Short-term outcomes following cytoreductive surgery and heated intra-peritoneal chemotherapy at Waikato

Jasen Ly, Linus Wu, Ralph Van Dalen, Simione Lolohea

ABSTRACT

AIM: Pseudomyxoma peritonei is a rare disease that affects 1–2 per million population per year. Treatment with cytoreductive surgery with heated intraperitoneal chemotherapy (CRS with IPC) has been well described. The purpose of this study was to look at the short-term outcomes following CRS with IPC for all such patients treated in Waikato.

METHOD: Records for all patients presenting to surgery for CRS with IPC were retrospectively reviewed. CRS with IPC was performed in accordance with the techniques described by Sugarbaker. Data recorded included patient characteristics, characteristics of surgical treatment and early post-operative outcomes.

RESULTS: Sixty-eight patients underwent 72 procedures. Fourteen patients were deemed unresectable at surgery and were treated palliatively. The median age was 57 with the majority being female (59%). The median time, from the decision made for surgery to CRS with IPC, was three months. The median prior surgical score was 1 and the median peritoneal cancer index (PCI) was 19.5. The median operating time was 9.08 hours (5.43–15.20). The majority of patients (76%) had pseudomyxoma peritonei, while the remainder had a combination of other appendiceal, colorectal, ovarian, gastric and primary mesothelial primaries. The major complication rate was 24% and the 30-day mortality rate was 1.4%. The median hospital stay was 12 days.

CONCLUSION: Short-term outcomes following CRS with IPC at Waikato are comparable to those published in the literature. Further follow-up is anticipated for the publication of survival and recurrence data.

Cytoreductive surgery with heated intraperitoneal chemotherapy (CRS with IPC) has been well established as a standard of care for the treatment of pseudomyxoma peritonei.1,2 Previously recognised as a fatal disease, the potential for cure through this technique can be attributed to Sugarbaker and the work performed by other high-volume centres.1–4 Traditional debulking procedures resulted in no chance for cure and, except for palliation, can largely be considered historical with survival rates as low as 34% and 15% having been reported at three and five years.5–7 With CRS with IPC, a recent multi-institutional review published in 2012 demonstrated survival rates of 63% and 59% at 10 and 15 years, together with major complication and mortality rates as low as 24% and 2% respectively.1

Classically, pseudomyxoma peritonei has been divided into low- and high-grade subtypes with numerous classification systems having been described previously such as that by Ronnett, Misdraji and Bradley.8–10 Commonly cited in the literature is that by Ronnett whereby pseudomyxoma peritonei is classified as either disseminated peritoneal adenomucinosis (DPAM) or peri- toneal mucinous carcinomatosis (PMCA), with numerous studies demonstrating a significantly poorer overall survival with the high-grade subtype (PMCA).1,3,8–10–15 The more recent WHO and AJCC equivalent describes pseudomyxoma
peritonei as either low-grade or high-grade mucinous adenocarcinoma, and this reflects the slow but malignant potential of the disease, and the ultimately fatal outcome without treatment.8

While much of the literature describes CRS with IPC in relation to the treatment of pseudomyxoma peritonei, there is increasing evidence to support the use of the technique for peritoneal metastases secondary to other malignant diseases. This includes both colorectal cancer and peritoneal malignant mesothelioma, and to a lesser degree metastatic ovarian and gastric cancer.16–19

Waikato is one of only two centres in New Zealand receiving nationwide referrals for cytoreductive surgery. Recently, Wheeler et al published their experience of 25 patients with pseudomyxoma peritonei over a 12-year period at Wellington Hospital from 1997 to 2011.15 They demonstrated an overall five-year survival rate of 64%, and had 17 Clavien-Dindo grade 3 or 4 complications in seven of the 25 patients, with no 30-day mortality. In slight contrast, Waikato has been performing cytoreductive surgery with the addition of heated intraoperative intraperitoneal mitomycin C, similar to the techniques described by Sugarbaker and that by other major centres performing cytoreductive surgery internationally.20 The technique was first introduced at our institution in 2008 and the following study examines our experience with CRS with IPC over the subsequent seven-year period to 2014.

Method

A prospective database of all patients referred for treatment to both Waikato (public) and Braemar (private) hospitals since 2008 was kept by a single surgeon. This database was retrospectively analysed from a combination of clinic letters, patient progress notes and pathology, radiology and operative reports. The information was divided into three categories and included pre-operative patient characteristics, characteristics of surgical treatment and post-operative outcome. Pre-operative patient characteristics included basic demographic features, mode of presentation, time since the decision to operate to surgery, prior surgical score, number of prior operations, prior chemotherapy and histology. Characteristics of surgical treatment included the peritoneal cancer index, number of visceral resections, number of peritonectomies, completeness of cytoreduction score, type of IPC, stoma formation, intraoperative transfusion requirement and duration of operation. Post-operative outcome included post-operative complications, 30-day mortality and duration of hospital stay.

Referrals for treatment were received from other centres throughout New Zealand as well as from within the Waikato region. Patients were seen at the outpatient clinic in Waikato and investigated with a combination of CT scans, colonoscopy, staging laparoscopy and tumour markers if not already performed in the referring centre. Details of their mode of presentation as well as number and type (as denoted by a prior surgical score) of previous surgery were usually documented in the outpatient clinic or referral letter. Once the decision had been made that a patient was a candidate for surgery, they were placed on the waiting list, consented for CRS with IPC and were given an anaesthetic appointment for review. The prior surgical score as described by Sugarbaker is a score from PSS-0 to PSS-3 and was assigned to patients according to the extent of previous surgery performed (PSS-0: biopsy only or laparoscopy plus biopsy, PSS-1: prior exploratory laparotomy, PSS-2: exploratory laparotomy with some resection, PSS-3: attempted complete cytoreduction).21,22

Patients were admitted to hospital the day before surgery and given full bowel preparation. Cytoreductive surgery was performed by three surgeons according to the techniques described by Sugarbaker.21,22 The patients were positioned in the modified Lloyd Davis position with the left arm abducted such that fixed table-based retraction could be used for exposure as well as for formation of the ‘coliseum’ for IPC. Intraoperatively, all patients were given a peritoneal cancer index (PCI) score, which is derived from the summation (up to 39) of the lesion size score (LSS 1:<0.5cm, LSS 2: 0.5–5cm, LSS 3:>5cm or confluent nodules of tumour) in the 13 abdomino-pelvic regions as described by Sugarbaker.21,22 For pseudomyxoma peritonei, a completeness of cytoreduction score of either 0 or 1 was attempted, while for other malignancies
a completeness of cytoreduction score of 0 was attempted. This score relates to the extent of residual disease present (CC-0: no disease, CC-1:<0.25cm, CC-2:0.25–2.5cm, CC-3>2.5cm).\textsuperscript{21,22} If the disease process was deemed incurable, palliative debulking was either attempted or the procedure was abandoned without intraperitoneal chemotherapy.

Once cytoreduction was complete, a ‘coliseum’ was set up for the instillation of intraperitoneal chemotherapy, before the construction of anastomoses. Ring-based fixed table retraction was used to which the skin was sutured with interrupted 1–0 nylon to prevent spillage of chemotherapy. Layers of opsite were then placed over the ring-based retractor and abdominal wall to fashion the watertight ‘coliseum’. Tubing consisted of one infl ow tube and three outfl ow tubes, a temperature probe and a smoke evacuator. Mitomycin C was delivered by a perfusionist for 90 minutes at 41–42ºC at a dose of 10mg/m\textsuperscript{2} for women and 12.5mg/m\textsuperscript{2} for men. The dose was reduced by 33% in those who had received heavy prior chemotherapy, had marginal renal function, were aged over 60, had extensive prior intraoperative trauma to the small bowel surfaces or who had prior radiotherapy. The addition of cisplatin was used for patients with malignant mesothelioma and gastric cancer. Once chemotherapy was complete, the construction of any anastomoses was performed, drains were placed, the abdomen was closed, and any stomas were fashioned. Chest drains were not routinely inserted unless there had been a definite diaphragmatic perforation.

Post-operatively, patients were transferred to a high dependency unit for 48–72 hours. The use of TPN was not routine as has been described in other centres.\textsuperscript{15,23} DVT prophylaxis was commenced immediately post-operatively and included compression stockings, sequential calf compressors and prophylactic dose clexane. Diet and mobilisation were progressed according to clinical assessment. Urine output was monitored strictly, especially in cases where cisplatin had been used where a higher urine flow rate was achieved. Convalescent care at the referring hospital was considered upon discharge for patients outside of the Waikato region. Post-operative complications were recorded and classified according to the Clavien-Dindo classification.

Following discharge, patients were seen at six weeks and the post-operative histology was reviewed at a fortnightly pathology multidisciplinary team meeting, which was attended by pathologists, surgeons and a medical oncologist. Follow up consisted of four-monthly CEA, CA19-9

\textbf{Figure 1:} Peritoneal cancer index.\textsuperscript{22}
and CA125. CT scans were performed at one, two and three years. Patients with recurrent disease discovered on surveillance were discussed and considered for either no treatment, systemic chemotherapy or further CRS with IPC.

Results
Since 2008, 72 operations were performed on 68 patients with the intention of performing CRS with IPC. Fourteen patients were deemed to be incurable at the time of surgery and either had a palliative debulking procedure (8) or the procedure was abandoned (6). Fifty-eight cases of CRS with IPC were performed on 54 patients, 16 of which were performed in a private hospital (Braemar Hospital). Four cases were redo operations whereby further CRS with IPC was performed for four patients who developed recurrent disease.

Patient characteristics
Referrals were received from all throughout New Zealand, although a reasonable proportion were from within the Waikato region (36%). Mode of presentation was most commonly abdominal pain (44%) or distension (25%). There were 28 (41%) men and 40 (59%) women with a median age of 57 years (30–80) and BMI of 28 (20–45). Median ASA was 2. From the time the decision was made that a patient was a candidate for CRS with IPC, patients received their operations at a median of three months, ranging from one to 12 months. The median number of prior operations was one, and the median prior surgical score was one. Fourteen patients received systemic chemotherapy prior to being operated on, five of whom turned out to be incurable. Five of these 14 patients (one of whom was incurable) had pseudomyxoma peritonei, five had colorectal cancer (two of whom were incurable), two had ovarian cancer (one of whom was incurable), one had gastric cancer and one had an adenocarcinoid of the appendix.

<table>
<thead>
<tr>
<th>Referral centre</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waikato</td>
<td>26</td>
</tr>
<tr>
<td>Auckland</td>
<td>13</td>
</tr>
<tr>
<td>Christchurch</td>
<td>7</td>
</tr>
<tr>
<td>Dunedin</td>
<td>5</td>
</tr>
<tr>
<td>Whangarei</td>
<td>4</td>
</tr>
<tr>
<td>Hawke’s Bay</td>
<td>2</td>
</tr>
<tr>
<td>Timaru</td>
<td>1</td>
</tr>
<tr>
<td>Invercargill</td>
<td>2</td>
</tr>
<tr>
<td>Taranaki</td>
<td>2</td>
</tr>
<tr>
<td>Tauranga</td>
<td>4</td>
</tr>
<tr>
<td>Rotorua</td>
<td>2</td>
</tr>
<tr>
<td>Palmerston North</td>
<td>2</td>
</tr>
<tr>
<td>Wellington</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Number by referral location.
Characteristics of surgical treatment

Of the 58 operations where CRS with IPC was performed, the median PCI at laparotomy was 19.5 (3–39). The PCI for those with incurable disease was not well documented and therefore not included. Table 3 shows the completeness of cytoreduction for each histological type.

Heated intraoperative intraperitoneal chemotherapy with mitomycin C was used in 54 cases, while mitomycin C with cisplatin was used in the four cases of peritoneal mesothelioma and gastric cancer. The median operative time was 9.08 hours (range 5.43–15.20 hours). The median number of visceral resections was two and the median number of peritonectomies was four. Thirty of the 58 cases treated with CRS with IPC required a stoma of some type (21 end ileostomies, seven loop ileostomies, two end colostomies). Twenty-three patients required a blood transfusion with a median of four units of red blood cells, five units of fresh frozen plasma, one unit of platelets and two units of cryoprecipitate.

Table 3: Total numbers by histological type and completeness of cytoreduction.

<table>
<thead>
<tr>
<th></th>
<th>Complete</th>
<th>Incomplete</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomyxoma peritonei</td>
<td>40</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>Appendix adenocarcinoma</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Adenocarcinoid</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Post-operative outcome

Thirty patients (42%) experienced complications, three of which occurred in the 14 incurable patients (one medication side effect, one relook laparotomy for a wound complication and one death). Seventeen patients (24%) had either grade 3 or 4 Clavien-Dindo complications. One out of the 72 cases died within 30 days as above (incurable patient), giving an overall 30-day mortality rate of 1.4%. Of 11 cases requiring a return to theatre (15.2%), the reasons were anastomotic leak (3), bowel obstruction (1), gastric perforation (1), enterotomy (1), bleeding (1), bile leak (1), wound complications (2) and removal of a drain end (1).

The median duration of hospital stay was 12 days (range five to 104 days), although was only 8.5 days (five to 21 days) for those who had incurable disease.

Table 4: Number of patients with complications, grouped by most severe complication by Clavien-Dindo grading.

<table>
<thead>
<tr>
<th>Clavien-Dindo grading</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>6</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>5</td>
</tr>
<tr>
<td>Grade 3b</td>
<td>11</td>
</tr>
<tr>
<td>Grade 4a</td>
<td>1</td>
</tr>
<tr>
<td>Grade 5</td>
<td>1</td>
</tr>
<tr>
<td>Total 30</td>
<td></td>
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</table>

Discussion

Pseudomyxoma peritonei is a rare disease, but worldwide there has been increasing experience with treatment with CRS with IPC, with good long-term outcome.\(^\text{11,12,24-28}\) In this article, we presented our early experience with the technique, not only for patients with pseudomyxoma peritonei, but also for a small series of patients with adenocarcinoid of the appendix, malignant mesothelioma and metastatic colon, gastric and ovarian cancer.

Traditionally, CRS with IPC has been considered a morbid, expensive and time-consuming procedure. The potential for multiple major visceral resections and peritonectomy procedures, long operating times and intensive post-operative care has led to criticisms regarding the safety, cost effectiveness and general acceptance of the technique.\(^\text{27-30}\) Overcoming these issues at our own institution has therefore required a significant collaborative effort between administrative, nursing, medical and allied health staff. At the present time, our experience with CRS with IPC is also no doubt early by international standards, and there is a recognised learning curve associated with the procedure that improves with experience and translates to decreased morbidity and improved survival over time.\(^\text{3,5,12}\) This relates not only to surgical expertise, but also importantly to patient selection, interpretation of pathology, anaesthetic, nursing and medical post-operative care.\(^\text{33}\)

To date, we have had a series now of 58 cases over a seven-year period that have been treated with CRS with IPC. Our short-term outcomes with respect to operative times, transfusion requirements and hospital stay are comparable to those published.\(^\text{1,4,15,24,25,34}\) We had a 30-day mortality rate of 1.4%, comparable to that published by Moran’s group of 5% in their early experience of 123 patients, and a major complication rate of 24%.\(^\text{24}\) In 2009, Chua et al published the morbidity and mortality outcomes of 24 institutions, 11 of which were considered high-volume tertiary centres with between 103 and 460 cases at the time of publication.\(^\text{27}\) Overall mortality rates ranged from 0 to 17%, with sub analysis of high-volume centres demonstrating mortality rates of between 0.9 to 5.8%. The most common causes of death were sepsis and multi-organ failure from surgical complications. The overall rate of grade 3/4 complications ranged from 0 to 52%, and for high-volume centres ranged from 12 to 52%, with the most common complications being sepsis, fistula, abscess, ileus, perforation, anastomotic leak, DVT/PE, haematological toxicity and renal insufficiency. Rates of reoperation ranged from 0 to 23% in the perioperative period, which in our series was 15.2%.

At our institution, we have only ever used heated intraoperative intraperitoneal chemotherapy (HIPEC) with mitomycin C, adding cisplatin for patients with malignant mesothelioma and gastric cancer. The main advantages of HIPEC are even exposure of the peritoneal surface to chemotherapy before the formation of adhesions and the
ability to use hyperthermia. Heat theoretically decreases the interstitial pressure of the tumour tissue to increase penetration of the chemotherapeutic agent, increases the cytotoxicity of the chemotherapeutic agent and has a direct cytotoxic effect on tumour tissue.21,22 The systemic absorption of mitomycin C is also limited because of its high molecular weight and in our series we encountered no complications related to cytotoxicity, though both renal and haematological toxicity have been reported. In the literature, renal toxicity ranged from 1.3–5.7% and haematological toxicity between 4.6–18.6%.30 The principal disadvantages of HIPEC are the increased operative times, the need for specialised perfusion equipment and personnel, and the limited number of heat stable chemotherapeutic agents available for use.21,22

The alternatively described technique is early post-operative intraperitoneal chemotherapy (EPIC), either alone or in combination with HIPEC.34,36 EPIC requires less operative time, equipment and personnel, has a broader range of available agents, and patients can receive multiple cycles of treatment beginning as early as the day after surgery. Port complications may, however, interfere with the ability to complete the intended duration of EPIC, and post-operative adhesions may interfere with chemotherapy distribution. Patients may also develop uncomfortable abdominal distension and special precautions are required during the administration of chemotherapy, which is undertaken on either the ward or in ICU.

Due to the relatively short follow-up data of our series at the time of publication, we did not examine the survival outcomes for our cohort of patients. In the multi-institutional review by Chua et al in 2012 of 2,298 patients with pseudomyxoma peritonei, the median overall survival was 16.3 years with 3-, 5-, 10- and 15-year survival rates of 80%, 74%, 63% and 59% respectively.4 Studies which reported on overall survival and performed multivariate analyses of associated factors found that older age, major post-operative complications, debulking surgery (CC 2/3), prior chemotherapy and high-grade subtype were independent predictors of poorer overall survival.1,11,12,26

We also did not report on the number of recurrences at the end of the follow-up period, though we did include four patients in our study who had repeat CRS with IPC for recurrent disease. In the above study by Chua et al, the median progression-free survival was reported as 8.2 years, with prior chemotherapy, the high grade subtype, major post-operative complications, higher PCI and debulking surgery being predictors of poorer progression-free survival on multivariate analysis.1 Repeat CRS with IPC in selected patients has been shown to be feasible, and in some patients’ third time and even fourth time CRS with IPC may be possible with improved survival.32 In this particular study by the Sugarbaker group, recurrence was most frequently noted in the small bowel initially and then in the pelvis at subsequent CRS with IPC, with focal recurrences being more common than diffuse. Patients were generally operated on within a few months of diagnosis, translating to better performance status, lower reoperative PCI, and tumours that were relatively easier to remove by complete cytoreduction. While timely surgery may be possible for patients from within the Waikato region, it may be difficult to achieve for patients referred from elsewhere in New Zealand.

Current evidence suggests that CRS with IPC also has a role in the treatment of other malignancies with peritoneal surface disease,16–19,38–41 and our series includes patients with adenocarcinoid of the appendix, appendix adenocarcinoma, malignant mesothelioma and metastatic colon, gastric and ovarian cancer. Emerging evidence into the use of the technique is particularly important in colorectal cancer, in whom patients are traditionally expected to have a dismal prognosis and are generally treated with a palliative intent. In a recent systematic review, however, the potential for a doubling in the median survival of patients with peritoneal disease treated with CRS with IPC was demonstrated compared to systemic chemotherapy.19 Only patients with a relatively lower PCI are considered to benefit from treatment (<20), and the main problem at the present time is in identifying which patients will benefit from CRS with IPC, and in establishing suitable scoring systems and algorithms for referral and treatment. Currently the peritoneal surface disease severity score (PSDSS) is one such prognostic scoring system that has been incorporated into a suggested algorithm for
treatment. In addition there is a move to try to identify patients with colorectal cancer at high risk for peritoneal recurrence in whom a staged relook could be performed with a view to offering them CRS with IPC. In a study by Elias et al, 41 patients were treated in this manner, with 23 going on to have CRS with IPC, giving an overall five-year survival of 90%.

This study demonstrates our institution’s short-term outcomes following CRS with IPC. By comparison, we have yet to gain the volume and experience achieved by other international centres performing CRS with IPC, though we hope to achieve this with time and in the near future will report on our overall and disease-free survival outcomes. Furthermore, as CRS with IPC has been accepted as standard of care for patients with pseudomyxoma peritonei, we anticipate that this increased awareness will lead to an increase in the number of referrals. Coupled with increasing interest in CRS with IPC for colorectal cancer, this will mean the need for a more streamlined and protocolised national referral process, proper patient selection, prompt patient treatment, clear guidelines for post-operative follow up, equal accessibility to discussion and treatment of recurrent disease, and further audit and review of our outcomes.

Competing interests: Nil.

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