Thirty-Three Long-Term Survivors After Cytoreductive Surgery in Patients With Peritoneal Metastases From Colorectal Cancer: A Retrospective Descriptive Study

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Abstract

Background

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) improves survival in selected patients with peritoneal metastasis (PM) from colorectal cancer (CRC). However, little has been reported on characteristics and clinical course of long-term survivors with CRC-PM beyond 5 years. The objective of this study was to describe the clinical and oncological features affecting long-term survival of CRC-PM after comprehensive treatment.

Methods

Between January 1990 and April 2015, CRC-PM patients who underwent CRS with or without HIPEC in two Japanese tertiary hospitals and who survived longer than 5 years after the first CRS for PM were retrospectively investigated. Clinicopathological parameters and therapeutic details involved in long-term survival were reviewed. Patients were defined as cured if the recurrence-free interval was > 5 years after the last operation for metastases.

Results

Thirty-three patients with a median peritoneal cancer index (PCI) of 4 (range, 1–27) were included. Complete cytoreduction was achieved in all 33 patients, and none had a rectal primary. Recurrence was observed in 19 patients (57.6%) at a median of 2.6 (range, 0.7–7.4) years. Sixteen patients (48.5%) were considered cured, of whom two never developed re-recurrence after the second surgery. The median PCI of cured group was 2 (range, 1–8).

Conclusions

Long-term survival and cure were obtained after CRS in selected patients with CRC-PM. Low PCI, complete cytoreduction, and non-rectal primary are associated with long-term survival and cure in PM from CRC.

Introduction

Colorectal cancer (CRC) represents the third most frequent cancer diagnosis and second most frequent cause of cancer-related mortality throughout the world (1). An estimated 2%–4% of patients have synchronous peritoneal metastasis (PM) (2-4), and approximately 20% develop metachronous PM during the course of their disease (5). PM was traditionally considered a terminal event, and patients were palliated with chemotherapy or minor surgical procedures. The overall estimated survival in untreated cases was 6 months (2, 6, 7), whereas with contemporary systemic chemotherapy, the median overall survival (OS) has been prolonged to 20 months (8-10).

Over the past two decades, several centers worldwide have adopted extensive cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC), aiming for cure in patients with PM. With this approach, long-term survival has been reported in CRC-PM, with a median OS of 20–63 months (11-20). A randomized trial proved the survival benefit in CRC-PM patients undergoing CRS/HIPEC over systemic chemotherapies (21), although the study encountered the criticism that the study cohort included appendiceal primary carcinoma, which is biologically different from CRC.

Selecting the appropriate candidates for CRS and HIPEC is vital to achieve long-term survival in CRC patients with PM. Several studies revealed the various features associated with survival benefits in detail (22-26), although there has been little research which focused on long-term survivors diagnosed with CRC-PM.

The data on oncologic outcomes in CRC-PM patients surviving beyond 5 years are sparse. Therefore, the aim of this study is to describe the characteristics of long-term survivors among patients with PM from CRC, with the goal of finding clinical and pathological factors associated with survival longer than 5 years after CRS.

Methods

Patients

This was a retrospective study of CRC-PM patients who had undergone CRS with or without HIPEC in two Japanese tertiary hospitals. Inclusion criteria were the following: (1) histopathologically-proven PM from CRC; (2) treated with CRS between January 1990 and April 2015; and (3) survived longer than 5 years after the first CRS for PM. Patients with PM from appendiceal carcinoma were excluded. We defined patients who met the inclusion criteria as long-term survivors and patients who had a recurrence-free survival (RFS) ≥5 years after the last operation for metastases as cured patients. Because there is no official definition of long-term survival and cure in CRC-PM patients, we used an OS and RFS of ≥5 years as our criteria.

Surgical Treatment and Intraperitoneal Chemotherapy

All patients were treated by cytoreduction according to the Sugarbaker technique after intraperitoneal exploration (27). The extent of intraoperative tumor volume was measured using the peritoneal cancer index (PCI) described by Jaquet and Sugarbaker (28). PCI after January 1997 was prospectively recorded, while in the cases before 1997, estimated PCI was measured using operation records and pathological reports. The intent of CRS was to remove all visible intraperitoneal disease (completeness of cytoreduction). At the completion of surgery, the completeness of cytoreduction (CCR) score was recorded (28): CCR-0 (no residual macroscopic tumor); CCR-1 (residual tumor deposits < 2.5 mm in diameter); and CCR-2 (residual tumor deposits > 2.5 mm in diameter). After completing CRS (CCR-0 or CCR-1), HIPEC was performed with the open coliseum technique with 4 liters of physiological saline (0.9%) as perfusate (29). The target temperature was 42.5–43.5°C, and treatment time was 30–60

minutes. The drug regimen varied based on patient factors and prior neoadjuvant therapies. Commonly, 5-fluorouracil (5-FU), oxaliplatin, mitomycin C, and cisplatin were used alone or in combination.

Data collection

Between January 1997 and April 2015, the prospective institutional database was searched to identify eligible patients. A standard data form before 1997 was retrospectively completed. The data comprised the following: onset of PM, primary tumor location, histology, lymph node metastasis, PCI, CCR, HIPEC drug, preoperative and postoperative chemotherapy, site of recurrence, recurrence-free survival (RFS), reoperation for recurrence, PCI and CCR at reoperation, and overall survival. The primary tumor located in the cecum, ascending colon, or transverse colon were defined as right-sided colon cancer, and those located in the splenic flexure, descending colon, or sigmoid colon were defined as left-sided colon cancer. Follow-up involved a clinical examination, tumor marker measurement, and imaging when required, every 3 months in the first 2 years, every 6 months for the next 3 years, and annually thereafter until any oncological event. The details of recurrence and consequent management details were noted, and follow-up frequency was modified based on the last event.

This retrospective study was approved by the ethics review committee for clinical studies of our institution. Our study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. The patients involved in this study provided written informed consent authorizing the use and disclosure of their protected health information.

Statistical analysis

The closing date of follow-up for this study was the 30 April 2020. OS was calculated from the date of the first CRS for PM until the patient's death or last follow-up. RFS was measured from the date of CRS until the date of first recurrence or last follow-up, including death. Continuous variables were given as median (range). Categorical data are given as frequencies and proportions.

Results

Patients' characteristics

Between January 1990 and April 2015, 236 patients underwent primary CRS with or without HIPEC for CRC-PM. Of these patients, 33 patients (14.0%) meeting the inclusion criterion of survival beyond 5 years after CRS constituted our study population. Patient demographics are summarized in **Table 1**.

The group consisted of 21 women and 12 men, with a median age of 59 (range, 33–75) years. The onset of PM was synchronous in 7 patients and metachronous in 26 patients. The primary tumor was located in the right colon in 17 patients, and in the left colon in 16 patients. Notably, none of the patients had a primary tumor in the rectum. Histological diagnoses were well to moderately differentiated tubular adenocarcinoma, mucinous adenocarcinoma (MC), and signet ring cell carcinoma (SRCC) in 24, 7, and 2 cases, respectively. Lymph node metastases were observed on pathology in 21 patients. The median PCI

in this cohort was 4 (range, 1–27). Categorizing PCI in this cohort, 28 patients (84.8%) had PCI ≤ 10, 4 (12.1%) had PCI 10–19, and 1 patient (3.1%) had PCI ≥ 20. The median PCI of the cured subgroup was 2 (range, 1–8). Among the 16 cured patients, 15 patients (93.8%) had PCI 1–5.

Treatment Factors

Table 1 shows the treatment factors, and **Table 2** summarizes the details of the treatment schedule. Most of the patients received systemic chemotherapy: 28 (84.8%) of the 33 patients received preoperative and postoperative chemotherapy. Modern chemotherapy agents (fluorinated pyrimidine plus oxaliplatin or irinotecan, ± bevacizumab or panitumumab) were used in 22 patients (66.7%) receiving preoperative regimens and in 12 patients (36.4%) receiving postoperative regimens. Five patients underwent preoperative intraperitoneal chemotherapy with cisplatin and/or docetaxel.

CCR-0 was achieved in all 33 patients, and 26 patients received HIPEC. Seven patients did not undergo HIPEC because of deterioration of their general condition secondary to massive bleeding during the CRS procedure. The HIPEC regimens were cisplatin plus mitomycin C in 18 patients, 5-FU plus oxaliplatin in 7 patients, and mitomycin C plus 5-FU in 1 patient.

Patient outcomes

The median follow-up duration was 6.9 (range, 5.1–28.8) years. Patients' prognoses are presented in **Table 2,** and a flow chart is shown in **Figure 1**. The 14 patients who did not develop recurrence after the first CRS and the 2 patients who survived at least 5 years after the last operation without a second recurrence were considered "cured". Among the long-term survivors, 5 patients survived beyond 10 years after the first CRS.

Tumor recurrence occurred in 19/33 cases at a median of 2.6 (range, 0.7–7.4) years. The sites of recurrence included isolated peritoneum (n = 6), abdominal wall (n = 4), abdominal lymph nodes (n = 3), liver (n = 1), lung (n = 1), and multiple sites (n = 4).

In this group of 19 patients with recurrence after CRS, 5 were treated with palliative systemic therapy and 14 with a second surgical procedure (CRS/metastasectomy). Median PCI in the second operation was 2 (range, 0–14). Twelve patients achieved CCR-0, and one each achieved CCR-1 and CCR-2. In the group who underwent secondary cytoreduction or metastasectomy, 11 developed a second recurrence. Among these 11 patients with re-recurences, 6 patients died of a cancer-related cause, and 5 patients were alive with disease at the last follow-up.

Discussion

In our cohort of patients with CRC-PM who underwent extensive CRS and perioperative chemotherapy including systemic and intraperitoneal chemotherapy, 14.0% (33/236) survived beyond 5 years. Sixteen of 33 patients remained recurrence-free more than 5 years after the last surgery for metastases and were considered "cured". Additionally, 5 patients in this cohort survived more than 10 years. Our study proves

that long-term survival and cured status are possible in an appropriately selected sub-set of patients with PM from CRC.

Despite the adoption of CRS and HIPEC in many centers worldwide, this approach is still met with criticism. One of the arguments against CRS and HIPEC is high morbidity and mortality risk of these procedures (30-32). However, whether patients with PM from CRC can attain equivalent long-term survival with systemic therapy alone is doubtful (8-10). A comprehensive approach with a combination of neoadjuvant systemic chemotherapy, CRS/HIPEC, and adjuvant systemic therapy may provide long-term survival in CRC-PM patients.

OS in CRC-PM patients treated with CRS is strongly associated with achieving complete cytoreduction. Several studies showed that patients with complete cytoreduction (CCR-0 or CCR-1) have a better survival outcome than patients with incomplete cytoreduction (CCR-2 or CCR-3) (33-35). Others reported survival differences between CCR-0 and CCR-1 in CRC-PM patients (36). In our study, all 33 patients received CCR-0 resection, which reaffirms that complete cytoreduction with no macroscopic disease is important to achieve long-term survival.

PCI, which describes the extent and distribution of peritoneal disease, is one of the most important prognostic indices. Several investigators have suggested that better outcomes are obtained after CRS and HIPEC with a PCI < 10 (37, 38), and worse survival with a PCI >17 (39, 40). The median PCI in our cohort was 4, and 87.9% (29/33) of the long-term survivors had a PCI $\leq$ 10. Moreover, all patients in the cured group had a PCI $\leq$ 8. These facts suggest that higher PCI is a negative prognostic factor for long-term survival.

It has been assumed that PMs from rectal origin behave differently from colonic origin PMs regarding survival. Previous studies demonstrated that PMs from primary rectal cancer were associated with a poor prognosis compared with primary colonic origin (41-44). In our cohort, none of the 33 long-term survivors had a primary tumor in the rectum, and our findings are similar to those in previous studies. The indications for CRS and HIPEC for rectal cancer PM might have to be more restrictive than for colonic PM.

Other important findings in our study were, first, that well to moderately differentiated tubular adenocarcinoma was the most frequently diagnosed histology of CRC followed by MC and SRCC. In our cohort, 7 patients had MC, and 2 had SRCC. Histological differences between mucinous and non-mucinous regarding prognosis are controversial. Some investigators suggested that mucinous carcinoma patients had a worse prognosis (45-47) while others did not (48, 49). Of the 7 MC patients in our cohort, 3 were cured of disease, and 4 were not, indicating that CRC-PM patients with MC histology can obtain long-term survival and cure. The negative impact of SRCC in CRC-PM has been described in multiple studies, with the median OS in these patients ranging from 7 to 13 months even if patients are treated with CRS and HIPEC (35, 44, 50-52). It is rare to witness 5-year survival in SRCC. The 2 SRCC patients in our cohort experienced 62- and 71-month survival, respectively. The proportion of SRCC patients who are eligible for CRS and consequently experience long-term survival is currently low. More detailed reporting and further research are required to identify potential long-term survivors.

Second, in our cohort, patients who had lymph node metastases constituted more than one-half of long-term survivors and the subgroup of cured patients. It has been proposed that regional lymph node metastasis has a negative prognostic impact on survival (36, 53-55). The recently-developed COMPASS (colorectal peritoneal metastases prognostic surgical score) reported by Simkens et al. includes nodal status among the four clinical factors (PCI, nodal status, histology, and age) used to predict outcomes after CRS and HIPEC in CRC-PM (56). However, lymph node meatastases in isolation cannot be considered an exclusion criterion (38). With standardization of techniques for total mesorectal excision and complete mesocolic excision, which removes tumors en bloc with lymphatics, local recurrence has decreased (57, 58). In our patient population, the majority (21/33, 63.6%) of patients presented with lymph node metastases, and 10 of 20 patients were categorized into the cured group. It is reasonable to support that CRC-PM patients with lymph node metastasis can achieve long-term survival and cure.

Third, 84.8% (28/33) of our patients received preoperative systemic therapy, and 93.9% (31/33) received systemic chemotherapy during the course of their management. Kujipers et al. noted that OS and progression-free survival were better in subjects receiving systemic therapy irrespective of the timing of its administration (pre-/post-CRS and HIPEC) (59). The fact that 93.9% of our cohort received systemic therapy underscores the importance of multimodal treatment in CRC-PM. One of the criticisms of the recent PRODIGE-7 trial, which questioned the role of HIPEC in the clinical management of PM from CRC, was the use of oxaliplatin in both neoadjuvant chemotherapy and HIPEC (60). Previous chemotherapy regimens with oxaliplatin could cause alterations in the cancer cell genome and in oxaliplatin sensitivity (61). These findings suggest that HIPEC with oxaliplatin may be ineffective. Therefore, our practice is to consider different drug regimens (cisplatin + mitomycin C) if neoadjuvant chemotherapy with oxaliplatin exceeds 4–6 cycles.

Readers may question the frequency of low PCI in our study group, and question whether HIPEC was required in such cases. First, because our hospitals are tertiary referral centers, our waiting period for surgery is approximately 6–12 weeks, and systemic therapy is initiated during this period. This potentially reduces the size and extent of PM, and there is a consequent reduction in PCI. However, the decision to perform CRS and HIPEC is based on the initial PCI calculation from imaging or laparoscopy. Second, patients responding favorably to preoperative chemotherapy could have had a favorable tumor biology that benefitted from this extensive procedure. While complete cytoreduction for optimal outcomes is vital, the role of systemic therapy in achieving tumor shrinkage and providing maintenance after CRS cannot be underestimated.

This study had several major limitations. First, because our study was retrospective in design, selection biases were introduced, due to the exclusion of patients with unresectable PM. Second, as a descriptive study, this current research lacked any comparison of control groups for statistical analysis of effectiveness of CRS/HIPEC and prognostic factors. Finally, the definition of long-term survival and cure is not officially defined and was based only on survival times. However, the data in this study allowed a detailed assessment of the clinical features among long-term survivors in CRC-PM patients.

Conclusions

we described the characteristics and clinical course of long-term survivors who underwent CRS with or without HIPEC for CRC-PM. Our findings suggested that low PCI, CCR-0, and PM from colonic primary are associated with long-term survival and achieving cure in PM from CRC. It is important to continue identifying long-term survivors who enjoy the benefit of CRS. Further studies are required in order to verify what factors have significant influence on long-term survival and cure.

Abbreviations

CCR, complete cytoreduction; CRC, colorectal cancer; CRS, cytoreductive surgery; FU, fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; MC, mucinous adenocarcinoma; OS, overall survival; PCI, peritoneal cancer index; PM, peritoneal metastasis; RFS, recurrence-free survival; SRCC, signet ring cell carcinoma.

Declarations

Acknowledgements

Not applicable

Authors' contributions

YK and YY designed the study. YK, YY, HI, SS, AM, and MI performed data acquisition. YK, SY and KH performed data analysis and interpretation. YK and NP prepared the manuscript. KH and YY revised the paper critically. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available without restriction. Researchers can obtain data by contacting the corresponding author.

Ethics approval and consent to participate

This study of was approved by the institutional review boards; was also conducted in accordance with the Declaration of Helsinki and all patients signed the informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1, 2 and 3 is only available as a download in the Supplemental Files section.

Figures

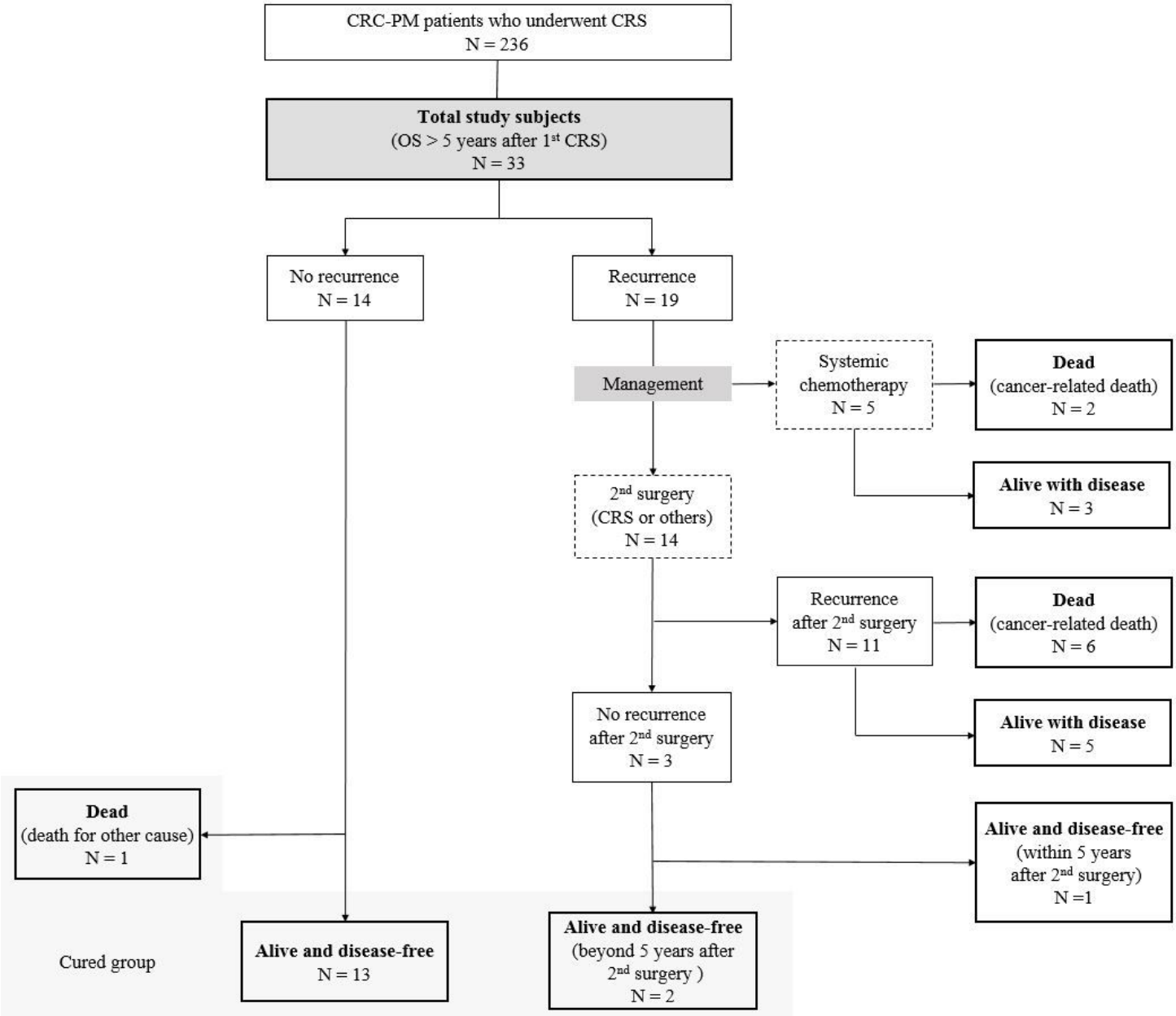

Figure 1

Flow diagram of patient enrollment. Abbreviations: CRC, colorectal cancer; CRS, cytoreductive surgery; OS, overall survival; PM, peritoneal metastasis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx