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

Yasuyuki Kamada (y_kamada@kuhp.kyoto-u.ac.jp)
Kyoto University Graduate School of Medicine Faculty of Medicine: Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu

Koya Hida
Kyoto University Graduate School of Medicine Faculty of Medicine: Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu

Haruaki Ishibashi
Kishiwada Tokushukai Hospital

Shouzou Sako
Kishiwada Tokushukai Hospital

Akiyoshi Mizumoto
Kusatsu General Hospital

Masumi Ichinose
Kusatsu General Hospital

Naveen Padmanabhan
Apollo Cancer Institutes

Shinya Yoshida
Kyoto University Graduate School of Medicine Faculty of Medicine: Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu

Yutaka Yonemura
Kishiwada Tokushukai Hospital

Research

Keywords: Peritoneal metastasis, Colorectal cancer, Long-term survivors, Cytoreductive surgery, HIPEC

DOI: https://doi.org/10.21203/rs.3.rs-104732/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
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-recurrences, 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 ≤ 10. Moreover, all patients in the cured group had a PCI ≤ 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 metastases 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.

Funding

None

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.

Author details

1 Department of Surgery, Graduate School of Medicine, Kyoto university, Kyoto, Japan

2 NPO to support Peritoneal Surface Malignancy Treatment, Japanese/Asian School of Peritoneal Surface Oncology, Kyoto, Japan

3 Department of Regional Cancer therapy, Peritoneal Surface Malignancy Center, Kishiwada Tokushukai Hospital, Kishiwada, Japan

4 Department of Regional Cancer therapy, Peritoneal Surface Malignancy Center, Kusatsu General Hospital, Shiga, Japan

5 Department of Surgical Oncology, Apollo Cancer Institutes, Chennai, India

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424

2. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002;89:1545-50.

3. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717-25.

4. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2012;99:699-705.

5. van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol. 2014;38:448-54.

6. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer. 1989;63:364-7.

7. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCape 1 multicentric prospective study. Cancer. 2000;88:358-63.

8. Klaver YL, Simkens LH, Lemmens VE, Koopman M, Teerenstra S, Bleichrodt RP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and
without targeted therapy. *Eur J Surg Oncol.* 2012;38:617-23.

9. van Oudheusden TR, Razenberg LG, van Gestel YR, Creemers GJ, Lemmens VE, de Hingh IH. Systemic treatment of patients with metachronous peritoneal carcinomatosis of colorectal origin. *Sci Rep.* 2015;5:18632.

10. Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. *J Clin Oncol.* 2012;30:263-7.

11. Ung L, Chua TC, David L M. Peritoneal metastases of lower gastrointestinal tract origin: a comparative study of patient outcomes following cytoreduction and intraperitoneal chemotherapy. *J Cancer Res Clin Oncol.* 2013;139:1899-908.

12. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol.* 2008;15:2426-32.

13. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol.* 2004;22:3284-92.

14. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer.* 2010;116:5608-18.

15. Cashin PH, Graf W, Nygren P, Mahteme H. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study. *Eur J Surg Oncol.* 2012;38:509-15.

16. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol.* 2009;27:681-5.

17. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. *Cancer.* 2010;116:3756-62.

18. Hompes D, D’Hoore A, Van Cutsem E, Fieuws S, Ceelen W, Peeters M, et al. The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. *Ann Surg Oncol.* 2012;19:2186-94.

19. Cavaliere F, Valle M, De Simone M, Deraco M, Rossi CR, Di Filippo F, et al. 120 peritoneal carcinomatoses from colorectal cancer treated with peritonectomy and intra-abdominal chemohyperthermia: a S.I.T.I.L.O. multicentric study. *In Vivo.* 2006;20:747-50.

20. Moran B, Cecil T, Chandrakumaran K, Arnold S, Mohamed F, Venkatasubramaniam A. The results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1200 patients with...
peritoneal malignancy. *Colorectal Dis.* 2015;17:772-8.

21. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21:3737-43.

22. Hallam S, Tyler R, Price M, Beggs A, Youssef H. Meta-analysis of prognostic factors for patients with colorectal peritoneal metastasis undergoing cytoreductive surgery and heated intraperitoneal chemotherapy. *BJS Open.* 2019;3:585-94.

23. Kwakman R, Schrama AM, van Olmen JP, Otten RH, de Lange-de Klerk ES, de Cuba EM, et al. Clinicopathological Parameters in Patient Selection for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Cancer Metastases: A Meta-analysis. *Ann Surg.* 2016;263:1102-11.

24. Cavaliere F, De Simone M, Virzi S, Deraco M, Rossi CR, Garofalo A, et al. Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. *Eur J Surg Oncol.* 2011;37:148-54.

25. Yonemura Y, Canbay E, Ishibashi H. Prognostic factors of peritoneal metastases from colorectal cancer following cytoreductive surgery and perioperative chemotherapy. *ScientificWorldJournal.* 2013;2013:978394.

26. Elias D, Mariani A, Cloutier AS, Blot F, Goéré D, Dumont F, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. *Eur J Surg Oncol.* 2014;40:1467-73.

27. Sugarbaker PH. Peritonectomy procedures. *Ann Surg.* 1995;221:29-42.

28. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996;82:359-74.

29. Turaga K, Levine E, Barone R, Sticca R, Petrelli N, Lambert L, et al. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol.* 2014;21:1501-5.

30. Shida D, Yoshida T, Tanabe T, Tsukamoto S, Ochiai H, Kanemitsu Y. Prognostic Impact of R0 Resection and Targeted Therapy for Colorectal Cancer with Synchronous Peritoneal Metastasis. *Ann Surg Oncol.* 2018;25:1646-53.

31. Piso P, Nedelcut SD, Rau B, Königsrainer A, Glockzin G, Ströhlein MA, et al. Morbidity and Mortality Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Data from the DGAV StuDoQ Registry with 2149 Consecutive Patients. *Ann Surg Oncol.* 2019;26:148-54.

32. Newton AD, Bartlett EK, Karakousis GC. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a review of factors contributing to morbidity and mortality. *J Gastrointest Oncol.* 2016;7:99-111.
33. Ihemelandu C, Sugarbaker PH. Management for Peritoneal Metastasis of Colonic Origin: Role of Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy: A Single Institution's Experience During Two Decades. *Ann Surg Oncol.* 2017;24:898-905.

34. Sugarbaker PH. Peritoneal Metastases from Gastrointestinal Cancer. *Curr Oncol Rep.* 2018;20:62.

35. Winer J, Zenati M, Ramalingam L, Jones H, Zureikat A, Holtzman M, et al. Impact of aggressive histology and location of primary tumor on the efficacy of surgical therapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol.* 2014;21:1456-62.

36. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2010;28:63-8.

37. Yan TD, Morris DL. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for isolated colorectal peritoneal carcinomatosis: experimental therapy or standard of care? *Ann Surg.* 2008;248:829-35.

38. Rivard JD, McConnell YJ, Temple WJ, Mack LA. Cytoreduction and heated intraperitoneal chemotherapy for colorectal cancer: are we excluding patients who may benefit? *J Surg Oncol.* 2014;109:104-9.

39. Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. *Ann Surg Oncol.* 2015;22:2958-64.

40. Faron M, Macovei R, Goéré D, Honoré C, Benhaim L, Elias D. Linear Relationship of Peritoneal Cancer Index and Survival in Patients with Peritoneal Metastases from Colorectal Cancer. *Ann Surg Oncol.* 2016;23:114-9.

41. Tonello M, Ortega-Perez G, Alonso-Casado O, Torres-Mesa P, Guíñez G, Gonzalez-Moreno S. Peritoneal carcinomatosis arising from rectal or colonic adenocarcinoma treated with cytoreductive surgery (CRS) hyperthermic intraperitoneal chemotherapy (HIPEC): two different diseases. *Clin Transl Oncol.* 2018;20:1268-73.

42. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. *J Am Coll Surg.* 2006;203:878-86.

43. Gomes da Silva R, Cabanas J, Sugarbaker PH. Limited survival in the treatment of carcinomatosis from rectal cancer. *Dis Colon Rectum.* 2005;48:2258-63.

44. Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. *Br J Surg.* 2004;91:739-46.

45. Hugen N, van de Velde CJ, de Wilt JH, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. *Ann Oncol.* 2014;25:651-7.

46. Bagante F, Spolverato G, Beal E, Merath K, Chen Q, Akgül O, et al. Impact of histological subtype on the prognosis of patients undergoing surgery for colon cancer. *J Surg Oncol.* 2018;117:1355-63.
47. Green JB, Timmcke AE, Mitchell WT, Hicks TC, Gathright JB, Ray JE. Mucinous carcinoma—just another colon cancer? *Dis Colon Rectum.* 1993;36:49-54.

48. Langner C, Harbaum L, Pollheimer MJ, Komprat P, Lindtner RA, Schlemmer A, et al. Mucinous differentiation in colorectal cancer—indicator of poor prognosis? *Histopathology.* 2012;60:1060-72.

49. Le QT, Fu KK, Kaplan M, Terris DJ, Fee WE, Goffinet DR. Treatment of maxillary sinus carcinoma: a comparison of the 1997 and 1977 American Joint Committee on cancer staging systems. *Cancer.* 1999;86:1700-11.

50. Chua TC, Pelz JO, Kerscher A, Morris DL, Esquivel J. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. *Ann Surg Oncol.* 2009;16:2765-70.

51. Pelz JO, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL, et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. *BMC Cancer.* 2010;10:689.

52. Van Sweringen HL, Hanseman DJ, Ahmad SA, Edwards MJ, Sussman JJ. Predictors of survival in patients with high-grade peritoneal metastases undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Surgery.* 2012;152:617-24

53. Braam HJ, van Oudheusden TR, de Hingh IH, Nienhuijs SW, Boerma D, Wiezer MJ, et al. Patterns of recurrence following complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *J Surg Oncol.* 2014;109:841-7.

54. Chua TC, Yan TD, Ng KM, Zhao J, Morris DL. Significance of lymph node metastasis in patients with colorectal cancer peritoneal carcinomatosis. *World J Surg.* 2009;33:1488-94.

55. Baumgartner JM, Tobin L, Heavey SF, Kelly KJ, Roeland EJ, Lowy AM. Predictors of progression in high-grade appendiceal or colorectal peritoneal carcinomatosis after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2015;22:1716-21.

56. Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res.* 2017;9:259-66.

57. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg.* 1982;69:613-6.

58. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. *Colorectal Dis.* 2009;11:354-64

59. Kuipers AM, Mehta AM, Boot H, van Leerdam ME, Hauptmann M, Aalbers AG, et al. Perioperative systemic chemotherapy in peritoneal carcinomatosis of lymph node positive colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Oncol.* 2014;25:864-9.
60. Quenet F, Elias D, Roca L, Goere D, Ghouti L, Pocard M, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol* 2018;36:LBA3503.

61. Andreou A, Kopetz S, Maru DM, Chen SS, Zimmitti G, Brouquet A, et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. *Ann Surg.* 2012;256:642-50.

**Tables**

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