Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei and Appendix Tumours

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Abstract Pseudomyxoma peritonei (PMP) is the intra-peritoneal accumulation of mucus due to mucinous neoplasia, most often from a ruptured mucinous appendiceal neoplasm. A similar syndrome is caused by appendix cancer and other gastrointestinal malignancies. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) provides long-term survival in selected patients with these conditions. The management of the appendiceal neoplasm prior to development of peritoneal involvement is initially discussed. This is followed by an overview of the management of peritoneal disease caused by appendiceal neoplasms. The principles and basic techniques of CRS and intraperitoneal chemotherapy (both intraoperative and post operative) are then discussed. Survival outcomes from several large studies are summarised. Prognostic factors are also discussed. We report our basic outcome data for the 345 patients with PMP or appendix cancer treated at our institution. Finally, the promising upcoming treatment of mucolytic therapy is discussed. We conclude that appendiceal neoplasms, although rare can cause significant morbidity and mortality. With optimal management long-term survival is possible in the majority of patients. The key to treatment is complete cytoreduction and use of hyperthermic intraperitoneal chemotherapy.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · HIPEC · Peritoneal surface malignancy · Appendiceal neoplasms · Mucocoele · Peritonectomy · Surgical oncology · Surgery · Pseudomyxoma peritonei · PMP

Introduction

Epithelial appendiceal neoplasms make up approximately 1–2 % of lower gastrointestinal tumours [1]. They constitute a spectrum of disease ranging from the simple unruptured appendiceal mucocoele (Figs. 1 and 2) to the aggressive peritoneal mucinous metastasis from appendiceal carcinomas [2]. The established treatment for peritoneal involvement of these tumours is complete cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) [3].

Origin of Pseudomyxoma Peritonei

Pseudomyxoma peritonei (PMP), sometimes referred to as the “jelly-belly” syndrome, is the intra-peritoneal accumulation of mucus due to mucinous neoplasia [4]. It most often develops from a ruptured mucinous appendiceal neoplasm [5]. For many decades it was thought that ovarian neoplasms caused PMP. This is due to the frequency with which women with PMP present with an ovarian mass (39 %) [6]. In recent times, using advanced immunohistochemical techniques, it has become clear appendiceal mucinous neoplasms cause the vast majority of cases of PMP [5, 7–10].

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Fig. 1 Appendiceal mucocoele removed intact. Histopathology showed a low-grade appendiceal mucinous neoplasm

Management of the Unruptured Mucocoele

Traditionally it has been taught that in the case of an appendix neoplasm a right hemi-colectomy should be performed in order to obtain an adequate sample of lymph nodes. In the case of low-grade appendiceal neoplasm it has been shown that it is not necessary to perform right hemicolectomy as these tumours do not metastasise to lymph nodes [11, 12]. The main aim of surgery on the intact mucocoele is to remove it without rupture. Removal of the intact low-grade appendicular neoplasm can usually be considered curative [13], however a recent small case series of patients with low-grade appendiceal

neoplasms without rupture reported that one out of the six patients developed PMP [14].

Management of the Ruptured Mucocoele

Intraoperative rupture may result in significant long-term morbidity and increased mortality for the patient. Spilling of the mucocoele may lead to development of extensive peritoneal disease. The ruptured appendix should be removed and all mucinous ascites evacuated. There is little evidence on how best to manage these cases. At our centre we take a two-tiered approach. Firstly, we consider HIPEC the best treatment. However the reality is that often these cases are being performed as emergencies and HIPEC is not available. In addition patients will not usually have consented to HIPEC. Therefore in practice we insert a peritoneal catheter and plan to administer Early Postoperative Intraperitoneal Chemotherapy (EPIC). If neither of these options were available then we would recommend transfer or early referral to a centre that has the capability to provide these treatment options. We recommend performing the minimal amount of surgery required to remove the appendix. There should be minimal disruption of tissue planes in order to maximise chance of cure should PMP develop [15]. The appendix and the ascites should be removed, a peritoneal port inserted, and then a discussion with the patient and a multidisciplinary team should inform the subsequent management. Close surveillance is subsequently required.

Histological Types of Epithelial Appendiceal Neoplasm: Terminology

There is inconsistency in the terminology used to describe the underlying pathology in appendiceal neoplasms with peritoneal spread [4, 16]. The term pseudomyxoma peritonei (PMP) has been used to describe not only the disease characterised by mucinous ascites caused by a mucinous appendiceal neoplasm but also to refer to the syndrome of mucinous ascites caused by a number of different primary cancers (e.g. colon, small bowel, stomach, ovary) [17, 18]. We use the term PMP to describe the intra-peritoneal accumulation of mucus due to a ruptured mucinous appendiceal neoplasm. PMP can be divided into two histopathologic types based primarily on invasion and cellular characteristics: diffuse peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis [19]. DPAM is caused by a ruptured low-grade mucinous appendiceal neoplasm and is characterised by wide-spread extracellular mucus and mucinous epithelial cell

Fig. 2 CT of low-grade appendiceal mucinous neoplasm

deposition on to the peritoneum that adheres to, but does not invade into, visceral or parietal peritoneum [2, 20]. PMCA is caused by an invasive appendiceal mucinous neoplasm (often referred to as high-grade or appendix cancer) and is characterised by invasive peritoneal lesions [7]. An intermediate or hybrid type, has been described where the tumour is predominately low-grade and of DPAM type but there are areas consistent with PMCA (less than 5 % of all fields) [7]. We group the intermediate type with PMCA as it has an invasive component. This is consistent with recent publications [2]. Differentiation between DPAM and PMCA is very important as it has a very strong effect on prognosis. This is discussed below.

Appendix Cancer Subtypes

The histologic subtype of malignant appendiceal neoplasm is very important in staging. Signet ring cell carcinoma of the appendix has been shown to have the worst prognosis [21]. The rare appendix adenocarcinoid (also called Goblet cell carcinoid) behaves more like appendix adenocarcinoma than the less aggressive carcinoid [22, 23].

Peritoneal Cancer Index (PCI)

The main staging tool for peritoneal surface malignancy is the peritoneal cancer index (PCI) [2]. The PCI divides the abdomen and pelvis up into nine regions and the small bowel up into four (proximal and distal jejunum and ileum). Each of these regions is given a score between 0 and 3 (see Fig. 3). A score of zero represents no peritoneal disease. A score of 1 is assigned for nodules between 0 and 0.5 cm, a score of 2 indicating nodules between 0.5 and 5 cm, and a score of 3 if greater than 5 cm of peritoneal disease is found. The maximum score is therefore 39 [15]. The PCI is estimated during the preoperative workup based on CT or MR imaging, but the definitive PCI can only be scored at operation.

Fig. 3 Peritoneal cancer index

PCI has a variable prognostic value in PMP. With DPAM there is a strong correlation between increased survival and a PCI of less than 20 [2]. This association is not as strong for PMCA. There is similar survival for patients with PMCA whether they have high or low volume disease. For all cases of PMP caused by appendiceal primaries we currently have no PCI limit although a limit might be considered for the more aggressive signet ring cell cancer of the appendix [24].

Preoperative Workup

Preoperative workup for possible cytoreductive surgery and HIPEC involves blood work, imaging, and anaesthetic assessment. Tumour markers (specifically CEA, CA 19-9 and CA125) are performed for all patients. CEA and CA 19-9 are elevated in the majority of patients with appendiceal primary tumours and peritoneal disease [25]. Normal levels of CEA and CA 19-9 have been shown to be associated with improved survival and decreased rates of recurrence. Our unit has shown that CA 19-9 is an independent prognostic indicator in DPAM. Five-year overall survival was 90 % for those with normal CA 19-9 levels compared to 58 % when the marker is elevated [26].

For the patient who has a low-grade appendiceal neoplasm as the primary tumour the only imaging routinely required is a CT scan of the chest, abdomen, and pelvis [27]. Recently a new prognostic scoring system has been developed to attempt to predict the likelihood of completeness of cytoreduction based on preoperative CT features including scalloping of liver (see Fig. 4), spleen, pancreas or portal vein, and foreshortening of the small bowel mesentery [28]. However

Fig. 4 Scalloping of the liver in high volume PMCA

none of these features are an exclusion from operation. The only adequate way to assess operability and possibility of complete cytoreduction is intraoperatively.

Patients with suspected or proven appendix cancer are evaluated with an FDG-PET scan, dedicated liver imaging and routine CT of the chest, abdomen, and pelvis. The purpose of this is to detect liver metastases, extra-abdominal disease, and establish a preoperative estimate of PCI [29]. More recently it has been suggested that diffusion restriction MRI may more accurately predict PCI in patients undergoing preoperative workup for cytoreductive surgery [30].

Exclusion criteria for cytoreduction and HIPEC include: presence severe comorbidities; presence of extra-abdominal disease; and for appendix cancer, the inability to perform complete or near complete cytoreduction, inability to preserve 1.2 m of small bowel (more required if gastrectomy is performed).

Liver Metastases

Patients with DPAM will not have liver metastases however those who have PMCA might and need to be evaluated as such. In our centre we routinely use catheter based hepatic angiography or MRI with liver specific contrast agents. If liver metastases are detected they will be assessed for suitability for synchronous resection during the cytoreductive surgery. Liver metastases do not necessarily exclude a patient from being treated with curative intent. There is little published data on liver treatment of intrahepatic liver metastases in cytoreductive surgery and HIPEC in PMCA caused by appendix cancer. There are several published series on the treatment of colorectal cancer with peritoneal and liver metastases that support synchronous cytoreductive surgery with HIPEC and minor liver resection [31–36]. Our own data also support this [37, 38].

Cytoreductive Surgery and HIPEC

The goal of cytoreductive surgery is to remove all visible malignancy. Complete cytoreduction may require five peritonectomy procedures to be performed within the single operation [2, 39]. These include the anterior parietal peritonectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, pelvic peritonectomy, greater omentectomy, omental bursectomy, stomach surface, small and large bowel mesentery and surface, and lesser sac. Each of these peritonectomy procedures may be accompanied by multiple visceral resections [40]. The only surgical instrument used that may be unfamiliar to some is the ball-tipped diathermy [41]. The advantage of the ball-tipped diathermy is that it has a blunt tip and it also has a greater surface area providing greater electrodestruction and haemostasis.

The following outline the basic steps in performing the cytoreductive surgery. Each of the peritonectomy procedures for different regions clearly overlaps with the adjacent region. Detailed technical description is beyond the scope of this review but is available elsewhere [40–46].

The patient is placed in a supine position with both arms placed on arm-boards. A nasogastric tube, indwelling urinary catheter, arterial line, and central venous catheter will all have been inserted prior to positioning the patient. The patient is then draped in non-sterile impermeable plastic sheeting in order to reduce the chance of contact between the patient's skin and the chemotherapy in the event of a HIPEC leak. After this the patient is prepped and draped in the routine fashion.

A midline xiphoid to pubis incision is made in order to completely expose the abdominal and pelvic cavities. In a patient with DPAM and a high volume of mucinous ascites an extraperitoneal approach to the initial dissection is carried out. The parietal peritoneum may be separated from the anterolateral abdominal wall musculature without entering the peritoneal cavity. This enables complete removal of the anterolateral parietal peritoneum and should include both diaphragms (See Fig. 5). After this the peritoneum is opened. Adhesions are divided, mucinous ascites removed, and the entire abdominopelvic cavity is inspected. Only once the abdominopelvic cavity is adequately exposed can a PCI assessment be made as imaging frequently underestimates the volume of disease [47, 48]. After the PCI is recorded a decision regarding the operability of the disease is made. For PMCA the only factor that would deem a patient inoperable would be the inability to remove all of the disease and maintain at least one to 1.5 m of small bowel. If a partial gastrectomy is performed during the operation then more than 1.5 m of bowel should be preserved. In DPAM the inability to removal all disease is not a contraindication to cytoreduction

Fig. 5 Extraperitoneal approach to opening the abdomen in a patient with high volume DPAM

and HIPEC as near complete cytoreduction is still associated with prolonged survival however every attempt should be made to achieve complete cytoreduction. If a region of peritoneum is unaffected by disease then it is not necessary to routinely remove that area of peritoneum. For example diaphragm stripping is not performed if there is not macroscopic disease. This is the same for both DPAM and PMCA.

Anterior Parietal Peritonectomy

If the opening has been performed using the extraperitoneal approach then the majority of the anterolateral parietal peritoneum has already been separated from the muscle and fascia to which it was attached. If not then the peritoneum is dissected as required. A large self-retaining ring retractor set is used to assist with this process. The retractors are steadily advanced along the anterior abdominal wall providing optimal traction at the point of dissection [44]. The stripping of peritoneum extends from the midline of the anterior abdominal wall through to the paracolic gutters, both hemi-diaphragms, and the pelvis.

Omentectomy

Greater omentectomy is always performed during cytoreductive surgery, as it is a very common site of tumour cell deposition. Even if the greater omentum appears macroscopically normal it is likely to harbour tumour cells. This procedure is usually performed early in the operative procedure as the greater omentum frequently is of large volume and removal of it will greatly increase exposure.

Left Upper Quadrant Peritonectomy

Left upper quadrant peritonectomy frequently involves stripping of the left diaphragm, +/- splenectomy +/- distal pancreatectomy, and removal of disease from the surface of the pancreas. If splenectomy is performed the splenic artery and vein will be tied with care taken not to injure the tail of the pancreas. It has been recently shown that distal pancreatectomy in cytoreductive surgery and HIPEC is safe [49]. The group found an increase in post-operative morbidity but not mortality. They concluded that distal pancreatic involvement in peritoneal carcinomatosis should not exclude an attempt at complete cytoreduction.

Right Upper Quadrant Peritonectomy

Right upper quadrant peritonectomy involves complete mobilisation of the liver in order to fully inspect the right hemi-diaphragm. If the peritoneum overlying the right hemi-

diaphragm is involved then it is stripped. Disease involving the capsule of the liver is treated via electrodestruction and stripping of the liver capsule as required.

It should be noted that where the diaphragm is opened during diaphragmatic stripping it should be left open for the HIPEC in order to allow the HIPEC to deal with the thoracic contamination. The diaphragmatic defect should be repaired after HIPEC.

Pelvic Peritonectomy

Frequently the pelvic peritonectomy involves anterior resection, total abdominal hysterectomy and bilateral salpingo-oophorectomy, and bladder stripping. The ovaries are a common site of tumour deposition. It is not uncommon to find large Krukenberg tumours [46]. If there is disease suspected on the ovaries of a female who is yet to complete her family an attempt is made to remove only the disease and preserve the ovaries. In the context of invasive cancer this approach should be used with caution due to the frequency of microscopic metastatic deposits on the ovaries. When both ovaries are removed in a patient who is yet to complete her family intra-operative egg harvesting is occasionally used.

Small Bowel

Where possible the small bowel is preserved in order to maintain an adequate length of gut for absorption of fluids and nutrition. Where it is not possible to remove the disease from the surface, such as when there are large nodules at the mesenteric border of the small bowel, then resection of the involved small bowel should be performed, preserving as much small bowel as possible [43].

Notable Areas Where Tumour may be Hidden

There are several notable areas to which the cytoreductive surgeon must pay particular attention, as they are difficult to visualise and also frequently harbour peritoneal disease. These include the recess between segment one of the liver and the inferior vena cava, the recesses adjacent to the duodenojejunal flexure, the rectouterine recess, and the retropyloric area [45]. In addition it is necessary to open the hepatic bridge and inspect the fold containing the ligamentum teres on its way towards the left portal vein [42].

The Role of Right Hemicolectomy

Routine right hemicolectomy has been shown to be unnecessary for mucinous appendiceal neoplasms (both DPAM and PMCA) [12]. If the primary tumour is unable to be safely

removed via simple appendicectomy then a wider resection may be required (e.g. caecectomy, ileocaecal resection, or right hemicolectomy). One study did not show any survival advantage for right hemicolectomy compared to appendicectomy in 501 patients undergoing CRS and HIPEC with appendix primary tumours (both DPAM and PMCA) [12]. If the primary tumour is located at the base of the appendix then right hemicolectomy should be performed. These tumours are more likely to be of a non-mucinous subtype that is more likely to metastasise to lymph nodes [12, 50].

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

After the cytoreductive surgery has been performed but prior to performing anastomoses and closure it is necessary to bathe the abdominal cavity in hyperthermic chemotherapy. The principle of HIPEC is to provide a high locoregional concentration of chemotherapy to penetrate the remaining microscopic disease (Fig. 6). Hyperthermia is used as it has direct cytotoxic effects as well as synergistically increases the effect of the chemotherapy. It has been shown that HIPEC can penetrate to a depth of 3–5 mm [51–53]. Intraperitoneal delivery of chemotherapy allows much higher concentrations to be delivered to the tissues than could be achieved safely with systemic administration. The chemotherapy is perfused into the peritoneal cavity along with additional crystalloid perfusate in order to fill the abdominal cavity with the chemotherapy solution. This dilutes the chemotherapy however will result in greater distribution. The possible effect of the variation in concentration is an area for future research.

Fig. 6 The HIPEC set up. An open technique is used with the skin edges brought up to the Bookwalter ring retractor using nylon sutures. Plastic sheeting is also sutured in place to reduce occupational exposure. Inflow and outflow catheters are seen, along with temperature probes and a smoke evacuator

There is variation between centres in the agents and doses used for HIPEC [51]. In our centre the first agent of choice for DPAM is mitomycin C (See box 1). For PMCA we use oxaliplatin HIPEC with simultaneous administration of intravenous 5-fluorouracil (See box 2). There is no consensus as to the correct dose for HIPEC. Other centres give doses of mitomycin C up to 35 mg/m² however this is associated with significant rates of bone marrow suppression [54]. A recent review by González-Moreno highlights this variation [51].

After HIPEC

Anastomoses are performed after the HIPEC. At our institution we perform side-to-side, functional end-to-end anastomoses using a GIA stapler. All staple lines are oversewn. Seromuscular defects that were created during the removal of surface bowel disease from the small bowel are oversewn. These defects are marked with a suture prior to HIPEC in order to make identification after HIPEC easier. It is only after the chemotherapy that oversews and repairs are performed in order to maximise the potential for the HIPEC to penetrate planes that have been breached. Once repairs have been made leak tests on the bowel and bladder may be performed.

At the conclusion of the operation a completeness of cytoreduction (CC) score is given. CC0 indicates a complete cytoreduction with no visible peritoneal disease. CC1 indicates nodules smaller than 0.25 cm persisting, CC2 indicates nodules between 0.25 and 2.5 cm remaining, and CC3 indicates nodules greater than 2.5 cm remain or a confluence of unresectable tumour within the abdominopelvic cavity [2]. CC0 and CC1 are considered complete cytoreduction, as the intraperitoneal chemotherapy is able to penetrate the small nodules in a CC1 cytoreduction.

Operation Record

It is important to ensure that key details of the operation are recorded clearly. We suggest that all operation notes for

Box 1 Intraperitoneal chemotherapy protocol for DPAM

HIPEC for DPAM. 'Adapted Classical Sugarbaker Protocol'

Day 1

HIPEC: Mitomycin C 12.5/m² over 90 mins in 1 L Plasma Lyte 148 in conjunction with hyperthermia.

Day 2–6

EPIC: 5FU 650 mg/m² IP + 50 mEq sodium bicarbonate in 1 L Plasma Lyte 148 (23 h dwell time)

Box 2 Intraperitoneal chemotherapy protocol for PMCA

HIPEC Protocol for PMCA (Appendix cancer) or Refractory Cases of DPAM

Day 1

Folinic acid 50 mg intravenously approximately 1 h prior to HIPEC.

5-Fluorouracil 400 mg/m² intravenously administered concurrently during HIPEC

HIPEC with Oxaliplatin 350 mg/m² over 30 mins in 500mls of 5 % Dextrose with hyperthermia

No EPIC

cytoreductive surgery and HIPEC must include the PCI, the type of primary tumour (DPAM or PMCA), the completeness of cytoreduction score (CC), the details of the chemotherapy, site of any residual disease, and the length of remaining bowel.

Early Post-Operative Intraperitoneal Chemotherapy (EPIC)

In addition to HIPEC there is an option to administer Early Post-operative Intraperitoneal Chemotherapy (EPIC). This may administered as early as postoperative day one if the patient is well enough to tolerate the administration of EPIC. In our centre EPIC consists of 5 days of 5-FU delivered via a peritoneal catheter inserted at the time of cytoreductive surgery and HIPEC. The intraperitoneal chemotherapy remains in situ for 23 h before being allowed to drain for one hour. This process is repeated for a further 4 days (see Box 1). There is variation amongst centres in the use of EPIC [51]. In our centre EPIC is only used in conjunction with mitomycin C HIPEC. We do not use EPIC when oxaliplatin is used for HIPEC.

Early Morbidity and Mortality

Most papers reporting morbidity in CRS and HIPEC use the Clavien-Dindo classification which defines Grade 3 complications as requiring surgical, endoscopic, or radiological interventions and Grade 4 complications as a life-threatening complication requiring ICU management [55, 56]. Cytoreduction and HIPEC is associated with a level of morbidity that has shown to be comparable to other major abdominal surgery such as pancreaticoduodenectomy [57] and less than that for pelvic exenteration surgery [58]. A well-established centre reported a mortality of 2 % and grade

IV morbidity rate of 19 % for patients undergoing cytoreduction surgery and HIPEC for appendix neoplasms [59]. A recent systematic review of reported morbidity and mortality of patients undergoing CRS and HIPEC for many different primary tumours reported a mean mortality of 2.9 % and a mean combined grade III/IV morbidity of 28.8 % [56, 57]. The top five complications in this review were reoperation, ileus, abscess, fistula, and haematological toxicity. For the last 400 patients undergoing CRS and HIPEC at our centre the mortality rate has been 1 %..

Long-Term Outcomes

A large retrospective multi-institutional registry study reported 5-year survival of 81 % for DPAM and 59 % for PMCA [60]. They also showed that high PCI and incomplete cytoreduction (CC2/3) are independent predictors of poorer progression free survival. The Basingstoke unit reported 5-year survival of 87 % in patients with DPAM who were able to undergo complete (CC0/1) cytoreduction ($n = 289$) compared to 34 % in those who underwent major debulk ($n = 152$, CC2/3) [61]. Of note only 29 % of patients who underwent a major debulk received HIPEC. Elias et al. report a five-year survival of 63.2 % for PMCA ($n = 41$) [62]. Other factors associated with increased survival include low grade tumour (DPAM vs. PMCA), PCI less than 20 in PMP, complete cytoreduction, and limited surgery prior to CRS and HIPEC [2]. Recently we have shown that elevated tumour marker CA 19-9 is an independent prognostic indicator of worse outcome in PMP [26].

Results from our Institution

At our institution we have performed CRS and HIPEC on 345 patients with PMP caused by primary appendiceal neoplasms (Table 1). Our five-year overall survival for DPAM and PMCA was 81 % and 49 % respectively. If only patients in whom we were able to obtain a complete cytoreduction are included the five-year survival is 85 % and 60 % respectively. Overall survival curves for DPAM and PMCA are shown in Fig. 7. Multiple studies have demonstrated that that main factor determining long-term survival is the ability to achieve a complete cytoreduction (CC0/1) [23, 60–62]. One multi-institution registry study showed a five-year survival of 85 %, 80 %, and 24 % for CC0, CC1, and CC2/3 respectively [60]. Our unit has five- year survivals for DPAM of 91 %, 78 %, and 28 % for CC0, CC1, and CC2 respectively. For PMCA we have a five-year survival of 61 %, 35 %, and 17 %

Table 1 Patient characteristics for DPAM and PMCA at our institution

	DPAM <i>n</i> = 180*	PMCA <i>n</i> = 165
Female (<i>n</i> , %)	103 (57 %)	87 (53 %)
Age (mean in years)	54.1	54.4
PCI (mean)	23.7	22.4
CC0 (<i>n</i>)	91	93
CC1 (<i>n</i>)	79	64
CC2/3 (<i>n</i>)	8	8
1 year survival	95 %	90 %
3 year survival	88 %	65 %
5 year survival	81 %	49 %

*CC score missing from 2 records

for CC0, CC1, and CC2 respectively. See Fig. 8 for survival curves. Our results for all primary cancers have recently been published [63].

Follow up

All patients undergoing cytoreduction and HIPEC for epithelial appendicular neoplasms require close postoperative follow up with CT scans and tumour markers. Patients are initially seen regularly and have CEA and CA 19-9 measured [25]. In the event of tumour recurrence it has been shown that reoperation is appropriate [64]. Although the need for reoperation due to disease recurrence is a poor prognostic factor

compared to absence of disease recurrence it has been shown that patients who undergo repeat cytoreductive surgery with HIPEC have significantly longer survival than those who do not [64].

Learning Curve

Several major centres have published data that clearly demonstrates a learning curve both regarding operative and oncological outcomes [65–67]. A recent study from Italy found that it took between 60 and 158 cases to overcome the learning curve with regards to completeness of cytoreduction, grade 3–5 morbidity, and procedure related mortality [67]. A Swedish group found greater than 200 cases are required to overcome the learning curve [66]. Most recently the group from the University of Pittsburgh, USA, published their findings that approximately 180 cases are required to improve operative outcomes and approximately 90 cases to improve oncologic outcomes [65].

Future Directions

Mucolytic Therapy

Our laboratory is currently exploring the use of mucolytic agents in the treatment of DPAM. The two agents that show the most promise are bromelain and N-acetyl cysteine (NAC). Bromelain is a cysteine proteinase extracted from the fruit and stem of pineapple plant (*Ananas comosus*) [68]. N-acetyl

Fig. 7 Overall survival curve for DPAM (blue) and PMCA (green). Logrank *p* < 0.000

Fig. 8 Survival curves by completeness of cytoreduction (CC) for DPAM and PMCA

cysteine (NAC) is a sulfur-containing protein widely used for the treatment of paracetamol toxicity [69]. NAC is also used as a mucolytic agent in chronic obstructive pulmonary disease, cystic fibrosis and other respiratory infections where excessive mucin is secreted [70].

Our previous published studies have shown that, both in vitro and in vivo, a combination of bromelain 300 µg/ml and NAC 250 mM can effectively solubilise the soft variety of patient PMP mucin [71, 72]. When tested in vitro, all soft mucin disintegrated completely into an amber coloured semi-transparent liquid, on incubation with 300 µg/ml bromelain +250 mM NAC for 3 h at 37° Celsius at a pH of 7. Semi-hard and hard mucin also partly disintegrated, however with residual material remaining. When tested in vivo using a rat

model with implanted intraperitoneal mucin, at 72 h the enzymes completely dissolved all soft mucin whilst partially dissolving semi-hard and hard mucin. No toxicity was observed. Future studies will be conducted using intraperitoneal delivery of these mucolytic agents in patients with DPAM.

Conclusions

Appendiceal neoplasms causing peritoneal disease are rare however if they are optimally managed long-term survival is possible in the majority of patients. The key to treatment is complete cytoreduction and use of hyperthermic intraperitoneal chemotherapy.

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