Outcomes and prognostic factors of cytoreductive surgery and perioperative intraperitoneal chemotherapy in high-volume peritoneal carcinomatosis

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ABSTRACT

Background and objectives: The management of patients with extensive appendiceal mucinous neoplasms and mesothelioma is controversial. Our aims were to analyze overall survival (OS), disease-free survival (DFS) and independent prognostic factors associated with high peritoneal cancer index (PCI) status in patients who underwent cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC).

Methods: A prospectively-maintained database for patients with appendiceal neoplasms and mesothelioma undergoing CRS/PIC from year 1996 to 2018 was retrospectively analyzed. Patients who achieved complete cytoreduction were stratified into limited (PCI < 30) and extensive (PCI ≥ 30) disease groups.

Results: 260 female and 235 male patients were identified. The 5-year survival for low-grade appendiceal mucinous neoplasms (LAMN) was significantly higher in the low PCI group (96.2% vs. 63.5%, p < 0.001). There was no difference in the OS across both groups in high-grade appendiceal mucinous neoplasms (HAMN) (63 vs. 69 months; p = 0.942) and mesothelioma (72 vs. 42 months; p = 0.058). Overall mortality was 2%. Grade III/IV complications were significantly higher in extensive disease (68% vs. 36.6%, p < 0.001). On multivariate analysis, use of EPIC and blood transfusion (>8 units) were independent positive and negative prognostic factors, respectively, associated with OS. Meanwhile, use of EPIC conferred benefit in DFS while increased blood transfusion (>8 units) and elevated preoperative CA125 were predictive of a poor DFS.

Conclusion: Long-term survivals following CRS/PIC are achievable with acceptable mortality and higher morbidity rates in extensive appendiceal mucinous neoplasms and mesothelioma. High PCI status does not preclude treatment with CRS/PIC.

Introduction

Peritoneal carcinomatosis (PC) is defined as dissemination of malignant tumor on peritoneal lining. Once regarded as a terminal condition [1], a combined approach of cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC) has largely become the standard of treatment for PC of appendiceal, peritoneal mesothelioma, colorectal and ovarian origins in highly selective patients [2]. CRS entails an extensive aggressive debulking surgery that aims to eliminate macroscopic malignant tumors [3]. Eradication of microscopic neoplastic deposits that are otherwise not resected with CRS will be achieved by PIC. This can be delivered intraoperatively as hyperthermic intraperitoneal chemotherapy (HIPEC), postoperatively as early postoperative intraperitoneal chemotherapy (EPIC), or both. The multimodal approach has been proven to be a viable option that can confer survival benefits in appropriate patients with PC [4–8].

Peritoneal cancer index (PCI) describes the extent of peritoneal deposits, represented by a score that integrates distribution and size of tumors in 13 abdominopelvic regions [3]. PCI is known to be an important prognostic indicator in PC [9–11]. High PCI may imply difficulty in achieving a complete cytoreduction [12] and severe postoperative complications [13]. Our recent published institutional experience suggested that lower PCI was associated with better survival outcomes [14]. For example, the 5-year survivals of mesothelioma for PCI 0–10, 11–20 and >20 were 100%, 53% and 24% respectively. Chua et al. demonstrated a five-survival of 64% in appendiceal PC patients with a PCI >30, 72% for 21–30, 83% for 11–20 and 88% for 0–10 [9]. Based on these findings, some centers have considered extensive disease – PCI greater than 20 – to be a relative contraindication for CRS/PIC [10,15,16]. Alternatively, some surgeons do not regard PCI as a limiting factor if complete cytoreduction is deemed achievable. Although complete cytoreduction (CC < 2) is always the aim regardless of the pathology, CRS and HIPEC...
can often lead to positive progression-free survival in patients with mesothelioma as long as CRS can reduce the size of nodules to 1 cm or smaller [17]. However, for gastrointestinal malignancy, surgery with incomplete cytoreduction is less than ideal.

The utility of PCI as a selection criterion for CRS/PIC has not been universally adopted because there are disadvantages using PCI in this setting. PCI cannot be directly correlated with tumor resectability and it does not take into account the biology of the cancer which is a crucial prognostic determinant [3]. Therefore, the primary aim of this study was to investigate the survival outcomes of patients with extensive PC treated by CRS/PIC as defined by PCI limit of 30 in our center. We narrowed the focus on appendiceal mucinous neoplasms and peritoneal mesothelioma. The secondary aim of this study was to analyze the prognostic factors that are associated with overall and disease-free survival in high-volume disease (PCI ≥30).

Materials and methods

Patients and selection

This retrospective study was approved by the ethics committee of South Eastern Sydney Local Health District (QAQI/18/078) as part of clinical studies in Abdominal and Peritoneal Cancers. The patients were formally consented to partake in the prospective data collection during preoperative surgical consultations. From a prospectively maintained database between January 1996 and March 2018, patients with appendiceal neoplasm and peritoneal mesothelioma undergoing CRS with PIC at our center were included in this study. The intraperitoneal chemotherapy regime was guided by the tumor types.

Appendiceal mucinous neoplasms are classified as low-grade appendiceal mucinous neoplasms (LAMN) or high-grade appendiceal neoplasms (HAMN) [18]. The classification of LAMN and HAMN was based on the WHO 5th Digestive System Tumors guideline [19]. The reported outcome of appendiceal neoplasms in our study was referred to the primary appendiceal tumor of peritoneal metastases. Most of our patients have their primary tumors removed prior to referral to our center and the histopathology slides were reviewed in our center and confirmed prior to CRS/PIC. The type of HIPEC was decided before the operation aiming to remove all macroscopic peritoneal disease [3]. The extent of peritoneal disease was measured during the laparotomy using the PCI, which ranged from 0 to 39 [3]. CRS was performed according to the Sugarbaker technique by aiming to remove all macroscopic peritoneal disease [3]. All sites and volumes of residual disease following CRS were recorded prospectively using the completeness of cytoreduction score (CC) [21]. It was scored from 0 to 3 with CC-0 (no residual tumor) and CC-1 (residual tumor deposits <2.5 mm) being considered complete cytoreduction.

Preoperative management

Potential surgical candidates underwent preoperative investigations which included physical examinations, blood tests, computed tomography (CT) scans of the chest, abdomen and pelvis. Additionally, patients with high-grade appendiceal tumors or raised tumor markers underwent either CT portography or MRI primovist and PET scan.

Procedure

Cytoreductive surgery

The extent of peritoneal disease was measured during the laparotomy using the PCI, which ranged from 0 to 39 [3]. CRS was performed according to the Sugarbaker technique by aiming to remove all macroscopic peritoneal disease [3]. EPIC was used in LAMN or HAMN of soft tumor consistency with 5FU (650 mg/m²) for days 2–6 postoperatively either in the intensive care unit or high dependency unit setting. EPIC was applied to other cancers under certain circumstances, for example, when there is a lack of availability of HIPEC (emergency cases) and contraindication to oxaliplatin or MMC.

Perioperative intraperitoneal chemotherapy

HIPEC was performed in the context of complete cytoreduction (CC0 and CC1). The chemoperfusate was delivered at a temperature of approximately 42°C using oxaliplatin (350 mg/m²) at a duration of 30 min for HAMN. In contrast, mitomycin C (MMC; 12.5 mg/m²) was used for 90 min in LAMN. Both cisplatin (100 mg/m²) and MMC (12.5 mg/m²) were administered simultaneously for 90 min for mesothelioma.

Postoperative management

Perioperative complications were classified using the Clavien-Dindo Classification [22] of surgical complications (Grade I: no intervention; Grade II: medical management; Grade III: invasive intervention such as radiological procedures; Grade IV: life-threatening complications warranting urgent return to theater or intensive care unit (ICU) admission).

After discharge, follow up was conducted by medical and surgical oncologists to review progress, tumor markers and CT scans (chest, abdomen and pelvis), when appropriate. These patients were scheduled for 3-monthly intervals for the first year and then 6-monthly intervals thereafter.

Data

Clinical data for selected patients were extracted from the database. Only patients who underwent index CRS/PIC were
Patients with incomplete cytoreduction (CC-score $\geq 2$) were excluded due to limited numbers, together with those who did not receive HIPEC. Selected patients were divided into two groups for comparisons according to the volume of PCI: a low (<30) and a high PCI group ($\geq 30$). Overall survival (OS) time was obtained in the unit of months from the initial operation to last time of contact or death whereas disease-free survival (DFS) time was calculated in the unit of months from the initial operation to time of recurrence.

### Statistical analysis

All statistical analyses were performed using SPSS for Windows version 25 (IBM Corporation, New York, NY). Patient characteristics were described using frequency and descriptive analyses. Clinicopathological factors of the two corresponding groups were analyzed using the $X^2$ test and Students’ t-test for categorical and continuous variables, respectively. Survival analyses of low- and high-volume disease were estimated using the Kaplan-Meier curves and log-rank test for comparison. In high PCI group, prognostic factors affecting OS and DFS were investigated utilizing a Cox regression model. Significant parameters ($p < 0.10$) were chosen for multivariable analysis. $p < 0.05$ was considered statistically significant.

### Results

#### Patient characteristics and perioperative outcomes

The median follow-up for the cohort was 31 months (range: 0–190). A total of 495 patients were included in the study with approximately two-third of patients ($n = 320$) in the low PCI group (Figure 1). Patient characteristics and clinicopathological factors are summarized in Tables 1 and 2, respectively, stratified according to low and high PCI groups.

The cohort in high PCI groups had significantly higher mean PCI and higher proportion of CC-1 patients (72%) leading to increased operating hours and use of blood products including packed red cell (>8 units) and fresh frozen plasma (FFP; >10 units). The admissions in ICU, high dependency unit (HDU) and hospital were relatively longer and grade 3–4 morbidity complications were more frequent when PCI was $\geq 30$. High-volume PC was also associated with elevated level of tumor markers (CEA, CA125, CA19.9 and combination of the three). There was no difference in readmission rates between the two groups following discharge from hospital. However, high volume disease was associated with higher morbidity of complications (grade III/IV) compared to low volume disease (68% vs 36.6%; $p < 0.001$).

#### Long-term survivals

Table 3 summarize the OS and DFS of different diagnoses stratified by tumor burden. The survival outcome of CRS/PIC for LAMN was excellent in the low PCI group demonstrating a 10-year survival of 81.8%. On the other hand, no patients survived more than 10 years in the high PCI group (Figure 2). Patients with low PCI also performed more favorably at 3- and 5-year follow-up (99.2% vs 80.1%; 96.2% vs 63.5%) ($p < 0.001$). Similarly, DFS was significantly better when the tumor burden was lower (Figure 2). The median DFS was 143 months in low PCI group compared to 41 months in high PCI group. In comparison, there was no significant distinction of OS in patients with HAMN regardless of the extension of disease.

![Figure 1. Flowchart showing total number of patients included in the study after exclusion of those with incomplete cytoreduction and without HIPEC.](image-url)
peritoneal disease \( p = 0.942 \); Figure 2). Median DFS for HAMN in low PCI group was significantly improved compared to the high PCI group (23 months vs 19 months; \( p < 0.001 \); Figure 2).

The median OS for peritoneal mesothelioma was 72 months and 42 months in low and high PCI groups, respectively, without statistical significance between the two groups \( p = 0.058 \); Figure 3). The same trend was noted for

| Table 1. Study population characteristics and perioperative numbers. |
| --- |
| **Patient characteristics** | **Low PCI (<30) (n = 320)** | **High PCI (>30) (n = 175)** | **p Value** |
| Gender | | | |
| Female | 182 (56.9%) | 78 (44.6%) | 0.009 |
| Male | 138 (43.1%) | 97 (55.4%) | |
| Mean age (SD) | 51.63 (12.62) | 56.07 (12.72) | <0.001 |
| Diagnoses | | | |
| LAMN | 143 (44.7%) | 60 (34.3%) | 0.034 |
| HAMN | 130 (40.6%) | 92 (52.5%) | |
| Mesothelioma | 47 (14.7%) | 23 (13.1%) | |
| Mean PCI score (SD) | 16.15 (8.17) | 35.07 (3.20) | <0.001 |
| cc-score | | | |
| 0 | 241 (75.3%) | 49 (28%) | <0.001 |
| 1 | 79 (24.7%) | 126 (72%) | |
| EPIC | | | |
| Yes | 163 (50.9%) | 85 (48.6%) | 0.615 |
| No | 157 (49.1%) | 90 (51.4%) | |
| Preoperative CEA | | | |
| Normal | 212 (70.2%) | 46 (27.2%) | <0.001 |
| Elevated | 289 (90.3%) | 90 (51.4%) | |
| Preoperative CA125 | | | |
| Normal | 209 (70.4%) | 40 (24.1%) | <0.001 |
| Elevated | 289 (90.3%) | 90 (51.4%) | |
| Preoperative CA19.9 | | | |
| Normal | 233 (79.8%) | 80 (47.9%) | <0.001 |
| Elevated | 289 (90.3%) | 90 (51.4%) | |
| Three elevated tumor markers (CEA, CA19.9, CA125) | | | |
| Yes | 25 (8.4%) | 71 (42.5%) | <0.001 |
| No | 271 (91.6%) | 96 (57.5%) | |

SD: standard deviation; LAMN: low-grade appendiceal mucinous neoplasm; HAMN: high-grade appendiceal mucinous neoplasm; CC: completeness of cytoreduction; PCI: peritoneal carcinomatosis index; EPIC: early postoperative intraperitoneal chemotherapy.

| Table 2. Comparisons of clinicopathological factors in low and high PCI groups. |
| --- |
| **Clinicopathological factors** | **Low PCI (<30) (n = 320)** | **High PCI (>30) (n = 175)** | **p Value** |
| Blood transfusion | | | |
| ≤8 units | 289 (90.3%) | 90 (51.4%) | <0.001 |
| >8 units | 31 (9.7%) | 85 (48.6%) | |
| FFP transfusion | | | |
| ≤10 units | 279 (87.2%) | 87 (49.7%) | <0.001 |
| >10 units | 41 (12.8%) | 88 (50.3%) | |
| Morbidity | | | |
| Grade 1–2 | 203 (63.4%) | 56 (32%) | <0.001 |
| Grade 3–4 | 117 (36.6%) | 119 (68%) | |
| Mean length of stay (SD) | 24.0 (18.576) | 37.16 (23.992) | <0.001 |
| Mean length of ICU stay (SD) | 3.67 (7.239) | 7.13 (12.119) | <0.001 |
| Mean length of HDU stay (SD) | 3.75 (3.661) | 4.94 (5.132) | 0.003 |
| Mean operating hours | 8.25 (2.43) | 11.09 (2.31) | <0.001 |
| Readmission rate | | | |
| Yes | 101 (31.8%) | 59 (34%) | 0.638 |
| No | 219 (68.2%) | 116 (66%) | |
| Blood transfusion | | | |
| ≤8 units | 289 (90.3%) | 90 (51.4%) | <0.001 |
| >8 units | 31 (9.7%) | 85 (48.6%) | |
| FFP transfusion | | | |
| ≤10 units | 279 (87.2%) | 87 (49.7%) | <0.001 |
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| No | 219 (68.2%) | 116 (66%) | |

SD: standard deviation; ICU: intensive care unit; HDU: high dependency unit.
Table 3 highlights both the univariate and multivariate analyses of OS and DFS in the high tumor burden group. Relevant factors associated with lower OS on univariate analysis were gender ($p = 0.017$), mesothelioma ($p = 0.01$), CC-score ($p = 0.006$), use of EPIC ($p < 0.001$), elevated preoperative CEA ($p = 0.05$), and quantity of blood transfusion ($p = 0.028$). On multivariate analysis, use of EPIC (HR 0.39, 95%CI = 0.21–0.73, $p = 0.004$) and blood transfusion >8 units (HR 1.77, 95%CI = 1.03–3.03, $p = 0.038$) were independent prognostic factors associated with OS.

Univariate analysis also displayed poorer DFS involving gender ($p = 0.014$), mesothelioma (0.005), CC-score ($p = 0.032$), use of EPIC ($p < 0.001$), elevated preoperative CA125 ($p = 0.049$) and utilization of blood products such as packed red cell ($p = 0.001$) and FFP ($p = 0.013$). On multivariate analysis, use of EPIC conferred benefit in DFS (HR 0.48, 95%CI = 0.26–0.89, $p = 0.021$) while elevated preoperative CA125 (HR 2.35, 95%CI = 1.14–4.85, $p = 0.021$) and increased blood transfusion >8 units (HR 2.11, 95%CI = 1.03–4.31, $p = 0.042$) were predictive of a poor DFS.

### Discussion

PCI is widely known as a significant prognostic determinant in PC in the current literature [9–11]. However, the implementation of PCI as a selection criterion for CRS/PIC has not been globally accepted and remains controversial in the peritonectomy community. In this study, we expanded on the analysis with an aim to clarify the impact of PCI on the long-term survival outcomes of patients with LAMN, HAMN and mesothelioma. The 5-year survival for LAMN was significantly higher in the low PCI group (96.2% vs. 63.5%, $p < 0.001$) however, there was no difference in the OS across both groups in HAMN (63 vs. 69 months; $p = 0.942$) and mesothelioma (72 vs. 42 months; $p = 0.058$).

Firstly, PCI cutoff for extensive peritoneal disease is not formalized or defined in the current literature. In our study, we chose PCI ≥ 30 as a cutoff to define high volume disease in our institution. We recognized that from the cytoreductive surgical point of view, the ability to achieve complete cytoreduction is a more important and significant prognostic factor for survival. When PCI is more than 30, complete cytoreduction is exceptionally challenging. This was also previously reflected by Benhaim et al. [23]. In their study, a PCI threshold of 28 was chosen to define extensive disease, as complete cytoreduction was increasingly difficult to achieve beyond this. They described three surgical conditions to achieve complete cytoreduction: (a) conserving at least the upper part of stomach (b) clearing the hepatic pedicle and (c) conserving a sufficient length of small bowel to avoid short bowel syndrome. This would correspond to at least all 13 regions of abdomen with a PCI score more than 2 for DFS in patients with peritoneal mesothelioma. Although median DFS was lower in low PCI group, it was not conclusive statistically to suggest a benefit ($p = 0.088$; Figure 3).
each region and a minimum score of 3 in the locations of difficult clearance (hepatic pedicle or upper part of the stomach). We formerly published outcomes of CRS and PIC comparing three PCI groups (PCI 20–24 vs. PCI 25–29 vs PCI ≥ 30) [24]. We were able to demonstrate a good survival among all three cohorts without statistical difference. Therefore, we accepted PCI ≥ 30 as a cutoff for extensive disease.

Appendiceal mucinous neoplasm is primarily classified into LAMN and HAMN based on its histological subtypes [25]. Outcomes in appendiceal mucinous neoplasms are heavily influenced by the tumor biology [9,10]. Our study reveals that patients with a high tumor burden for LAMN and HAMN can achieve good survival benefits. Albeit a significant decrease of OS in the high PCI group (≥30), approximately two-thirds of patients with LAMN survived after 5 years of the initial CRS/PIC with a median OS of 83 months. Similarly, these patients had good 5-year DFS at 37.1%. Interestingly, within the HAMN subtype, there was no statistical difference in the OS across both low- and high-volume disease. More than half of the patients survived beyond 5 years in both low and high PCI groups. This is in accordance with multiple studies in the literature [12,23,24,26–31]. Benhaim et al. reported a 5-year OS of 70% when CRS/PIC were offered to patients with extensive PMP [23], although these patients were not stratified into individual histological subtypes. These findings are encouraging and suggest that patients with appendiceal mucinous neoplasms will still
benefit from CRS/PIC regardless of the PCI status as long as complete cytoreduction (CC ≥ 1) can be achieved. Therefore, extensive disease should not preclude CRS/PIC, and referral to a specialized peritoneectomy center is advised to determine suitability for surgery.

PCI should not be used as a crude threshold to guide patient selection for CRS/PIC. Rather, it was found to correlate with the ability to achieve a complete cytoreduction [27]. There is a linear relationship between PCI and completion of CRS. Further analysis, though, did not demonstrate any association of survival with PCI status as long as complete cytoreduction had been achieved. El Halabi and authors reported 5-year OS of 0% in high-volume HAMN patients with incomplete cytoreduction. In contrast, 5-year OS was 45% in this group when complete cytoreduction was achieved [28]. This was echoed in a separate study. Patients with high-grade, high-volume appendiceal neoplasms had comparable OS when compared with high-grade, low-volume appendiceal neoplasms (56 vs. 52 months, $p = 0.393$) when complete cytoreduction was achieved [29]. As a result, treatment for PC of appendiceal origin with CRS/PIC should be individualized and offered on a case-to-case basis, especially if surgeons are confident a complete cytoreduction can be achieved during the pre-operative workup.

The DFS for HAMN in the high PCI group was significantly lower compared to the low PCI group. This is consistent with a recent study by Kitai et al. The authors analyzed clinical outcomes of 49 patients with PC of appendiceal origin and a high-tumor burden. The recurrence-free survival was noted to be significantly worse in the high-volume disease group. This is perhaps related to the cytoreduction rate. In our series, the probability of leaving residual tumor deposits was significantly higher (CC-1) if the disease was extensive. The presence of residual neoplastic tumors would mean an earlier recurrence. High volume disease is also likely to be more aggressive due to tumor heterogeneity [32].

In the present study, we found no difference in the OS and DFS of mesothelioma following CRS/PIC across low and high PCI groups. The median OS was lower at 42 months in the high PCI group, compared to 72 months in the low PCI group, albeit without significant statistical difference ($p = 0.058$). Meanwhile, the median RFS in the high and low PCI groups were 14 and 29 months, respectively. These figures were comparable to the majority of studies in a systematic review [11] that investigated outcomes of CRS/PIC in mesothelioma as a cohort, rather than focusing in high-volume disease. Similarly, this may be related to completeness of cytoreduction in our cohort. As previously reported in a multi-institutional study

### Table 4. Prognostic factors influencing OS and DFS in high PCI group.

| Variables       | Overall survival | Disease-free survival |
|-----------------|------------------|-----------------------|
|                 | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                 | HR (95% CI) | p-Value | HR (95% CI) | p-Value | HR (95% CI) | p-Value | HR (95% CI) | p-Value |
| Gender          |                 |          |              |          |              |          |              |          |
| Female          | Ref             | 0.017    | Ref          | 0.204    | Ref          | 0.014    | Ref          | 0.094    |
| Male            | 1.88 (1.12–3.14) | –        | 1.43 (0.82–2.49) | –        | 1.89 (1.14–2.14) | –        | 1.59 (0.93–2.73) | –        |
| Age             | 1.01 (0.99–1.04) | 0.203    | –            | –        | 1.00 (0.98–1.03) | 0.679    | –            | –        |
| Diagnoses       |                 |          |              |          |              |          |              |          |
| LAMN            | Ref             | –        | Ref          | –        | Ref          | –        | Ref          | –        |
| HAMN            | 1.27 (0.73–2.22) | 0.404    | 1.26 (0.69–2.31) | 0.448    | 1.32 (0.75–2.32) | 0.333    | 1.44 (0.74–2.81) | 0.284    |
| Mesothelioma    | 2.44 (1.24–4.78) | 0.01     | 1.02 (0.36–2.89) | 0.972    | 2.62 (1.34–5.14) | 0.005    | 1.73 (0.72–4.14) | 0.224    |
| PCI             | 1.02 (0.94–1.10) | 0.675    | –            | –        | 1.01 (0.94–1.09) | 0.847    | –            | –        |
| CC-score        |                 |          |              |          |              |          |              |          |
| 0               | Ref             | 0.006    | Ref          | 0.250    | Ref          | 0.032    | Ref          | 0.575    |
| 1               | 2.53 (1.31–4.87) | 1.51     | (0.75–3.05)  | 1.99     | (1.06–3.72)  | 1.23     | (0.60–2.52)  |          |
| EPIC            |                 |          |              |          |              |          |              |          |
| No              | Ref             | <0.001   | Ref          | 0.004    | Ref          | 0.001    | Ref          | 0.021    |
| Yes             | 0.31 (0.18–0.53) | 0.39     | (0.21–0.73)  | 0.40     | (0.24–0.67)  | 0.48     | (0.26–0.89)  |          |
| Preoperative CEA|                 |          |              |          |              |          |              |          |
| Normal          | Ref             | 0.05     | Ref          | 0.708    | Ref          | 0.237    | Ref          | –        |
| Elevated        | 0.59 (0.35–1.00) | 0.86     | (0.38–1.93)  | 0.73     | (0.43–1.23)  | –        | –            |          |
| Preoperative CA125|              |          |              |          |              |          |              |          |
| Normal          | Ref             | –        | –            | –        | Ref          | 0.049    | Ref          | 0.021    |
| Elevated        | 1.44 (0.73–2.85) | 0.297    | –            | –        | 1.98 (1.00–3.92) | 2.35     | (1.14–4.85)  |          |
| Preoperative CA19.9|          |          |              |          |              |          |              |          |
| Normal          | Ref             | 0.889    | –            | –        | Ref          | 0.494    | –            | –        |
| Elevated        | 1.04 (0.63–1.71) | 0.049    | –            | –        | 1.19 (0.72–1.97) | 2.35     | (1.14–4.85)  |          |
| Elevated CEA, CA19.9, CA125| |          |              |          |              |          |              |          |
| No              | Ref             | 0.713    | –            | –        | Ref          | 0.237    | –            | –        |
| Yes             | 1.10 (0.67–1.81) | 3.36     | (0.82–2.28)  | –        | –            | –        | –            |          |
| Blood transfusion|              |          |              |          |              |          |              |          |
| ≤8 units        | Ref             | 0.028    | Ref          | 0.038    | Ref          | 0.001    | Ref          | 0.042    |
| >8 units        | 1.75 (1.06–2.87) | 1.77     | (1.03–3.03)  | 2.29     | (1.38–3.78)  | 2.11     | (1.03–4.31)  |          |
| FFP transfusion |                 |          |              |          |              |          |              |          |
| ≤10 units       | Ref             | 0.226    | –            | –        | Ref          | 0.013    | Ref          | 0.578    |
| >10 units       | 4.37 (0.82–2.27) | 0.713    | –            | –        | 1.89 (1.14–3.11) | 1.23     | (0.59–2.55)  |          |
| Morbidity       |                 |          |              |          |              |          |              |          |
| Grade 0–2       | Ref             | 0.177    | –            | –        | Ref          | 0.053    | Ref          | 0.336    |
| Grade 3–4       | 1.47 (0.84–2.55) | 0.89     | –            | –        | 1.74 (0.99–3.04) | 1.37     | (0.72–2.61)  |          |

Ref: reference; CI: confidence interval; LAMN: low-grade appendiceal mucinous neoplasm; HAMN: high-grade appendiceal mucinous neoplasm; CC: completeness of cytoreduction; PCI: peritoneal carcinomatosis index; FFP: fresh frozen plasma; EPIC: early postoperative intraperitoneal chemotherapy.
that included 405 patients with mesothelioma, CC-score was independently associated with improved survival \([4]\). Unfortunately, we were not able to provide data on the different subtypes of mesothelioma in this series which is a known prognostic factor for mesothelioma.

EPIC was found to be an independent prognostic factor of OS (OR 0.39, 95%CI 0.21–0.73, \(p = 0.004\)) and DFS (OR 0.48, 95%CI 0.26–0.89, \(p = 0.021\)) in patients with high-volume disease. This was likely specific to appendiceal mucinous neoplasms given EPIC was only administered in 5 mesothelioma patients in this study. The use of EPIC is not universal in the treatment of PC due to reported higher complication rates and prolonged hospital admission \([33,34]\). In contrast, we strongly advocate EPIC for patients with LAMN and HAMN of soft tumor consistency in our institution. We previously demonstrated that there was a marked benefit in 5-year OS for patients with LAMN who received a combined HIPEC and EPIC therapy than those who received HIPEC alone (93.0% vs. 64.5%; \(p < 0.001\)) without major differences in the mortality and morbidity \([35]\). Not using EPIC in the treatment of appendiceal PC was associated with recurrence \([36]\). Furthermore, our analysis suggests that elevated preoperative CA125 level is associated with poor DFS (OR 2.35, 95%CI 1.14–4.85, \(p = 0.021\)). Among 62 patients with PMP undergoing CRS/PIC, Baratti concluded that normal preoperative CA125 correlated to the likelihood of achieving adequate cytoreduction \([37]\). This is intriguing because the inability to achieve adequate cytoreduction would explain a lower DFS in our cohort.

Increased blood transfusion (>8 units) decreased the OS (HR 1.77, 95%CI = 1.03–3.03, \(p = 0.038\)) and DFS (HR 2.11, 95%CI = 1.03–4.31, \(p = 0.042\)) by approximately one-half- and two-fold, respectively. This may be explained by transfusion-related immune modulation (TRIM), which is a result of the inflammatory and immunosuppressive nature of blood products. They blunt the recipients’ innate immunity that regulates local tumor control, thereby promoting growth of malignant tumors \([38]\). A study involving patients with mesothelioma and PMP treated with CRS/PIC demonstrated that blood transfusion is an independent prognostic factor for worse OS and DFS. There is a dose-dependent effect such that even low amounts of transfusion (1 U–2U) affect survival outcomes following CRS/PIC \([39]\).

Overall mortality in our study was 2% while high-grade complications (grade 3–4) occurred in 44.2% of patients. This is consistent with those in CRS/PIC specialized centers \([40]\). Nevertheless, performing CRS/PIC in high-volume disease is not without its risks. In our series, the postoperative grade 3–4 morbidity was significantly higher in the high PCI group (68% vs 36.6%, \(p < 0.001\)). Additionally, the mean operating hours and the mean length of hospital, ICU and HDU stay were significantly longer in the high PCI group. We suspect this was due to more extensive surgical resection, malnourishment and poor condition in patients with high-volume disease. Patients in the high PCI group were also significantly older which may have delayed the recovery phase of surgery. Extensive CRS was associated with higher rate of blood and FFP transfusions. Ultimately, the decision to treat a patient with high tumor burden is multifaceted and should be guided by a multi-disciplinary approach. Many factors including likelihood of a complete cytoreduction, tumor subtypes, nutritional status and medical co-morbidities should be taken into consideration. It is paramount to balance and discuss the survival benefits of CRS/PIC and risks of potential morbidity during the informed consent process.

There are several limitations within this study. Firstly, the series design is retrospective and selection bias may be introduced. The data should be interpreted with caution. The lack of uniform classifications of appendiceal PC historically could have led to some inconsistencies in the histological subtyping of surgical specimens. Some data from patient and treatment perspectives, such as histological subtypes of mesothelioma and status of prior therapy, were missing from our analysis, thereby reducing the impact of our statistics. Lastly, the learning curve involving CRS/PIC is widely documented \([41,42]\). The surgical performance in our center has improved with exposure and experience. Hence, the outcomes of this study may not be applicable to other centers.

**Conclusion**

Long-term survival outcomes following CRS/PIC are achievable with acceptable mortality in patients with extensive (PCI ≥ 30) appendiceal mucinous neoplasms and mesothelioma. The postoperative morbidity in these patients, though, is significantly higher than those with limited disease. High PCI status does not preclude treatment with CRS and PIC. The management should be individualized and approached in a multi-disciplinary setting. Benefits of surgery and risks of complications should be considered.

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