

*Diagnosis and Treatment of
Pseudomyxoma Peritonei*

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1 List of original publications

This thesis is based on the following publications, which are referred to in the text by their roman numerals (I, II, III and IV):

- I Järvinen P, Järvinen H, Lepistö A. Survival of patients with pseudomyxoma peritonei treated by serial debulking. *Colorectal Disease* 2010; 12: 868 – 873.
- II Järvinen P, Lepistö A. Clinical presentation of pseudomyxoma peritonei. *Scandinavian Journal of Surgery* 2010; 99: 213 – 216.
- III Järvinen P, Ristimäki A, Kantonen J, Lepistö A. Feasibility of radical cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei of appendiceal origin. *Scandinavian Journal of Surgery* 2013; 102: 145 – 151.
- IV Järvinen P, Ristimäki A, Kantonen J, Aronen M, Huuhtanen R, Järvinen H, Lepistö A. Comparison of serial debulking and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei of appendiceal origin. *International Journal of Colorectal Disease* 2014; 29: 999 – 1007.

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2 Abstract

Pseudomyxoma peritonei (PMP) is best treated by surgery. It was formerly treated by serial debulking. The current gold standard is complete cytoreductive surgery (CRS) to be followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Improved survival figures for patients treated by CRS and HIPEC combined have been reported recently. The aim of this PhD research was to evaluate (I) the outcome of patients treated by serial debulking in Helsinki University Central Hospital, (II) investigate the clinical manifestation of the disease, (III) assess the feasibility of CRS and HIPEC modality in combination, and (IV) compare results of serial debulking and CRS with HIPEC in patients with PMP.

The surgical data and the survival outcome of 33 patients that were treated by serial debulking were analyzed in study I. The symptoms and signs of 82 patients with PMP were investigated in study II. Study III included 90 patients, who were evaluated in our facility and then given HIPEC when practicable. The characteristics that were associated with technically successful administration of HIPEC were analysed. The outcome of 87 patients treated in the HIPEC era was compared with those treated before the HIPEC era in study IV.

The 5-year and 10-year overall survival (OS) rates were 67% and 31%. Four patients (12%) presented with no apparent evidence of disease at the completion of follow-up (I). The most common symptom of PMP was abdominal pain in 23% of the cases (II). Of 53 women, 26 (49%) underwent their initial operations because of presumed ovarian tumour. Of 29 men, 13 (45%) underwent their initial operations with a suspicion of PMP. Of the 90 patients assessed, 56 (62%) were feasible for HIPEC (III). Low-grade tumour ($P=0.013$), age under 65 ($P=0.004$), and serum CEA under $5.0\mu\text{g/L}$ ($P=0.003$) were associated with successful administration of HIPEC. The 5-year OS rates were 69% for the HIPEC era and 67% for the debulking era (IV). The proportion of patients who presented with no evidence of disease was higher for the HIPEC-era group than for the debulking-era group (54% vs. 24%).

Patients who were treated by CRS and HIPEC combined managed well, but it is unfeasible to deliver HIPEC to every patient. A comparison of the 5-year OS rates of HIPEC era with those of the debulking era showed them to be approximately equal, when the whole patient population was included for the comparison. The natural progression of PMP is slow and thus the survival difference may only become apparent in follow-up periods in excess of 5-years. The proportion of patients who had undergone curative treatment may be higher in the HIPEC era.

3 Abbreviations

5-FU = 5-fluorouracil

C = Celsius

CC = completeness of cytoreduction

CA 12-5 = carbohydrate antigen 12-5

CA 19-9 = carbohydrate antigen 19-9

CEA = carcinoembryonic antigen

CK = cytokeratin

CRS = cytoreductive surgery

CT = computed tomography

CTCAE = Common Terminology Criteria for Adverse Events

DFS = disease-free survival

DSS = disease-specific survival

EPIC = early postoperative intraperitoneal chemotherapy

DPAM = disseminated peritoneal adenomucinosis

HAM = human alveolar macrophage

HIPEC = hyperthermic intraperitoneal chemotherapy

HUCH = Helsinki University Central Hospital

LAMN = low-grade appendiceal mucinous neoplasm

LOH = loss of heterozygosity

MANEC = mixed adenoneuroendocrine carcinoma of appendix

MCP-L = low grade mucinous carcinoma peritonei

MCP-H = high grade mucinous carcinoma peritonei

mL = milliliter

M-LMP = mucinous neoplasm of low malignant potential

MMC = mitomycin C

MRI = magnetic resonance imaging

M-UMP = mucinous neoplasm of uncertain malignant potential

OS = overall survival

PALGA = Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief

PC = peritoneal carcinomatosis

PCI = peritoneal cancer index

PET = positive emission tomography

PFS = progression-free survival

PMCA = peritoneal mucinous carcinomatosis

PMCA-I/D = peritoneal mucinous carcinomatosis with intermediate or discordant features

PMP = pseudomyxoma peritonei

SC = systemic chemotherapy

WHO = World Health Organization

4 Review of the literature

The challenging disease of Pseudomyxoma peritonei (PMP) is best treated by surgery and was formerly treated by serial debulking [1]. The current gold standard is complete cytoreductive surgery (CRS) to be followed by hyperthermic intraperitoneal chemotherapy (HIPEC) [2]. Improved survival figures for patients treated by CRS and HIPEC combined have been reported in a recent meta-analysis [3]. However, it is worth considering the historical background to this disease in order to understand the difficulties and complexities of diagnosing and treating it.

4.1 Historical background

The term “pseudomyxoma” comprises the prefix pseudo-, (from the Greek “false, lying”), -myx- (muxe from the Greek “mucus”), and suffix -oma (from the Greek “process” or “action”. Oma also means tumour in contemporary medical nomenclature. Thus, pseudomyxoma peritonei is a mucoid tumour of the peritoneum that resembles but is not, myxoma. Myxoma is instead a rare tumour of the primitive connective tissue and is located most commonly in the heart.

The first descriptions of PMP are dated in the 19th century. One of the first persons attributed to having described a benign mucocele of the appendix was the Bohemian nobleman and pathologist Karl von Rokitansky in 1842. His original article could not be traced, but Weaver described Rokitansky’s contribution to oncology in 1937 [4]. A gynaecologist named Werth introduced the term pseudomyxoma peritonei and reported the syndrome to be related to an ovarian neoplasm in 1884 [5]. In 1901, Frankel reported the association between pseudomyxoma and appendiceal cysts [6]. Woodruff and McDonald proposed in 1940 that the aetiology of PMP is malignant appendiceal mucocele and reported that its peritoneal spread was metastatic [7]. During the 20th century there was debate about whether the origin of PMP was the appendix or the ovary [8, 9]. The current opinion is, that the appendix can be identified as the origin in the majority of cases [10, 11].

4.2 Definition

PMP is a clinical term. It is characterized by the accumulation of mucinous ascites within the peritoneal cavity. An epithelial neoplasm arises within the appendiceal lumen and consequently the lumen *per se* becomes occluded. This occlusion finally causes a rupture in the wall of the appendix and therefore mucus containing epithelial cells is spilled within the abdominal cavity [12]. In the majority of cases, this process is subclinical [13]. The natural progression of the disease is usually moderately slow, although rapid advancement is also seen on occasions. The speed of progression is related to the histology of the tumour. The typical course of disease comprises tumour spread on the peritoneal surfaces, but invasion of the organs is also seen, especially in cases with a high-grade histology. Haematogeneous metastases are rarely seen. Nevertheless, those that can be seen are found in the livers or lungs of patients with high-grade histology. Eventually the progressive amount of mucus causes dyspnea, gastrointestinal obstruction, malnutrition, hydronephrosis, and other organ malfunctioning. The condition is lethal without surgical intervention.

4.3 Epidemiology

PMP is an uncommon syndrome. A population based study conducted by Smeenk et al. used the nationwide database of the Netherlands and reported an annual incidence of PMP approaching 2 per million [14]. Another Dutch study, in which data were retrieved from the Eindhoven Cancer Registry noted an increase in age-standardized incidence of appendiceal mucinous adenocarcinoma that varied between 0.6 to 1.9 per million in women and from 0.4 to 1.0 per million in men [15]. The study period was 1980 to 2010 and the data cover a large part of the southern Netherlands, which comprises about 2.3 million inhabitants. The increasing trend in the incidence was explained by the increasing awareness of PMP and better registration of the specific diagnosis. Notably, only malignant tumours were included in their study. Thus, the incidence they reported would be assumed to give an underestimation, if the whole spectrum of PMP regardless the histological grade were to have been analyzed.

The study by Smeenk et al. noted that a total of 167 744 appendectomies were performed in the Netherlands in the 10-year period of 1995 to 2005 [14]. A search was undertaken in the nationwide pathology database of the Netherlands (PALGA) and an appendiceal lesion was identified in 1482 of those specimens (0.9%). Thus, the annual incidence of appendiceal lesion is 9 per million. Of 1482 patients with an appendiceal lesion, 138 (9%) developed PMP. The chance of developing PMP was related to the type of lesion. Patients with a mucinous epithelial neoplasm developed PMP in 114 cases (20%), patients with non-mucinous epithelial neoplasm developed PMP in 13 cases (3%), and patients with mucocele in 11 cases (2%).

To the best of my knowledge, no data of epidemiology of PMP in Finland has hitherto been published.

4.4 Classification

The classification of PMP is indeed challenging. Various classification schemes have been proposed and have been used to grade PMP [16-20]. The following section will examine more closely the schemes considered to be the most relevant for the debate on classification. The studies presented were chosen to represent different aspects of the debate.

Ronnett's criteria for three distinct PMP groups were introduced in 1995 [18]. These criteria have since been widely used in the literature on PMP. According to the criteria, PMP can be divided into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA-I/D) by histopathological features. The peritoneal lesions in the DPAM group consist of scant, histologically low-grade mucinous epithelium within abundant mucin. The epithelium displays minimal mitotic activity and cytological atypia. The peritoneal lesions of the PMCA group consist of mucinous epithelium forming glands and/or signet ring cells. The amount of epithelium is more abundant than for the DPAM group. Cytological atypia and architectural complexity are sufficient to establish a diagnosis of mucinous carcinoma. Invasion of other organs/lymph nodes often manifest. The PMCA-I group consists of lesions

demonstrated predominantly as features of DPAM. However, focal areas of well-differentiated mucinous carcinoma are present. The PMCA-D group consists of peritoneal lesions with mucinous adenocarcinoma, often with signet ring cell differentiation and without low-grade epithelium. Despite the peritoneal lesions, the primary lesion in the appendix lacks evidence of invasive features.

Bradley et al. published a series of 101 patients with mucinous ascites related to primary appendiceal lesions in 2006 [21]. First, those authors classified the patient population into three groups: DPAM, PMCA, or PMCA-I according to Ronnett's criteria. There was the one exception of the signet-cell component. Those cases with the presence of signet cell were classified as PMCA and not as PMCA-I. Second, Bradley et al. unified DPAM and PMCA-I as one group and PMCA as the other. The amalgamated DPAM and PMCA-I group was re-graded to low grade mucinous carcinoma peritonei (MCP-L). The PMCA group with an addition of cases with signet-cell component was re-graded to high-grade mucinous carcinoma peritonei (MCP-H). The rationale for the amalgamation of the DPAM and PMCA-I categories was that there was no difference in the five-year overall survival (OS) between the groups ($61.8 \pm 9.2\%$ vs. $68.2 \pm 12.1\%$, $P=0.27$). On the other hand, the difference in five-year overall survival between PMCA and DPAM/PMCA-I combined was evidently significant ($37.7\% \pm 11.2$ vs. $62.5\% \pm 7.8$, $P=0.004$).

Pai and Longacre proposed their differential diagnosis spectrum of appendiceal mucinous neoplasms in 2005 [16]. They presented four distinct groups: mucinous adenoma, mucinous neoplasm of uncertain malignant potential (M-UMP), mucinous neoplasm of low malignant potential (M-LMP), and mucinous carcinoma. They considered mucinous adenoma lesions, which involve appendiceal mucosal surface and are composed of mucin-rich epithelium. Cytological atypia is mild or moderate. There is no invasion by the epithelium into the muscular wall nor is there a presence of epithelium on the serosa. According to Pai and Longacre's definition, mucinous adenoma is restricted to those cases without epithelium involvement in extra-appendiceal mucin. Consequently, if the appendix is surgically excised, no further treatment is required. In the case of M-LMP, however, neoplastic cells are sprayed beyond the appendix. Microscopic investigation does not reveal any significant difference in individual cells between mucinous adenoma and M-LMP. Therefore, the

differential diagnostics between these two groups is challenging. It is impossible to definitely exclude the possibility of extra-appendiceal spread of epithelial cells, even if no macroscopic tumour can be seen on the peritoneal surfaces. The group that falls between M-LMP and mucinous adenoma, was designated M-UMP by Pai and Longacre. They also restricted the use of this category to those cases with extremely well-differentiated mucinous neoplasms but which also had an uncertain stage of invasion. In contrast, mucinous carcinoma exhibits architectural complexity and high-grade cytological atypia with high mitotic activity. Destructive invasion is seen in most cases, if not all. The borders between mucinous adenoma, M-UMP, and M-LMP are rather indistinct. There is always uncertainty as to whether the epithelial cells have sprayed on peritoneal surfaces, thus the division of histologically comparable homogeneous group of lesions by invasiveness might be somewhat irrelevant. On the other hand, a clear dividing line can be drawn between the mucinous carcinoma and the other groups.

The WHO 2010 classification [19] of pseudomyxoma peritonei is straightforward and rather similar to that of the Bradley group's classification [19]. The lesion can be classified according to the definition as low-grade or high-grade pseudomyxoma. The alternative terms low-grade and high-grade mucinous adenocarcinoma can be used as well. The WHO avoids the use of the term DPAM, since the concept of ruptured adenoma can be seen as an understatement for a condition that commonly is lethal. The primary appendiceal lesions are classified as low-grade appendiceal mucinous neoplasm (LAMN) or mucinous adenocarcinoma. For the previously mentioned reason, the WHO avoided the use of term adenoma in case of LAMN as well. Principally, LAMN is related to low-grade PMP, whereas mucinous adenocarcinoma is related to high-grade PMP.

Table 1.

Different classification schemes of PMP.

Classification	Year	Number of classified groups	Groups
Ronnett	1995	3	DPAM: PMCA-I/D: PMCA:
Bradley	2006	2	MCP-L: MCP-H:
Pai & Longacre	2005	4	M-UIMP: M-LIMP:
WHO	2010	2	Low grade: High grade:

4.5 Aetiology

PMP is currently regarded as a condition that is derived from the appendix at least in the vast majority of cases [11, 22]. Synchronous ovarian lesions are frequently seen in female patients, which has led to confusion about the true origin of PMP [23]. There are histopathological, immunochemical, and molecular genetic studies that suggest the appendix as an origin in those cases with synchronous tumour of appendix and ovary [10, 22, 24]. Most cases of PMP showed positive expression for cytokeratins (CK) 18 and 20 when immunohistochemical expression was tested whereas the reaction was mostly negative for CK 7. The expression of human alveolar macrophage (HAM) 56 tended to be negative and that of carcinoembryonic antigen CEA positive. Thus, the pattern of immunoreactivity was distinct from primary ovarian tumour and similar to appendiceal adenoma [22]. The PMP cases demonstrated identical K-ras mutations in appendiceal adenoma and corresponding synchronous ovarian tumour when K-ras mutations were identified. The loss of heterozygosity (LOH) was observed in the ovarian tumour when the LOH on specific chromosomes was examined, whereas both alleles were retained in the matched appendiceal lesion in most cases. This finding supports the conclusion that ovarian lesions are metastatic [10].

The abundant expression of the MUC2 and MUC5AC genes were determined by both immunohistochemistry and *in situ* hybridization when O'Connell et al. studied gene expression of PMP cases [25]. The expression of MUC-2, in particular, explains the copious amounts of extracellular mucin found in PMP. Appendiceal goblet cells express both MUC2 and MUC5AC, but mesothelial cells and the cells of the ovarian surface express only MUC5AC. This gene expression pattern suggests that PMP is of appendiceal origin and not of ovarian or mesothelial origin. The cases of PMP were also compared to the control cases with normal appendix and *in situ* hybridization studies obtained strong MUC2 and MUC5AC signals both in PMP cells and goblet cells of the normal appendix. Nongoblet cells of the appendix showed no MUC2 signal. This finding suggests that the goblet cells of the appendix are the origin of PMP.

There are several studies that report a non-appendiceal origin of PMP. For example, PMPs that arise from mature cystic teratoma, pancreas, urachus, and colon in addition

to ovaries have been reported [26-28]. Therefore, PMP is not synonymous with appendiceal neoplasm with peritoneal spread, even though the appendix can be generally identified as the site of origin.

4.6 Clinical presentation

The clinical manifestations of PMP are manifold. The classic sign is increased abdominal girth, which is caused by the accumulation of gelatinous ascites. The disease may sometimes be presented as “jelly belly” at the time of diagnosis. This is characteristic of the progressive state of disease in which the most of the abdomen is filled with ascites and tumour [23]. The chief complaint may be a newly-onset hernia as a consequence of increased intra-abdominal pressure. The abundant tumour may sometimes cause intestinal obstruction. Appendicitis may be the first manifestation of PMP. PMP lesions may also cause pain in the flank(s) due to obstruction of the ureter. Mucinous ascites may flow into the scrotum mimicking hydrocele. A large proportion of diagnoses are established co-incidentally: ultrasonography or CT-scan performed for any reason may reveal PMP. A typical finding is an ovarian mass found by transvaginal ultrasonography during routine gynaecological examination. During surgery, there might be unexpected deposits of mucus on the peritoneal surfaces.

4.7 Diagnostic methods

4.7.1 Radiological imaging

The gold standard for imaging PMP is computed tomography (CT), preferably with a contrast medium [29-31]. A CT may identify appendiceal mucocele in the early stage of the disease that can often be calcified and accompanied by mucus in the ileocaecal region. Progressing PMP is characterized by visceral and mesenteric sparing. Gastric antrum, lesser omentum, left subphrenic region, spleen, rectum and sigma are entangled by the tumour mass in the terminal stage of the disease. The primary tumour is rarely seen in the appendix at this stage. What is emblematic for the terminal stage is the aforementioned scalloping of the hepatic margin, and a displacement or compression of the intestines by the abundant mucus [23].

There are reports of the usefulness of ultrasound in the diagnosis of PMP [32, 33]. Echogenic ascites reflect the gelatinous nature of the fluid. The ascites is not mobile. Bowel loops are positioned centrally and posteriorly by the surrounding mass instead of floating freely. There may be a septated appearance to the ascites. Scalloping of the hepatic margin may be present in PMP, although other conditions that cause peritoneal spread may also induce this effect [32, 34]. Some authors have noted ultrasonography to be more beneficial for guide paracentesis [30]. The needle biopsies commonly produce less information than expected when no mucus or no cells within the mucus are aspirated. The quantity of epithelial cells within the mucus may be low even in high-grade disease, thus the final evaluation about the grade should not be made from biopsy alone [23].

The role of colonoscopy in the diagnosis of PMP is minimal. Tumours of the appendix are infrequently seen in colonoscopy and rarely yield a diagnostic biopsy [35].

4.7.2 Tumour markers

Circulating tumour markers have a prognostic value in PMP. They are also useful instruments in follow-up after surgery.

Koh et al. reported that the elevation of carbohydrate antigen 19-9 (CA 19-9) was negatively associated with OS in patients with the DPAM subtype of PMP [36]. Not only did the marker manifest positivity above the laboratory reference range (>40 U/mL), the absolute level of CA 19-9 was also prognostically significant. The prognostic value of CA 19-9 was not noted in the PMCA group of the same study. Van Ruth et al. have suggested CA 19-9 to be a more useful tumour marker than CEA for follow-up [37]. Those authors also noted that patients who never attained normal CA 19-9 levels after surgery were more prone to recurrence of the disease at 1 year (53% vs 15%).

Canbay et al. noted that elevated carcinoembryonic antigen (CEA) levels measured preoperatively associated with the peritoneal cancer index (PCI, Heading 5.2.4.3), with cytoreductive surgery scores, with progress free survival and with OS [38]. Moreover, Alexander-Sefre et al. noted that CEA was the most commonly elevated tumour marker in PMP, which was contrary to that suggested about the usefulness of CA 19-9 [39]. Those authors also noted that elevated CEA prior to complete tumour removal predicted early recurrence. The 2-year recurrence free interval in those with elevated and normal CEA, were 53% and 94%, respectively.

Taflampas et al. analyzed the elevation of preoperative serum marker levels of CEA, CA19-9, and CA12-5 in a study with a population of 519 patients [40]. The patients with normal marker levels (131/519) had significantly higher mean disease-free (DFS) and OS than those who had elevated levels of all three markers (109/519). The mean DFS and OS figures were 168 months and 125 months for patients with normal markers versus 65 months and 55 months for patients with all three markers elevated.

4.8 Treatment

Some authors of an early study had suggested follow-up only, without surgery, for PMP, but this former approach did not achieve wide acceptance [9]. Systemic chemotherapy (SC) alone has generally not been considered useful in PMP, because therapeutic levels of cytostatic agents are hard to attain in tumour cells surrounded by mucin accumulations [23, 41-43]. Surgical debulking has traditionally been the standard approach for patients with PMP [44, 45]. The debulking protocol is consisted for the surgical removal of gross disease. Complete radicality is uncommon, however, and relapses will develop in most cases. The relapses lead to increasingly difficult subsequent operations, after adhesions, scarring, and distortion of the anatomy has developed and the disease has progressed. The timing of iterative operations is driven mostly by symptoms. In the end, further surgery is impossible. The short-term results are rather favourable with 53% - 85% OS at 5-year follow up [44, 45]. However, the 10-year OS figures are more modest with survival rate of 21% - 32% [44, 45].

4.8.1 Complete cytoreductive surgery

The peritonectomy procedures, as originally described by Sugarbaker, consist of six different resections that are used to remove the tumor from peritoneal surfaces [46]. These resections are as follows: greater omentectomy-splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy-cholecystectomy with stripping of the omental bursa, pelvic peritonectomy with sleeve resection of the sigmoid colon, and antrectomy. These procedures are used on every single patient to an extent that is sufficient for the removal of the tumour. (Figures 1-5).

During the operation, the extent of the disease and the radicality of the surgery is assessed and scored. The scoring systems are reported in detail (5.2.4). There are typical situations, when radical surgery is technically impossible. Indeed, tumour burden locating in the hepatic hilum or in the lesser omentum can be surgically unresectable. The extensively disseminated disease in the abdominal cavity that especially affects the small intestine may prevent radical surgery. Surgery with a radical end-result is a

fundamental part of successful combined therapy, as it is a prerequisite for the administration of HIPEC in most cases. If the tumour is not completely resected from the abdominal cavity during the cytoreductive surgery, the chemotherapeutic agent will not eliminate the disease. The cytoreduction is considered complete when residual tumour nodules are sized under 0.25cm at the most.

The current practice includes complete cytoreductive surgery to be followed by HIPEC. To the best of my knowledge, only one series about complete cytoreductive surgery without HIPEC has been published [47]. This retrospective series that emanated from New Zealand included 25 patients with PMP. The 5-year overall survival (OS) was 64% for the study population. The OS was 92% for those with DPAM pathology and 33% for those with PMCA.

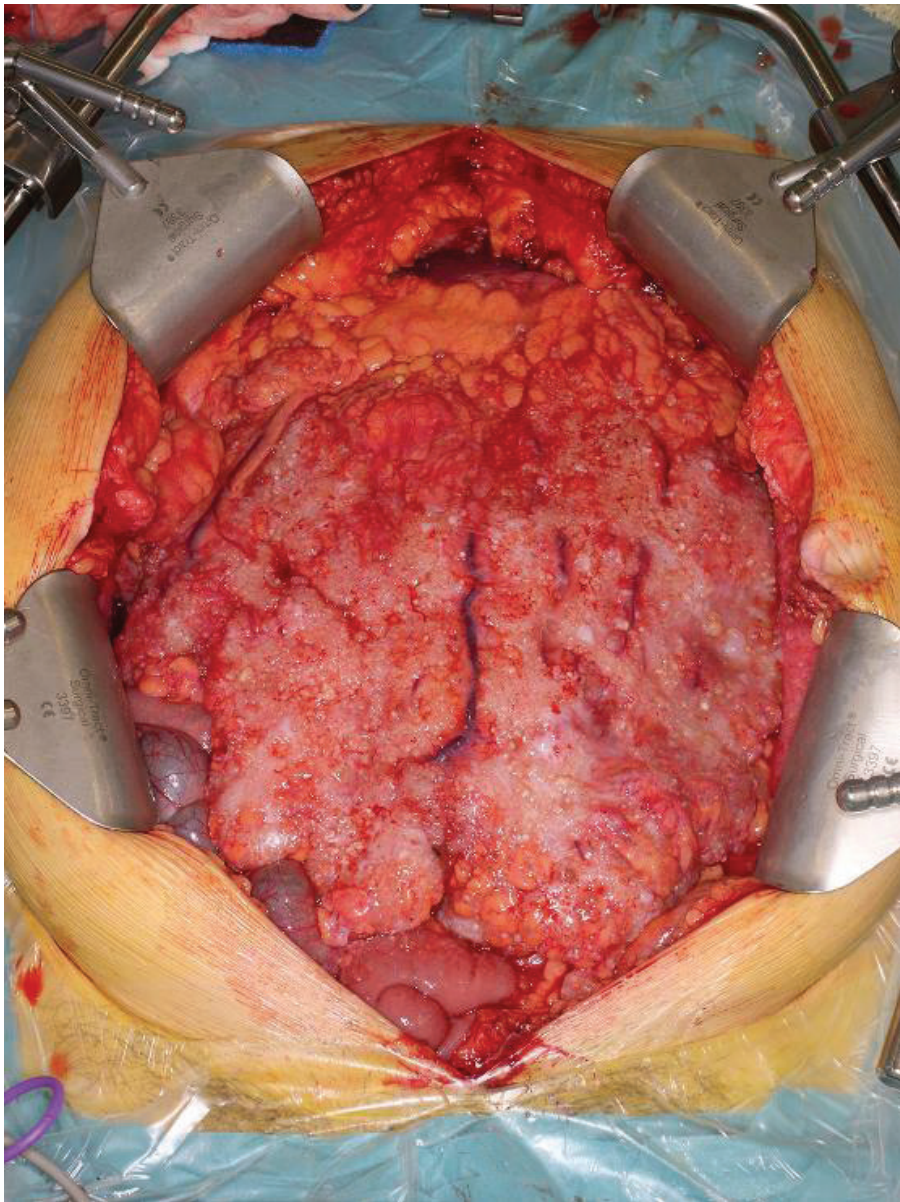
4.8.2 HIPEC

Intraoperative HIPEC was initiated at the Washington Hospital Center in 1992 [48]. The administration of a chemotherapeutic agent is timed after complete cytoreductive surgery is finished but before the construction of any anastomoses. Perfusion drains are placed through the abdominal wall at specific sites: the right subdiaphragmatic space, the left subdiaphragmatic space, and two in the pelvis (Figure 6). One additional spiral-ended (Tenckhoff) catheter is positioned within the abdomen. The Coliseum technique involves the elevation of the edges of the abdominal incision onto the self-retaining retractor by a running suture. A plastic sheet is then sewed to that suture and a cavity for chemotherapy is consequently formed. An incision in the plastic sheet is made and a portal is then attached, which allows manual access into the cavity (Figure 7). The perfusion is then performed for 90 min (Figure 8) and the surgeon secures the distribution of chemotherapeutic agent manually during that time. The chemotherapeutic agent used in the original setting was mitomycin C (MMC), as reported by Sugarbaker and his co-workers. The target temperature of the intraperitoneal fluid is 41°C to 42°C. There are at least three reasons, why chemotherapy solution should be heated: the tissue penetration of the chemotherapeutics is increased, the cytotoxicity of the chemotherapeutics is increased, and also because of the inherent anti-tumour effect of heat itself [49]. The manual

distribution of chemotherapeutic agent for 90 minutes affords several advantages: all surfaces of the abdomen and pelvis are uniformly affected by the chemotherapeutic agent and heat, diuresis can easily be monitored during the administration of agents that can affect renal functioning, hyperthermic therapy lasting 90 minutes causes mechanical disruption of cancer cells within blood clots and fibrin accumulations, and the moderately long time allows the normalization of many physiological parameters (temperature, haemodynamics, coagulation, etc.) [49].

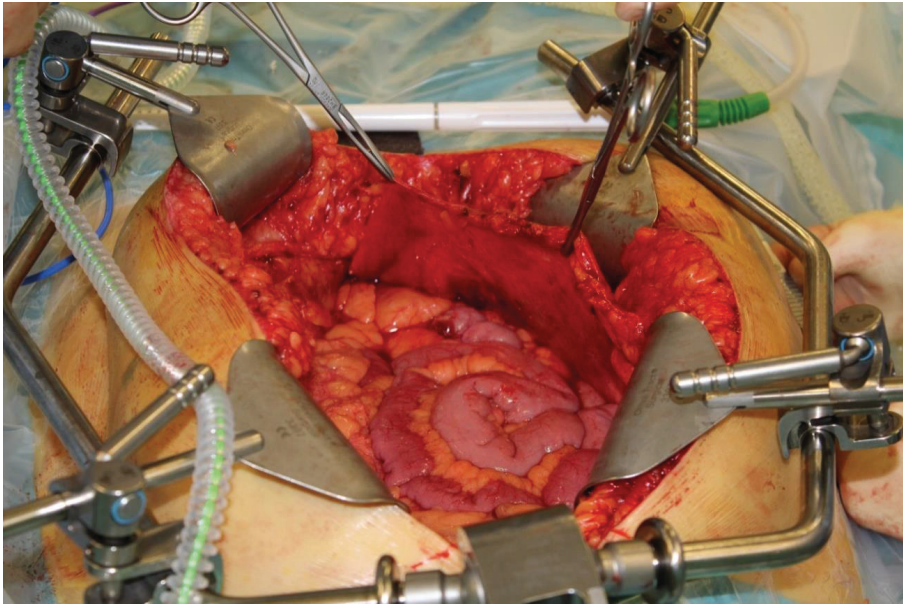
Elias et al. have reported other chemotherapeutic regimens for HIPEC than that originally described by Sugarbaker [50, 51]. For instance, Elias et al. described the use of oxaliplatin instead of MMC in different regimens. Intraperitoneal oxaliplatin was administered either alone, in combination with intraperitoneal irinotecan, or after administration of intravenous 5-fluorouracil (5-FU) with leucovorin. The 5-FU is assumed to potentiate the activity of oxaliplatin. The 5-FU and oxaliplatin cannot be administered simultaneously within the abdominal cavity because of the pH incompatibility. Thus, 5-FU is administered intravenously. The target temperature of HIPEC in their protocol was 43°C and the duration was 30 minutes. The cytotoxicity of various drugs for PMP cells was tested *in vitro* [52]. Those findings suggested a combination of cisplatin and doxorubicin for treating PMP. These results encouraged Andréasson et al. to perform HIPEC treatment for some patients using the combination of cisplatin and doxorubicin over 90 minutes [53].

Figure 1.

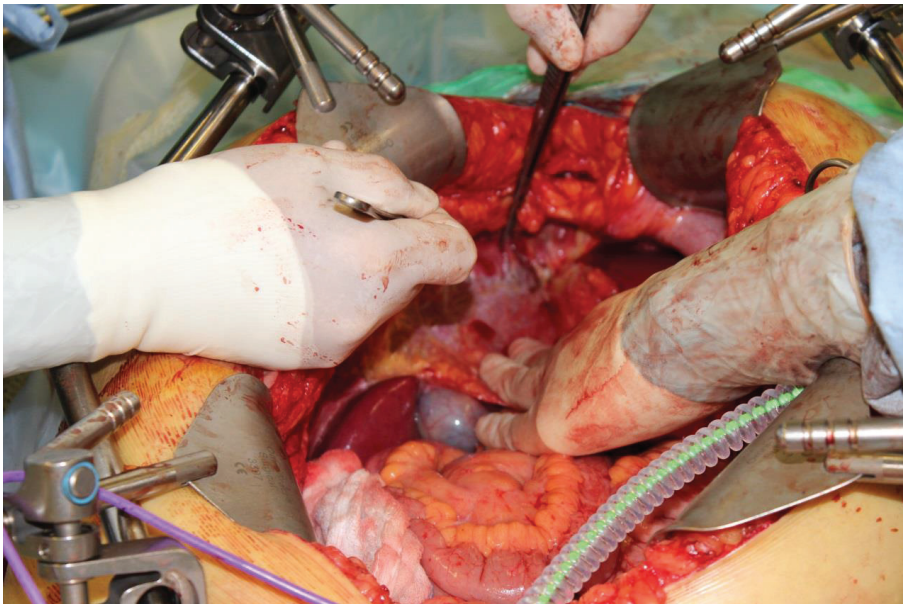


The view of PMP patient's abdominal cavity immediately after the midline incision and after the positioning of a retractor.

Figures 2 and 3.



Stripping the right anterior peritoneum.

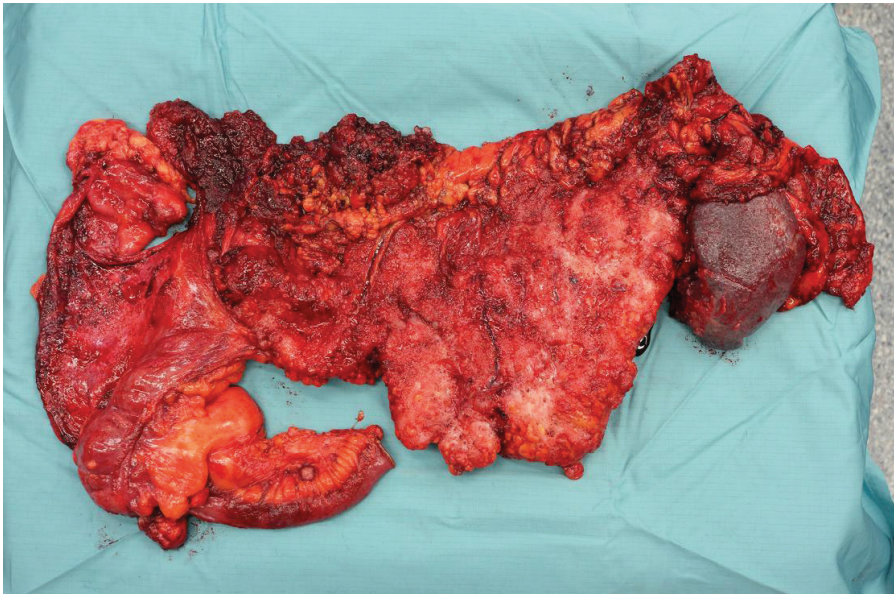


Stripping the right subphrenic peritoneum.

Figures 4 and 5.

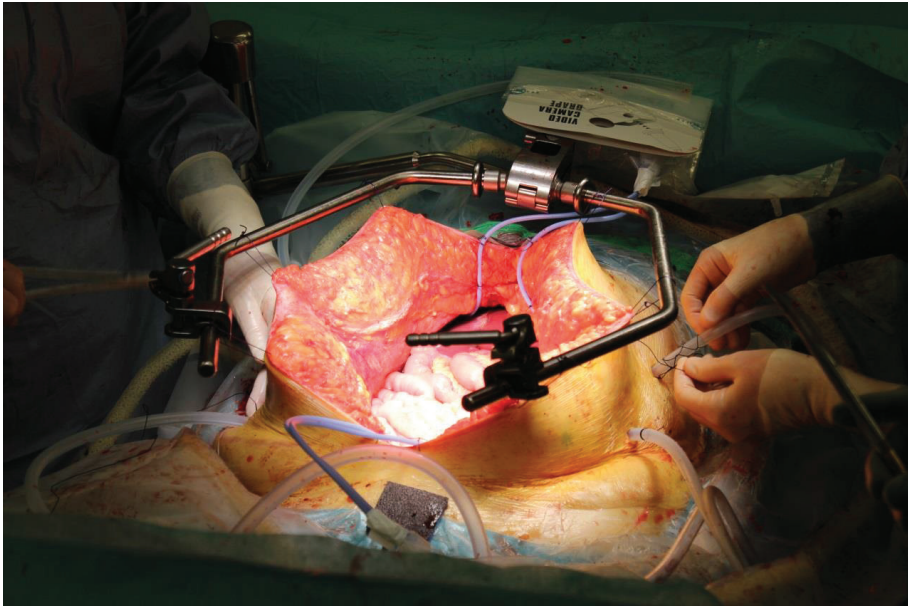


En bloc resection of the terminal ileum, the right hemicolon, and the right parietal peritoneum.

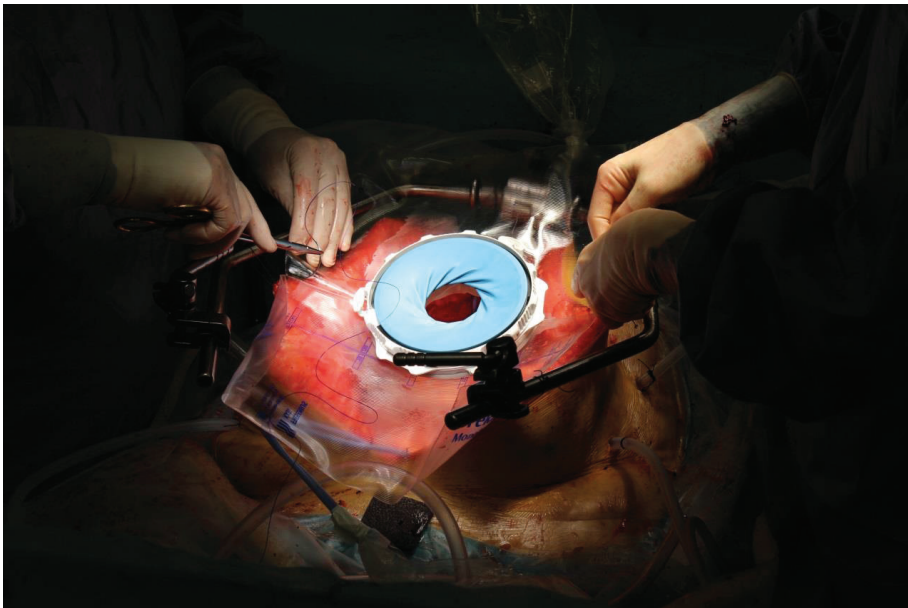


The resection of terminal ileum, colon, and spleen affected by PMP.

Figures 6 and 7.

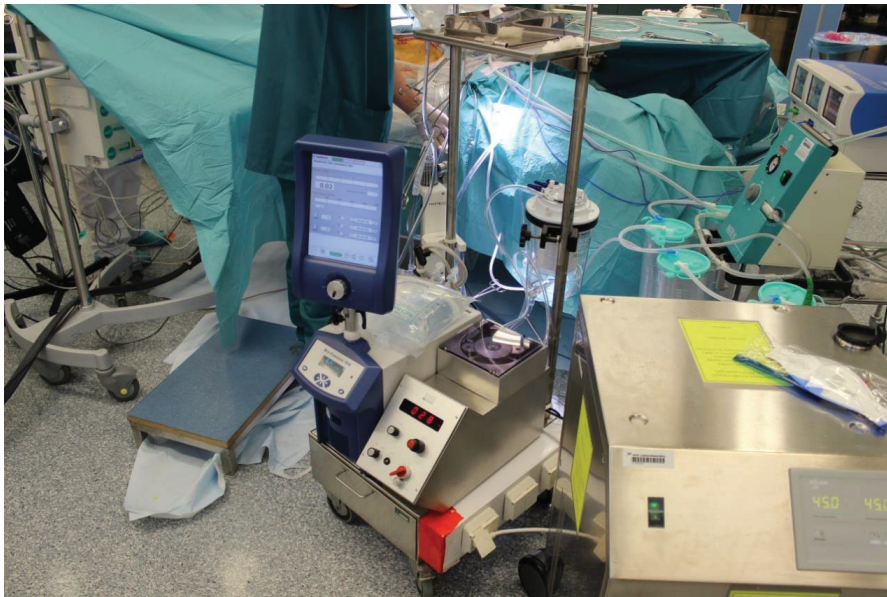


Placing the catheters for chemotherapy.



The closed Coliseum technique.

Figure 8.



The perfusion facility.

4.8.3 Complications of the complete CRS and HIPEC combined treatment

High rates of complications have been reported after the administration of CRS and HIPEC [53-60]. Non-surgical complications include *inter alia* neutropenia, sepsis, pleural effusion, respiratory insufficiency, and thromboembolism. Surgical complications include anastomotic leakage, bowel perforation, haemorrhage, fistula formation, bile leakage, abscess formation, and wound dehiscence. The complication rates of some studies are enlisted in table 2.

Sugarbaker et al. reported a series of 356 procedures with CRS and HIPEC [61]. In that series, grade IV adverse events occurred in 67 (19%) of the procedures. The distribution of those complications was as follows: haematological 28%, gastrointestinal 26%, cardiovascular 16%, pulmonary 9%, genitourinary 8%, infections 5%, neurological 4%, and IV catheter 4%. Events that resulted in a return to the operating room were recorded for 40 (11%) of the procedures. The distribution of causes for return to the operating room was as follows: fistula 29%, anastomotic leak 19%, compartment syndrome 19%, postoperative bleeding 18%, pancreatitis 3%, bile leak 3%, fasciitis 3%, urine leak 3%, and negative exploration 3%.

Thromboembolisms are featured complications in HIPEC [57]. Not only are deep venous thromboses encountered, pulmonary embolisms and portal vein embolisms also occur. Special attention should be paid to anti-thrombotic treatment during the perioperative course. The wearing of anti-embolic pump stockings in combination with intensified low-molecular weight heparin are offered with the purposes of avoiding such complications.

Neutropenia frequently follows HIPEC [62]. Intraperitoneal chemotherapy with MMC causes less toxicity than systemic administration. Even so, a 39% incidence of neutropenia was reported after such therapy by Lambert and co-workers in 2009 [62]. Those authors also noted that female gender and MMC dose per surface area were independent risk factors for MMC-induced neutropenia. Despite this, neutropenia was not found to be associated with an increased risk of operative mortality or increased

hospital stay. The only infection type neutropenia was associated with was urinary tract infection, but no other types were associated with neutropenia upon univariate analysis.

Anastomotic leak represents a typical gastrointestinal complication after CRS and HIPEC combined treatment, which results in a substantial portion of cases requiring re-operation [61]. The construction of any anastomoses is postponed till after the intraperitoneal chemotherapy has finished in order to avoid these complications. Hand-sewn seams are preferred over stapled seams.

Table 2.

Rate of complications after CRS and HIPEC.

Authors	Year	Country of origin	Center	Rate of any complications	Rate of major complications ¹
Kuijpers et al. [54]	2013	Netherlands	Multicenter	NA	34% ^{2 3}
Andreásson et al. [53]	2012	Sweden	Uppsala	47%	35%
Vaira et al. [55]	2009	Italy	Milan	45%	NA
Iversen et al. [56]	2013	Denmark	Aarhus	52%	NA
Youssef et al. [57]	2011	UK	Basingstoke	56%	7%
Elias et al. [58]	2010	France	Multicenter	NA	40%
Chua et al. [59]	2009	Australia	Sydney	NA	49%
Güner et al. [60]	2005	Germany	Hannover	36%	NA

NA, not available.¹CTCAE grade 3-4 or similar; ²69% were affected by PC of colorectal carcinoma and the remaining 31% suffered from PMP; ³Grade 5 was also included.

4.8.4 Systemic chemotherapy

The benefit of SC in patients with PMP is unknown because no prospective trials have been published [63]. The data concerning SC are discordant. Two rather old reports found the use of SC was not beneficial when used in conjunction with debulking surgery. Gough et al. reported that the use of SC had an adverse effect on OS in 56 patients treated by debulking surgery, radiation and/or chemotherapy upon analysis by a Cox model [44]. Smith et al. found no difference in survival rates between the patients who received operative treatment only and those who received postoperative SC in a series of 17 patients who had undergone palliative debulking surgery for PMP of appendiceal origin [43]. It is notable that the SC was delivered by very heterogeneous regimens within both these studies and some of the patients also received intraperitoneal chemotherapy. One of the largest retrospective reports about SC was obtained from a multicenter international study of 2298 patients with PMP of which 2054 had been treated by CRS and HIPEC [64]. SC was administered to 377 patients before the cytoreduction. They found that earlier chemotherapy treatment was an independent predictor of poorer progression-free survival (PFS) and OS as analyzed by the Cox model. Contrary to those reports of no or negative effect of SC, there are studies that report some benefit from SC. Shapiro et al. reported a series of 186 patients who were considered ineligible for CRS and/or HIPEC [65]. They noted a disease control rate of 56% with modern SC regimens. The authors of that study concluded that SC may have a role in a patient population that comprises suboptimal candidates for CRS and HIPEC, although they recognized a need for randomized trials. Farquharson et al. revealed that 38% of patients with advanced unresectable PMP benefited from SC as indicated by a reduction in mucinous ascites or a stabilizing disease [66]. Blackham et al. studied the role of SC in conjunction with CRS with HIPEC [63]. Postoperative SC seemed to improve PFS in patients with high-grade PMP treated by CRS and HIPEC in comparison with CRS and HIPEC alone (13.6 months vs. 7.0 months, $P=0.03$) and also in comparison with pre-operative SC (13.6 months vs. 6.8 months, $P<0.01$). On the other hand, the Blackham group's results did not support the routine use of perioperative SC in low-grade PMP (Median OS 107 months vs. 72 months, $P=0.47$).

In conclusion, there is limited evidence that SC is beneficial in advanced inoperable PMP and in high-grade PMP. Even so, the duration of SC and the preferable pattern in addition to the specific medication need further investigation. A randomized double blind trial would be optimal to meet this aim.

4.8.5 Results of complete CRS and HIPEC combined treatment

The results of some of the main studies regarding the CRS and HIPEC combined treatment published since 2005 are summarized in table 3. The main treatment protocol is generally rather similar in all the centers that provide HIPEC. Even so, there are specific differences in chemotherapy protocol, histological classification of the tumour, follow-up time, reporting of the surgical completeness, and so forth. Some centers only provide HIPEC for patients after complete cytoreduction [50]. Other centers proceed with HIPEC after complete and sometimes also after incomplete cytoreduction [53]. Some studies reported only for those patients with complete CRS followed by HIPEC. When only those cases that are successfully treated by HIPEC are reported and those with incomplete CRS are excluded, the results become biased. First, the results of the studies include only the successful cases are not comparable with those studies that also include cases with non-radical CRS. Second, when only successful cases are reported, the outcome of the CRS and HIPEC combined treatment are exaggerated.

The poorest outcome for 5-year OS shown in table 3 was obtained from a small German series that also included patients with non-radical CRS [60]. All 28 patients in the series received HIPEC. The study is not only the smallest series in the compared investigations, it is also the oldest and thus represents the early era of combined modality treatment. The best outcome was obtained from the Italian series of 53 patients, who underwent radical surgery combined with HIPEC [55]. The 10-year OS in that series was as high as 84.5%. A minority of the studies report 10-year OS figures, whereas the majority of studies report 5-year OS. The survival outcomes are not fully comparable because of the heterogeneity of the patient populations. Despite the lack of uniformity in the patient demographics of the different series, the conclusion of the comparison is clear. The survival rate is excellent for those patients who were able to undergo complete CRS and HIPEC combined treatments.

Table 3.

Summary of survival results after CRS and HIPEC combined

Authors	Year	Country of origin	Center	Number of patients with PMIP treated by CRS + HIPEC	5-year OS	10-year OS	Percentage of patients with no macroscopic residual tumour (R0 or R1)	Percentage of patients with complete CRS (CC-0 or CC-1)	Percentage of patients with unfavourable pathology of high grade or PMCA
Kuijpers et al. [54]	2013	Netherlands	Multicenter	300	65%	NA	80%	NA	16%
Andréasson et al. [53]	2012	Sweden	Uppsala	110	74%	NA	72%	NA	46%
Vaira et al. [55]	2009	Italy	Milan	60	94% ¹	84.6% ¹	NA	100%	NA
Iversen et al. [56]	2013	Denmark	Aarhus	29	73%	NA	NA	100%	14%
Youssef et al. [57]	2011	UK	Basingstoke	280	87% ²	74% ²	NA	100%	NA
Elias et al. [58]	2010	France	Multicenter	301 (255) ³	79% ⁴	NA	NA	93% ⁵	22% ⁶
Chua et al. [59]	2009	Australia	Sydney	106 (83) ³	75% ⁷	36% ⁷	NA	91% ⁵	10% ⁵
Güner et al. [60]	2005	Germany	Hannover	28	43% ⁸	NA	40%	NA	NA

NA, not available; ¹only 53 were included in the survival analysis because of otherwise short follow-up; ²the survival was calculated for 289 patients with complete CRS of which 280 received HIPEC; ³the first number represents the number of patients treated by HIPEC or early postoperative intraperitoneal chemotherapy (EPIC) and the number in parentheses represents the number of patients treated by HIPEC; ⁴the survival was calculated for 255 patients treated by HIPEC; ⁵the percentage is calculated from the number of patients treated by HIPEC or EPIC; ⁶only 266 were reported; ⁷the survival was calculated for 106 patients treated by HIPEC or EPIC; ⁸extrapolated from the Kaplan-Meier curve.

There are certain aspects that still require attention. There are a limited number of studies with a follow-up that exceeds 10 years. The natural progression of PMP is slow and consequently the true efficacy of HIPEC is only likely to emerge after a long follow-up time. The survival of patients treated by serial debulking may sometimes be rather favourable as well. Therefore, the debate on the efficacy of using HIPEC should still be continued. The long-term results of HIPEC must be widely evaluated. The whole patient population includes patients who are ineligible for HIPEC and who also should be included in that analysis. Only after such a critical and comprehensive analysis, would it be possible to draw valid conclusions about the efficacy of HIPEC. It is presumed that the CRS and HIPEC combined treatment can withstand the most critical evaluation when treating patients with PMP.

There were reports of several affecting factors upon analyzing the outcome in patients with PMP in detail. The extent of the disease is obviously a factor that has impact on the treatment. Elias et al. reported, that a PCI over 24 had a significant impact on the disease-free survival [50]. A high PCI value was found to be an independent factor for a poorer PFS in a large multi-center study reported by Chua et al. [64]. Smeenk et al. noted that the affected regions associated with decreased disease-specific survival (DSS) probability were the left subdiaphragmatic region and the subhepatic region [41]. In the case of tumour lesions that exceeded the size of 5cm and involved the small bowel, the DSS was affected. The histopathological grade of the tumour has also been reported to affect survival in many studies [20, 64, 67]. Dayal et al. reported that tumour morphology of a high grade was an independent negative prognostic factor as indicated by multivariate analysis [68]. The large multi-center study reported by Chua et al. showed that the histological subtype of PMCA was an independent predictor for a poorer outcome for both PFS and OS as evaluated by multivariate analysis [64]. Strong evidence supports that the surgical result has an impact on survival. Andréasson et al. reported a comparison between 110 patients treated by cytoreductive surgery and 40 patients treated by debulking surgery [53]. In that study, they adjusted for the following prognostic factors: sex, histopathology, PCI, Prior Surgical Score, type of surgery, intraperitoneal chemotherapy regimen, and surgical outcome. Those authors used a Cox proportional hazard model and found that only the surgical outcome had an impact on survival. The multi-center study reported by Chua et al. indicated that incomplete

cytoreduction (CC-2 or CC-3) was an independent predictor for poorer outcome for both PFS and OS in multivariate analysis [64]. Dayal et al. demonstrated a 10-year OS of 64% for patients who had undergone complete CRS in comparison with 22% for those who were maximally debulked [68]. Elevated serum tumour markers were found to have an effect on survival. Dayal et al. observed that elevated CA12-5 was a significant negative prognostic factor in univariate analysis [68]. Kusamura et al. documented that preoperative circulating tumour marker levels of CA12-5 > 125 U/mL and CA19-9 > 89 U/mL independently affected OS using a multivariate analysis Cox model [69]. Moreover, elevated preoperative CEA levels have been found to affect OS. in the Cox model reported by Canbay et al. On the other hand, elevated CA12-5 and synchronous elevation of all three markers of CA12-5, Ca19-9, and CEA were factors associated with early recurrence after HIPEC [70].

4.8.6 Follow-up after surgery

To the best of my knowledge, hitherto no scientifically evaluated follow-up protocol after HIPEC for the patients with PMP has been published. It is obvious that patients with PMP should be followed-up after surgery for the progression or recurrence of the disease and associated conditions. The suggested methods for follow-up after surgical treatment include physical examination, CT, and determining serum tumour markers [23].

Physical examination may reveal new tumour deposits in the scars or the abdomen, abdominal distension, or newly-onset hernias. Patients may have abdominal complaints that are related to relapse or to disease progression.

The natural choice for the imaging instrument is CT. First, it is considered the gold standard for imaging PMP and therefore it is also useful in follow-up. Second, practically every patient will have undergone CT prior to HIPEC. Consequently, there will be reference images stored to compare with during the follow-up. According to the consensus statement on the treatment of PMP, other imaging methods such as MRI, PET, or CT-PET have little or no value in follow-up after treatment [2]. PET provides limited value in the diagnostics of low-grade lesions, which is often the classification of

PMP [71]. MRI is more expensive and time consuming than CT. Some authors have suggested MRI, particularly for preoperative staging and classification purposes [72].

Pre-operative elevation of tumour markers is known to associate with an increased risk of recurrence and reduced survival after complete CRS [40]. The CEA and CA19-9 markers seem to be especially useful for the detection of progression [23]. The elevation of tumour markers after surgery usually signifies activation of PMP.

There is no definitive consensus on the timing of follow-up visits after surgery. A proposed starting point for further follow-up is three months after surgery, which includes CT, clinical examination, and serum tumour markers determinations. Follow-up visits should be biannual in the first year and yearly in the subsequent years. In the case of a suspected relapse, the examinations should be immediately performed regardless of the protocol [23].

In our center, the first follow-up visit is scheduled for three months after surgery, and it includes clinical examination and serum tumour markers (CEA, CA19-9). The second follow-up visit is at six months after surgery, and it includes clinical examination, serum tumour markers determination, and CT. The subsequent follow-up visits are repeated every six months for up to two years and they include the same examinations as for the six-month follow up visits. After two years follow visits are given annually. The total duration of the subsequent follow-up is considered individually for each patient and varies from five to ten years. Our aim is to optimize the balance with minimizing radiation, coping with hospital resources, and early detection of relapses.

4.9 Summary

Pseudomyxoma peritonei (PMP) is a clinical condition. The estimated incidence is 1-2 per million annually. The abdominal cavity is progressively filled by ascites and mucinous tumour. The symptoms and signs of PMP may include: an increase of abdominal girdle, newly-onset hernia, vague abdominal complaints, flank pain, bowel obstruction symptoms, appendicitis, ovarian mass and hydrocele. Moreover, many cases are diagnosed co-incidentally. The tumour is derived from the appendiceal epithelium in the vast majority of cases, but other origins have also been reported in a minority of cases, including: PMP arising from mature cystic teratoma, pancreas, urachus, colon, and ovaries have been reported. Many histological classification schemes have been proposed. According to the WHO 2010 definition, the tumour can be classified as low grade and high grade. The tumour causes organ malfunctioning, mostly by compression as the disease progresses. The disease is best treated by surgery. The classic surgical approach was to debulk the tumour iteratively until further surgery becomes impracticable. The contemporary approach comprises radical cytoreductive surgery (CRS). The CRS is immediately followed by hyperthermic intraperitoneal chemotherapy (HIPEC) during surgery. The CRS and HIPEC combined treatment was first introduced by Paul H. Sugarbaker from the Washington Cancer Institute. Improved survival has been reported for patients treated by CRS and HIPEC in combination. However, not all patients are eligible for combined CRS and HIPEC. If those patients who are not eligible for HIPEC are included in the analysis, then the survival outcome is not as good as it was when only the successful cases were included. Unbiased evaluation of the real benefits of the CRS and HIPEC combination is very important. The natural progression of PMP is slow, and the true efficacy of CRS and HIPEC combined is seen only after long-term follow-up.

5 The present investigation

5.1 Aims of the study

The main purpose of the present study was to analyze the diagnosis and treatment of PMP. Specific aims were:

1. To evaluate the outcome of patients with PMP that were treated by serial debulking.
2. To explore the clinical manifestations of PMP that lead to a diagnosis.
3. To analyze the feasibility of CRS and HIPEC combined treatments in patients with PMP.
4. To compare the outcome of serial debulking and CRS with HIPEC in consecutive patients with PMP for two time periods.

5.2 Materials and Methods

5.2.1 Patients

The protocols for studies III and IV was approved by the Helsinki university Central Hospital (HUCH) ethics committee (permission number 265/13/03/02/2011). Studies I and II were performed as retrospective chart studies and therefore without the need for ethics committee approval. All patients studied had the clinical condition of PMP. They underwent surgery or consideration concerning surgery between 1984 and 2011 in Helsinki University Central Hospital. Study I included 33 consecutive patients treated by the classic approach of serial debulking between the years 1984 and 2008. They all underwent surgery in our unit. Study II consisted of a consecutive series of 82 patients with PMP. The clinical presentation of PMP of those patients was analyzed. The patient population in study III comprised 90 patients who underwent consideration for CRS and HIPEC. Of those 90 patients, 87 were also included in study IV. The outcome of the

treatment was also analyzed in study IV. The outcome was then compared with the patient population of study I. The specific patient characteristics of studies I – IV are presented in table 4.

Table 4.

Characteristics of patients for studies I to IV inclusive

Study	I	II	III	IV
Patient number	33	82	90	33
Sex distribution	17 women (52%) 16 men (48%)	53 women (65%) 29 men (35%)	58 women (64%) 32 men (36%)	17 women (52%) 16 men (48%)
Tumour morphology	NA	NA	LG 57 (63%) HG 33 (37%)	NA LG 55 (63%) HG 32 (37%)
Median age at diagnosis (range)	50yr (25-73)	52yr (25-87)	58yr (30-87)	50yr (25-73)
Time period years	1984 – 2008	1984 – 2009	2007 – 2011	1984 – 2013
Median follow-up time (range)	4.7yr (0.4-17)	NA	NA	5.9 (0.6-21.4)yr 2.8 (0 – 5.5)yr

NA, not available; LG, low-grade tumour; HG, high-grade tumor; yr, years

5.2.2 Diagnosis and Classification

PMP is a clinical entity. The diagnosis of PMP in this study was based on operative findings, pathological sampling, and radiological investigations. The initial diagnostics were performed either in our unit or in referral units.

Histological samples were not reviewed, but the original pathological assessments were used in studies I and II. We performed a re-assessment for pathological samples for the patient population in studies III and IV. The cases were re-assessed using WHO 2010 criteria for classification. Cases with diagnoses other than PMP of appendiceal origin were excluded. The other origins for peritoneal carcinomatoses found in the re-assessment were: mixed adenoneuroendocrine carcinoma of appendix (MANEC), ovary, colon/rectum, ileum, and unknown. Those patients with malignant peritoneal mesothelioma and benign cystic mesothelioma were also excluded.

5.2.3 Treatment

Repeated interval debulking was the standard treatment protocol for patients with PMP (I, IV) before the adoption of the combination treatment of complete cytoreductive surgery followed by HIPEC. Complete tumour resection was the aim, particularly in the initial surgery, but only for those cases for which the disease was amenable for that procedure. The successive surgeries were performed, when the symptoms necessitated. The peritonectomy procedures were not notably performed. Maximal debulking surgery was also offered to those patients in the HIPEC era who were excluded from CRS preoperatively or who had undergone a non-radical attempt at CRS (III, IV).

The first patient received complete CRS followed by HIPEC combination for PMP in January 2008 (IV). After adopting HIPEC, every patient with demonstrable PMP were evaluated and considered for CRS and HIPEC combined (III, IV). When no medical or surgical contraindications were observed, an attempt at CRS to be followed by HIPEC

was scheduled (III, IV). Medical contraindications for CRS with HIPEC were poor overall status, severe co-morbidities, and, in limited cases, advanced age. The surgical contraindication that prevented an attempt at CRS with HIPEC was an extensively disseminated disease without any realistic probability for complete CRS upon examination by either radiological investigations or during prior surgeries.

The HIPEC was administered only after complete cytoreduction was achieved (III, IV). The chemotherapeutic agent was MMC at the standard dosage of 30mg/m². A modified version of the Coliseum technique was used for administering the chemotherapeutic solution [48]. The target temperature of intraperitoneal solution was 42 - 43°C and the duration was for 90 minutes. SC was not routinely used prior to or after HIPEC. Only a limited number of selected cases with non-radical surgery or with relapsed PMP received SCs.

5.2.4 Scoring systems

5.2.4.1 The Clavien-Dindo classification of surgical complications

Postoperative complications during the hospital stay were recorded and graded in study IV for those patients who had undergone surgery. The grading was performed according to the Clavien-Dindo classification of surgical complications published by Dindo et al. [73]. The streamlined classification is as follows:

- Grade I refers to any deviation from the normal postoperative course that does not need intervention.
- Grade II refers to complications requiring pharmacological treatment.
- Grade III refers to complications that require surgical, endoscopic or radiological intervention.
- Grade IV refers to life-threatening complications; and
- Grade V refers to a death of a patient.

When the patient had several complications, the most severe complication was reported.

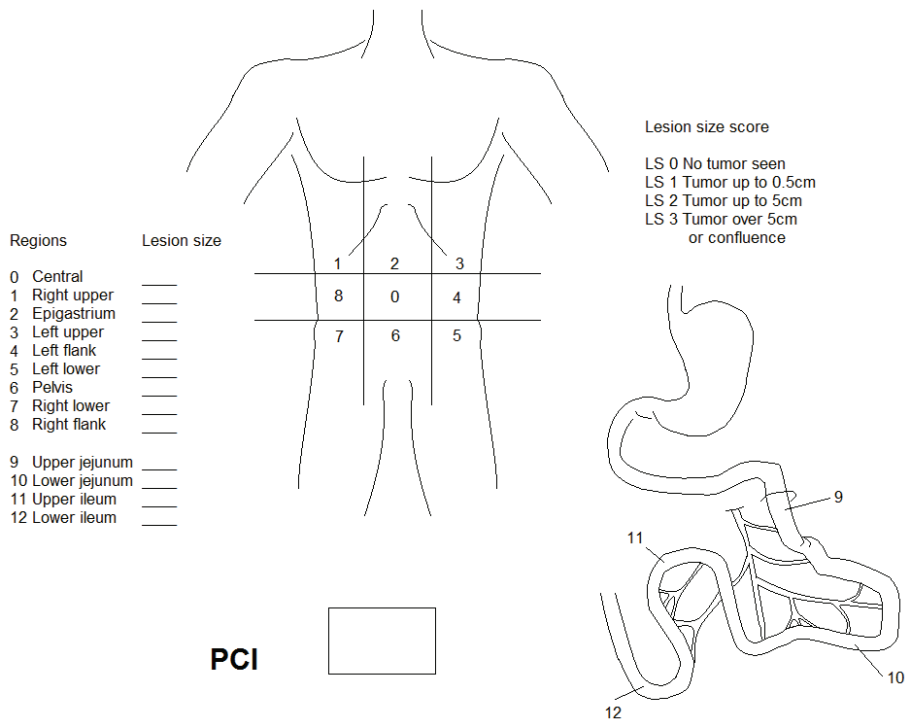
5.2.4.2 The completeness of cytoreduction scoring system

The radicality of cytoreductive surgery was assessed for those patients who underwent surgery with an intention of radical operation in studies III and IV. The radicality of surgery can obviously be scored only after an effort of cytoreductive surgery has been made. Our scoring was based on previously published cytoreduction scores [74]. The scoring was as follows: CC-0 signified that no visible tumour remained; CC-1 signified that tumours under 0.25 cm remained; CC-2 signified that tumours between 0.25 and 2.5 cm remained; CC-3 signifies that tumours over 2.5 cm remained. The scores CC-0 and CC-1 were further classified as radical and the scores CC-2 and CC-3 as non-radical.

5.2.4.3 The peritoneal cancer index (PCI)

The peritoneal cancer index was used to assess those patients who underwent an attempt at CRS and HIPEC in studies III and IV. The index was determined intraoperatively after exploration of the abdomen and pelvis [75]. The abdominopelvic area is divided into 13 regions that are numbered from 0 to 12. The presence or absence of tumour nodules in each of the 13 regions were determined. The size of the lesion in each region was also assessed. The lesion size was scored from 0 to 3: 0 indicated no visible tumour; 1 indicated nodules less than 0.5 cm; 2 indicated nodules between 0.5 and 5 cm; and 3 indicated tumour nodules over 5 cm. The summation of scores of each region resulted in the final PCI score. Thus, the maximum would be 39 (13 x 3).

Figure 9.



The PCI score.

5.2.4.4 Statistical analyses

The overall survival was analyzed according to the Kaplan-Meir survivorship method (I, IV). The end point was the death of a patient. The comparisons between the survival curves were assessed by a log-rank test (IV). The distribution of genders was tested by one-variable χ^2 test (II). Characteristics associated with successful HIPEC administration: age, CEA, morphology, and gender were tested by 2 x 2 χ^2 test (III), in addition to the proportion of patients with no-evidence of disease (IV). The comparison of populations was performed by Mann-Whitney U-test in the case of a delay between the diagnosis and assessment (III), in the case of a number of re-operations (IV) and the Student's t-test was used to compare means for PCI and age (III). The test for comparison of the means was chosen according to the Kolmogorov-Smirnov test of normality (III, IV). The 30-d mortality after the initial operation was tested by using the Fisher's exact test (IV).

5.3 Results

5.3.1 The outcome of the debulking series (I)

A consecutive series of 33 patients with PMP underwent a total of 113 operations. The study did not include patients who had non-surgical treatment only. The mean number of operations per patient was 3.4 (range 1 – 10). Re-operation resulting from a major complication occurred for 3/113 surgeries. Those re-operations were indicated for haemorrhage within the abdominal cavity, anastomotic leakage, and dehiscence of the surgical wound. No postoperative deaths were recorded after the initial operation. The 30-d operative mortality for all 113 operations was 2.7% (3/113). Those three deaths respectively occurred in the terminal phase of PMP after the 3rd, 4th, and 8th operation. The 5- and 10-year OS rates were 67% and 31%, respectively. At the completion of the follow-up in study I, there seemed to be four patients with no evidence of disease.

5.3.2 Clinical manifestations (II)

Clinical presentation of PMP at the first appointment was recorded and grouped for 82 consecutive patients. The sex distribution was: 53 women (65%) and 29 men (35%). The groupings for symptoms and signs were (Table 1 in study II): abdominal pain (19 patients); acute abdomen (17 patients); newly onset hernia (10 patients); increased abdominal girth (14 patients); coincidental diagnosis (11 patients); and other (11 patients). The presumed diagnoses of the 82 patients prior to initial surgery were recorded. Suspected PMP was the cause for the initial operation in 23/82 cases (28%) and formed the most common indication for surgery among men with 13 of 29 cases (45%). Suspected ovarian tumour was the most common cause for surgery in females and accounted for nearly half 26/53 (49%) of the cases. Thirty-five patients underwent a CT-scan, of which PMP was demonstrable in 18 cases (51%).

5.3.3 The feasibility of HIPEC (III)

A prospective series of 90 patients was offered HIPEC when feasible. HIPEC was successfully delivered to 56 of 90 patients (62%). An attempt at HIPEC was performed on 69 patients (77%), conventional surgery without an attempt at HIPEC was delivered to 11 patients, and 10 patients were referred back or transferred to palliative care without surgery. A radical end-result was achieved in four of those 10 cases who had received conventional surgery.

Low-grade tumour morphology ($P=0.013$), age under 65 years ($P=0.004$), and preoperative serum carcinoembryonic antigen (CEA) level under $5.0\mu\text{g/L}$ ($P=0.003$) were associated with successfully delivered HIPEC. Mean PCI was lower (18.9 vs. 32.6, $p < 0.001$) and age was younger (54.3 years vs. 61.6 years, $p = 0.003$) in patients who underwent successful HIPEC than for those patients who did not. No gender-related effect was detected. The mean delay between the diagnosis and the treatment decision was longer among patients who were treated by other methods than HIPEC, although the difference was not statistically significant (24.1 months vs. 18.3 months, $P=0.124$).

5.3.4 Comparison of serial debulking and HIPEC (IV)

The HIPEC-era group consisted of 87 patients who were offered HIPEC when feasible after the adoption of HIPEC as a treatment for PMP in Helsinki University Central Hospital in 2008. The control group of 33 patients that were treated by serial debulking was formed before the HIPEC era began.

Of 87 patients, 56 received HIPEC, 12 were treated non-radically while attempting HIPEC, 9 were debulked, and 10 were referred back or transferred to palliative care without surgery. The 33 patients in the control group were treated uniformly by serial debulking. The results after treatment are represented in table 5.

There was no difference in 5-year OS between the debulking-era group and the HIPEC-era group. The mean number of re-operations was lower for the HIPEC-era group (1.6 vs. 0.8, $P=0.01$). There were more patients who subsequently seemed to present with no evidence of disease in the HIPEC-era group than in the debulking-era group (54% vs. 24%, $P<0.01$), although the follow-up time was shorter for the HIPEC-era group. The 30-day operative mortality rates were low for both groups and no statistically significant difference was found (2.6% vs. 0%, $P=1.0$). Two patients died after the initial operation in the HIPEC-era group. Of these, one patient died of peritonitis after debulking surgery, whereas the other died of multi-organ-failure after receiving CRS with HIPEC.

It is remarkable that the number of patients who presented with no evidence of disease at completion of follow up in the debulking-era group was higher in the updated data (IV) than in the original data (I) (8/33 vs. 4/33, $P<0.01$). This is possibly because in those cases with altered status, the radical surgical result may have not been achieved in the initial operation but only after subsequent operation(s) that took place after the completion of study I.

Table 5.

Outcome after treatment and OS at 5-year and at 10-year follow-up.

Group	Debulking-era group	HIPEC-era group
5-year OS	67%	69%
10-year OS	39%	NA
30-d mortality after initial operation at our unit	0 / 33 (0%)	2 / 77 (2.6%)*
Complications after surgery	NA	No complications 24.7%* Grade I 2.6% Grade II 11.7% Grade III 50.6% Grade IV 7.8% Grade V 2.6%
The mean number of re-operations	1.6 ± 0.3	0.8 ± 0.2*
The number of patients with no evidence of disease at the end of follow-up	8 / 33 (24%)	47 / 87 (54%)
The median follow-up time	71 months	33 months

NA, not available; *calculated only for 77 operated patients.

5.4 Discussion

5.4.1 Diagnosis and preoperative assessment (II, III)

The diagnosis of PMP is difficult. The clinical symptoms and signs of PMP are varied and are commonly preoperatively misdiagnosed as other conditions (II). Sometimes the diagnosis is definite only after pathological assessment and even then a definitive diagnosis may still be challenging for the pathologist. According to our unpublished data, a substantial portion of cases with PMP had their classification altered when the grading was systematically reviewed.

Abdominal pain was the most common symptom of PMP in our study (II). The diagnosis of acute appendicitis before the initial operation was suspected in 9% of the cases. As many as 49% of the female patients underwent their initial operation for a suspicion of ovarian tumour. In the series reported by Esquivel and Sugarbaker, suspected appendicitis was the most common presentation and it accounted for 27% of the cases [13]. Those authors also noted that 44% of the women in their study had their diagnosis of PMP confirmed while being evaluated for an ovarian mass.

There are some particular problems in the diagnostics of PMP. The diagnosis is sometimes established only after pathological assessment and not pre- or intra-operatively. In such cases, the intra-operative staging of the disease may have been done inadequately. When a surgeon thinks he is operating on a patient with an acute appendicitis, he is not likely to perform a staging laparotomy routinely. The accuracy of CT is limited in revealing small tumour deposits on the peritoneal surfaces (II), therefore a 2nd-look laparoscopy for staging purpose is sometimes a good option. This especially applies to those cases for which serum tumour markers are elevated after the surgery and the result of CT-scan is normal. What has to be remembered is that even negative diagnostic laparoscopy is not definite because a small lesion can still exist undetected within the abdominal cavity. Staging laparoscopy may also have a role in determining the feasibility of HIPEC. In particular, affluent tumour deposits of the

small intestine prevent HIPEC can be revealed by staging laparoscopy. It is probable that those patients with the high-grade disease, and thus a more invasive and aggressive disease, would benefit from a staging laparoscopy before an attempt at HIPEC [76]. The purpose of laparoscopy in such cases would then be to avoid unnecessary laparotomies, and on the other hand, enable necessary and timely HIPEC treatments. However, the abundant amounts of mucin that are often present may hinder the laparoscopic evaluation of the tumour load. Regardless of the method used, the preoperative assessment of the feasibility of HIPEC is difficult to achieve (III). The final success of complete cytoreduction is always evident only after an attempt at one has been carried out.

5.4.2 Debulking surgery (I, IV)

Debulking surgery is a form of cytoreductive surgery, with the intention to reduce tumour bulk maximally. Sometimes, even a radical surgical result is achieved. Survival analysis in study I showed a 10-year OS rate of 31%. The survival data were updated, after five more years of follow-up, in study IV and the 10-year OS rate was found to be 39%. This might suggest that more effort was focused on achieving maximal cytoreduction in the later cases of the series than in the earlier cases. The philosophy of treating patients with PMP has undergone a drastic change after adopting the complete cytoreductive surgery followed by HIPEC combination modality. It is probable that the pursuit of maximal cytoreduction is still achieved in patients treated by debulking in the 21st century even though the surgical approach is not as aggressive as in it is for complete cytoreduction.

Miner et al. reported a series of 97 patients with PMP that had been treated by function preserving debulking [45]. They achieved optimal cytoreduction in 55% of the cases. Even though, PMP recurred in 91% of cases and 10-year OS was 21%. As much as 90% of those patients who survived over 10 years had low-grade histology. Our 10-year OS rate of 39% is substantially more favourable than that reported in their study. The

proportion of patients who presented with no evidence at the completion of follow-up is also higher in our series (24% vs. 12%).

The combination of cytoreductive surgery and HIPEC is presently considered as the treatment of choice for PMP [2]. The precise role of HIPEC in the combined modality treatment is actually unknown. Some authors stated that HIPEC has a particularly critical role in achieving long-term remission [77]. Patients treated successfully by combined modality treatment manage well, but as to what part of this is due to the optimal cytoreduction and what is due to HIPEC remains unclear. A study from New Zealand reported a 5-year survival rate of 64% in patients treated by CRS without HIPEC [47]. The outcome of such a study reporting a patient population treated by CRS alone without HIPEC could be compared with an investigation reporting patient population treated by CRS and HIPEC combined. A large multi-center study on 2298 subjects, already cited under heading 4.8.4., reported 5-year OS of 74% for patients treated by CRS and HIPEC [64]. At first sight these two studies appear to be comparable. Unfortunately, unknown numbers of patients were excluded from both these studies. Patients treated by palliative debulking were excluded from the series from New Zealand, as were the patients whose disease was considered technically unresectable. Thus, upon closer inspection the survival results of the two studies are not fully comparable. The series from New Zealand about CRS without HIPEC is the only one that has been published to the best of my knowledge. Evidence from comparisons between CRS only treatment with that of the CRS and HIPEC combined treatment is very scarce. Indeed, a prospective comparison between CRS only and CRS with HIPEC combined would be the best way to clarify the effects of HIPEC. Such a comparison would be informative, but would raise ethical questions, because HIPEC is presumed to benefit patients with PMP. Nevertheless, patients who are not eligible for the combined modality treatment may still benefit from maximal debulking surgery [68]. We noted the rather favourable 5-year survival rate of 67% (IV) in debulked patients. Debulking is still an option in a proportion of patients who are ineligible for the combined modality treatment, because of medical contraindications or whose disease is technically unresectable.

5.4.3 CRS and HIPEC combined (III, IV)

Although the CRS and HIPEC combined treatment is currently considered as the treatment of choice for patients with PMP, it is impracticable to deliver it to every patient with PMP. In our study (III), complete cytoreduction was achieved in 60 out of 90 cases (67%) and HIPEC was successfully delivered to 56 (62%) patients with PMP. Ten patients (11%) were treated non-operatively, but all had had an earlier limited operation. A prospective database from Basingstoke England included 748 patients who underwent surgery for PMP [68]. The number of patients who did not undergo surgery was not reported. Complete cytoreduction was achieved in 543 (73%) cases and HIPEC was delivered in 448 (60%) cases. A large multi-center study on 2298 patients excluded an unknown number of patients who were deemed medically unfit to undergo radical surgery or whose disease was considered technically unresectable preoperatively [64]. Optimal cytoreduction (CC-0 or CC-1) was achieved in 1904 cases (83%). Intraperitoneal chemotherapy (HIPEC, EPIC or both) was administered in 2094 cases (91%). Therefore, a proportion of patients had not undergone complete CRS before receiving intraperitoneal chemotherapy. Consequently, the protocol of that study is fundamentally different from our protocol of delivering HIPEC only to patients after optimal CRS. A series from Uppsala included 152 patients who underwent surgery for PMP [53]. Two cases with “open and close” laparotomy were excluded. The number of excluded patients who were preoperatively considered unfit for surgical treatment was unknown, however. Cytoreduction with no macroscopic residual tumour was achieved in 79 patients (52%).

The results of these studies are typical findings after delivering complete CRS. Some studies do not report the original number of patients who were preoperatively excluded or excluded even after an attempt at surgery. What must be emphasized is that in such studies, the accurate assessment of success of CRS remains undetermined. Whether or not the actual number is reported, there is the phenomenon that a substantial and similar portion of patients with PMP are not eligible for complete CRS in every study and in every situation. The comparison of the rate of complete CRS delivered is difficult to ascertain between the centers. Health care systems are different. Some tertiary care

centers receive unselected referrals whereas the others accept only referrals of patients who have already been evaluated as fit for surgery. In some health care systems, debulking surgery may also be delivered in secondary care hospitals whereas tertiary care hospitals may have the sole responsibility for any attempt at delivering CRS and HIPEC.

Our 5-year OS rate of 93% for those who had undergone CRS and HIPEC is very good and fully comparable with the results of other centers. Three other European studies that included only patients with complete CRS are those reported by Vaira et al. from Italy, Iversen et al. from Denmark, and Youssef et al. from the UK [55-57] who reported 5-year OS rates of 94%, 73%, and 87% respectively. There are also series published that show lower rates of complete cytoreduction and some of those reported more modest survival rates as well. Andreásson et al. reported a 5-year OS of 74% with 72% complete CRS rate, Kuijpers et al. reported a 5-year OS of 65% with 80% complete CRS rate, and Güner et al. reported a 5-year OS of 43% with 40% complete CRS rate [53, 54, 60]. One of the largest studies that reported 10-year OS rates is the international multi-center study published by Chua et al. who obtained a 10-year OS rate of 63% for 2298 patients [55, 64]. One of the highest survival rates was reported by Vaira et al. who obtained a 10-year OS rate of 84.5% [55, 64].

We noted major complications (grade 3-5) in 47 (61%) for operated patients during the HIPEC-era (IV). The rate is considerably higher than the rate of 24% reported by Chua et al. [64]. Though, the most common complication in our study was pleural effusion, which resulted in 36 grade 3 complications. If those cases whose only complication was pleural effusion that can be relatively easily treated by puncture were to have been excluded, the major complication rate would have been much more favourable. The high numbers of grade 3 complications found in the present study were categorized to the Clavien-Dindo classification system, which is rigorous for the pleural effusion complication. For example, Common Terminology Criteria for Adverse Events (CTCAE) V4.03 would have rated postoperative pleural effusion aspirated by radiologist as only a grade 2 complication. It should also be noted that the grade 4 complication rate in our study was only 7.8%, whereas Chua et al. observed a grade 4

complication rate of 10% [64]. The postoperative mortality rate of 2.6% is acceptable, since only two postoperative deaths occurred during the HIPEC-era of which one was recorded after CRS and HIPEC combined treatment and the other after debulking surgery alone. Chua et al. observed a comparable postoperative mortality rate of 2% [64].

5.4.4 Comparison of the two modalities

When the whole population of patients with PMP was included in the analysis, there was no difference in short-term survival between the serial debulking method and CRS and HIPEC combined treatment. When only those patients who had received both CRS and HIPEC, are included in the analysis, the survival benefit is evident even after the rather short follow-up of five years. It is possible that given the slow progression of the disease a follow-up lasting more than five years would also reveal a survival benefit even when patients with unsuccessful HIPEC are included in the analysis.

The present study noted, that more patients presented with no evidence of disease in the HIPEC-era group than for the debulking-era group. This might suggest that the number of patients who had undergone a curative treatment is also higher. The natural progression of the disease is slow, therefore some of the patients currently presenting with no evidence of disease may still suffer a relapse in the future. Consequently, the final evaluation of the curative potential of CRS with HIPEC combined modality would only be apparent after long follow-up times.

The number of re-operations was lower among patients who underwent CRS and HIPEC in comparison with those who underwent serial debulking only. This finding is plausible. The intention of serial debulking is more palliative in intent than radical therefore the need for a succeeding operation is more urgent than when a radical end-result had been achieved. On the other hand, the complication rate for HIPEC is usually higher than the complication rate for debulking surgery and complications often

necessitate re-operations over and above those required for disease progression. Regardless of this, the number of re-operations in our study was actually lower in the HIPEC-era group.

These findings demonstrate that HIPEC can be considered the treatment of choice for selected patients with PMP.

5.4.5 Possible sources of bias in the present study

Classification of PMP is known to be challenging. A pathologist's re-assessment was not performed in studies I and II, thus we cannot exclude the possibility of diagnostic bias in those studies. If the pathological samples in studies I and II had been screened, some of the cases would probably have been deemed PMP of non-appendiceal origin.

Our unit was the only facility that provided HIPEC in Finland during the 2008 to 2013 period (studies III and IV). The treatment of PMP in Finland prior to that period was not centralized (studies I and II). Even after the commencement of HIPEC treatments in Finland, the numbers of patients treated in primary and secondary care units remains unknown. It is still possible, that patients in poor condition, or with disseminated disease at the time of diagnosis, were not referred to a tertiary care unit. Consequently, it is nearly impossible to conduct a study that involves every patient with PMP in our health care system.

5.4.6 Where to treat patients with PMP?

The combination of CRS and HIPEC is expensive, requires a high level of specialization, consumes hospital resources, and is challenging even in optimal circumstances. It is obvious, that HIPEC should be performed in specialized tertiary care units only. On the other hand, serial debulking surgery is less demanding on

hospital resources. Moreover, there is no evidence to suggest that the only facility that provides debulking surgery should be a tertiary care unit. Nevertheless, the assessment as to whether or not to attempt HIPEC should only be taken and carried out in specialized centers. The final decision about the treatment modality is often taken intra-operatively during an attempt at HIPEC. Therefore, the concept of the strict centralization of treatment of patients with PMP is the most plausible approach for successfully treating this challenging disease.

5.4.7 Future studies

The present study did not reveal survival differences in OS rates between the debulking-era group and the HIPEC-era group after 5 years of follow-up (IV). However, the rate of patients who presented with no evidence of disease was higher for the HIPEC-era group. Thus, it is probable that those patients with no demonstrable PMP will survive longer than those with the disease. The natural progression of PMP is slow, thus the true survival benefit of the combined CRS with HIPEC treatment will become apparent only after follow-up lasting more than 5 years. After a prolonged follow up, the updated survival figures of both debulking-era and HIPEC-era groups should be compared.

Since the adoption of HIPEC in Finland, the number of referrals has shown a huge increase when compared with the number of referrals during the debulking era (IV). According to our unpublished data, the number of new cases of verified PMP of appendiceal origin exceeds the expected incidence in Finland. This effect is not explained by the PMP cases being diagnosed earlier and then only recently referred to our unit. The incidence of newly-diagnosed cases, in particular, is greater than the observed incidence of 1-2 / 1 000 000 annually [14]. This finding should be further analyzed and the age-adjusted incidence should be determined.

Apart from patients with PMP, patients with other peritoneal malignancies have received CRS and HIPEC combined treatment in our unit. Selected patients with peritoneal mesothelioma, MANEC, carcinosis of colorectal and ovarian aetiology are also treated using the combined modality treatment. The outcome of those surgeries

should be analyzed and compared with each other and with the results of the other centers providing the same treatments.

Our unit has collected a comprehensive database of patients with PMP. In addition to surgical data pathological samples were also collected during the present investigation. The present investigation noted that patients with low-grade histology managed better than those with high-grade histology (III, IV). It would be of interest, to find whether there were other factors than histological grade that affect survival. The wide pathological database implemented during the present investigation will enhance further immunohistochemical studies of the samples collected. For example, protein expression patterns of the samples would be interesting to study. Those patterns would include protein expression of V600E mutated BRAF, MLH1, MSH2, MSH6, SMAD4, and p53. It is possible that some of those proteins that show high frequencies of abnormal immunostaining are associated with survival as an independent factor.

5.5 Conclusions

1. The 5-year OS of patients treated by serial debulking is comparable with those of patients treated by cytoreductive surgery and HIPEC combined modality, when the whole patient populations were included in the analysis (I, IV).

2. The diagnosis of PMP in the subclinical early phase is difficult and rarely achieved. Careful patient examination including CT is highly recommended prior to the initial operation if there is any suspicion of intra-abdominal tumour (II).

3. Only two thirds of patients were eligible for complete cytoreduction and HIPEC combined treatment. The other one third of patients required treatment by other methods (III).

4. Although the 5-year survival rates of serial debulking and HIPEC are comparable, there are advantages to using HIPEC. Patients successfully treated by CRS and HIPEC manage well. The proportion of patients who presented with no evidence of disease was higher in patients treated by CRS and HIPEC combined than in patients who received serial debulking only at short follow-up time. This might indicate that there will be a survival benefit in favour of HIPEC in longer follow-up (IV).

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8 Corrigenda to original articles

I

This corrigendum is in reference to the manuscript **Survival of patients with pseudomyxoma Peritonei treated by serial debulking** Colorectal Dis 2010; 868-873, DOI: 10.1111/j.1463-1318.2009.01947.x, by P.Järvinen et al. In the published version of abstract (results) the number of operations should be “3.4” instead of “3.2”. A corrected version of the table is displayed below:

The patients underwent an average of 3.4 ± 0.4 operations (range 1–10).

III

This corrigendum is in reference to the manuscript **Feasibility of Radical Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy For Pseudomyxoma Peritonei of Appendiceal Origin** Scand J Surg 2013;102:145-151, DOI: 10.1177/1457496913490463, by P. Järvinen et al. In the published version of Table 3 the headings “Mean age” and ‘Mean PCI’ were interchanged. A corrected version of the table is displayed below:

TABLE 3. Comparison of means in patients undergoing successful HIPEC and other treatment modalities.

	Mean age ± S.E.	Median	(Range)	Student's t-value	P	N
HIPEC	54.3 ± 1.27	54	(30-73)			56
No HIPEC	61.6 ± 2.18	61	(36-87)	3.09	0.003	34
Total						90
	Mean PCI ± S.E.	Median	(Range)	Student's t-value	P	N
HIPEC	18.9 ± 0.83	20	(5-29)			56
No HIPEC	32.6 ± 1.64	34	(16-39)	7.24	<0.001	13
Total						69*
	Mean delay† ± S.E.	Median	(Range)	Mann- Whitney U	P	N
HIPEC	18.3 ± 3.86	7	(0-149)			56
No HIPEC	24.1 ± 7.82	3.5	(0-191)	1136.5	0.124	34
Total						90

HIPEC = hyperthermic intraperitoneal chemotherapy. S.E. = Standard error. PCI = peritoneal cancer index. *PCI was determined only in 69 patients who underwent an attempt at combined modality treatment. †Delay between diagnosis and assessment for feasibility of HIPEC is presented in months.

IV

This corrigendum is in reference to the manuscript **Comparison of serial debulking and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei of appendiceal origin** *Int J Colorectal Dis* 2014;29:999-1007, DOI: 10.1007/s00384-014-1933-8 by P. Järvinen et al. The unit in the legend should be “months” instead of “years” in the published version of Figure 4.

