of 6 months within the initial 5 years when most disease recurrence for those with PC would occur. This is to ensure that recurrences confined to the peritoneal cavity are diagnosed when they are still resectable and fairly low volumed. As PMP is a fairly indolent disease, the recurrence may occur later and hence we propose that annual surveillance imaging is performed for up to 10 years.

The prognosis for peritoneal-based malignancy can vary. Peritoneal surface malignancy like primary peritoneal carcinoma or pseudomyxoma peritonei from primary appendiceal carcinoma usually spell better prognosis. However, peritoneal carcinomatosis from gastrointestinal or ovarian cancer primaries tends to have significantly more dismal prognosis.

Qualifying patients for a second CRS and HIPEC requires careful selection criteria based on disease factors like disease subtype and their natural history, initial disease staging, and patient factors like ECOG status and comorbidities. CRS and HIPEC is a technically feasible surgical option but subjecting patients to a repeat procedure requires meeting of stringent criteria of favorable prognostic factors, such as a disease-free interval of more than 12 months, disease subtypes with favorable histologies and good functional status.

Conclusion

In selected patients who have undergone a complete CRS and HIPEC for their peritoneal-based malignancy and

develop recurrence confined to the peritoneum, second CRS and HIPEC may be feasible and confer a survival benefit. Close surveillance of patients who have already undergone CRS and HIPEC is advocated for early diagnosis of recurrent disease and may be warranted for beyond 5 years in pseudomyxoma peritonei.

Conflict of interest The authors declare that they have no conflict of interest.

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