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Case Report

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Unconventional Indications

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Received: August 31, 2015; **Published:** October 20, 2015

Abstract

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS and HIPEC) has been well established in the treatment of peritoneal carcinomatosis of ovarian, colorectal, appendiceal, gastric, mesothelioma and primary peritoneal origin. However, there are conditions where CRS and HIPEC may play a role achieving cure or increasing survival of the patients. Here, we explore the option of using CRS and HIPEC in the management of peritoneal sarcomatosis, mucinous adenocarcinoma of the small bowel and uterine sarcomas, with the associated literature review.

Keywords: *Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Peritoneal sarcomatosis, uterine sarcoma; Adenocarcinoma*

Introduction

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy havegained acceptance for the treatment of peritoneal carcinomatosis of ovarian, colorectal, appendiceal, gastric, mesothelioma and primary peritoneal origin [1]. CRS and HIPEC have also been describedfor selected cases of peritoneal sarcomatosis, mucinous adenocarcinoma of the small bowel and uterine sarcomas [2-4]. Here, we present fourpatients treated at our institution, with unconventional indications for CRS and HIPEC and describe their clinical course and outcomes.

Case 1: Small bowel adenocarcinoma

Mr A was a 51 year old Chinese male, with no significant past medical history, who initially presented with anaemia and a haemoglobin level of 7.5 g/dL (normal: 14.0-18.0 g/dL). This was associated with generalised body weakness, vomiting four to five hours after a meal, and significant loss of weight of 15 kg in two months. Oesophagogastroduodenoscopy and colonoscopy were unremarkable, and acomputed tomography (CT) scan of the abdomen was performed, that showed a proximal jejunal tumour in the right upper abdomen adjacent to the hepatic flexure and inferior to the gallbladder causing upper gastrointestinal obstruction (Figure 1). His case was discussed at the multidisciplinary tumor board meeting (MDT), where surgical, medicalandradiation oncologists, along with oncologic radiologists and pathologists were present.A preliminary diagnosis of small bowel obstruction secondary to a jejunal tumour was made, and a recommendation for surgery was given. He underwent a laparotomy, and intra-operatively, a 4 cm jejunal tumor, involving the transverse colon, was found, 30 cm from the duodeno- jejunal flexure. He underwent anen- bloc segmental resection of small bowel and right hemicolectomy. Histology confirmed a well to moderately differentiated adenocarcinoma of the jejunum with invasion into the adjacent colon. Peritoneal fluid cytology post- tumour resection was negative for malignancy. Margins were free oftumour and0 out of 33 Lymph nodes were positive (pT4N0). The tumour had normal expression of DNA mismatch repair proteins MLH-1, MSH-2, MSH-6 and PMS 2. His post- operative recovery was uneventful and he was counselled for adjuvant chemotherapy by the medical oncologist, but declined. He remained well and disease-free on six- monthly clinical examination and surveillance ct scans until 17 months post- operatively when he presented with

colicky abdominal pain. A CT thorax, abdomen and pelvisrevealed a new soft tissue mass adjacent to the ileocolic anastomotic site, suspicious for local recurrence and a new ill-defined hypodensityin segment II of the liver, suspicious of metastasis (Figure 2). A Colonoscopy was performed, and this showed a stricture at the anastomotic site that revealed high grade dysplasia on biopsy. A PET-CT showed an FDG avid hypodensity at the capsular surface of segment II of his liver, a mass at the right hemicolectomy anastomotic site and also a left paracolic gutter mass suspicious for a peritoneal deposit (Figure 3). His case was discussed at the MDT, and the patient was counselled for CRS and HIPEC. Intra- operatively, his peritoneal cancer index (PCI) (Figure 4) was 9, and he underwent a redo right hemicolectomy with resection of the previous ileocolic anastomosis, left hemicolectomy, resection of 30 cm of jejunum, stripping of the left paracolic peritoneum, and resection of the segment II subcapsular lesion.His completeness of cytoreduction score (CC) was 0. This was followed by HIPEC with mitomycin 20 mg at 41 degrees Celsius for 60 minutes. Histology of the resected anastomotic site was positive for adenocarcinoma and the liver resection specimen showed metastatic adenocarcinoma on the hepatic capsule invading into the liver parenchyma. The specimen was compared to the initial resected specimen and it showed identical morphology, consistent with metastatic recurrence. His post- operative recovery was once again unremarkable. He declined intravenous chemotherapy but completed 8 cycles of oralXeloda. His latest CT scan, 24 months from the initial surgery and 7 months from the CRS and HIPEC, shows no recurrence.

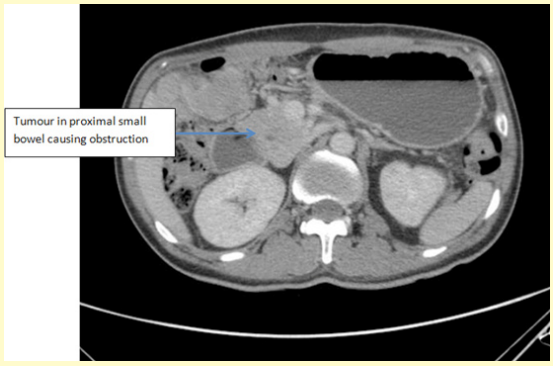

Figure 1: *Computed tomography (CT) scan of the abdomen showing the tumour in the proximal small bowel causing intestinal obstruction.*

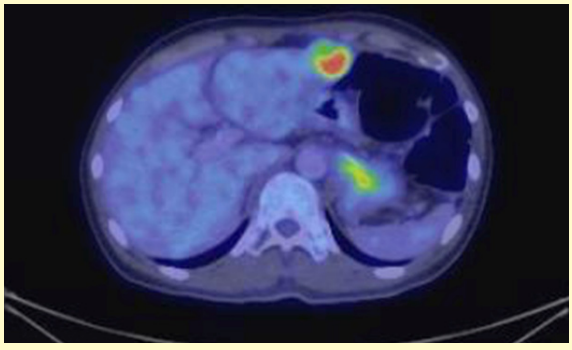

Figure 2: *Positron emission tomography (PET) scan of the abdomen showing the lesion at the capsular surface of hepatic segment II suspicious for peritoneal deposit.*

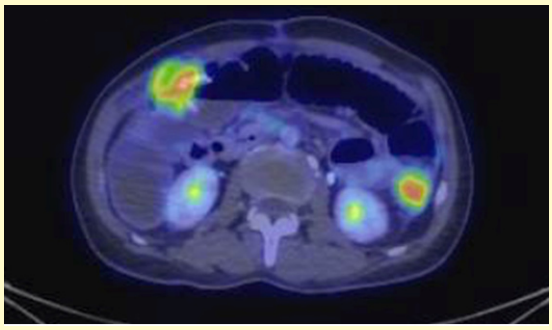

Figure 3: *PET scan showing local recurrence at site of right hemicolectomy anastomosis and left paracolic gutter metastasis.*

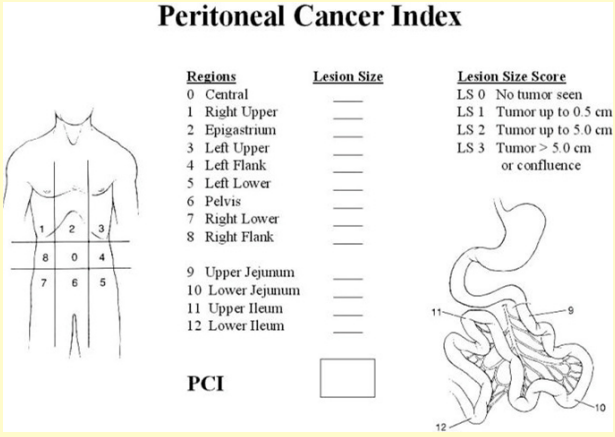

Figure 4: *Peritoneal Cancer Index [15].*

Case 2: Peritoneal leiomyosarcoma

A 57 year old Chinese female with a past medical history of dyslipidaemia and cataract, presented with right iliac fossa pain of one year duration, which worsened one day prior to presentation. The pain was colicky in nature, radiating to the right flank, and associated with nausea and vomiting. She sought advice from her general practitioner who did a bedside ultrasound scan which showed a large pelvic mass and she was referred to the general surgical service.Of note, she did not have any recent loss of appetite, loss of weight, bleeding per rectum or any family history of malignancy. On examination, her abdomen was soft, but tender over the right side of her abdomen and there was a palpable pelvic mass. A CT scan of the abdomen and pelvis was done, which showed a large pelvic neoplasm arising from the right adnexa, intimately associated with the right ovarian pedicle and right lateral wall of the uterus (Figure 5). Blood investigations were grossly normal, including the Cancer Antigen–125 (CA125) level which was 8.5 U/mL (normal < 35 U/mL). She was referred to the consultant gynaecologist, with a working diagnosis of ovarian tumour, and surgery was recommended. She was counselled appropriately and after preparation, underwent a laparotomy. Intraoperative findings were that of a large 16 cm mobile mass, arising from the right ovary, adherent to the small bowel mesentery and right ureter. She underwent a total abdominal hysterectomy bilateral salphingo-oopherectomy, infracolicomentectomy and bilateral pelvic lymph node dissection. There was an inadvertent transection of the right ureter during the surgery, which was repaired with a primary end to end anastomosis. Post-operatively, she recovered well and was discharged on post-operative day 6. The pathology showed a leiomyosarcoma arising from the mesentery, with a mitotic count of 24/10 hpf, and all the harvested pelvic lymph nodes (21 in total) were negative for malignancy. Immunohistochemistry showeda strong diffuse

positive reaction for smooth muscle antibody (SMA) and focal strong positive reaction for desmin, DOG-1, CD117 (for gastrointestinal stromal tumour), MNF-116 (for sarcomatoid carcinoma), CD10 (for endometrial stromal sarcoma) and CD34 (for haemopoietic cells) negative. She was seen by the medical oncologist and in view of the histology, was advised for close surveillance. She remained asymptomatic during her follow-up, but it was noted on a CT thorax abdomen and pelvis performed 8 months post-operatively, that there was a heterogeneously enhancing mass in the right hemipelvis, adjacent to the small bowel and suspicious for peritoneal recurrence (Figure 6). Her case was discussed at the MDT, and a recommendation for CRS and HIPEC was made, in view of the peritoneal origin of her tumor. She was counselled for surgery andunderwent cytoreductive surgery and HIPEC, which involved peritonectomy, small bowel resection, and cholecystectomy. Her PCI score was 9 and CC score was 0. HIPEC was withcisplatin 16 mg at 39 degrees Celsius for 60 minutes. Oral feeds were established on post- operative day 4 and she was discharged on day 9. Histology was that of metastatic leiomyosarcoma. She declined adjuvant chemotherapy after CRS and HIPEC. Ona surveillance CT scan 4 months later, was found to have evidence of disease recurrence, withperitoneal nodules and enlarged common iliac lymph nodes. She has since started on chemotherapy with gemcitabine and taxotere with pegfilgrastim. She is currently alive, 14 months since her first surgery and 6 months post CRS and HIPEC, and still on chemotherapy.

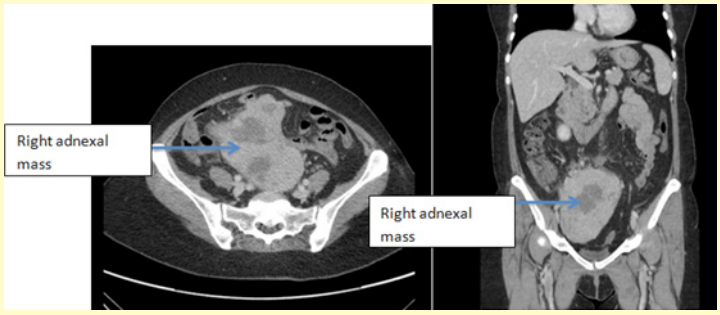

Figure 5: *CT scan showing the right adnexal mass.*

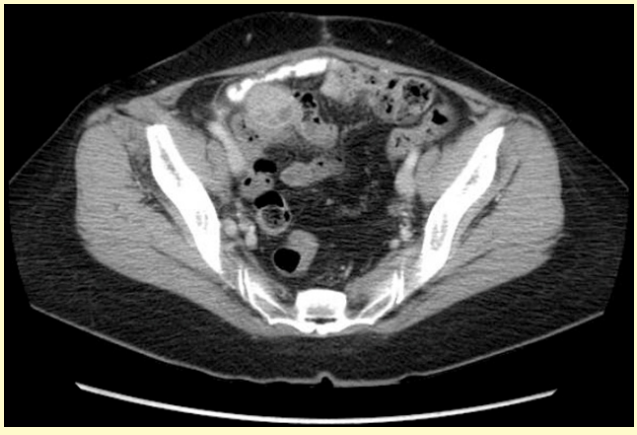

Figure 6: *CT scan showing heterogeneously enhancing mass in the right hemipelvis, adjacent to the small bowel and suspicious for recurrence.*

Case 3: Peritoneal synovial sarcoma

A 44 year old Indonesian male, with no significant past medical history, smoker of 30 pack years and drinks alcohol regularly (hard liquor), initially presented with left sided abdominal pain and a palpable mass per abdomen. He had no quantifiable loss of appetite and loss of weight, nor any gastrointestinal symptoms such as altered bowel habits and bleeding per rectum. He subsequently sought medical advice in Indonesia, upon which a CT scan of his abdomen was obtained. This showed a large mass intra- peritoneally, between the spleen and the stomach. Open biopsy was done in Indonesia and the histology was reported as adenocarcinoma. Post-operatively, he sought medical advice from our institution, and the biopsy specimen was re-read by a consultant pathologist specialising in sarcoma pathology. The histology was confirmed to be synovial sarcoma as the Fluorescence in situ Hybridization (FISH) test for SS18 gene was positive. He returned to Indonesia to have debulking surgery and adjuvant treatment with sunitinib. Six months after the initial surgery, his PET scan showed local recurrence of the disease and he underwent distal pancreatectomy, splenectomy, and resection of the tumour, followed by adjuvant radiotherapy. The following surveillance CT scan done six months after his second surgery showed no new recurrence. However, three months later, he was noted by his family members to be losing weight and a repeat CT scan showed new lesions in the peritoneum [Figure 7] and around the right kidney [Figure 8]. He was then counselled for chemotherapy and started on doxorubicin and ifosfamide, which he completed 6 cycles of. A repeat CT scan showed that there were no new nodules in the peritoneum but the size of the present nodules had increased slightly. His case was discussed at our MDT meeting for consideration of CRS and HIPEC, and the decision was to offer the patient the option of CRS and HIPEC in view of his young age and absence of distant metastases. He was agreeable for the option of surgical intervention and underwent CRS and HIPEC 27 months after his initial surgery. The intraoperative PCI score was 9 and the CC score was 0. He underwent small bowel resection, right hemicolectomy, resection of right retroperitoneal tumour, and peritonectomy as the tumour was involving multiple loops of small bowel, adhering to the transverse colon, sigmoid colon and bladder. HIPEC was done with cisplatin 67mg, for duration of 60 minutes at 40 degrees celsius. The final histology was that of recurrent synovial sarcoma. In the immediate post-operative period, he developed acute kidney injury and acute respiratory distress syndrome and required management in the surgical intensive care unit. He was administered intravenous corticosteroids in a bid to overcome the severe systemic inflammatory response syndrome, and made a rapid and remarkable recovery with minimal sequelae. He was discharged on post- operative day 15 and returned home to Indonesia subsequently. He is currently well, and four months post-operative CRS and HIPEC, and due for his repeat CT scan in two months' time.

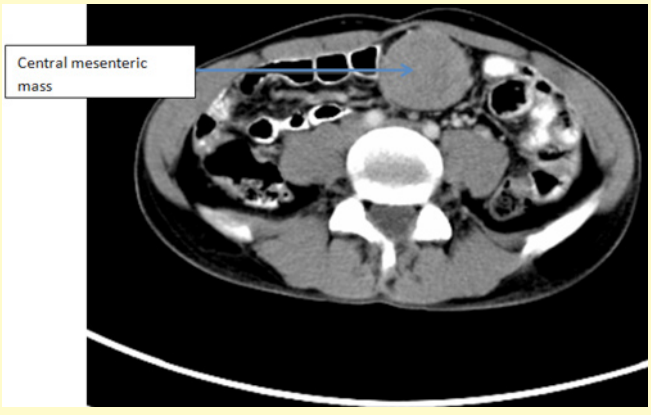

Figure 7: *Recurrent mass in the anterior central mesentery.*

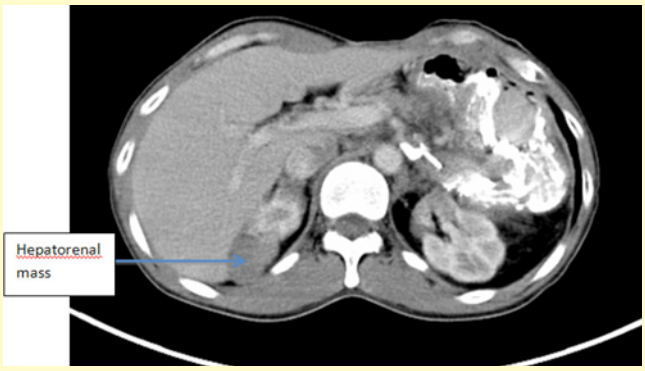

Figure 8: *Showing the mass at the hepatorenal region, histology consistent with recurrent synovial sarcoma.*

Case 4: Endometrial adenocarcinoma

A 46 year old premenopausal Chinese female with no significant medical history, presented with a new onset of menorrhagia. She did not have any recent loss of appetite or weight, did not take any oral contraceptive pills, and was not on anticoagulation. On examination, her abdomen was soft, non- tender, and there were no palpable masses. Blood investigation showed her CA125 level to be 47.3 U/mL (normal: 0-35 U/mL). A CT scan of her abdomen and pelvis was done and this showed an enlarged ovary measuring 5cm which was predominantly cystic with irregular septations and worrisome for malignancy. There was also a bulky uterus seen on the CT scan. Cervical smear showed atypical squamous cells. Colposcopy showed areas of hypervascularity but histology confirmed cervicitis. Endometrial curettage was done and histology was that of endometroid adenocarcinoma. She underwent a total abdominal hysterectomy and salphingo-oopherectomy with pelvic lymph node dissection by the gynaecologist. Histology was that of Grade 3 endometroid adenocarcinoma with multiple small foci of clear cell carcinoma, and all 23 lymph nodes were negative for malignancy. She completed 6 cycles of adjuvant chemotherapy with carboplatin and paclitaxel. After a disease-free interval of 47 months, she re-presented with crampy abdominal pain, radiating to the left groin. She did not have any symptoms of urinary tract infection and had normal bowel habits. On examination, her abdomen was soft, non- tender, with no rebound or guarding. Bowel sounds were active and a digital rectal examination did not reveal any significant findings. A CT scan was done, and it showed a new heterogenous nodule in left pelvic side wall and peritoneal nodules around the right hepatic lobe (Figure 9). Her case was discussed at the multidisciplinary meeting, and the impression was that of recurrent ovarian cancer and the recommendation was for surgery. She was counselled accordingly and was agreeable for CRS and HIPEC. Intra- operatively, there was a left pelvic wall nodule closely related to the left ureter, diaphragmatic nodules and nodules on the peritoneal surface of the liver. CRS involved stripping of the right diaphragmatic peritoneum, liver capsule and left pelvic peritoneum. The remaining peritoneal surface and bowels appeared free from tumour. Her PCI score was 5 and CC score was 0. HIPEC was given with cisplatin 50 mg for 60 minutes. Post-operatively, she was planned for early intra- peritoneal chemotherapy (EPIC) with carbotaxel. However, she only received EPIC for 3 days as her creatinine was found to be increasing, with the highest value reaching 128 mmol/L (baseline 55 mmol/L). Her creatinine subsequently improved with hydration. Her post- operative recovery was unremarkable, and she was started on oral feeds by post-operative day 5 and discharged on post- operative day 16. Histology of the nodules were metastatic poorly differentiated adenocarcinoma, consistent with endometroid subtype. Tumour cells were positive for estrogen receptors (2 +, > 90%), and progesterone receptors (3 +, > 90%). She then received adjuvant chemotherapy with paclitaxel for 4 cycles. She remained well and disease-free on surveillance scans until her latest CT scan, performed 45 months post CRS and HIPEC, and 91 months since her initial diagnosis that showed a 8 mm nodule at the subcapsular region of segment 4/8 of the liver. Amagnetic resonance imaging (MRI) scan of the abdomen confirmed the single subcapsular disease recurrence with no other peritoneal deposits. Her CA125 level was noted to be 6.5 U/mL. After discussion at the MDT, the decision was for a repeat CRS and HIPEC which was performed. Intra- operatively, there was only a single peritoneal deposit which was successfully removed (PCI score 3, CC score 0).

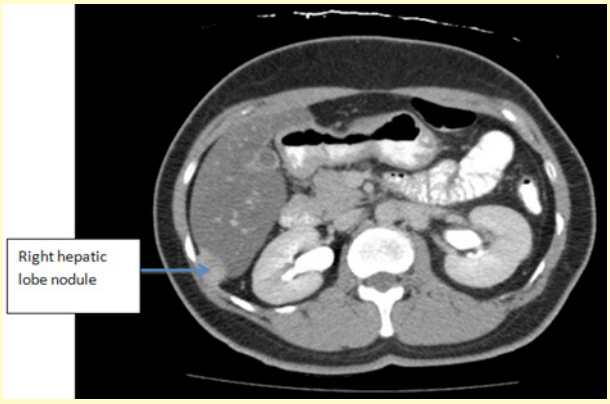

Figure 9: *CT scan showing a new right hepatic lobe enhancing nodule suspicious for recurrent tumour.*

Discussion

Peritoneal carcinomatosis carries an unfavourable prognosis and if left untreated, will cause great morbidity and mortality due to the progressive involvement of the peritoneal surface and intra-abdominal organs [1]. Patients may present with no other systemic metastases and this has moved clinicians to search aggressively for a treatment option for this subset of patients. The treatment of peritoneal metastases has evolved from CRS in late 1960s and 1970s, to hyperthermicintra- peritoneal chemotherapy in the 1980s, and subsequently combining both modalities as the definitive surgical technique by Dr Sugarbaker [1]. Since then, we have seen significantly improved survival rates for selected patients with peritoneal carcinomatosis who have undergone CRS and HIPEC. Currently, CRS and HIPEC is utilised in the treatment of peritoneal carcinomatosis of colorectal, appendiceal, ovarian, gastric, primary peritoneal, and mesothelioma origin [1]. Attempts at treating peritoneal metastasis of small bowel and endometrium origin, and also peritoneal sarcomatosis have been made but there is no high-level evidence to show the effectiveness of CRS and HIPEC in improving overall survival for these patients.

Small bowel carcinoma is a rare tumour, accounting for less than 2% of all the tumours in the gastrointestinal tract [5]. This includes adenocarcinoma (most common and accounts for nearly half of all small bowel neoplasms), carcinoids, sarcomas and stromal tumours. Despite it being rare, the incidence of small bowel cancer is rising. According to the United States National Cancer Database, incidence of small bowel cancer in the USA rose from 11.8 to 22.7 cases/million people from 1973 to 2004 [6]. Certain recognized risk factors include Peutz-Jeghers syndrome, Familial Adenomatous Polyposis (FAP), Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Crohn's and Coeliac disease [6-7]. Presentation is usually nonspecific and hence, patients are diagnosed in later stages of the disease. Approximately 50% of small bowel adenocarcinomas are found in the duodenum [6], with a slight preference for the second and third portions [7]. Those found in the ileum and jejunum seem to be associated with Crohn's or coeliac disease [7]. Treatment for localised small bowel adenocarcinoma is complete surgical resection of the primary tumour with locoregional lymph node resection [6]. For metastatic disease however, chemotherapy is currently the mainstay of treatment, and has been shown to prolong survivalin several small case series [6]. Literature search showed that The Washington Cancer Institute has had experience with 6 patients with either mucinous or intestinal type adenocarcinoma of the small bowel with peritoneal seeding, treated with CRS and HIPEC [2]. The median survival after CRS and HIPEC was 12 months compared to 9 months for those on palliative chemotherapy [2]. It is difficult to organise large scale studies to come up with the best mode of treatment for advanced small bowel carcinoma as the disease itself is rare. However, CRS and HIPEC should be considered for patients who have advanced disease limited to the peritoneum, high performance status and lack of comorbid disease, allowing them to tolerate the procedure with minimal morbidity or mortality.

Intra-abdominal sarcomas make up 30% of all soft tissue sarcomas, and 50-70% of these patients will face recurrences which will eventually lead to intra-peritoneal dissemination or sarcomatosis [8-9]. Peritoneal sarcomatosis (PS) is associated with poor prognosis, with a median survival of 6-15 months with palliative treatment [8]. As treatment options are limited, CRS and HIPEC have been attempted to prolong the survival of these patients. The MD Anderson Cancer Center looked into CRS and HIPEC as a treatment option in 28 patients with PS [9]. Despite the aggressive surgical approach, they found that patients still recurred with a disease free survival interval of 4.4 months and overall survival duration 16.9 months [9]. They have also proceeded to do a study of CRS and HIPEC in the paediatric age group who have been diagnosed with peritoneal sarcomatosis. CRS and HIPEC provided the patients with a longer overall survival period from less than a year in those undergoing only chemotherapy and radiotherapy to a median of 39 months [10]. In another study by Salti et al, patients with low volume disease and who had undergone complete cytoreduction had a disease- free survival of 31 months [8]. Published duration of disease- free and overall survivals of a patient with peritoneal sarcomatosis is variedas they are dependent on disease histology, extent of disease, completeness of cytoreduction and chemoperfusion techniques [11]. Some of the results are encouraging, and until further studies are available to determine the best management for patients with PS, CRS and HIPEC can be considered in selected patients.

Advanced gynaecological cancers of epithelial ovarian origin have been treated with CRS and HIPEC with good results [12-13]. There are few studies however, which look at the outcomes of endometrial carcinoma with peritoneal metastases, treated with CRS and HIPEC, even though it is the most common cancer of the female reproductive tract. With peritoneal seeding, the median survival of the patient is approximately one year, compared to a 90% 5 year survival of patients with stage 1 disease [14]. Endometrial carcinoma with peritoneal spread would require multimodality treatment including surgery, systemic chemotherapy, brachytherapy, radiation or even hormonal therapy. With CRS and HIPEC, results from a small study showed that the median overall survival was 19.4 months (range 1.5-124.8 months). The major determining factor of the success of CRS and HIPEC were intraoperative PCI score and the CC score; with a PCI score of >10, the patients survived less than 48 months [14]. Hence, with the evolution of CRS and HIPEC and evidence of improved overall survival for these patients, it should be considered as a treatment option for patients with endometrial carcinoma with limited peritoneal metastases.

Conclusion

CRS and HIPEC is fast becoming an accepted treatment modality for peritoneal carcinomatosis of colorectal, ovarian, gastric and primary peritoneal origins. However, this procedure can also be considered for other cancers localised to the peritoneal cavity. A few institutions have reported small case series of the use of CRS and HIPEC in the treatment of peritoneal sarcomatosis, mucinous adenocarcinoma of the small bowel and uterine sarcomas [2-4], and longer follow-up time for these unconventional indications, would serve to show its effectiveness and the positive impact on survival it can have, on select patients with localised peritoneal diseases.

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Volume 1 Issue 1 October 2015