*Original Article*

# Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Colorectal and Appendiceal Peritoneal Metastasis: The Experience of China Medical University Hospital

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***Key Words***
Colorectal appendiceal peritoneal metastasis;
Cytoreductive surgery;
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Survival;
Risk factors

***Purpose.*** The aim of this study was to evaluate the safety and oncological survival of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for colorectal and appendiceal peritoneal metastasis.
***Methods.*** We report a retrospective, single-center, case series from our prospective database. We reviewed the data of patients with colorectal and appendiceal peritoneal metastasis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy at our hospital between 2016-2021. The exclusion criteria were peritoneal cancer index > 15, old age (> 80 years), Eastern Cooperative Oncology Group performance status > 1, completeness of cytoreduction score ≥ 2, unresectable extraperitoneal metastasis, and palliative or prophylactic hyperthermic intraperitoneal chemotherapy. The relationships between clinical variables and tumor relapse were examined using univariate and multivariate analyses.
***Results.*** Of the 96 consecutive patients who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, the overall morbidity was 34.4%, with major complications in 11 patients (11%). The mean duration of hospital stay was 12.8 days. The median relapse-free survival and peritoneal recurrence-free survival were 16.37 ± 2.17 and 21.77 ± 10.67 months, respectively. The 5-year overall survival rate, relapse-free survival, and peritoneal recurrence-free survival was 51.4%, 21.6%, 42.9%, respectively. Multivariable analysis identified more prior systemic chemotherapy (odds ratio, 2.08) and complete cytoreductive score = 1 (odds ratio, 2.39) as independent risk factors for tumor relapse.
***Conclusions.*** Our experience demonstrated the safety of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy and its acceptable oncologic survival. However, further randomized studies are required to validate our findings.

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Colorectal peritoneal metastases (CRPM) occur in up to 20% of colorectal cancers (CRCs) and 70% of recurrent CRCs. Ten to thirty percent of recurrent CRPM is limited to the peritoneum, with a median

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survival of 7 months.[1] Since the mid-1990s, cytoreductive surgery has been considered an alternative procedure for peritoneal surface malignancy, but its difficult technique and high surgical morbidity have inhibited its development.[2,3]

With accumulated experience of cytoreductive surgery, postoperative intensive care, and better chemotherapeutic agents, both perioperative morbidity and mortality have significantly decreased, and consequently, overall survival has been prolonged.[4,5] Verwaal published the first randomized trial comparing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) to systemic chemotherapy with palliative surgery for patients with CRPM and demonstrated statistically significantly longer overall survival in the CRS/HIPEC group (22.3 vs. 12.6 months, $p = 0.032$).[6]

Thereafter, CRS/HIPEC was recommended by the National Comprehensive Cancer Network® (NCCN®) guidelines as an alternative therapeutic method in experienced centers for selected patients with peritoneal metastases for whom R0 resection can be achieved.[7] The success of CRS/HIPEC is based on the underlying principle of CRPM being a locoregional disease, not a "true" metastasis.[8] Hence, complete resection of the macroscopic tumor by CRS and eradication of the microscopic disease by HIPEC can potentially make the patient tumor-free.

This study aimed to evaluate the surgical safety and oncological survival of CRS/HIPEC in patients with colorectal and appendiceal cancer with peritoneal metastasis (CRAPM) in our hospital. We also analyzed the risk factors for tumor recurrence after CRS/HIPEC in these patients.

# Materials and Methods

## Study population and design

We conducted a retrospective, single-center case series study based on our institution's prospective patient registry database. Between April 2016 and April 2021, data of patients with peritoneal metastasis (PM) from appendiceal or colorectal adenocarcinoma treated with CRS/HIPEC at our tertiary referral hospital were analyzed. Patients younger than 80 years with an Eastern Cooperative Oncology Group (ECOG) score of less than 2 were included in this study. Before surgery, eligibility for CRS/HIPEC was discussed at a multidisciplinary colorectal team conference. We excluded patients with a peritoneal cancer index (PCI) > 15, a completeness of cytoreduction score (CCS) ≥ 2, unresectable extraperitoneal metastasis, and those who underwent palliative or prophylactic HIPEC. Our primary end point was tumor relapse-free survival (RFS) after CRS/HIPEC and evaluation of the related risk factors. Secondary end point included early postoperative results (major surgical morbidity and duration of hospital stay) and survival (overall survival (OS) and peritoneal recurrence-free survival (periRFS)). This study was approved by the Institutional Review Board of China Medical University Hospital, Taichung, Taiwan (CMUH110-REC2-033).

## CRS/HIPEC procedures

### Preoperative survey

Preoperative computed tomography (CT) of the chest, abdomen, and pelvis were performed routinely to evaluate the resectability of CRAPM and detect distal metastasis. Positron emission tomography (PET) was used only for suspected extraperitoneal metastases. Cardiac echograms were arranged for patients aged > 70 years or with a history of hypertension. Colonoscopy was also performed to establish the preoperative pathological tissue proof for colorectal or appendiceal cancer or colon status evaluations.

Nutritional status (body weight, sarcopenia, albumin, and prealbumin levels) were analyzed routinely prior to CRS/HIPEC. For cases of malnutrition, a preoperative parenteral nutrition supplement was administered for at least 1 week. Thorough laboratory tests including complete blood count (CBC), differential count (DC), biochemistry, and tumor markers were performed.

### Preoperative preparation

All patients underwent preoperative antegrade bowel preparation (Fleet® Phosphosoda or Bowel-

Klean® powder) in the evening before surgery. Antibiotic prophylaxis with cefmetazole (2 g) was administered intravenously 30 minutes before the operation, and then re-administered every 4 hours during surgery.

**Surgical procedure for CRS**

Surgery began with a complete exploration of the abdominal cavity by laparoscopy or laparotomy in cases of extensive peritoneal adhesions, and the PCI score was used to determine the extent of CRAPM. Cytoreductive surgery is defined as resection of all visible peritoneal tumors, with excision of involved organs as necessary, or with electrofulguration of millimetric implants on intestinal surfaces (Fig. 1a). Total omentectomy, appendectomy, and oophorectomy were performed routinely for menopausal women regardless of the presence or absence of metastatic nodules. Regional parietal peritonectomy was performed as described by Sugarbaker.[9] Total pelvic peritonectomy, a combination of intrapelvic organ and parietal peritoneal resection, was performed for pelvic tumor seeding or tumoral invasion of the cul-de sac, as previously published by our team.[10] The goal of surgery was to achieve complete cytoreduction (CC-0) or CC-1 with HIPEC (CC-0, no macroscopic lesion remaining; CC-1, remaining lesion < 2.5 mm). Bowel anastomoses were typically performed before the HIPEC procedure. Combined hepatectomy for liver metastasis (LM) is performed with CRS/HIPEC simultaneously if complete resection is possible.

**Procedure for HIPEC**

For colorectal cancer/appendiceal cancer, oxaliplatin is our first choice of HIPEC regimen, except for patients with a history of oxaliplatin allergy or resistance to neoadjuvant chemotherapy including oxaliplatin, cancer histology of mucinous/signet ring cells, or second HIPEC treatment with previous use of oxaliplatin. The alternative regimens were mitomycin C (MMC) with or without cisplatin.

At our institution, both closed and open HIPEC methods (Fig. 1b, 1c) were used. The concentrated chemotherapy solution was circulated at 43 °C throughout the abdomen using a PERFORMER HT hyperthermic perfusion system (RanD Biotechnology Corporation, Medolla [MO], Italy). We introduced two inflow and two outflow drains placed in both the subphrenic fossa and Douglas pouch, respectively. Two temperature probes were inserted into the abdominal cavity through the upper and lower abdominal incisions. HIPEC was administered for 60 minutes (oxaliplatin or cisplatin + mitomycin C) or 90 minutes (mitomycin C only) according to the different regimens. The dose of oxaliplatin was 460 mg/m$^2$. For mitomycin C, divided doses of 17.5, 8.8, 8.8 mg/m$^2$, total 35 mg/m$^2$ was used. First dose of 17.5 mg/m$^2$, the second dose of 8.8 mg/m$^2$ at 30 minutes, and the third dose of 8.8 mg/m$^2$ at 60 minutes, totally 35 mg/m$^2$ were given dividedly. For cisplatin with mitomycin C, dosage was cisplatin 100 mg/m$^2$ with MMC 15 mg/m$^2$. The patient's core temperature and adequate volume status was carefully monitored by anesthetists during HIPEC.

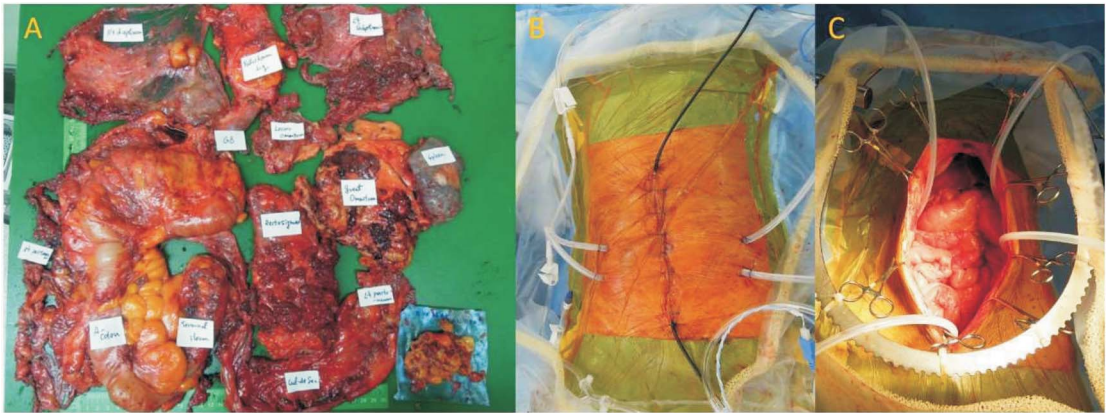


**Fig. 1.** (A) Specimen of CRS + HIPEC. (B) Close HIPEC and (C) Open HIPEC.

### Postoperative care

Patients were routinely admitted to the intensive care unit (ICU) postoperatively. If the patient tolerates the procedure, extubation and oral feeding were attempted on postoperative day 1 (POD1) after which the patient was referred to the ward. Whole blood examination was performed twice a week. Parenteral nutrition was administered to patients with paralytic ileus. All patients underwent systemic adjuvant chemotherapy and were followed up for ≥ 5 years.

### Statistical analysis

Continuous variables are reported as mean (± standard deviation), and categorical variables are reported as percentages. Probabilities of overall survival (OS), relapse-free survival (RFS), and peritoneal recurrence-free survival (Peri-RFS) were estimated using the Kaplan-Meier method. Independent risk factors for RFS were determined by multivariate Cox proportional hazards analysis, after all variables with $p < 0.05$ in the univariate analysis were entered.

## Results

### Patient characteristics

A total of 96 patients were enrolled in our study based on the inclusion and exclusion criteria. The demographic data are summarized in Table 1. There were 48 men and 48 women with a mean age of 56 years and a mean body mass index of 23.4 kg/m$^2$. Most patients had undergone prior abdominal surgery (74%) and had an American Society of Anesthesia score of I/II (52%). Interestingly, left-sided colonic neoplasms accounted for a higher proportion of primary tumors (appendix 9.4%, right-sided colon 36.5%, left-colon 42.7%, rectum 11.5%). Synchronous resectable extraperitoneal metastasis was noted in 28.1% of the patients (liver 16, ovary 11, solitary lymph node 4), and combined complete metastectomy was performed with CRS/HIPEC. Most of our patients had T4 lesions (72%), with aggressive histology (poor differentiation, mucinous, and signet-ring cell type) in 28%. RAS and

**Table 1.** Demographic data of CRC patients underwent CRS + HIPEC

| Variable | Frequency |
|---|---|
| Case numbers, total | 96 |
| Age at surgery, years | 56 |
| Sex | |
| Male | 48 (50) |
| Female | 48 (50) |
| Body mass index (kg/m$^2$) | 23.4 (15.5-35.4) |
| ASA status | |
| I/II | 50 (52) |
| III/IV | 46 (48) |
| Prior abdominal surgery | 71 (74) |
| Prior C/T more than two line | 19 (19.79) |
| Peritoneal metastasis factors | |
| Peritoneal cancer index, median (range) | |
| 1-5 | 45 (45.8) |
| 6-10 | 30 (31.3) |
| 11-15 | 22 (22.9) |
| Primary tumor location | |
| Appendix | 9 (9.4) |
| Right colon | 35 (36.5) |
| Left colon | 41 (42.7) |
| Rectum | 11 (11.5) |
| Time of peritoneal metastasis | |
| Synchronous PM | 38 (39.6) |
| Metachronous | 58 (60.4) |
| Pathological factors | |
| Primary tumor T classification | |
| T2 | 5 (5.2) |
| T3 | 22 (22.9) |
| T4 | 69 (71.9) |
| Primary tumor N classification | |
| N0 | 26 (27.1) |
| N1 | 32 (33.3) |
| N2 | 38 (39.6) |
| Histologic differentiation | |
| Well/moderate | 69 (71.9) |
| Poor/Muc./SRC | 27 (28.1) |
| RAS status | |
| Mutation | 47 (48.9) |
| B-raf status | |
| Mutation | 14 (15.4)* |
| Neoadjuvant chemotherapy | 42 (43.7) |

Values are presented as mean (standard deviation) or numbers (%).

CRS/HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; BMI, body mass index; ASA, American Society of Anesthesiologists; PCI, peritoneal cancer index; CC, completeness of cytoreduction; PM, peritoneal metastasis; SRC, signet ring cell.

* Data collection from 91 patients, data missing in 5 patients.

BRAF mutations were present in 48.9% and 15.4% of the patients, respectively. Most patients were administered systemic chemotherapy, and 19 patients (1.8%) had been administered at least two lines of systemic chemotherapy before CRS/HIPEC.

## Data on peritoneal metastasis

In our study, 39.6% of patients had synchronous peritoneal metastasis. The extension of peritoneal cancer was classified as PCI 1-5 (45 patients, 45.8%), PCI 6-10 (30 patients, 31.3%), and PCI 11-15 (22 patients, 22.9%). The mean PCI score was 7.2. Of all patients, 79.6% had complete cytoreduction (CC-0) and 20.8% achieved CC-1. Forty-two patients (43.7%) were administered neoadjuvant chemotherapy for peritoneal metastasis (Table 1).

## Surgical details

The intraoperative characteristics are shown in Table 2, including peritonectomy region, visceral resection, and HIPEC regimen and methods. The mean operation time and intraoperative blood loss were 662.4 minutes and 421.4 ml, respectively. Forty-three patients (44.8%) underwent laparoscopic-approach CRS/ HIPEC, and 71 (74%) patients had at least one bowel anastomosis. Twenty-four patients (25%) had intraoperative complications such as diaphragmatic perforation, massive bleeding, and iatrogenic vascular injury.

## Perioperative outcomes and morbidity

The short-term operative outcomes and surgical morbidity rates are shown in Table 3. Duration of intensive care unit stay, bowel function recovery, and hospital stay were 1.6, 3, and 12.8 days, respectively. Eleven patients (11.5%) required readmission 30 days after discharge due to paralytic ileus, infection, or abdominal discomfort. The overall morbidity rate was 34.4%, with major complications occurring in 11 patients (11%). As shown in Table 3, more medical complications were noted than surgical complications (26% vs. 18.8%). Although none of the patients had anastomotic leakage, there were cases of prolonged postoperative ileus (n = 6), intra-abdominal infection (n = 4), and neutropenia (n = 3). No 30-day mortalities were observed.

## Survival analysis

The median duration of follow-up was 28.4 (range 1.1-61.3) months for all patients following CRS/ HIPEC. The Kaplan-Meier survival curve showed that the median RFS and Peri-RFS were 16.37 ± 2.17 and 21.77 ± 10.67 months. The 5-years survival rates were 51.4%, 21.6%, and 42.9% for OS, RFS, and peri-RFS, respectively (Fig. 2, 3, 4).

**Table 2.** Summary of intraoperative characteristics

| Characteristics | N = 96 |
|---|---|
| PCI score | 7.2 ± 4.4 |
| Received systemic chemotherapy | |
| 0 | 34 (35.4) |
| 1 | 43 (44.8) |
| 2 or 3 | 19 (19.8) |
| Operative duration, mins | 662.4 ± 167.4 |
| Estimated blood loss, ml | 421.3 ± 113.3 |
| Laparoscopic surgery | 43 (44.8) |
| Bowel anastomosis | |
| 1 | 47 (49) |
| 2 | 24 (25) |
| 3 | 2 (2.1) |
| Subphrenic | 26 (27.1) |
| Pelvic | 66 (68.7) |
| Parietal peritonectomy | |
| Right anterior quater | 21 (21.9) |
| Left anterior quater | 14 (14.6) |
| Lessor sac | 10 (10.4) |
| Total hysterectomy | 21 (21.8) |
| Visceral resection | |
| Bilateral oopherectomy | 31 (32.3) |
| Partial hepatectomy | 25 (26.0) |
| HIPEC regimen | |
| MMC | 22 (22.9) |
| Oxaliplatin | 52 (54.2) |
| Cisplatin + MMC | 22 (22.9) |
| HIPEC method | |
| Open | 17 (17.7) |
| Close | 79 (82.3) |
| Intraoperative complications | 24 (25) |

Values are presented as median (range) or numbers (%).
PCI, peritoneal cancer index; CC, completeness of cytoreduction.

**Table 3.** Short-term operative outcomes and surgical morbidity

| Characteristics | N = 96 |
|---|---|
| Hospital stay, days | 12.8 ± 6.8 |
| ICU stay, days | 1.6 ± 0.7 |
| Time to 1st flatus passage, days | 3 ± 1.4 |
| Re-admission in 30 days | 11 (11.5) |
| Overall morbidity | 33 (34.4) |
| Minor* | 22 (22.9) |
| Major† | 11 (11.5) |
| Surgical complications | 22 (22.9) |
| Postoperative ileus | 6 |
| Intraabdominal abscess | 4 |
| Neurogenic bladder | 3 |
| Wound infection/hernia | 4/1 |
| Bowel perforation | 2 |
| Others | 4 |
| Medical complications | 25 (26.0) |
| High stoma output | 4 |
| Watery diarrhea | 3 |
| Jaundice | 4 |
| Acute kidney injury | 7 |
| Urinary tract/CVC infection | 4/2 |
| Neutropenia | 3 |

* Minor morbidities: Clavien Dindo Grade I/II.
† Major morbidities: Clavien Dindo Grade III/IV.

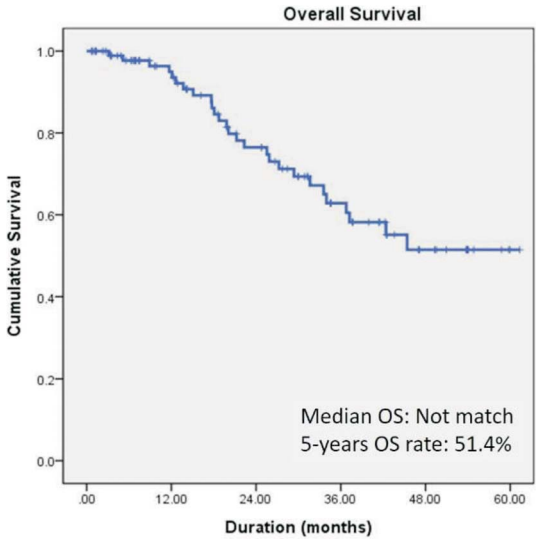


**Fig. 2.** Kaplan Meier curves of overall survival (OS).

## Risk factors for RFS

Univariate analysis revealed that a higher PCI score (> 10), CC score-1, intraoperative blood transfusion, prior administration of more regimens of systemic chemotherapy (≥ 2 lines), major complications and combined hepatectomy were associated with higher risk for tumor relapse (Table 4). HIPEC regimen was not associated with RFS according to the logistic regression analysis. Multivariate analysis found that prior administration of more regimens of systemic chemotherapy (OR = 2.08, 95% CI = 1.09-3.96, $p$ = 0.026), CC score < 1 (OR = 2.39, 95% CI = 1.04-5.46, $p$ = 0.004) and combined hepatectomy (OR = 1.90, 95% CI = 1.05-3.42, $p$ = 0.033) were independent risk factors for RFS.

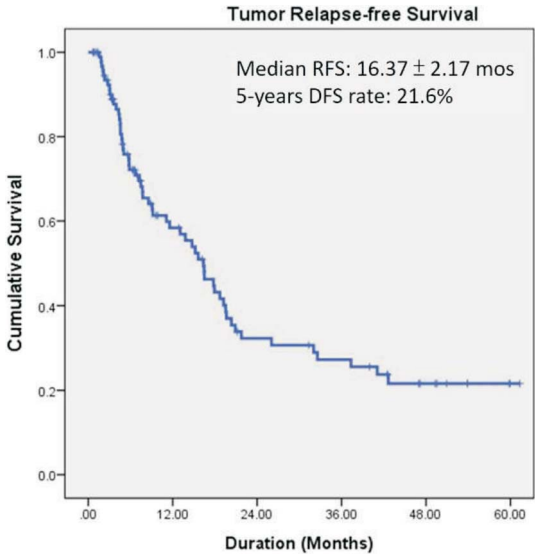


**Fig. 3.** Kaplan Meier curves of tumor relapse free survival (RFS).

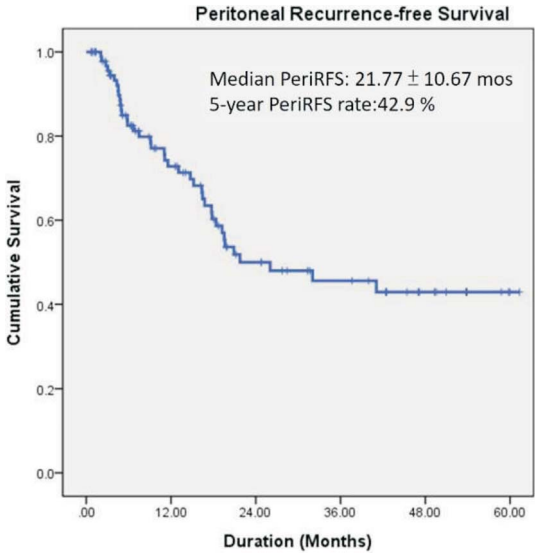


**Fig. 4.** Kaplan Meier curves of peritoneal recurrence-free survival (PeriRFS).

**Table 4.** Univariate and multivariate Cox regression analysis of risk factors for tumor Relapse according to patient's characteristics

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | N (%) | Odds ratio | *p* | Odds ratio | 95% CI | *p* |
| Age ≥ 60 – y/o | 39 | 1.20 | 0.503 | | | |
| Male | 48 (50) | 0.88 | 0.634 | | | |
| PCI score ≥ 11 | 22 | 2.14 | 0.019 | 1.30 | 0.61-2.77 | 0.490 |
| Left site of primary tumor | 52 | 0.79 | 0.370 | | | |
| Synchronous PM | 38 | 1.15 | 0.601 | | | |
| Tumor invasion – T4* | 69 | 1.06 | 0.853 | | | |
| Histology – Poor Diff. | 8 | 0.86 | 0.741 | | | |
| Type – mucinous | 20 | 1.02 | 0.942 | | | |
| RAS – mutation | 47 | 1.36 | 0.247 | | | |
| Prior C/T – more than 2 line | 19 | 2.54 | 0.003 | 2.08 | 1.09-3.96 | 0.026 |
| Neoadjuvant C/T | 42 | 1.07 | 0.799 | | | |
| CC score – 1 | 20 | 3.79 | < 0.001 | 2.39 | 1.04-5.46 | 0.040 |
| Laparoscopy – yes | 43 | 0.87 | 0.607 | | | |
| Combined hepatectomy – yes | 25 | 1.89 | 0.027 | 1.90 | 1.05-3.42 | 0.033 |
| Blood transfusion – yes | 33 | 1.98 | 0.014 | 1.53 | 0.85-2.76 | 0.156 |
| HIPEC regimen | | | | | | |
| Oxaliplatin | 52 | 0.68 | 0.191 | | | |
| Cisplatin + MMC | 22 | 0.69 | 0.439 | | | |
| Post-op major complications | 11 | 2.92 | 0.004 | 2.15 | 0.94-4.88 | 0.069 |

y/o, years-old; PCI, peritoneal cancer index; cm, centimeter; Diff., differentiation; Mod., moderate; C/T, chemotherapy; CI, confidence interval.
* Classified by the American Joint Committee on Cancer (AJCC) staging.

# Discussion

Our report confirms the surgical safety and survival benefit of CRS/HIPEC for CMUH in patients with CRAPM, as previously published.[6,11,12] In our series, the duration of hospital stay after CRS/HIPEC was 12.8 days and the overall morbidity was 34.4%, with no mortality. The median tumor relapse free survival after CRS/HIPEC was 16.37 ± 2.17 months, and the 5-year RFS rate was 21.6%; prior administration of more regimens of systemic chemotherapy (≥ 2 lines) (OR = 2.08) and CC score < 1 (OR = 2.39) were the independent risk factors for tumor recurrence after multivariate analysis.

The role of CRS/HIPEC in CRPM was established in the first randomized prospective trial by Verwaal et al. in 2003.[6] In the trial, 105 patients with CRPM were assigned to either systemic chemotherapy (5-Fluorouracil/Lecovorin) with or without palliative surgery or CRS/HIPEC with mitomycin C, followed by systemic chemotherapy groups. The initial results showed a median overall survival of 12.6 months and 22.3 months in the standard treatment and CRS/HIPEC groups, respectively ($p = 0.032$). A mortality rate of 8% was noted in the CRS arm. The study was updated in 2008 and reported statistically significantly longer disease-specific survivals in the CRS/HIPEC group than in the control group (22.2 vs. 12.6 months, $p = 0.028$).[11] However, this trial was criticized for its high mortality rate, and the chemotherapy regimen used was outdated by current standards.

Glehen et al. also conducted a retrospective multicenter study involving 506 patients who underwent CRS/HIPEC followed by oxaliplatin-based chemotherapy for CRPM in 2004.[12] The major morbidity and mortality rates were 22.9% and 4%, respectively, and OS was 19.2 months. With improvements in CRS/HIPEC in recent years, our study reported a lower surgical risk (11% major morbidity rate) and longer overall survival (51.4% 5-year OS rate). This may be related to accurate patient selection for CRS/HIPEC, the evolution of targeted agents, and perioperative chemotherapy. Therefore, current studies also recommend CRS/HIPEC as an alternative therapeutic method in experienced centers for selected patients with CRPM.[12-15]

In our analysis, the CC score was the major prog-

nostic factor for tumor recurrence and oncologic survival in patients who underwent CRS/HIPEC, as was the case in other studies.[8,16] Patients in whom CC-0 was not achieved during surgery had a significantly inferior OS.[21] Elias et al. showed a statistically significantly longer OS of 33 months for patients with CC-0 but OS of only 20 and 7 months for those with CC-1 and CC-2 or 3, respectively.[16] Therefore, every effort to achieve complete cytoreduction is important in CRAPM treatment.

Prior administration of more regimen of systemic chemotherapy (≥ 2 lines) was also an independent risk factor for tumor relapse in our study. Patients in this group had more advanced tumors that were refractory to prior systemic therapy; therefore, a poorer prognosis could be anticipated. Sugarbaker reported a similar finding in 1995.[9]

The peritoneal carcinomatosis index (PCI) score, established at the time of surgery, is widely used to evaluate the extent of disease and acts as a prognostic tool to predict patient survival. Da Silva et al. showed a statistically significant difference in survival between patients with a PCI above or below 20 (16 vs. 41 months, $p = 0.004$).[18] Elias et al. showed that the median survival time was 40 months for PCI of 1-6, 29 months for PCI of 7-12, 25 months for PCI of 13-19, and 18 months for PCI greater than 19.[16] In our study, we noted that PCI ≤ 10 was a positive prognostic factor for tumor relapse-free survival. Similarly, Yonemura et al. reported a median survival of 33.7 months and 5-years urvival rate of 40% for patients with PCI ≤ 10 compared to 10.5 months and 2.9% for those with PCI ≥ 11.[19]

Major postoperative complications are often recognized as negative prognostic factors for survival, similar to the finding in our study. Baratti et al. reported a statistically significant lower rate of 5-year disease-specific survival in patients with postoperative grade 3 to 5 morbidity than in those without such morbidity (14.3% vs. 52.3%, $p = 0.001$).[20] Simkens et al. also reported that major complications after CRS/HIPEC were significant risk factors for early recurrence (OR 2.3; $p = 0.046$) and were associated with lower OS in patents with major complications than in those without such complications (22.1 vs. 31.0 months, respectively; $p = 0.02$) [21].

In this study, intraoperative blood transfusion during CRS/HIPEC was also a negative risk factor for tumor relapse; it was associated with poor outcomes in other studies, such as higher morbidity rates;[23-25] major complications;[22] lower survival rates;[22,23,25] longer hospital and intensive care unit stay;[23,25] and increased reoperation rate, risk of renal impairment, and rate of postoperative infections.[23]

The concomitant presence of LM is considered a poor prognostic factor compared to patients with PM alone in our series and also in other studies.[12,26,27] To date, no standard management nor guideline has been established for patients with simultaneous LM and PM from colorectal cancer. Dico et al. showed the feasibility of the simultaneous treatment of liver resection and CRS/HIPEC in selected patients of mCRC with LM and PM, resulting in a 48 month median overall survival, and reasonable morbidity.[28] Maggiori et al. also suggested that in LM and PM, prolonged survival may still be achieved in highly selected patients with limited peritoneal disease (PCI < 12).[29]

## Conclusion

In conclusion, a novel therapeutic approach combining cytoreductive surgery and HIPEC is the most promising treatment for CRAPM. Our experience demonstrated the safety of CRS/HIPEC in short-term surgical outcomes and demonstrated its acceptable oncologic survival, especially in patients with R0 resection or those who had been administered fewer regimens of systemic chemotherapy. It offers hope for a cure to patients who were previously informed of a terminal stage cancer. However, the use of CRS/HIPEC and its modalities still need to be validated in randomized studies.

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**原　著**

# 腫瘤減積手術加腹腔內熱化療治療大腸直腸癌、闌尾癌併發腹膜轉移病患：中國醫藥大學附設醫院經驗分享

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**目的**　此研究之目的在於評估腫瘤減積手術併腹腔內溫熱化學治療用於治療大腸直腸癌及闌尾癌腹膜轉移的安全性及存活率。

**方法**　此為回顧性、單一醫學中心、病例系列 (case series) 研究，使用中國醫藥大學附設醫院的病患資料庫。時間從 2016 至 2021 年止，我們回顧了在此時間內接受過腫瘤減積手術併腹腔內溫熱化學治療的病患。受試者排除條件為腹膜轉移分數評估 > 15 分，年齡大於 80 歲，ECOG > 1，Completeness of cytoreduction score (CC score) ≥ 2，有無法切除乾淨的腹膜外轉移、緩和性及預防性的腹腔內熱化療。研究使用單變數及多變數分析探討腫瘤復發的危險因子。

**結果**　一共 96 位病患，整體的併發症機率為 34.4%，其中有 11 位病患產生嚴重併發症 (11%)。平均住院天數為 12.8 天。中位數腫瘤無復發存活期及中位數無腹膜腫瘤復發存活期分別為 16.37 ± 2.17 個月及 21.77 ± 10.67 個月。五年整體存活率 (OS)、無復發存活率 (RFS)、無腹膜腫瘤復發存活率 (Peri-RFS) 分別為 51.4%、21.6% 及 42.9%。多變量分析發現腫瘤復發的獨立危險因子為術前接受過較後線的化學治療 (使用超過兩線以上化學治療，OR: 2.08) 及完全減量評估分數為 1 分以上 (OR = 2.39)。

**結論**　我們的經驗證實了腫瘤減積手術併腹腔溫熱化學的安全性及可接受的腫瘤相關的存活期，然而，此結果仍需要隨機對照試驗證實。

**關鍵詞**　大腸直腸癌及闌尾癌腹腔轉移、腫瘤減積手術、腹腔內熱化療、存活率、危險因子。