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Original Article

# Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases – The Hong Kong experience and literature review

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ABSTRACT

*Introduction:* Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used to treat peritoneal metastases from appendiceal or colorectal origin. We evaluate our institution's experience and survival outcomes with this procedure, and its efficacy in symptom relief.
*Methods:* This is a single-centre retrospective observational study on patients with peritoneal metastases (PM) from appendiceal neoplasm or colorectal cancer who underwent CRS/HIPEC in Queen Mary Hospital. Our primary endpoints were overall survival (OS) and morbidity and mortality of this procedure; secondary endpoints included disease-free survival (DFS) and symptom-free survival.
*Results:* Between 2006 and 2018, thirty CRS/HIPEC procedures were performed for 28 patients – 17 (60.7%) had appendiceal PM while 11 (39.9%) had colorectal PM. The median peritoneal cancer index was 20; complete cytoreduction was achieved in 83.3% patients. High-grade morbidity occurred in 13.3% cases. There was no 30-day mortality. Two-year OS were 71.6% and 50% for low-grade appendiceal PM and colorectal PM patients ($p = 0.20$). Complete cytoreduction improved OS (2-year OS 75.4% vs 20%, $p = 0.04$). Median DFS was 11.8 months. Median symptom-free duration was 36.8 months; patients with complete cytoreduction were more likely to remain asymptomatic (82.9% at 1 year, vs 60% in incomplete cytoreduction group, $p < 0.01$). 91.7% low-grade appendiceal PM patients and 58.4% colorectal PM patients remained asymptomatic at post-operative one year ($p = 0.31$).
*Conclusion:* CRS/HIPEC is beneficial to appendiceal PM and selected colorectal PM patients – improving survival and offering prolonged symptom relief, with reasonable morbidity and mortality. Complete cytoreduction is key to realising this benefit.



## 1. Introduction

Peritoneum is the third most common site of metastases in colorectal cancer.[1] Five percent patients have synchronous peritoneal metastases (PM) at initial diagnosis; 19% develop metachronous PM after curative primary resection, with 8% being isolated metastasis.[2,3] Conventionally regarded as a terminal disease with dismal prognosis, treatment for colorectal PM is often palliative. Compared to solid organ metastases, PM have poorer response to systemic therapy and inferior prognosis. Contemporary systemic chemotherapy (oxaliplatin- and irinotecan-based) with targeted therapy attains median survival of 16.3 months for isolated PM, compared with 19.1 and 24.6 months for isolated liver and lung metastases.[4] Patients with PM also frequently suffer from debilitating ascites and local complications like bowel obstruction and enteric fistulae.[5] It is not easy to alleviate their symptoms; palliative surgery comes at the cost of high morbidity and mortality, as well as prolonged hospitalization.[6]

Selected patients with colorectal oligo-metastases to liver or lung enjoy long-term survival after curative metastatectomy, provided complete resection is attained. A similar concept has been increasingly adopted to colorectal PM. With isolated low-volume PM considered a loco-regional disease instead of systemic, a

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multimodal therapeutic approach optimizing loco-regional disease control improves outcomes in selected patients.[7]

The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIEPC), a synergistic approach combining radical surgery with regional chemotherapy, has altered the treatment landscape. CRS aims to remove all macroscopic peritoneal disease; this is achieved by resection of tumour-coated viscera and parietal peritoneum (peritonectomy). HIPEC targets the residual microscopic lesions – intraperitoneal administration allows delivery of a higher concentration of chemotherapeutics to peritoneal disease with less systemic toxicity, while mild hyperthermia enhances the drugs' cytotoxicity and penetration into tumour nodules.[8]

CRS/HIPEC was first used to treat appendiceal mucinous neoplasm with pseudomyxoma peritonei (PMP) – a condition caused by transmural appendicular mucinous tumours secreting mucin in the peritoneal cavity, leading to gelatinous ascites. This approach has replaced serial debulking surgeries as the standard of care for PMP.[9] Five-year overall survival reached 84% in recent large retrospective studies, but high recurrence rates up to 28% were quoted.[10,11] This technique also proved valuable for a subgroup of colorectal PM patients. It was first shown CRS/HIPEC in addition to systemic 5-fluorouracil/leucovorin improved median survival from 12.6 to 22.3 months.[12] A prematurely terminated randomized trial subsequently demonstrated addition of CRS/HIPEC offered superior 2-year overall survival when compared to systemic oxaliplatin-based chemotherapy alone (54% vs 38%, $p = 0.04$).[13] Large multicentre retrospective studies attained median survival times of 30–38 months.[14,15] Nevertheless, controversies exist on this treatment modality. Firstly, it carries significant morbidity and mortality; major complications and death occurred in up to 52% and 5.8% patients in high-volume centres,.[16] Secondly, the value of HIPEC on top of CRS has been questioned for colorectal PM. The preliminary results of PRODIGE-7 trial showed combining oxaliplatin-based HIPEC with CRS had no survival advantage over optimal CRS alone, but was associated with more late complications. It is worth mentioning both arms of PRODIGE-7 had an unexpectedly long survival of 41 months, highlighting the benefit of complete surgical cytoreduction.[17] Current major guidelines in Europe and the United States recommend complete CRS/HIPEC performed in experienced centres as an appropriate treatment option for selected patients with limited colorectal PM.[18,19]

We started performing CRS/HIPEC for appendiceal PMP patients since September 2006; with growing evidence, we have extended its application to colorectal PM starting from March 2016. The aim of this study is to evaluate the efficacy and safety of CRS/HIPEC in our centre. In addition, we investigate whether this approach is effective in relieving obstruction and other symptoms for these patients. We conclude by reviewing latest evidence in the literature, with a focus on Asian-Pacific experience.

## 2. Methods

### 2.1. Study population and data collection

This is a single-centre retrospective observational study. All patients with PM of appendiceal or colorectal origin who underwent CRS/HIPEC in Queen Mary Hospital between 2006 and 2018 were prospectively identified and included. The following data were extracted from medical records: patient demographics and symptoms; tumour pathology and previous treatment; their operative findings including peritoneal cancer index, PCI (a scoring system that ranges from 0 to 39, and quantifies the extent of peritoneal disease based on tumour sizes and their distribution along 13 regions within the peritoneal cavity[20]); procedural details including completeness of cytoreduction (CC-score; no residual disease [CC-0] or <2.5 mm residual disease [CC-1] signify complete cytoreduction, while surgery leaving behind tumours $\geq$ 2.5 mm [CC-2 or CC-3] is considered incomplete[8]). The postoperative outcomes including complications, symptoms, disease recurrence and mortality were noted in detail.

### 2.2. Preoperative evaluation and patient selection

All patients considered for CRS/HIPEC underwent either CT thorax/abdomen/pelvis or PET-CT to assess the extent of disease. Their age, comorbidities and performance status, as well as tumour biology were taken into consideration during patient selection for this ultra-major procedure. Therapeutic decision was made by a multidisciplinary team comprised of surgeon, oncologist and radiologist. Extra-abdominal metastases, extensive small bowel/mesentery involvement, and high-volume peritoneal disease precluding CC-0 or 1 cytoreduction were absolute contra-indications to CRS/HIPEC. For colorectal PM, presence of synchronous liver metastases and a PCI$\geq$ 20 (either from imaging or exploratory laparotomy) were relative contraindications as they were associated with poor outcomes[21]; under such circumstances, we only offer CRS/HIPEC to young, fit patients who lack alternative treatment option (e.g. further systemic therapy is expected to be futile).

### 2.3. Surgical technique

Via a midline laparotomy, the extent of intraperitoneal disease was assessed and PCI was documented. If complete cytoreduction was feasible, CRS was performed by resecting all peritoneum and viscera coated by disease. In patients with appendiceal PM, peritonectomy procedures include right upper quadrant peritonectomy, left upper quadrant peritonectomy, pelvic peritonectomy, lesser omentectomy with omental bursectomy, and anterior parietal peritonectomy.[8] In patients with colorectal PM, unaffected peritoneal surfaces are left intact rather than performing a full peritonectomy. Right hemicolectomy, rectosigmoid resection, greater omentectomy, splenectomy, hysterectomy and oophorectomy (in female patients), and occasionally gastrectomy may be needed to remove all macroscopic disease over visceral peritoneum.

HIPEC was administered before any intestinal anastomosis. We adopted the closed technique since 2014 – inflow and outflow cannulas were placed in the abdomen, the skin was temporarily closed watertight, the abdominal cavity was rinsed with a heated solution till temperature reached 42 °C, and then mitomycin C-based chemotherapy was added.[22] For appendiceal PM, 12.5 mg/m$^2$ body surface area (male) or 10 mg/m$^2$ (female) mitomycin C was given for 60 min. For patients with colorectal PM, totally 40 mg mitomycin would be given, with 30 mg given for the first hour and a further 10mg added for another 30 min.[23] We use mitomycin C because of its favourable pharmacokinetic properties (large-sized molecule that is not rapidly absorbed systemically, ability to maintain high peritoneal concentration with low systemic toxicity, stability at high temperatures, and synergistic effect with heat) and its proven benefit for HIPEC.[8,12] A continuous flow of heated chemotherapeutic solution was maintained by a hyperthermic pump, to ensure all peritoneal surfaces were adequately exposed. After flushing out the chemotherapeutic agent, the abdomen was reopened for bowel anastomosis and repair of serosa tears, before final closure of the abdominal incision.

### 2.4. Follow-up

Postoperatively, patients were seen at clinic every two to three months with CEA and CA19-9 blood tests. Surveillance CT scans

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were performed every 6 months to look for any intraabdominal recurrence.

### 2.5. Outcomes and statistical analyses

The outcomes analysed were:

1. Perioperative outcomes – completeness of cytoreduction, incidence of complications as per the Clavien-Dindo classification, and 30- and 90-day mortality rates.
2. Overall survival (OS) and disease-free survival (DFS).
3. Symptom-free survival (SFS), defined as the time from operation to recurrent symptoms requiring treatment or hospitalization (e.g. abdominal distension, intestinal obstruction) or death.

Statistical analysis was performed using IBM SPSS Statistics 24 (IBM Corp., Armonk, NY). Survival was analysed using the Kaplan–Meier method; the log-rank test was used to determine if survivals between two groups were different, and statistical significance was accepted at $p$-value <0.05. Comparison was also made against a control group of 8 appendiceal PM patients who were considered for CRS/HIPEC but only had debulking in the study period, with a median PCI of 30.

## 3. Results

Between 2006 and 2018, 30 procedures were performed for 28 patients with PM of appendiceal or colorectal origin, with 2 patients undergoing repeat CRS/HIPEC for recurrence. Seventeen (60.7%) had appendiceal PM and 11 (39.3%) had colorectal PM.

### 3.1. Patient and tumour characteristics

Nine appendiceal PM patients presented with appendicitis (5) or appendicular mass (4), while others presented with abdominal distension or raised tumour markers. Most appendiceal PM (14, 82.4%) were diagnosed synchronous to the primary appendiceal neoplasm, and had their pathological diagnosis established in appendectomy specimens before CRS/HIPEC (Table 1).

Seven (63.6%) colorectal PM patients developed PM metachronous to their primary cancer– at a median interval of 24 months (range 6.8–36 months). Amongst the four with synchronous PM and colorectal primary, two also had liver metastases on initial diagnosis. Both patients had their colorectal primary resected first, then underwent induction chemotherapy before concomitant hepatic wedge resection and CRS/HIPEC. One patient had liver metastasis on initial diagnosis of sigmoid cancer; she underwent

**Table 1**
Patient Disease and Operative details.

| | Appendiceal PM | Colorectal PM | Total | $p$-value |
|---|---|---|---|---|
| | n=17 (60.7%) | n=11 (39.3%) | n=28 | |
| Age, median, years (range) | 58 (35–75) | 61 (44–78) | 58 (35–78) | 0.470 |
| Sex, male | 5/17 (29.4%) | 2/11 (18.2%) | 7 (25%) | 0.668 |
| Primary appendiceal mucinous neoplasm | | | | |
| - Low-grade, LAMN | 12/17 (70.6%) | | | |
| - High-grade, HAMN and carcinoma | 5/17 (29.4%) | | | |
| Diagnosis of PM | | | | 0.020 |
| - Synchronous to primary tumour | 14/17 (82.4%) | 4/11 (36.4%) | 18/28 (64.3%) | |
| - Metachronous to primary tumour | 3/17 (17.6%) | 7/11 (63.6%) | 10/28 (35.7%) | |
| Previous procedures for diagnosis/treatment | | | | |
| - Appendectomy for appendiceal PM | 14/17 (82.4%) | | | |
| - Colectomy for colorectal cancer | | 9/11 (81.8%) | | |
| - Peritoneal nodule excision/omentectomy | 10/17 (58.8%) | 2/11 (18.2%) | 12/28 (42.9%) | 0.054 |
| For colorectal cancer | | | | |
| - Poorly-differentiated adenocarcinoma | | 5/11 (45.5%) | | |
| - Metastases on diagnosis of primary | | 6/11 (54.5%) | | |
| - Previous systemic chemotherapy | | 11/11 (100%) | | |
| ◦ 1st line | | 6/11 (54.5%) | | |
| ◦ 2nd line | | 5/11 (45.5%) | | |
| CRS/HIPEC performed | n=19 | n=11 | n=30 | |
| Preoperative symptoms | 11/19 (57.9%) | 3/11 (27.3%) | 14/30 (46.7%) | 0.105 |
| - Abdominal distension | 8/19 (42.1%) | 2/11 (18.2%) | 10/30 (33.3%) | 0.246 |
| - Tumour pain | 3/19 (15.8%) | 1/11 (9.1%) | 4/30 (13.3%) | 1.00 |
| Peritoneal Cancer Index (PCI), median (range) | 24 (8–32) | 9 (2–20) | 20 (2–32) | <0.001 |
| - < 10 | 2/19 (10.5%) | 6/11 (54.5%) | 8/30 (26.7%) | 0.028 |
| - 10-19 | 4/19 (21.1%) | 4/11 (36.4%) | 8/30 (26.7%) | 0.417 |
| - ≥ 20 | 13/19 (68.4%) | 1/11 (9.1%) | 14/30 (46.7%) | 0.002 |
| Complete cytoreduction (CC-0/ 1) | 15/19 (78.9%) | 10/11 (90.9%) | 25/30 (83.3%) | 0.626 |
| Operative time, median, mins (range) | 791 (276–1427) | 360 (198–571) | 504 (198–1427) | <0.001 |
| Intra-operative blood loss, median, ml (range) | 2600 (50–6000) | 800 (50–3000) | 1650 (506,000) | 0.002 |
| Multi-visceral resection[a] | 11/19 (57.9%) | 3/11 (27.3%) | 14/30 (46.7%) | 0.142 |
| Extensive peritonectomy[b] | 11/19 (57.9%) | 1/11 (9.1%) | 12/30 (40%) | 0.018 |
| Procedures performed | | | | |
| - Colectomy | 11/19 (57.9%) | 4/11 (36.4%) | 15/30 (50%) | 0.450 |
| - Rectal resection | 12/19 (63.2%) | 5/11 (45.5%) | 17/30 (56.7%) | 0.346 |
| - Hysterectomy & bilateral oophorectomy | 6/19 (31.6%) | 1/11 (9.1%) | 7/30 (23.3%) | 0.215 |
| - Small bowel resection | 1/19 (5.3%) | 6/11 (54.5%) | 7/30 (23.3%) | 0.004 |
| - Splenectomy | 9/19 (47.4%) | 0 | 9/30 (30%) | 0.011 |
| - Gastrectomy | 4/19 (21.1%) | 0 | 4/30 (13.3%) | 0.268 |
| - Liver resection | 0 | 2/11 (18.2%) | 2/30 (6.7%) | 0.126 |
| - Stoma | 12/19 (63.2%) | 2/11 (18.2%) | 14/30 (46.7%) | 0.044 |

[a] Defined as resection of viscera other than right colon and rectum.
[b] Defined as performing 3 or more of the following procedures - right upper quadrant peritonectomy, left upper quadrant peritonectomy, pelvic peritonectomy, lesser omentectomy with omental bursectomy, and anterior parietal peritonectomy.

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**Table 2**
Postoperative outcomes.

| | |
|---|---|
| Length of ICU stay, median, days (range) | 4 (0-20) |
| Length of hospital stay, median, days (range) | 18 (5–60) |
| Postoperative complications, grade II[a] | 5/30 (16.7%) |
| - Intraabdominal collection/sepsis, prolonged antibiotics | 3 |
| - Prolonged ileus, parenteral nutrition | 2 |
| Postoperative complications, grade III-IV[a] | 4/30 (13.3%) |
| - Small bowel perforation, surgical repair | 1 |
| - Respiratory failure, tracheostomy/mechanical ventilation | 1 |
| - Colorectal anastomotic stricture, endoscopic dilatation | 1 |
| - Suspected anastomotic leak, negative laparotomy | 1 |
| 30-day readmission | 1/30 (3.3%) |
| 30-day and 90-day mortality | 0 |

[a] Defined according to Clavien-Dindo classification.

staged curative resection, but developed isolated metachronous PM 10 months later. Eight (72.7%) colorectal PM patients received para-adjuvant systemic chemotherapy (XELOX ± bevacizumab) before CRS/HPEC; majority (7/8, 87.5%) had moderate to poor response.

### 3.2. Performance of CRS/HIPEC

The median PCI of the whole cohort was 20 (range 2–32). Complete cytoreduction (CC-0/1) was achieved in 25 of the 30 (83.3%) procedures. This was accomplished by multi-visceral resection and extensive peritonectomy in 14 (46.7%) and 12 (40%) procedures respectively. For colorectal PM patients, the median PCI was 9 (range 2–20) and ten (90.9%) patients had CC-0/1 cytoreduction. Other operative details were listed in Table 1.

### 3.3. Early postoperative results and morbidity following CRS/HIPEC

The median hospital stay was 18 days (5–60) and 30-day readmission rate was 3.3%. Clavien-Dindo grade II or above complications occurred after 9/30 procedures (morbidity rate 30%) (Table 2). Two had re-laparotomy: one had small bowel perforation mandating bowel resection, while the other had suspected peritonitis but laparotomy was negative. There was no procedure-related thirty- or ninety-day mortality.

### 3.4. Survival and oncological outcome

After a median follow-up of 23.4 months (range 4.5–135), eleven (37.9%) patients died and nine were tumour-related. Two- and projected five-year OS for the whole cohort were 62.7 ± 10% and 51.5 ± 11% respectively. Stratified by pathology, two-year OS for low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal neoplasm (HAMN)/appendiceal carcinoma and colorectal PM were 71.6 ± 14%, 60 ± 22% and 50 ± 17% respectively ($p = 0.20$) (Fig. 1a). Completeness of cytoreduction was significantly associated with OS: two-year survival was 75.4 ± 9.6% when CC-0/1 resection was achieved, compared to only 20 ± 17.9% in the CC-2/3 group ($p = 0.04$) (Fig. 1b).

Seventeen (70.8%) of the 24 patients who had complete cytoreduction experienced recurrence. Median DFS for LAMN, HAMN/appendiceal carcinoma and colorectal PM were 102.5, 13.8 and 5.1 months respectively. For appendiceal PM, all the recurrence (8/14, 57.1%) occurred within the peritoneal cavity. For the ten colorectal PM patients who had CC-0/1 cytoreduction, nine (90%) had disease recurrence – 3 at peritoneum, 3 to distal lymph nodes, 3 in liver, and one had pulmonary metastases; the median DFS was 5.1 months (95%CI 2.06–8.06 months).

### 3.5. Symptom-free survival

The median SFS after CRS/HIPEC was 36.8 months (95%CI 5.71–67.8 months) for the whole cohort. More than half (16/25, 64%) patients with complete cytoreduction remained alive and symptom-free, compared with median SFS of 15.4 ± 12.3 months among patients with CC-2/3 cytoreduction and 14.1 ± 2.6 months in the debulking control group. At one year, 82.9%, 60% and 62.5% patients were asymptomatic in the 3 groups respectively ($p$ <0.01) (Fig. 2a). CRS/HIPEC tended to offer longer-lasting symptom relief for LAMN

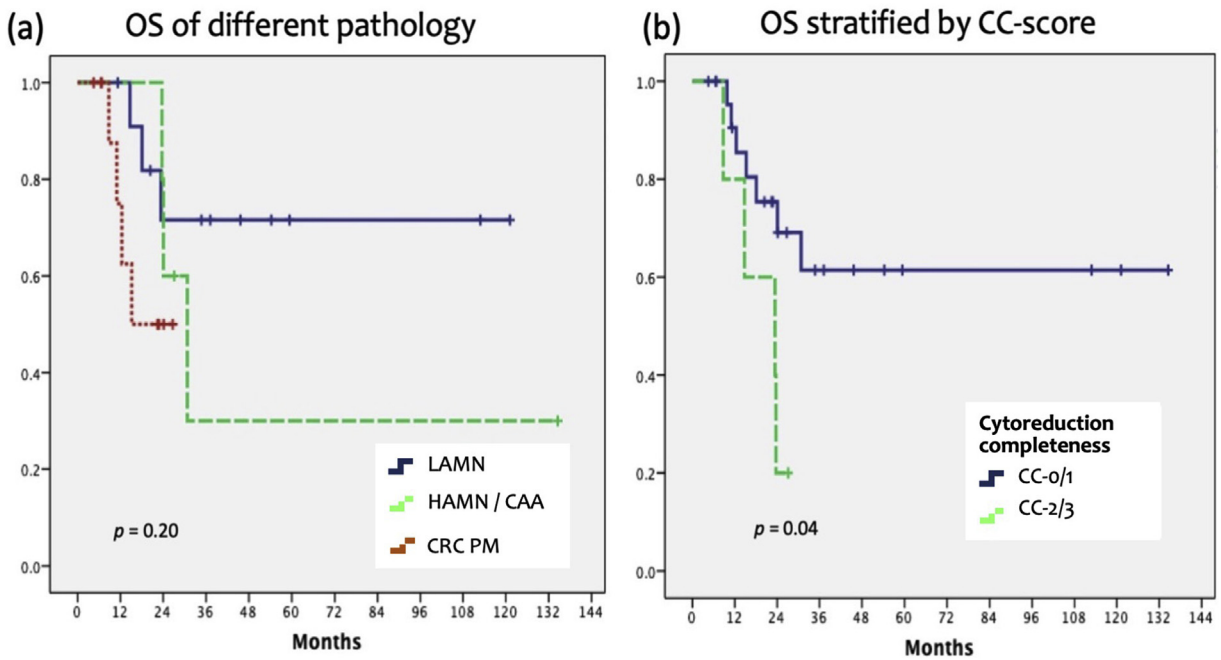


**Fig. 1.** Overall survival stratified by (a) different pathology, and (b) completeness of cytoreduction. LAMN: low-grade appendiceal mucinous neoplasm; HAMN: high-grade appendiceal mucinous neoplasm; CAA: appendiceal carcinoma; CRC PM: colorectal peritoneal metastases

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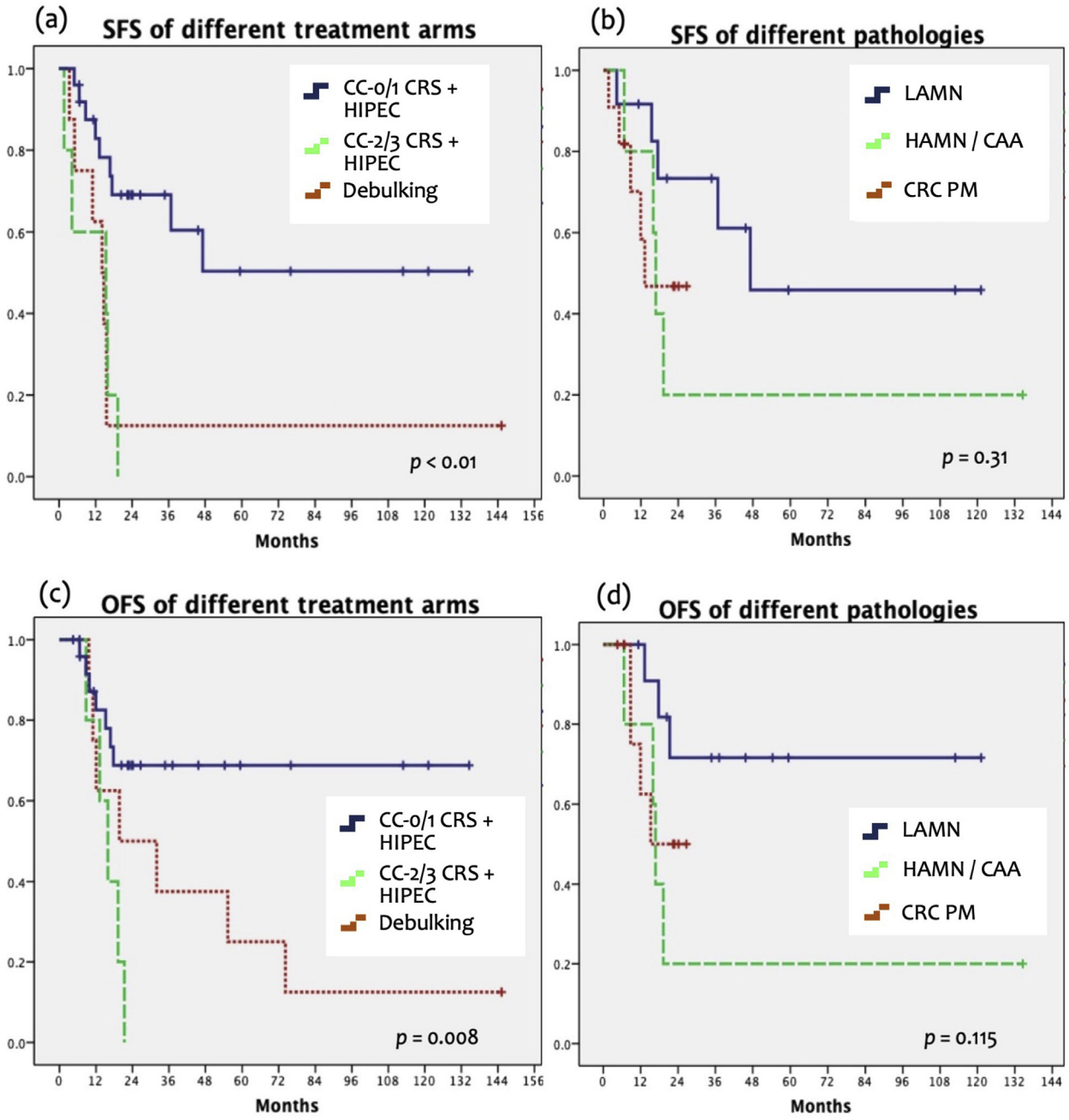


**Fig. 2. Symptom-free survival (SFS) and obstruction-free survival (OFS).** (a) SFS of different treatment arms. (b) SFS after CRS/HIPEC stratified by different pathologies. (c) OFS of different treatment arms. (d) OFS after CRS/HIPEC stratified by different pathologies. LAMN: low-grade appendiceal mucinous neoplasm; HAMN: high-grade appendiceal mucinous neoplasm; CAA: appendiceal carcinoma; CRC PM: colorectal peritoneal metastases

patients, compared to those having high-grade appendiceal tumours or colorectal PM (Fig. 2b). The median obstruction-free period for all patients was 55.3 months (95%CI 5.4–105.2 months). Patients with complete cytoreduction remained obstruction-free for longer – 82.5% (SE 8%) at 1 year (Fig. 2c). Among patients who had CRS/HIPEC for LAMN, none suffered from obstructive symptoms at post-operative 1 year (Fig. 2d).

## 4. Discussion

Appendiceal PM and colorectal cancer with PM as the only site of spread are now considered loco-regional disease. While current systemic therapies are not effective enough in keeping patients alive, CRS/HIPEC offers the hope of cure by eliminating macroscopic peritoneal tumours and improving regional disease control. It is the standard treatment for appendiceal PMP, based on 5-year survival rates of 43–84% in contemporary retrospective series.[9,24] For colorectal PM, increasing evidence suggests CRS/HIPEC plus systemic chemotherapy improves overall and progression-free survivals in selected patients. Recent large multicentre studies attained median survivals of 30–40 months (range 25–54 months) and 5-year survival rates of 28–44%.[25] While optimal cytoreduction is universally accepted as the cornerstone of this treatment modality, debate over the additional role of HIPEC has yet been settled,

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**Table 5**
Recent Asian-Pacific studies on CRS/HIPEC for appendiceal PM or Colorectal PM.

| | Year | Country | Pathology | No. of patients | % complete cytoreduction | Median FU (months) | Survival | Grade III or above complications |
|---|---|---|---|---|---|---|---|---|
| Yonemura[29] | 2013 | Japan | All colorectal PM | 142; 87 had HIPEC | 76.0% | N/A | 5yr OS 23.4%, median OS 24.4 months | 17.6%; operative mortality 0.7% |
| Huang[30] | 2014 | China | All colorectal PM *(Median PCI 21)* | 60 | 53.0% | 30 | 5yr OS 22.0%, median OS 16 months | 30.2%; no 30-day mortality |
| Alzahrani[31] | 2016 | Australia | 28.3% colorectal PM, appendiceal − 26.6% PMP, 23.1% adenocarcinoma *(Mean PCI 17)* | 675 | N/A | N/A | PMP − 5yr OS 80%, CA appendix − 5yr OS 42%, All appendix− median OS 59 months; Colorectal PM − 5yr OS 24%, median OS 28 months | 37.4%; 30-day mortality 1.2% |
| Tan[32] | 2017 | Singapore | 30% colorectal PM, 20% appendiceal *(Median PCI 12)* | 201 | 92% | 16 | 5-yr OS 55.1%, median OS 66 months. Appendix − median OS 136 months, Colorectal PM- median OS 36 months. 5-yr DFS 20.3%, median DFS 24 months | 25.8%; no 30-day mortality |
| Hsieh[33] | 2017 | Taiwan | 19.5% colorectal PM, 23.2% appendiceal *(Mean PCI 15.9 and 20.0 in two periods)* | 164 | 61.0% | 34 | 5yr-OS 35.8%; median OS 28 months. Appendix − 5yr OS 70.0%, median OS 77.6 months, Colorectal PM − 5yr OS 27.3% | 17.1%; operative mortality 3.7% |
| Narasimhan[34] | 2019 | Australia | Appendiceal − 68% PMP, 20% adenocarcinoma *(Median PCI 14)* | 172 | 74.2% | 37 | 5yr-OS 75%, median OS 104 months. Median DFS 63 months for complete cytoreduction group | 40.4%; peri-op in-hospital mortality 0.5% |

largely due to the heterogeneity of drugs and protocols used in HIPEC administration, plus lack of randomized trial data in the era of modern chemotherapy and targeted therapy. Given a recent randomized trial showed addition of HIPEC to CRS offered survival advantage in stage III ovarian cancer,[26] the negative finding of PRODIGE-7 trial was unexpected. Possible explanations include inappropriate choice of drug (oxaliplatin has uncertain efficacy when administered intraperitoneally), an exceedingly high drug dosage (which could contribute to a high rate of delayed complications), and problems in trial design (HIPEC was hypothesized to improve median OS by 18 months, on top of complete CRS; this overestimation of effect size obscured any potential subtle benefits of HIPEC).[27] More research effort should be directed at identifying the optimal drug and protocol for HIPEC for colorectal PM and establishing criteria to select the subgroup that will benefit most from HIPEC. Currently most Western guidelines recommend CRS plus HIPEC as a standard therapy for selected colorectal PM patients.[9,18,19]

Asian oncological societies also recommended consideration of CRS/HIPEC for patients with limited colorectal PM.[28] However, there is limited clinical evidence derived from Asian patients. We reviewed recent studies published by Asian-Pacific centres (Table 5). All six were retrospective cohort studies with limited median follow-up (16–37 months); at least 40% procedures in each study were for appendiceal or colorectal PM.[29–34] The median OS for appendiceal PM and colorectal PM were 59–136 and 13–36 months, whereas 5-year OS were 70–80% and 22–27% respectively. Our results were similar − LAMN patients had a 5-year OS rate of 71.6%; colorectal PM patients had a median OS of more than 15 months and a 2-year OS rate of 50%. In Asia, while the survival of appendiceal PM patients following CRS/HIPEC was comparable to that reported in Western centres, colorectal PM patients seemed to fare poorer. This could be related to differences in patient selection and tumour biology, as well as experience in performing this complex procedure. More studies, particularly large prospective trials, are required to establish the long-term oncological outcome of CRS/HIPEC in Asian patients.

Careful patient selection is paramount in maximizing oncological benefit while minimizing risks. According to the Chinese expert consensus, concurrent liver metastasis is considered a contraindication for CRS/HIPEC for colorectal PM.[35] Recent studies though showed CRS/HIPEC could achieve OS up to 49 months in selected patients with both peritoneal and liver metastases.[36] Provided the hepatic disease is limited and resectable, CRS/HIPEC may still be offered in an individual-tailored manner; nevertheless, survival and oncological outcomes were inferior to patients with isolated PM.[36] Similarly, poor response to neoadjuvant chemotherapy is considered a negative prognostic indicator, as this signifies underlying aggressive tumour biology.[21] The relatively short OS and DFS of our colorectal PM patients can be explained by our patient selection policy − three (27%) had synchronous liver metastases, and only 1 of 8 (12.5%) patients who underwent neoadjuvant chemotherapy had favourable tumour response. CRS/HIPEC was still performed because it was the only potentially efficacious treatment for these patients, for whom second- or third-line palliative chemotherapy would be futile.

Complete cytoreduction is the most important prognostic determinant. In our cohort, patients with CC score of 0 or 1 enjoyed significantly better OS. Survivals for those who had macroscopic residual tumour (CC-2/3 cytoreduction) were similar to controls who had debulking surgery. Therefore, if incomplete cytoreduction is likely, CRS/HIPEC should not be carried out. In such patients, a diagnostic laparoscopy for assessing disease extent may be helpful.[37]

Misperception of very high morbidity and mortality dissuades many surgeons and oncologists from referring suitable patients for CRS/HIPEC. With technological advances, these rates have improved to 22–34% and 0.8–4.1% in recent large series in the West.[38] An analysis on the US national surgical database showed CRS/HIPEC was a safer procedure than Whipple operation and esophagectomy.[39]

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The major morbidity and mortality rates in Asian-Pacific centres – 17.1–40.4% and 0–3.7% respectively (Table 5)[29–34] – were comparable to those in the West. Our results were similar, with a grade III or above complication rate of 13.3% and zero 90-day mortality. Given CRS/HIPEC has a learning curve requiring 180 cases to conquer,[40] we expect our morbidity and mortality rates will improve.

We showed CRS/HIPEC provides robust symptomatic relief, even in the context of disease recurrence. Almost half of our cohort suffered from abdominal distension or tumour pain preoperatively. All had total relief immediately after the procedure. The median SFS was 36.8 months, with complete cytoreduction predicting a longer symptom-free period and a lower likelihood of further palliative surgical procedures e.g. stoma creation, bypass or debulking. The procedure is effective in preventing intestinal obstruction particularly in LAMN, a debilitating symptom that frequently complicates the end stage of this indolent tumour.

There are inherent limitations to this retrospective small study: data capturing may be incomplete as patients might present to private doctors for symptoms or recurrence; the limited sample size might fall short of establishing certain correlations. Of note, subjects undergoing CRS/HIPEC represent carefully selected patients with good surgical risk and reasonable prognosis, while the control group comprises of appendiceal PM patients who had debulking mostly because of too extensive disease. There is an element of selection bias and the benefit of CRS/HIPEC could be overstated. However, we believe our study has good external validity as our patient selection criteria is not over-stringent and is comparable to those used by other institutes.

## 5. Conclusion

Our series reaffirms CRS/HIPEC offers survival benefit to patients with appendiceal PM and selected colorectal patients with small-to moderate-volume PM, with reasonable morbidity and mortality. Appropriate patient selection is the key to achieving good outcome, and complete cytoreduction is an important prognostic factor. In spite of a significant recurrence rate, CRS/HIPEC also provide robust symptomatic relief and long obstruction-free survival.

## Declaration of competing interest

We have no conflicts of interest to disclose. We would like to acknowledge Dr JWC Ho and Prof WL Law for starting the cytoreductive surgery/ HIPEC programme in our centre.

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