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HIPECology

Aspects of Postoperative Morbidity Following the HIPEC Procedure

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Abstract
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Peritoneal surface malignancy (PM), regardless of the dissemination site, was once considered a terminal condition. However, the introduction of a surgical approach with cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) with or without early intraperitoneal chemotherapy (EPIC) shifted the attitude from managing the symptoms of PM to disease treatment with curative intent. The magnitude of this combined therapy leaves the patients at risk for a diverse range of postoperative morbidities. Moreover, some small cohort studies argued that combining HIPEC with EPIC is associated with a higher risk of postoperative complications compared to HIPEC alone. The overall aim of the thesis was to investigate postoperative morbidity following the management of PM with CRS and HIPEC ± EPIC.

We investigated readmission morbidity within 6 months after CRS and HIPEC, using a national population-based register. The results of this study showed that morbidity causing HIPEC-related readmission was higher than expected, with almost half of the interventions occurring outside the HIPEC centre. Gastric resection and advanced age are independent predictors of morbidity and readmission. We analyzed postoperative coagulopathy and the risk for venous thromboembolic events (VTE) in a prospective study. Results revealed that significant postoperative changes in coagulation biomarkers occur with dynamic changes over 10 days postoperatively. The incidence of symptomatic VTE was low. Residual tumor at completion of surgery, and elevated D-dimer on day 2, were independent risk factors for postoperative VTE. Postoperative morbidity following HIPEC + EPIC was compared to morbidity following HIPEC alone in our propensity score matched study. Results showed that HIPEC + EPIC is associated with a prolonged hospital stay (LOS), but there was no statistically significant relevant increase in postoperative morbidity, reoperation rate or incidence of readmission. Finally, we also analyzed the impact of different strategies of intraoperative fluid management during CRS and HIPEC on postoperative outcomes. Goal-directed therapy (GDT) is associated with significantly improved LOS despite an increase in morbidity in some patients. GDT management does not affect the postoperative risk for hemorrhage, although the choice of an oxaliplatin-based HIPEC does. Personalized GDT based on patients' characteristics and surgery should be utilized during the management of CRS and HIPEC patients.

Keywords: CRS, HIPEC, readmission, EPIC, coagulopathy, VTE, goal-directed therapy (GDT), postoperative hemorrhage, oxaliplatin.

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Sic Parvis Magna"

Glory from Small Beginnings

-Sir Francis Drake

To Nadine, Dominic and Sophie, the source of my eternal happiness, to my family and kind helping friends. To the most beautiful soul that ever walked the planet, Mariam Al Khalifa: rest in peace. To Mother Earth for hosting us when no other planet could.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Dranichnikov, P., Graf, W., Cashin, PH. Readmissions after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy a national population-based study. *World J Surg Oncol*, 2020;18(1):67

II. Dranichnikov, P., Mahteme, H., Cashin, P., Graf, W. Coagulopathy and Venous Thromboembolic Events Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol.* 2021 Nov;28(12):7772-7782

III. Dranichnikov, P., Graf, W., Cashin, P. Morbidity Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastasis With or Without Early-Postoperative-Intraperitoneal Chemotherapy: A Propensity Score-Matched Study. Article in press. *Eur J Surg Oncol*. 10.1016/j.ejso.2022.02.004

IV. Dranichnikov, P., Semenas, E., Graf, W., Cashin, P. The Impact on Postoperative Outcomes of Intraoperative Fluid Management Strategies During Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Manuscript

Contents

Abbreviations

5-FU	5-Fluorouracil
APTT	Activated Partial Thromboplastin Time
CC0	Complete Cytoreduction
CCS	Complete Cytoreduction Score
CI	Confidence Interval
CRC	Colorectal Cancer
CRS	Cytoreductive Surgery
DPAM	Disseminated Peritoneal Adenomucinosis
DVT	Deep Vein Thrombosis
EPIC	Early Postoperative Intraperitoneal Chemotherapy
FFP	Fresh Frozen Plasmas
GDT	Goal-Directed Fluid Therapy
GI	Gastrointestinal Tract
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
IBD	Inflammatory Bowel Disease
ICD	International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive Care Unit
KPS	Karnofsky Performance Status Scale
LOS	Length of In-hospital Stay
MMC	Mitomycin C
N/A	Not Applicable
OR	Odds Ratio
PCI	Peritoneal Cancer Index
PE	Pulmonary Embolism
PIPAC	Pressurized Intraperitoneal Aerosol Chemotherapy
PM	Peritoneal Surface Malignancy

PMCA	Peritoneal Mucinous Carcinomatosis
PMP	Pseudomyxoma peritonei
PRBC	Packed Red Blood Cells
PSM	Propensity Score Matching
PT-INR	Prothrombin Time
SD	Standard Deviation
SMD	Standardized Mean Difference
SVV	Stroke Volume Variation
VTE	Venous Thromboembolic Events

Introduction

Peritoneal surface malignancy (PM), regardless of the dissemination site, was once considered a terminal condition, which was treated with systemic chemotherapy with palliative intent.[1, 2] PM is relatively rare as a primary disease.[3] However, it is more common as a disseminated malignancy from colorectal carcinoma, appendiceal neoplasms with pseudomyxoma peritonei, gastric cancer and advanced ovarian carcinoma. The introduction of the surgical approach with cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the mid-nineties shifted the attitude from managing the symptoms of PM to disease treatment with curative intent. There are now several randomized trials within the area of PM treatment, for ovarian, colorectal and gastric cancers. [4-13] CRS and HIPEC are performed at special centers located in major hospitals worldwide. The referral rate depends on the number of HIPEC centers present in each specific country. In Sweden, treatment with HIPEC started at Uppsala University Hospital (*UAS*) in 2003. Currently there are four Swedish HIPEC centers – UAS, Karolinska Hospital (Stockholm), Sahlgrenska University Hospital (Gothenburg), and Skåne University Hospital (Malmö-Lund).

Patients undergoing CRS and HIPEC often suffer from a disseminated malignancy to multiple peritoneal sites covering several intraabdominal organs.[14] The combination therapy of CRS and HIPEC is considered as standard treatment for PM of appendiceal origin, peritoneal mesothelioma [15, 16], and colorectal cancer.[17-20] However, treatment with CRS and HIPEC is a highly challenging procedure often associated with prolonged duration of surgery and multivisceral resections including peritonectomy procedures, in order to visibly clear the abdominal cavity and pelvis of malignant nodules.[1, 21-24] Thus, the majority of patients undergoing this combined procedure are at higher risk for intraoperative tissue and vascular damage, which often results in large volume blood loss and thus requires significant use of blood product support.[25] In addition, the prolonged postoperative care leaves patients undergoing CRS and HIPEC at high risk for a wide range of postoperative morbidities, in particular abdominal infection, anastomotic insufficiency, intraabdominal hemorrhage and thromboembolic complications. In general, morbidity following CRS and HIPEC varies in presentation. Some occurs within days postoperatively even before discharge, while other issues may be diagnosed later, months after the first discharge, such as gastrointestinal fistulas.

The definition of early versus late morbidity is complicated by the fact that the length of in-hospital stay (LOS) varies vastly with reported ranges from 7 to 118 days.[26, 27] The risk for prolonged in-hospital care after surgery, and the risk for rehospitalization for other similar complex gastrointestinal cancer surgeries such as pancreaticoduodenectomy and esophagectomy, have been well investigated.[14, 28-31] Chua et al. (2009) suggested that morbidity after CRS and HIPEC is similar to that of other major gastrointestinal surgeries, such as a Whipple's procedure.[32] Despite that fact, the frequency and tendency of rehospitalization for patients after CRS and HIPEC has been poorly investigated.[14]

Therapy in addition to CRS and HIPEC had been tested during a certain period of time by administering early postoperative intraperitoneal chemotherapy (EPIC). However, many institutions worldwide, including UAS, terminated the use of EPIC based primarily on results from French retrospective studies suggesting higher morbidity rate for patients treated with HIPEC + EPIC compared to those treated with HIPEC alone.[33, 34] All published studies are retrospective and most reported increased morbidity when adding EPIC after CRS and HIPEC. Soucisse et al. (2019) argued that the current retrospective evidence is entirely conflicting and encouraged ongoing studies to clarify EPIC's role in the treatment of patients with PM.[35] Before being able to evaluate the efficacy of EPIC in future trials, the added morbidity of the procedure when combined with HIPEC needs to be further elucidated.

The Healthy Peritoneum

The peritoneum is the largest and most complex serosal membrane of the human body. The healthy peritoneum plays an active part in almost all intraabdominal activities such as supporting the movements of intraabdominal organs, and assessing the balance of the abdominal cavity. It is involved in the inflammation process as well as contributing to the formation of postoperative fibrotic adhesion.[36] The peritoneum, however, is a target for metastasis from primary tumors of intraabdominal organs mainly of the gastrointestinal tract (GI), and the reproductive or genitourinary tracts due to the anatomical location. Although there are reported cases of peritoneal involvement from extra-abdominal primary tumors, those cases are uncommon.[37]

Basic knowledge of the healthy peritoneum is essential in order to have a better understanding of disease processes and malignant peritoneal involvement as well as the management of adverse events.

Embryology of the peritoneum and the peritoneal cavity

The development of the peritoneum starts in the fifth week of gestation at the gastrulation stage.[36] The embryonic construction of the gastrointestinal tract begins with the development of entoderm into a tube within the coelomic cavity, acquiring a single layer of mesodermal cells. These cells evolve from the space between the ectoderm and the endoderm. The posterior mesoderm merges into the dorsal mesentery, which eventually constructs the visceral peritoneum. Figure 1 demonstrates the entodermal canal within the layers of the mesoderm and ectoderm. The entoderm is attached posteriorly by the dorsal mesentery and anteriorly by the ventral mesentery. Mesodermal cells, which emerge to be the peritoneum at a later embryonic phase, line the coelomic cavity (which evolves later to the peritoneal cavity).[38]

The anterior mesoderm (splanchnic mesoderm) merges into the ventral mesentery which gradually disappears completely, leaving the liver's ligamentum falciforme as the only residue (Figure 2-a).

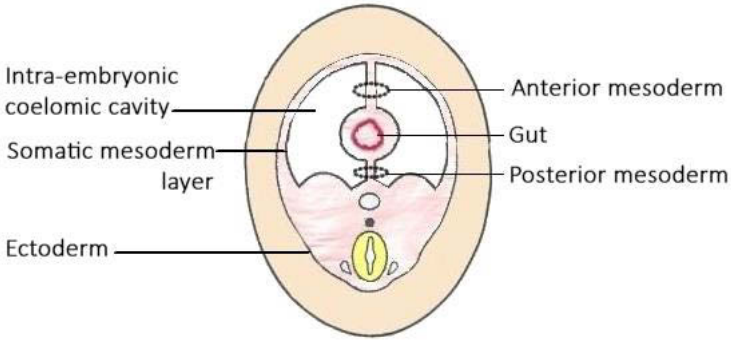
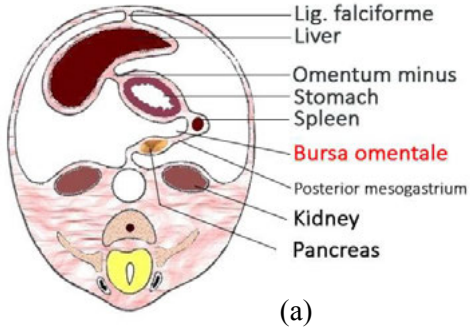
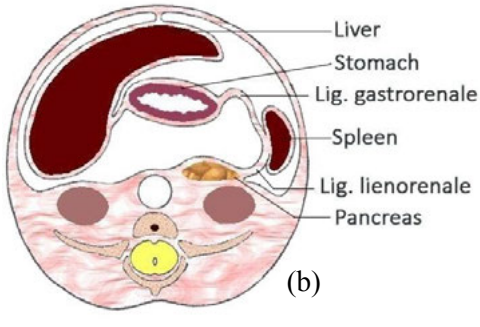


Figure 1 – Schematic image shows the entodermal canal within the layers of the mesoderm and ectoderm.[38]



(a)



(b)

Figure 2 – **(a)** Schematic image demonstrating the formation of the liver in the anterior mesentery in later embryonic phase. [39] **(b)** Schematic image of an abdominal configuration in the adult shows how the movement of liver to the right, the rotation of the stomach, spleen, ligamentum lienorenale and pancreas produce the borders of the bursa omentale.[38]

This anterior mesentery emerges into the ligamentum falciforme and the omentum minus which adhere the liver to the stomach. The spleen and dorsal part of the pancreas form in the posterior mesentery. The formation of the mesogastrium creates a folding sac with the posterior mesentery and forms the bursa omentale. In the retroperitoneum, the kidneys and adrenal glands emerge one on each side.

The liver emerges from the septum transversum (from which the diaphragm evolves), and gradually moves into the coelomic cavity carrying an investment of peritoneum. These small attachments of the liver to the septum transversum of the peritoneum construct the two ligaments of the liver: ligamentum triangulare and ligamentum coronarium (behind which are the "bare areas" of the liver) (Figure 3).

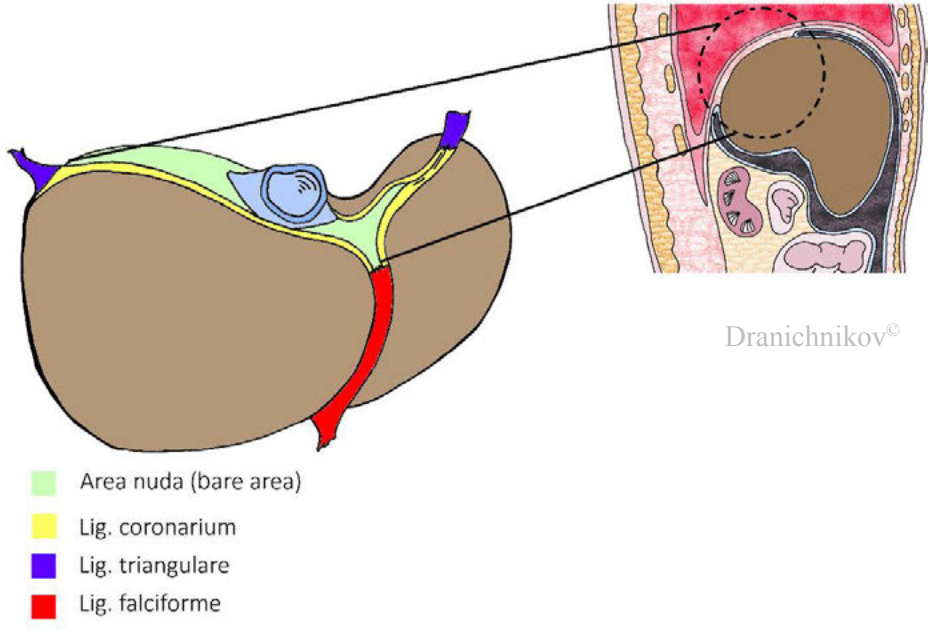


Figure 3 – Transvers illustration of the main ligaments of the liver demonstrating the anatomical localization of the area nuda (bare area) of the liver.

Blood vessels develop and supply the various early viscera through the posterior or dorsal mesentery.[38] The outcome of the gonadal ridges' proliferation and the migration of epithelial cells through the underlying mesenchyme throughout the sixth gestational week is the formation of indifferent gonads. The surface epithelium of the future gonads develops from the parietal mesothelium. In males, the gonads proliferate and form the future testes. In females the gonads continue to enlarge after splitting the future ovaries until they merge and shortly after develop into the reproductive organs, urinary bladder and the superior part of the vagina. The complex folding process of the parietal

mesothelium of the gonads with the underlying developing organs results in a perfectly covering layer of the peritoneum.[36]

The two portions of omentum, ligamentum gastrohepaticum and ligamentum gastroduodenale, develop from the anterior attachment of the mesentery limited to the liver and dorsally stomach, esophagus, and duodenum. The omentum minus is formed by the rotation of the stomach and duodenum and the posterior movement of the pancreas (Figures 2-a and 2-b).

The two pancreatic buds (the ventral and the dorsal) join together at the level of the head during the rotation of the duodenal C-loop. In the posterior mesentery the spleen and bursa omentale develop with the spleen being carried laterally. Eventually, the whole posterior mesentery containing the pancreas fuses with the posterior peritoneum.

The anterior wall of the bursa omentale consists of the omentum minus, parts of ligamentum gastroduodenale and ligamentum hepatoduodenale, the posterior wall of the stomach, the ligamentum gastrocolicum, and the mesocolon. The posterior wall of bursa omentale is enclosed by the peritoneum over the top of the pancreas. During the rotation of the bowel and the colon, the mesentery of the mesocolon moves posteriorly forming the retroperitoneum (Figure 4). The retroperitoneum to the side is divided into three parts: the anterior pararenal, posterior pararenal, and perirenal spaces. By the end of the fusion, these spaces remain intact and conform to the traditional anatomic concepts of the retroperitoneum and the peritoneum.[38]

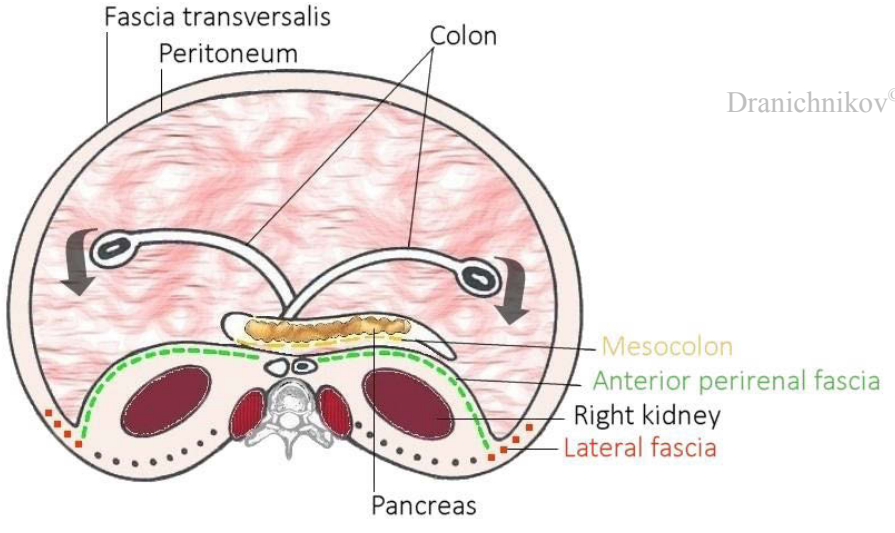


Figure 4 – Schematic illustration demonstrates the formation of the retroperitoneal colonic space.

Anatomy

The peritoneum is a thin, double-layered serosal membrane which covers the surface of the peritoneal cavity and its mesenteries (Figure 5). The peritoneum is continuous in males, resulting in a closed peritoneal cavity and discontinuous in females, resulting in a physiological opening at the ostia of the oviducts which allows communication between the peritoneal cavity and extraperitoneal pelvis, a communication which allows disease and metastasis extension from the extraperitoneal pelvis into the peritoneal cavity.[40]

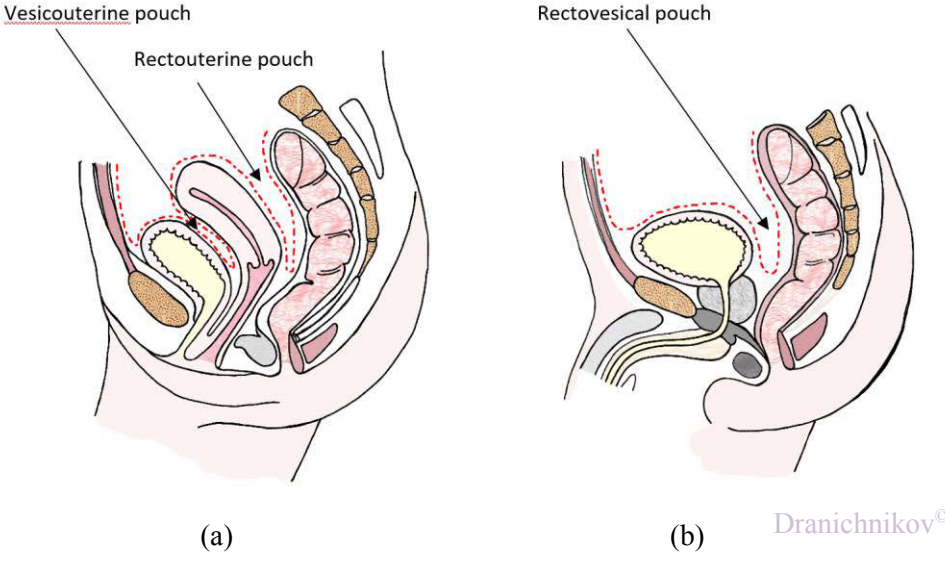


Figure 5 – A schematic sagittal illustration of the anatomy of the healthy peritoneum in the pelvic region of the female **(a)**, and male **(b)**.

Histology

The peritoneal serosal membrane is identical to other serosal membranes such as the pleura, pericardium, and tunica vaginalis which explains why similar tumours that affect the peritoneum can also be found in those organs.[41] A cross-section of the peritoneum is illustrated in Figure 6.[36] The structural composition of the peritoneum is very similar in both the visceral and parietal peritoneum. It consists mainly of 3 distinctive layers: the mesothelium, a basal lamina and the submesothelial stroma.[36]

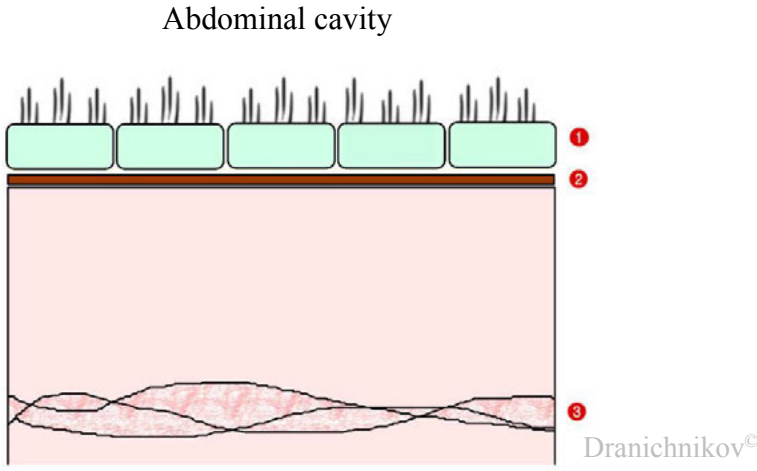


Figure 6 – (1) Mesothelial cells, (2) Basal lamina, (3) Submesothelial stroma.

Macroanatomy

The peritoneum is considered to be the largest serous membrane, with an estimated surface area of 1.8 m^2, that encloses the peritoneal cavity, with the exception for its ends close to the uterine tubes in females (Figure 7). It covers the viscera of the abdomen and pelvis either partially or completely.[42, 43] In general, the peritoneum is divided into two surfaces, the parietal peritoneum and the visceral peritoneum. The parietal peritoneum accounts for 30% of the peritoneal surface and covers the inner surface of the abdominal wall, while the visceral peritoneum, which accounts for about 70% of the total peritoneal surface, covers the visceral organs through a combination with the outer serosal layers of the organs (Figure 7).[36, 44]

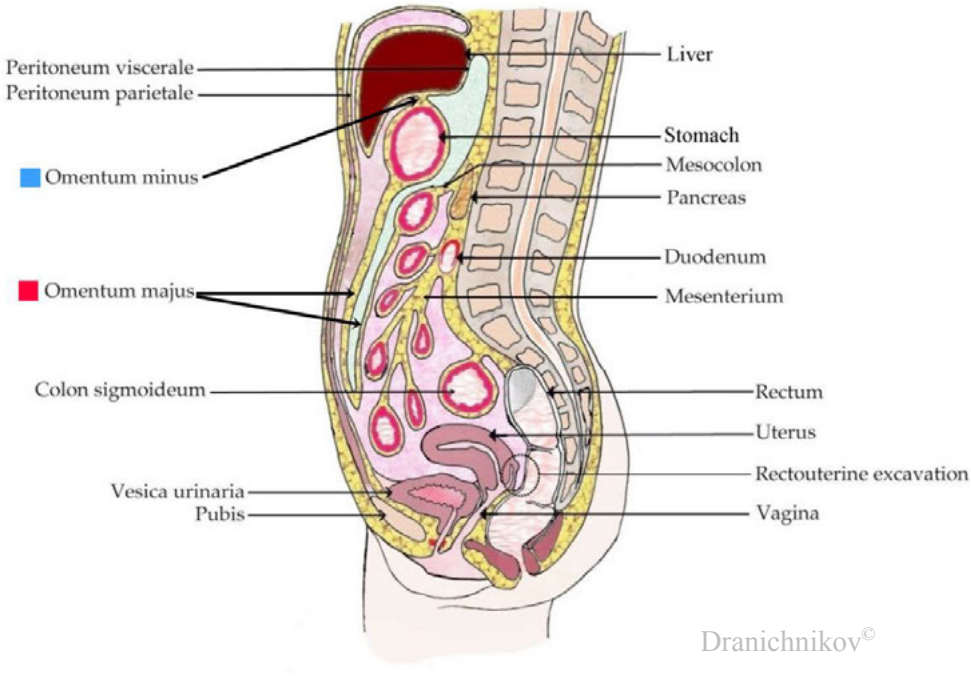


Figure 7 – Schematic sagittal section of the abdomen in the adult female illustrating the anatomy of the peritoneal surface including the anatomical localization of the omentum majus (red) and the omentum minus (blue).

In the female, the peritoneum runs in line with the reproductive organs and forms deep supportive tissue over the entire tuba uterina. This part of the peritoneum is mostly composed of mesovarium, mesosalpinx and the mesometrium, which is to some extent different when compared to the peritoneum lining the abdominal walls and the visceral organs. The peritoneum, however, becomes discontinuous at the end of the **fimbriae region of the tuba uterina**. Conversely, in the male the peritoneum is a completely closed sac.[36]

Blood and lymphatic circulation of the peritoneum

The peritoneum receives no more than 1%-2% of the cardiac outflow with an estimated total effective blood flow between 60 and 100 ml/min. The parietal layer of the peritoneum gets its blood supply mainly from the intercostal, epigastric and iliac arteries and drain the outflow into vena cava inferior. The visceral peritoneum gets its blood supply from the splanchnic, celiac and superior and inferior mesenteric arteries and drains into the portal vein.

The peritoneal outflow into the portal vein results in first-pass hepatic metabolism for all drugs and other solutes that are absorbed through the visceral peritoneum.[45]

The thoracic duct and the right lymphatic duct supply about 80% of all the lymphatic drainage of the abdominal cavity.[36]

Coagulation Cascade in a Nutshell

This doctoral thesis will investigate complications after CRS+HIPEC treatment of peritoneal metastases. Two important complications that will be examined are related to the coagulation cascade – venous thromboembolisms and postoperative hemorrhage. Consequently, the coagulation cascade is explained in more detail in this section.

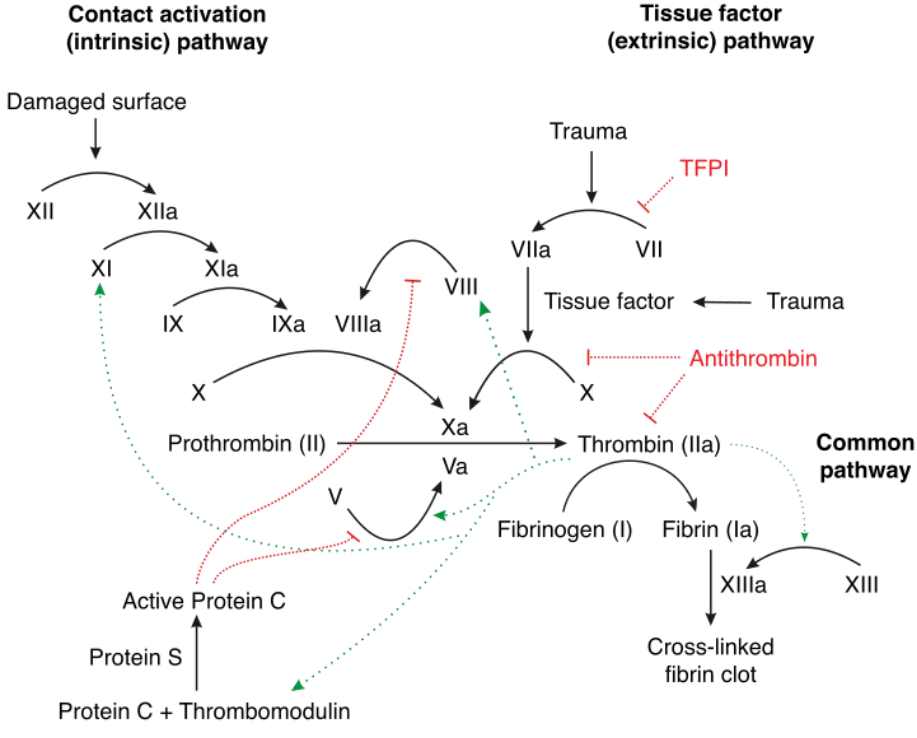


Figure 8 – Illustration summarizing the intrinsic and the extrinsic pathways of the coagulation cascade.

There are two distinct pathways triggering the coagulation cascade, the extrinsic and the intrinsic (Figure 8). These pathways converge to form the common pathway which leads to the activation of prothrombin (Factor II) to thrombin (Factor IIa).[46]

The activity of the extrinsic and the common pathway is clinically monitored by measuring the prothrombin time (**PT**) while the activated partial thromboplastin time (**aPTT**) assesses the integrity of the intrinsic and common pathway.[46] The extrinsic, or tissue factor, pathway is a "shortcut" pathway to the common pathway. Via this pathway, coagulation is initiated, bypassing several steps needed by the intrinsic pathway.[47]

This pathway is triggered by the interaction of factor VIIa with the tissue factor (TF or factor III) that can be presented automatically at the site of acute vascular injury.[46] The TF/factor VIIa complex leads directly to the activation of thrombokinase (factor X), which in turn forms an additional complex together with calcium ions (factor IV), platelet accelerator (factor V) and platelet factor 3 (PF3) to form the prothrombin activator complex. The last mentioned is the end product of both the extrinsic and the intrinsic pathways and the most essential complex to trigger coagulation by converting prothrombin (factor II) to thrombin (factor IIa). A study by Boisclair et al. (1993) on perioperative hemostasis during cardiopulmonary bypass surgery suggested that the main trigger to the coagulation cascade was via the extrinsic pathway as a response to the surgical cutting of blood vessels.[48] Thrombin then converts **fibrinogen** (factor I) to fibrin (factor Ia) which forms the cross-linked fibrin polymer after being reinforced and transformed to an insoluble mesh by fibrin stabilizing factor (FSF or factor XIII).[47, 49]

This interaction between the coagulation factors and the platelets leads to the formation of the thrombus in the blood vessel at the site of injury.[50]

After tissue restoration, the sequential action of thrombin, factor XIIIa and plasmin start to degenerate the thrombus in a sub-process of the coagulation cascade called termination. Termination leads to the inhibition of most enzymes in the procoagulant system by means of a physiological inhibitory system consisting mainly of the circulating protease inhibitor **antithrombin III** (ATIII).[46, 51] This process releases fibrin degradation product (FDP) and a specific protein segment called **D-dimer**. D-dimer represents the final product of the fibrinolytic system and thus plays a significant role in the clinical evaluation of thrombophilia after major surgical procedures.[51] Activity of the coagulation cascade can be measured and followed up by certain blood samples. Table 1 summarizes tools available for detecting abnormalities in the coagulation cascade.

Table 1 – Blood samples with value to detect abnormalities in certain steps of the coagulation cascade.

Compo-nent	**Standard value**	**Role in the coagulation cascade**
PT-INR	0.9-1.2	Measuring the activity of the extrinsic and common pathways.
aPTT	30-42 s	Measuring the activity of the intrinsic and common pathways.
Fibrinogen (Factor I)	2.0-3.6 g/L	Common pathway. Converted to a web-like substance called fibrin. Thrombogenic component.
Antithrom-bin	0.15-0.2 mg/mL	Inhibition of thrombin and factor Xa. Antithrombogenic component.
D-dimer	<0.5 mg/L	Thrombogenic component.
Platelets	150-350 10(9)/L	Adhere to the injured blood vessel wall and block the injured site. Thrombogenic component.
Erythro-cytes	4.30-5.70 10(12)/L	Laminar shearing with platelet margination. Interacting with endothelial cells and platelets, which may be involved in thrombosis. Interacting with fibrinogen/fibrin and affecting the lytic resistance of the thrombus.[52]

Physiology of the Peritoneum

The complexity of the peritoneum gives it a variety of functions. Most importantly, it facilitates the movements of intraabdominal organs as well as maintaining the balance of the abdominal cavity.[36] The peritoneum consists of a layer of mesothelial cells on a connective tissue base.[45] The peritoneal mesothelium also contains the peritoneal-plasma barrier of capillary walls and subserosal interstitium. The capillary walls are the most important component in controlling the permeability of large molecules through this barrier.[53] Under healthy conditions, the peritoneal cavity contains up to 75ml of clear and normally sterile watery fluid described as an ultra-filtrated blood derivate. This peritoneal fluid, produced daily, mainly helps to moisturize the peritoneal surfaces and substance exchange between the peritoneal cavity and the plasma.[36] Circulation of the peritoneal fluid follows a specific intraabdominal pattern. Respiratory movements create upward flow transferring the fluid from the lower to the upper abdomen, while gravity creates the downward flow transferring the fluid back to the lower abdomen.[36] The circulation pattern of the peritoneal fluid plays a major role in spreading metastatic disease. The peritoneal fluid contains several immune elements such as components of the complement cascade C3, C4 as well as immunoglobulin G. Moreover, it contains certain antimicrobial peptides such as human neutrophil peptide (HNP), human β defensins (HβD) and immune cells like macrophages, mast cells, eosinophils and lymphocytes. All these elements are produced by mesothelial cells which make the peritoneal fluid a sustainable physiological barrier against infection. Besides the physiological barrier and immune induction, the peritoneum also participates in selective fluid and cell transport processes, preventing adhesion and tumoral dissemination. It also participates **in trans**-cellular migration, as well as tissue repair and scarring, as mesothelial cells have the ability to change their phenotype in response to damage, as well as the ability to return to their normal form after tissue repair.[54]

The Malignancy of the Peritoneum

The peritoneum is a common location for metastases of epithelial cancers. Peritoneal surface malignancy (PM) can be a primary tumor of the peritoneum, such as a peritoneal malignant mesothelioma, which arises from the mesothelial cells of the peritoneum. Although the presentation of malignant mesothelioma is rare, with a worldwide annual incidence of approximately 2500 cases, it is considered an aggressive condition. In up to 50% of cases, it is caused by asbestos exposure and presented mainly in males ≥60 years old.[55] The secondary tumor of the peritoneum or the peritoneal metastasis is a heterogeneous group of quite different cancers (Figure 9).[56]

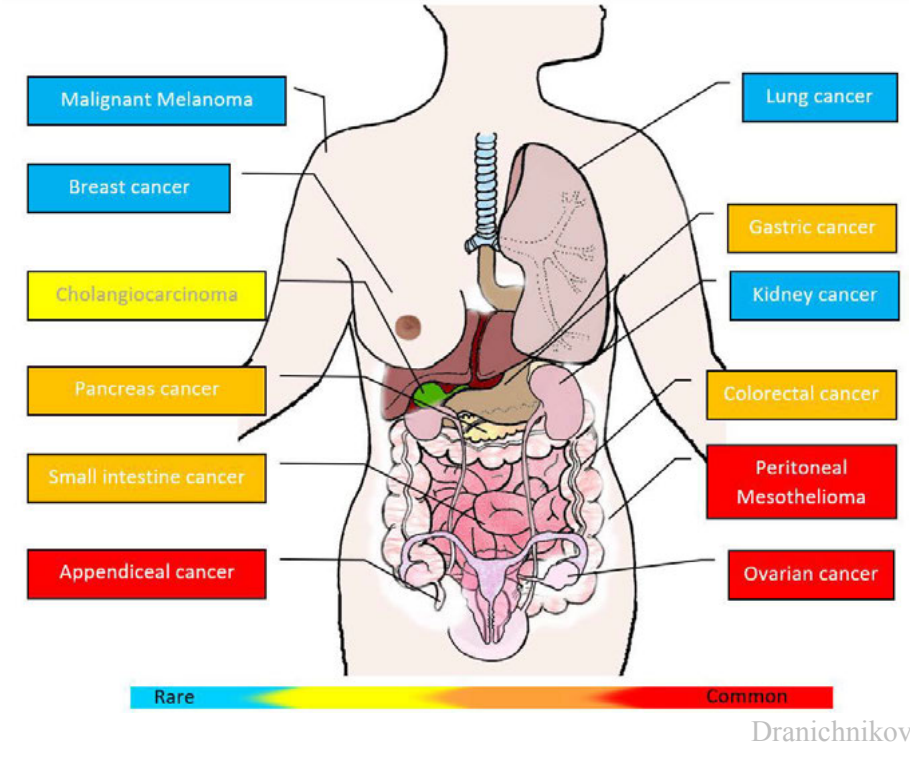


Figure 9 – Peritoneal surface malignancies can arise from primary tumors of the peritoneum (peritoneal mesothelioma) or disseminate as metastases from tumors of intra- or extraperitoneal origin. Color scale represents how commonly each primary tumor disseminates to the peritoneum and not how common the primary tumor is.

PM is often seen as multiple metastatic deposits which adhere to the peritoneal surfaces.[36] Peritoneal involvement arises most commonly from intraabdominal primary malignancies due to the anatomical location. Although there are some reported cases of peritoneal involvement from extraabdominal primary tumors, those cases are uncommon. The peritoneal anatomy, physiology, the movement pattern of the peritoneal fluid as well as the blood and lymphatic supply to the peritoneum all act as an open gate for dissemination of metastases to the peritoneal cavity.[37] The incidence of PM depends strongly on the prevalence of the underlying primary tumors.[56] As presented in Figure 9, primary tumors from the large bowel, ovaries and appendix are by far the most common contributors presenting in advanced stages of PM.

The worldwide incidence of ovarian cancer showed an increase over the past decade with an estimated incidence of PM from ovarian cancer of around 60–70%.[56] The exfoliation of malignant cells from the ovarian tumor into the peritoneum is the most common way of dissemination.[57] The highest average annual percentage presentation of PM from ovarian cancer was found in Brazil, at 4.4%.[56] Colorectal cancer (CRC) has a 4%–15% estimated incidence of peritoneal metastases as a synchronous disease. Moreover, there is an estimated risk that 8% of CRC patients will develop metachronous PM, while the risk is significantly higher, up to 25% of patients with recurrent CRC.[58] There are multiple routes for dissemination from CRC to the peritoneal surface including hematogenous metastasis or metastasis in the lymphatic fluid within the peritoneal cavity; serosal involvement of the primary tumor, or implantation of free cancer cells due to adherence molecules.[58]

The reported incidence of appendiceal mucinous tumors, which are the most common underlying cause of pseudomyxoma peritonei (PMP), is around 0.4–1.9 per 1,000,000 person-years.[56] PMP is a mucinous ascite produced by a specific glycoprotein encoded by MUC genes, with a distinguishing pattern of dissemination to the peritoneal surface.[58] Cancer involving other organs such as the small intestine, endometrium, lung and prostate can also cause PM (Figure 9), but occur less frequently.[27, 59]

Untreated PM or recurrent disease might lead to obstructive or paralytic ileus with a high risk for morbidity and mortality.[36]

Management of Peritoneal Malignancy

PM has been and remains a major challenge to manage and is, in many cases, difficult to treat mainly due to the complicated seeding of microscopic and macroscopic tumor depositions all over the abdominal cavity. The peritoneal nodules may present in different ways. Sometimes the PM spreads in a miliary pattern which is often difficult to remove completely by surgery. Other patterns with large nodule growth can be surgically removed more easily with better prognosis.[36] Several therapeutic approaches for PM have been investigated, tested and adopted over the past three decades. Additional intraperitoneal chemotherapy after cytoreductive surgery (CRS) is performed to target the microscopic residual disease as a curative approach, regardless of how that therapy is administered.[27]

However, the systemic toxicity and poor drug distribution to the peritoneal tumors limits the use of systemic chemotherapy after CRS.[60, 61] Thus, the use of hyperthermic intraperitoneal chemotherapy (HIPEC) emerged as a valuable treatment option in conjunction with CRS for well-selected patients with PM. Unlike the systemic administration of chemotherapy, HIPEC has certain advantages such as direct administration to the malignancy site, dose intensification, enhanced tissue penetration, as well as the synergistic cytotoxic effects of regional hyperthermia.[62] The choice of HIPEC agent or HIPEC regimen depends on the type of tumor causing the PM. HIPEC agents can be delivered as a single drug or combined with other drugs (both intraperitoneally or intravenously) or as additional early postoperative intraperitoneal chemotherapy (EPIC) (Table 2).[57]

Oxaliplatin is a platinum containing an alkylating agent with a molecular weight of approximately 397g/mol. When administered, it binds and prevents DNA replication in the tumor cell.[57] Oxaliplatin is commonly used (± irinotecan) as a HIPEC regimen for 30 min to treat PM with primary tumors from colorectal or gastric cancers. Treatment with oxaliplatin is often combined with 5-fluorouracil given intravenously together with calcium folinate to reach a synergistic effect.

Irinotecan is an antineoplastic enzyme inhibitor with a molecular wight of approximately 587 g/mol often used in combination with oxaliplatin as a HIPEC agent for treatment of PM with primary colorectal or pancreatic tumors. Irinotecan and its potent metabolite, 7- ethyl-10-hydroxy-camptothecin (SN-38), interfere with the tumor cells' DNA by inhibiting topoisomerase I,

leading to the formation of a cleavable complex which ends with DNA strand breaks and thus a cellular death.[63, 64]

Mitomycin C (MMC) is an antitumor antibiotic with a molecular weight of 334 g/mol. When administered, the bio-reduced MMC alkylates DNA by generating oxygen radicals followed by DNA interstrand cross-links, which results in inhibiting DNA synthesis. At higher concentrations, MMC is also capable of RNA inhibition and protein synthesis.[65] As a HIPEC agent, MMC is administered for 90 min to treat PM originating from appendiceal tumors.

Cisplatin is a platinum-based alkylating drug with a molecular weight of 300 g/mol and is used as a HIPEC agent (± doxorubicin) for treatment of patients with PM from peritoneal mesothelioma, ovarian cancer or gastric cancer. When administered, cisplatin adds alkyl groups causing cross-links in the DNA double-helix strands in the tumor cell which affect the strands' ability to uncoil, resulting in inhibition of DNA replication.[66]

Doxorubicin is a cytotoxic anthracycline antibiotic with a molecular weight of approximately 544 g/mol and is used in combination with Cisplatin as a HIPEC agent for treatment of PM with the primary tumor from ovarian or gastric cancer. When administered, doxorubicin binds to nucleic acids, inhibits topoisomerase II and forms oxygen free radicals. This results in preventing DNA replication, inhibiting protein synthesis and cellular toxicity.[67] Table 2 shows the most commonly used HIPEC and EPIC agents.

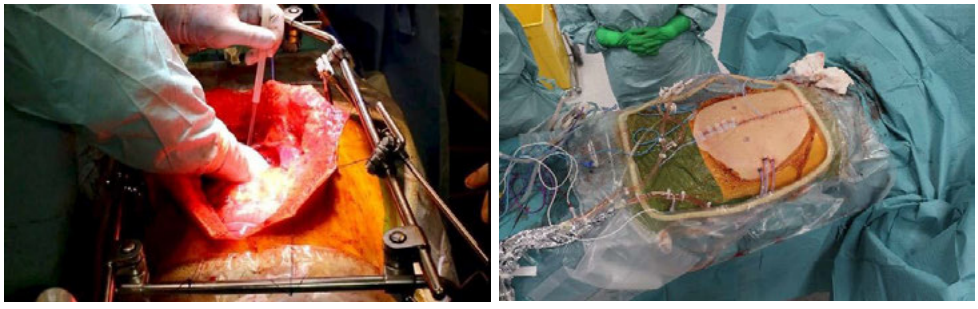
Table 2 – Different cytostatic agents used during HIPEC or EPIC.[57, 53]

Agent	**Type**	**Targeted tumor**	**HIPEC/EPIC**	**Penetration depth**	**AUC ratio***
5-Fluorouracil	Antimetabolite	Colorectal	EPIC	0.2mm	250
Cisplatin	Alkylating	Ovarian, gastric	HIPEC	1-3mm	7.8
Doxorubicin	Antitumor antibiotic	Ovarian, gastric	HIPEC	4-6 cell layers	230
Irinotecan	Topoisomerase inhibitor	Colorectal	HIPEC	N/A[a]	15[b]
Mitomycin C	Antitumor antibiotic	PMP	HIPEC	2-5mm	23.5
Oxaliplatin	Platinum compounds	Colorectal, gastric	HIPEC	1-2mm	16
Taxol	Plant Alkaloid	Mesothelioma, ovarian	EPIC	>80 cell layers	1000

* AUC, area under concentration vs. time curve (AUC ratio, peritoneal fluid AUC/systemic AUC).[53]
[a] N/A, not available
[b] AUC ratio of 4 irinotecan's active metabolite (SN-38).[53]

Area under the curve (AUC) is calculated by taking plasma concentration versus time, which expresses the measure of drug exposure. In the peritoneal cavity, the intraperitoneal to plasma AUC ratio of the drug reflects the amount of the drug in the peritoneal cavity as well as the amount absorbed into the circulation.[57] This gradient varies from a factor 10 to a factor 1000, depending mainly on the molecular weight of the drug and also on the renal and hepatic clearance.[53]

The administration of the intraabdominal chemotherapy during HIPEC can be done either with an open Coliseum technique (Figure 10-a) or a closed abdominal technique (Figure 10-b).



(a) (b)

Figure 10 – (a) Open Coliseum technique, Uppsala University Hospital, Dranichnikov©, **(b)** Closed HIPEC, Uppsala University Hospital, Cashin©.

In a multi-institutional analysis, Leiting et al. (2020) compared the outcome of the open Coliseum method to closed HIPEC head-to-head, but detected no significant differences concerning efficacy.[68]

In addition to HIPEC, several institutions, including Uppsala University Hospital, used to treat high tumor-volume patients with Early Postoperative Intraperitoneal Chemotherapy (EPIC). This was administered in the abdominal cavity through peritoneal drains over 5 days postoperatively, thus permitting prolonged direct administration, and enhancing prolonged tumor exposure to chemotherapy with low systemic toxicity. However, treatment with EPIC was discontinued in many institutions based on the results of French retrospective studies which suggested the correlation of higher morbidity rates for patients treated with HIPEC + EPIC compared to those treated with HIPEC alone.[33, 34] On the other hand, the role of using HIPEC after CRS still demonstrates notable efficacy for the treatment of PM arising from various malignancies in the abdomen, such as ovarian cancer [69, 70], colorectal cancer [71], pseudomyxoma peritonei [72], mesothelioma [73] and gastric cancer.[8, 74]

However, CRS with HIPEC is a demanding and complicated procedure with prolonged duration and multi visceral resections which cannot be performed on all patients. Aspects such as age, comorbidities, histology of the primary tumor, extraperitoneal metastasis, peritoneal cancer index (PCI) as well as completeness of cytoreduction score (CCS) limit the treatment to selected patients. PCI is one of the main tools used to quantify the intraabdominal disease and it has been found to be the most useful and accurate assessment of survival (Figure 11).[75]

The main principle of the PCI scoring system is to divide the abdomen into 13 regions. Each region is assigned a lesion size score (LSS).

However, all primary lesions are excluded from the LSS assessment. The sum of the total score for lesion sizes for all regions ranges from 0 to 39.[76]

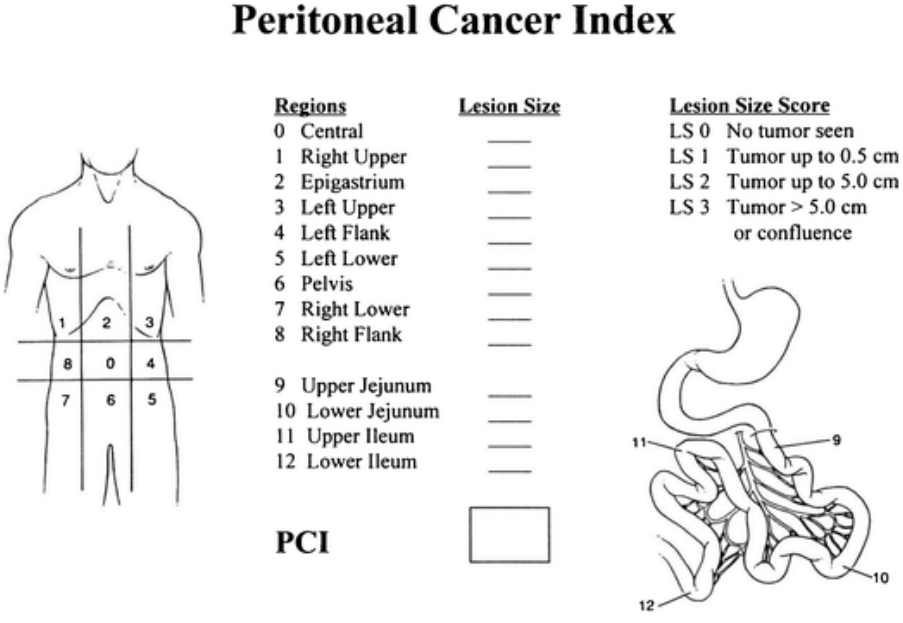


Figure 11 – Peritoneal cancer index (PCI) according to Sugarbaker.[67]

On the other hand, for prognosis assessment, the CCS is the most definitive instrument in PM management. After cytoreduction is completed, the CCS provides the surgeon with information about the prognosis, from no persisting tumor nodules after cytoreduction (CC0) to unresectable tumor nodules > 2.5 cm (CCS3) (Table 3).[75]

CCS has been proven to be a major prognostic indicator in both non-invasive and invasive PM and it has been shown to function accurately in PMP, CRC, sarcomatosis, and peritoneal mesothelioma.[75]

Table 3 – The completeness of cytoreduction score (CCS).[75]

CC score	Definition
0	No macroscopically visible peritoneal nodules remaining after CRS.
1	<2.5mm persisting tumor nodules after cytoreduction.
2	2.5mm – 2.5cm persisting tumor nodules after cytoreduction.
3	>2.5cm persisting tumor nodules after cytoreduction.

Recently, a new method of intraabdominal chemotherapy distribution has emerged, namely pressurized intraperitoneal aerosol chemotherapy (PIPAC). This also gives patients with unresectable PM an opportunity to undergo

intraabdominal chemotherapy with a minimally invasive approach. However, the use of PIPAC is still under investigation and its outcomes and survival rates have not been fully analyzed. Nevertheless, PIPAC might be considered as a possible palliative therapy for patients who are not eligible for CRS and HIPEC.[62]

The Impact of CRS and HIPEC on Fluid Balance

CRS with HIPEC is a challenging procedure associated with a long surgical incision which extends from the xiphoid process to the pubic bone (Figure 12); prolonged surgery time; multivisceral resection, and thus a higher risk for vascular damage.[25] This often leads to increased capillary leakage and results in major fluid shifts.[77, 78, 79]

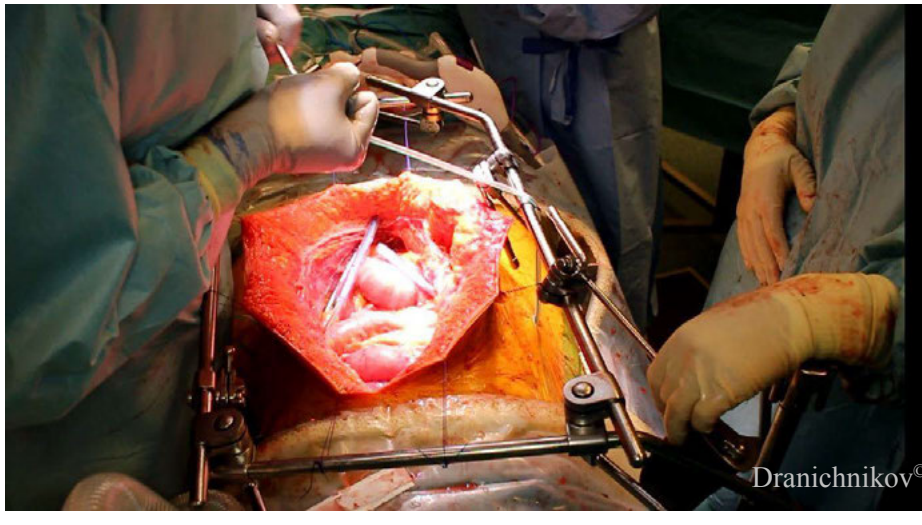


Figure 12 – The surgical incision during CRS and HIPEC operations often extends from the xiphoid process to the pubic bone.

Patients undergoing all kinds of major abdominal surgeries are at higher risk of fluid disbalance and dehydration, not only as a result of the procedure itself, but also due to the preoperative fasting as well as postoperative fluid and electrolytes loss.[80]

Historically, the overall mean operation duration of CRS and HIPEC was estimated as 8-14 hours.[25, 81] Sargant et al. reported that the majority of their operations (84.4%) had a duration of 6-12 hours while in 8.8% of cases, surgery time exceeded 12 hours.[82] However, many HIPEC centers have noted a decreased duration of these surgeries depending on the surgical team's increased experience and technical developments. An important part of the time-

consuming process is the HIPEC administration time, which might take 30-90 minutes depending mainly on the HIPEC regimen used. Raspe et al. (2012) estimated that blood loss during CRS and HIPEC varies between 200 and 9000 ml.[83] Other than the multiple surgical procedures during CRS, intraoperative blood loss during CRS and HIPEC can be related to the impairment of the coagulation cascade with increased prothrombin time and international normalized ratio (PT-INR); prolonged activated partial thromboplastin time (aPTT), along with decreased values of antithrombin III, fibrinogen as well as a number of thrombocytes.[84] Additionally, high fluid turnover results in protein loss and decreased levels of coagulation factors such as fibrin stabilizing factor (factor XIII). Those actions affect coagulation, resulting in an increased risk for postoperative bleeding. This effect might even be enhanced by the addition of HIPEC. However, until recently data were insufficient to confirm that.[83] Di Giorgio et al. (2008) estimated that mean intraoperative bleeding was 1494 ml for patients undergoing CRS with HIPEC, which required correction with a mean 3.4 units of PRBC and 5.2 units of plasma.[82] Pamela et al. (2018) reported intraoperative the mean blood products' correction rate as 1.1 units PRBC and 4.4 units of plasma.[25]

Intraoperative Fluid Management

Replacement of fluid losses during CRS and HIPEC is achieved through a combination of colloid/blood products and crystalloid solutions. Additionally, the length, surgical method (open vs closed), and choice of drug use during the HIPEC part of the treatment can also affect fluid management and the risk of postoperative morbidity. It has been suggested, for instance, that oxaliplatin may increase the risk of postoperative hemorrhage.[85] Uppsala University Hospital introduced goal-directed fluid therapy (GDT) in 2013 for the management of intraoperative blood and fluid balance for CRS and HIPEC patients. GDT treatment applied intraoperative hemodynamic monitoring using the FloTrac/Vigileo device or esophageal echo-Doppler, CardioQ device (Deltex Medical Ltd, Sussex, UK) to predict fluid responsiveness by dynamic preload parameters such as stroke volume variation (SVV) or aortic blood flow corrected flow time (FTc).[86] Studies have suggested that this approach could minimize the risks associated with both hypovolemia (e.g. renal dysfunction) and hypervolemia (e.g. tissue edema).[78, 87] To date, there has been only one small, randomized trial investigating GDT in HIPEC patients, by Colantonio et al. (2015) with 38 patients in the GDT arm and 42 in the standard fluid therapy arm.[87] The same study concluded that the use of GDT minimized the incidence of postoperative major abdominal morbidity (10.5% in GDT group, n=4 vs. 38%, n=16, p=0.005) and shortened LOS (19 days in GDT group vs. 29 days, p<0.0001).[87] Likewise, among the few observational studies published, cohort sizes are relatively small and have demonstrated conflicting results.[85, 88, 89] Castellanos et al. (2021) demonstrated that the use of too restrictive intraoperative fluid margins may actually increase the risk of major postoperative complications [89], while most studies have shown a benefit in LOS and morbidity.[85, 88]

However, Castellanos et al. (2021) used a very restrictive fluid management at < 9ml/kg/h in the GDT group, which is significantly lower than what we use in GDT groups at Uppsala University Hospital (16ml/kg/h in total fluid replacement). Eng et al. (2017) argued that the risk of complications was higher in patients receiving generous intraoperative fluid support compared to those receiving restricted amounts (31.5 vs. 22.0, p=0.02).[88] Although the impact of intraoperative fluid management during CRS and HIPEC is crucial, it has been poorly investigated and, as mentioned earlier, the few published reports demonstrate conflicted results. Moreover, to date there are no studies

analyzing the impact of different intraoperative fluid management approaches during CRS and HIPEC on overall survival.

Postoperative Morbidity

The majority of patients undergoing CRS and HIPEC are at a risk for a wide range of morbidities mainly due to the extensive peritonectomies and visceral resections that are performed in order to visibly clear the abdominal cavity and pelvis of malignant nodules.[1, 21, 22, 23] Morbidity in the form of surgical complications is common and has a significant impact on the quality-of-life of patients undergoing the procedure.[90] Patients undergoing CRS and HIPEC often suffer from a malignancy spreading to multiple peritoneal sites covering several intraabdominal organs, which results in several resections and reconstructions. Some complications present before hospital discharge (referred to as in-hospital morbidity) while other complications occur after discharge (considered as readmission morbidity). In-hospital morbidity has been studied, while frequency and tendency to rehospitalization for patients after CRS and HIPEC have been sparsely investigated.[14] Martin et al. (2016) reported a readmission rate of 14.9% within 30 days after CRS and HIPEC (n=32) and a higher readmission rate of 21.4% within 90 days (n=46). The same study argued that the main reason for readmission at all time points was enterocutaneous fistula (OR 24.9, CI 2.92-213, $p<0.01$).[14] Dreznik et al. (2018) reported a late readmission rate of 11% up to 90 days following CRS and HIPEC (n=25). The most common causes of readmission were surgical site infection (22.4%, n=13), dehydration (17%, n=10) and small bowel obstruction (12%, n=7).[91] Lee et al. (2020) reported a 15.9% readmission rate within 30 days following CRS and HIPEC (n=321) with failure to thrive (malnutrition/poor oral intake) as the main indication for readmission (29.9%, n=95), followed by infection (23.6%, n=75) and bowel obstruction (15.1%, n=48). However, the readmission rate between 31 and 90 days postoperatively was lower at 3.9% (n=78), with bowel obstruction (25.3%) as the main reason for readmission (n=19).[92]

The Impact of CRS and HIPEC on Coagulation

Postoperative coagulopathy has been considered as a crucial manifestation after major cancer surgery. Cancer patients face an increased risk for thromboembolic events after abdominal and pelvic surgery when compared with non-cancer patients undergoing similar surgery. For cancer patients, this risk is estimated as 2-fold for deep-vein thrombosis (DVT) and 3-fold for pulmonary embolism (PE).[93] Studies have shown that without thromboprophylaxis, the incidence of DVT is about 26% in abdominal surgery and 14% in gynecological surgery. This risk is evidently higher in cancer patients.[94] However, and even with thromboprophylaxis treatment, the risk of thromboembolic complications differs extensively between patients and the type and duration of malignancy.[95] Some tumor types are commonly associated with various thromboembolic complications such as gastrointestinal carcinomas as well as carcinomas of the ovary and lung. Patients who died of pancreatic cancer had a 30% incidence of thrombosis at autopsy. The risk was even higher (>50%) in patients with tumors in the body or tail of the pancreas. [46]

Peritoneal surface malignancy (PM) has been considered as a sign of advanced tumor stage.[96] Prior to the development of CRS and HIPEC, patients with PM were treated with palliative systemic chemotherapy or best supportive care.[2] The introduction of the surgical approach with CRS combined with HIPEC in the mid-nineties shifted the attitude from palliation to curative treatment of PM. However, the development of this treatment led to more aggressive surgery. [41, 97-100] Although treatment with CRS and HIPEC has improved the survival of PM patients, with an acceptable level of postoperative morbidity that is comparable to other complex gastrointestinal surgeries, the procedures are associated with high volume tissue damage and a variety of physiological changes as well as prolonged hospital stays affecting the cardiovascular system and coagulation cascade.[101, 102, 103] The occurrence of thromboembolic complications postoperatively after CRS and HIPEC, or any other major surgery, depends strongly on the balance between thrombogenic and fibrinolytic system function.[104]

Even though the main mechanisms involved in perioperative hypercoagulable stimuli are still unclear, either the exposure of the specific membrane protein called tissue factor (TF or factor III) from the injury site, or activated monocytes, is the most likely pathway in this setting. [46] Moreover, many

studies suggest a multifactorial contribution to the adaptable impairment of the coagulation system.[105, 106, 107]

Falanga et al. (2013), as well as Connolly et al. (2010), categorized thrombotic risk factors in cancer patients into three groups: **Patient-related** (high age, bed rest, obesity, previous thrombosis, prothrombotic mutation, high leukocyte and platelet count as well as comorbidities), **cancer-related** (site and stage of cancer) and finally **treatment-related** (surgery, hospitalization and prolonged immobilization, chemotherapy etc.)[95, 108]

The extent and duration of surgery as well as the degree of tissue damage, reduced liver perfusion, excessive blood loss and fluid replacement are some of the perioperative thrombogenic factors that shift the hemostasis out of balance and increase the coagulant and fibrinolytic activity, both peri- and postoperatively. Furthermore, the risks are considered to be higher for patients with a poor performance status prior to surgery, as well as co-morbidity and unhealthy lifestyle including high body-mass index and tobacco use.[109, 110] Widespread malignancy, extensive surgery, chemotherapy[46] and postoperative immobilization are the quadruple threat to patients undergoing CRS and HIPEC that increase risk for thromboembolic events both venous and arterial, including deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral vascular lesion (CVL) or nonbacterial thrombotic endocarditis with arterial emboli.

Despite the above-mentioned facts, studies on coagulopathy following CRS and HIPEC are rare.

Physiological coagulation is a multifaceted and well-balanced system of cellular and biochemical processes called hemostasis.[111] These processes range from the development of thrombosis to the restoration of the injury site and thrombolysis. Platelets are the main cellular component in hemostasis. In addition, erythrocytes or red blood cells (RBCs) play a rheological role in coagulation by involving laminar shearing with platelet margination as well as interacting with endothelial cells and platelets which may be involved in thrombosis and postoperative hemorrhage. [52]

Aim of the Thesis

The overall aim of the thesis was to investigate postoperative morbidity following the management of peritoneal surface malignancy with CRS and HIPEC ± EPIC. The following aspects were the main focus of the studies included in this thesis: readmission morbidity, coagulopathy and venous thromboembolism, comparing different intraperitoneal treatment strategies (HIPEC alone vs. HIPEC + EPIC) as well as comparing the outcomes after using two different intraoperative fluid management strategies.

Specific aims:

Paper I

- To analyze the national incidence of readmissions after CRS and HIPEC.
- To assess national overall morbidity rates and risk factors for morbidity requiring readmission or intervention.

Paper II

- To investigate changes in coagulation biomarkers after CRS and HIPEC and their predictive abilities for venous thromboembolic events.

Paper III

- To compare the length of stay, postoperative morbidity, reoperation rate and readmission after HIPEC+EPIC treatment compared to HIPEC alone.

Paper IV

- To compare the postoperative outcomes after CRS and HIPEC depending on the intraoperative fluid management strategy.
- To evaluate the risk of postoperative hemorrhage depending on HIPEC regimen.

Common Methods

Ethical considerations

All the studies included in this thesis followed the Declaration of Helsinki guidelines and were approved by the regional ethics committee for the Uppsala region, Sweden.

- **Paper I:** reference number 2015/367.
- **Paper II:** reference number 2007/073.
- **Paper III:** reference number 2015/367 and 2013/203.
- **Paper IV:** reference number 2013/203.

Cohort start and finish date

- **Paper I:** January 1st, 2004 - June 30th, 2014
- **Paper II:** November 8th, 2004- December 22nd, 2014
- **Paper III:** February 16th, 2004- December 22nd, 2014
- **Paper IV:** November 8th, 2004- December 21st, 2017

Data collection and eligibility requirements

Paper I

Data for Paper I were retrieved from Sweden's National Patient Register and the Cause of Death Register and included all patients with a Swedish social security number who underwent HIPEC. This was done by using the HIPEC ICD code JAQ10. As the code JAQ10 was not used consistently early on, when there was only one center in Sweden (Uppsala University Hospital), the cohort from the National Patient Register was combined with the local HIPEC register at Uppsala in order to minimize the risk for missing data. All hospital admissions were retrieved from the first HIPEC treatment/index HIPEC (some patients were treated several times) until six months postoperatively. Study observation ended on December 31st, 2014. Eligibility requirements for this study are summarized in Figure 13.

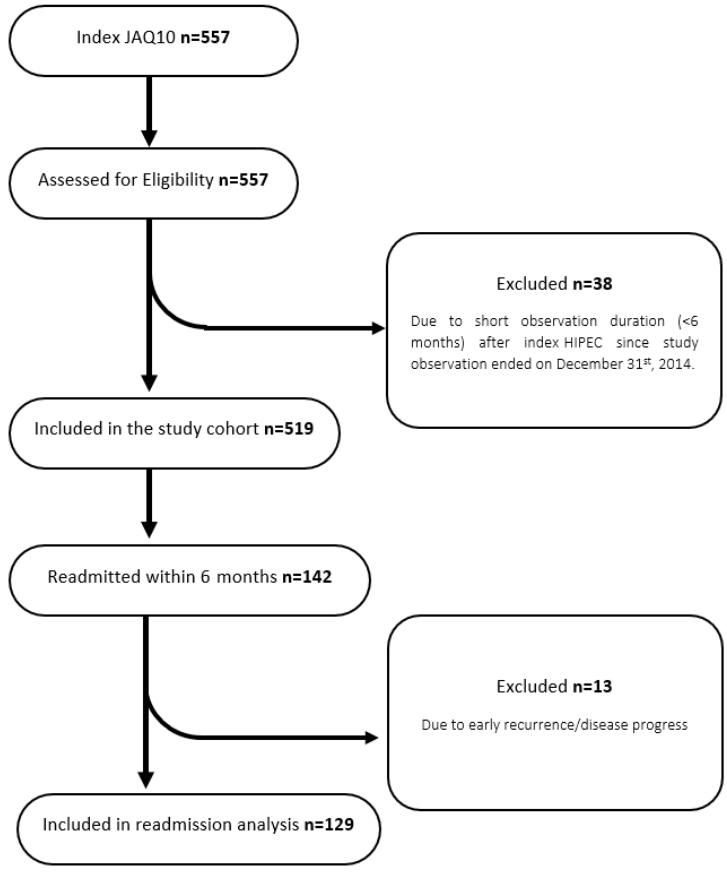


Figure 13 – Flowchart of study inclusion and readmission analysis

Paper II

Demographics, variables, laboratory values and surgical factors for Paper II were retrieved from the local HIPEC registry. Data for morbidity-related readmission within six months after CRS and HIPEC were retrieved from the National Swedish Patient Register as well as the Cause of Death Register by using the ICD operation code JAQ10 (intraoperative hyperthermic chemotherapy in the abdominal cavity).

Paper III

Data for Paper III were retrieved from the local HIPEC register at Uppsala University Hospital. Data concerning readmissions within six months of surgery were extracted using the National Patient Register using ICD-10 code JAQ10. Date and cause of death were taken from the National Cause of Death Register. Eligibility requirements for this study are summarized in Figure 14.

Only patients who underwent their first HIPEC procedure were included in the study.

Study inclusion criteria were: peritoneal malignancy (PM) regardless of primary tumor site; Karnofsky performance status (KPS) > 60, and absence of distant metastasis (except limited hepatic deposits that were possible to treat with a wedge resection) evaluated by preoperative radiological examination or pre-HIPEC surgical exploration and deemed eligible by a multidisciplinary tumor board.

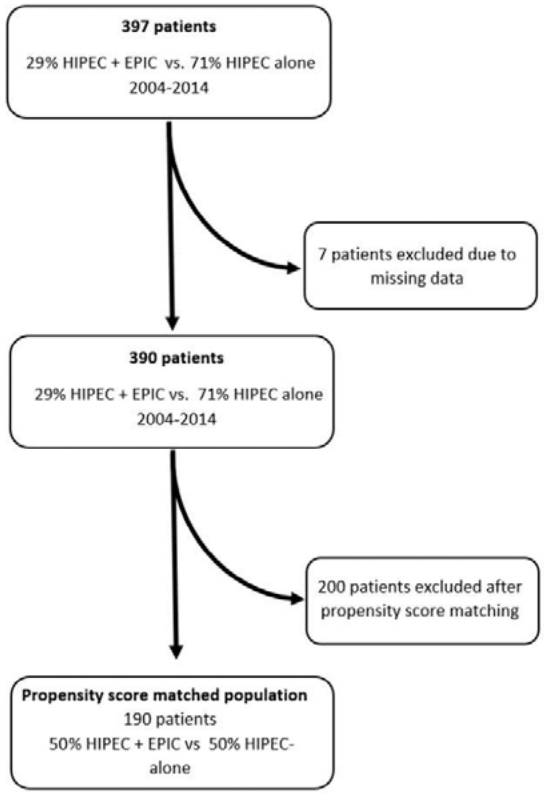


Figure 14 – Flowchart summarizing the inclusion and exclusion process in Paper III.

Paper IV

Data for Paper IV were retrieved from the local HIPEC register at Uppsala University Hospital. All fluid management variables were retrieved from the anesthesia and intensive care chart records at Uppsala University Hospital. Only one patient was excluded from the analysis of this study due to early and unexpected in-hospital mortality (suicide on postoperative day four). All cases

with a primary tumor site from the small intestine and gastric cancer were excluded from risk analysis due to the small number of cases.

General statistics

Descriptive statistics are presented as means, medians, percentages, and ranges. Statistical inferences between two groups (Papers III and IV) were tested using the Mann-Whitney U test (if variables not equally distributed) and Pearson Chi-square test for categorical variables, or using two-sample Student's t-test for normally distributed continuous variables. Standardized mean difference (SMD) was used in Paper III as a further measure of effect size.

Survival analyses (Paper IV) were done using Kaplan-Meier curves with log rank tests. Risk analysis was performed using univariate and multivariate logistic regression and results were presented as odds ratios (OR) and corresponding 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. Only clinically relevant variables with a significant p-value (< 0.05) were included in the multivariate logistic regression. The univariate variables with p-value <0.1 were included in the final multivariable risk analysis of postoperative hemorrhage in Paper IV.

Adjustments were made in Paper II using multiple imputations on PT-INR, APTT, fibrinogen, antithrombin, and D-dimer due to missing data (last value carried forward + mean + median/3).

Covariates used in Paper III included: sex, primary tumor site, preoperative chemotherapy, peritoneal cancer index (PCI), completeness of cytoreduction score and HIPEC regimen. Propensity score matching (PSM) was performed 1:1 using the nearest neighbor method with a caliper of 0.2. After matching, all standardized mean differences for the covariates were below 0.1 indicating adequate balance.

In Paper IV, multivariate analysis was performed for the endpoint of Clavien-Dindo morbidity Grade III-V, to adjust the odds ratio (OR) of the GDT group (vs pre-GDT group) in a logistical regression model using the following variables: age, ASA score, primary tumor site (small intestine and gastric cancer were excluded due to few cases in both groups), neoadjuvant chemotherapy, PCI, CCS, as well as HIPEC regimen used. Likewise, the same variables were used in the multivariable Cox regression model for overall survival.

Statistical analysis in Papers I-IV was performed using *Statistica* 64 software for Windows [Version 13.3, Dell Software, Round Rock, Texas, USA]. Additionally, propensity score matching (PSM) in Paper III was performed using the *MatchIt* package in RStudio Desktop 1.4.1717 for Windows [Northern Ave, Boston, USA].

Summary of Papers

Paper I: Readmission after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy - a National Population-Based Study.

Patients and Methods

The following information was registered from each hospital admission: age, gender, primary tumor site, coded surgical procedures, coded postoperative morbidity diagnoses, all reoperations or interventional coded therapies, the date for index surgical procedures as well as the date for reoperation and readmissions required for reinterventions.

The Swedish Cause of Death Register was used to ascertain the date and cause of death in the cohort. Interventions were categorized into radiological, endoscopic or surgical interventions. Hospital stays related to early recurrence, other anti-tumor treatment (or complications thereof) or hospice care were not considered. Univariate/multivariate logistical analyses were performed to identify risk factors for reinterventions and readmissions.

Results

A total of 519 patients were included in the analysis with a mean age of 56 years (range 13-78). In total, 150 HIPEC-related readmissions occurred in 129 patients (25%), with 83 interventions performed on 67 of them (i.e., 13% of the entire cohort required a readmission intervention within six months). Complications at readmission fell into three categories: gastrointestinal (n=95), cardiovascular (n=25) and miscellaneous (n=30).

An intervention during the first postoperative six months (both postoperative in-hospital and at readmission) was required in 34% of the patients (n=179) including 16% requiring a surgical reoperation (n=85). Of these 179 patients requiring an intervention, 83 patients (46%) received it at the referral hospital or during a readmission. In-hospital mortality was noted in five patients (1%). Risk analysis showed that age at treatment (OR 1.02, CI 1.00–1.03, p = 0.004) and any colonic resection (OD 1.85, CI 1.03–3.31, p = 0.03) were associated with a significantly higher risk for a HIPEC-related readmission. The risk for readmission requiring an intervention was significantly increased by advanced age at the time of treatment (OR 1.02, CI 1.00–1.04, p=0.02). Late HIPEC-related complications were noted with 48.7% of readmissions occurring between 90 days and 6 months.

A total of 438 in-hospital adverse events occurred in 261 patients (50%): 221 patients at the HIPEC center, 23 patients at the referral hospital, and 17 patients at both hospitals. One hundred and forty-five in-hospital interventions occurred in 112 patients: 96 patients at the HIPEC center, 12 patients at the referral hospital, and four patients at both hospitals. The mean number of days to an in-hospital surgical intervention (return to operating theater) was 11.9 (0-51). Univariate logistical analysis showed that gastric resection, splenectomy and number of resections had a significantly higher risk for in-hospital intervention (Table 4).

Table 4 – Univariate logistical regression using the three endpoints of the study.

Characteristics	**Risk for in-hospital intervention**	***p***	**HIPEC-related readmission**	***p***	**Readmission requiring intervention**	***p***
Age at treatment	0.98 (0.97-1.00)	0.13	1.02 (1.00-1.013	0.004	1.02 (1.00-1.04)	0.01
Gender Female Male	 ref 1.07 (0.70-1.64)	 0.74	 ref 1.07 (0.72-1.61)	 0.70	 ref 1.29 (0.76-2.20)	 0.33
Gastric resection (36)	2.87 (1.43-5.79)	0.003	1.17 (0.55-2.51)	0.67	1.38 (0.55-3.46)	0.48
Pancreatectomy (10)	2.50 (0.69-9.03)	0.16	2.04 (0.56-7.37)	0.27	2.97 (0.75-11.81)	0.12
Liver resection (95)	1.05 (0.61-1.80)	0.85	0.89 (0.52-1.50)	0.67	0.56 (0.26-1.23)	0.15
Cholecystectomy (154)	1.24 (0.79-1.94)	0.34	1.66 (1.09-2.53)	0.01	1.60 (0.94-2.73)	0.08
Splenectomy (181)	1.81 (1.18-2.78)	0.006	1.42 (0.94-2.14)	0.08	1.12 (0.66-1.92)	0.65
Small bowel resection (232)	1.16 (0.76-1.78)	0.46	1.47 (0.98-2.19)	0.05	1.74 (1.03-2.92)	0.03

Any colonic resection (365)	1.24 (0.77-2.00)	0.35	2.48 (1.50-4.12)	0.0003	2.3 (1.19-4.63)	0.01
Appendectomy (41)	0.88 (0.39-1.96)	0.76	0.83 (0.38-1.80)	0.65	0.32 (0.07-1.38)	0.12
Rectal resection (193)	1.38 (0.90-2.11)	0.13	1.90 (1.27-2.86)	0.001	1.77 (1.05-2.96)	0.02
Ureter resection (15)	0.25 (0.03-1.96)	0.19	2.06 (0.72-5.91)	0.17	3.56 (1.17-10.77)	0.02
Bladder resection (15)	0.25 (0.03-1.96)	0.19	2.73 (0.97-7.71)	0.05	2.54 (0.78-8.23)	0.11
Abdominal hernia repair (13)	2.35 (0.75-7.35)	0.13	1.35 (0.41-4.47)	0.61	1.23 (0.26-5.69)	0.78
Number of resections	1.11 (1.01-1.22)	0.02	1.20 (1.09-1.31)	0.00007	1.21 (1.08-1.36)	0.0007
Confidence interval between parentheses; N/A – not applicable						

Table 4 – Univariate logistical regression using the three endpoints of the study.

However, gastric resection was the only independent risk factor for in-hospital intervention in the multivariate logistical regression analysis (p=0.02, Table 5).

At the end of the study on December 31st, 2014, 61% of the cohort was still alive.

Table 5 – Multivariate logistical analyses according to three endpoints.

Characteristics	**Risk for in-hospital intervention**	***p***	**HIPEC-related readmission**	***p***	**Readmission requiring intervention**	***p***
Age at treatment	N/A	N/A	1.02 (1.00-1.03)	0.004	1.02 (1.00-1.04)	0.02
Gastric resection (36)	2.34 (1.13-4.87)	0.02	N/A	N/A	N/A	N/A
Splenectomy (181)	1.53 (0.90-2.59)	0.10	N/A	N/A	N/A	N/A
Small bowel resection (232)	N/A	N/A	1.09 (0.69-1.71)	0.69	1.26 (0.71-2.22)	0.41
Cholecystectomy (154)	N/A	N/A	1.16 (0.66-2.03)	0.58	N/A	N/A
Any colonic resection (365)	N/A	N/A	1.85 (1.03-3.31)	0.03	1.49 (0.68-3.26)	0.30
Rectal resection (193)	N/A	N/A	1.37 (0.82-2.26)	0.21	1.11 (0.59-2.11)	0.73
Ureter resection (15)	N/A	N/A	N/A	N/A	2.24 (0.70-7.11)	0.16
Number of resections	0.9 (0.86-1.09)	0.65	0.94 (0.80-1.10)	0.45	0.89 (0.76-1.04)	0.15
Confidence interval between parentheses; N/A – not applicable						

Discussion

The most important finding in this study was the number of interventions occurring in the referral hospital or during a HIPEC-related readmission. Forty-six percent of all patients (83/179) requiring an intervention in the first six months, did not receive it during the postoperative stay at the HIPEC center but at the referring hospital or during a readmission. As such, most morbidity studies underestimate the true morbidity and reoperation rate unless data from the referral hospital are considered.

The postoperative in-hospital intervention rate of 27% with a slight increase to 34% within six months is comparable to that seen in previous studies (Grades III/IV morbidity up to 52%).[32, 112] Likewise, the need for surgical intervention within the first six months (including both postoperative in-hospital and readmission) was 16%, which is also comparable to previous studies (11% - 26.8%).[2, 113, 114]

Readmissions, morbidity and mortality after CRS and HIPEC seem to differ from other abdominal surgical procedures. Some of the reasons are

identified in this study. Pancreaticoduodenectomy (considered to be the closest to HIPEC regarding complexity of procedure) has a risk of up to 21% for early hospital readmission within 30 days.[29] Ahmad et al. (2012) reported 15% readmission within 30 days and 19% within 90 days after the same procedure[28] while Bagante et al. (2018) reported a 23% readmission rate within 90 days after hepato-pancreatic surgery for malignant disease.[115] At 14%, our study had a very similar early readmission rate within 30 days, although it increased to 25% after six months.

A gastric resection was an independent risk factor for in-hospital intervention. A systematic review by Gill et al. (2011) of survival and morbidity in gastric cancer patients with peritoneal surface malignancy undergoing CRS and HIPEC reported an overall morbidity of 21.5%. Furthermore, the most reported complications were abscess, fistula, and anastomotic leak.[74]

The most common complications in our cohort of patients who had gastric resection (n=36) were abscess, anastomotic leak and wound dehiscence (n=15). The need for gastric resection should be evaluated in relation to the overall risk of other complications. It may increase the risk of in-hospital complications requiring an intervention by three-fold.

The multivariate analyses for HIPEC-related readmission showed that any colonic resection was a significant risk factor (p=0.03), while the same analysis for HIPEC-related readmission and readmission requiring an intervention both showed that age was the only independent significant risk factor (p=0.004 and p=0.02, respectively). Few studies have investigated morbidity after CRS and HIPEC in relation to age at treatment.[116, 117, 118]

Elias et al. (2007) reported no correlation between age and occurrence of intra-abdominal complications[118], while Beckert et al. (2015) reported that CRS and HIPEC are not associated with either Grades III–IV morbidity or surgery-related mortality in elderly patients.[116]

There may be a need to explore this aspect further, considering the increased risk for both HIPEC-related readmission and readmission requiring an intervention in elderly patients in this study.

Mortality within 30 days after CRS and HIPEC in Sweden is low, with a rate of only 0.2%. This is lower than the 30-day mortality rate (7.7%) presented by Ihemelandu et al. (2013).[119] Moreover, the in-hospital mortality rate is only 1%, which is at the lower end of mortality rates (0.9% to 5.8%) reported by several high-volume HIPEC centers.[120, 121]

Paper II: Coagulopathy and Venous Thromboembolic Events Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy.

Patients and Methods

A prospective cohort analysis. Complete baseline characteristics were recorded for all patients, including body mass index (BMI), smoking habits, medication that might affect hemostasis, previous thromboembolic events, previous abdominal surgery prior to CRS and HIPEC, and previous chemotherapy for PM disease.

Postoperative adverse events were classified according to Clavien-Dindo [122], but only Grades III-V were included in the analysis. The Caprini score (2005) [123] was used to assess the postoperative risk for VTE.

The time frame for postoperative adverse events was expanded to six months in order to investigate possible late HIPEC-related readmissions since the readmission rate between 90 days and six months in an earlier study was approximately 50%.[124]

The following blood tests were sampled on postoperative days (POD) 1, 2, 5, and 10: PT-INR, APTT, fibrinogen, antithrombin, D-dimer and platelet count. In addition, hemoglobin, erythrocyte, platelet and leucocyte counts were sampled at discharge. The following perioperative parameters were registered: primary tumor origin, liver resection, splenectomy, perioperative blood loss, perioperative erythrocytes and plasma transfusion, HIPEC regimen, intraabdominal temperature during HIPEC, early postoperative intraperitoneal chemotherapy (EPIC) if performed, duration of surgery, duration of in-hospital care, adverse events, interventions, duration of thromboprophylaxis, postoperative thromboembolic events as well as mortality.

Thromboprophylaxis treatment was given according to Uppsala County Hospitals' routine as a subcutaneous injection of Klexane® [Sanofi, Paris, France] 100mg/ml, 0.4ml once a day for a total treatment period of 4 weeks. In addition, mechanical prophylaxis including compression garments and routine physiotherapy were part of the postoperative care protocol.

Results

Three hundred and eighty patients with PM were included in the analysis. Mean age was 56. Thirty-one percent of the cohort had received neoadjuvant chemotherapy within three months prior to HIPEC (n=116). A complete cytoreduction to microscopic disease burden (CC0) was achieved in 264 patients (69%). Mean duration of surgery was 9.3 hours (range 4-18 hours). Mean length of hospital stay was 25.8 days (range 10-124 days). In total, 6% of VTEs occurred within 6 months (n=23). These patients had a median Caprini score of 8 (range 7-13) compared to 94% non-VTE patients who had a median Caprini score of 8 (range 6-15). Twelve of the VTEs occurred in hospital and 11 occurred within six months of the first discharge. Only 4% received a shortened postoperative anticoagulant therapy (2-3 weeks) due to the risk of

hemorrhage (n=17). However, none of those patients developed VTE within six months of their CRS and HIPEC.

Coagulation biomarkers PT-INR and APTT were elevated directly after surgery but returned to normal levels on POD 5 (Figure 15). Conversely, fibrinogen, platelet count, D-dimer, and anti-thrombin showed an increased level on POD 5 and a further increment up to POD 10 (Figure 16).

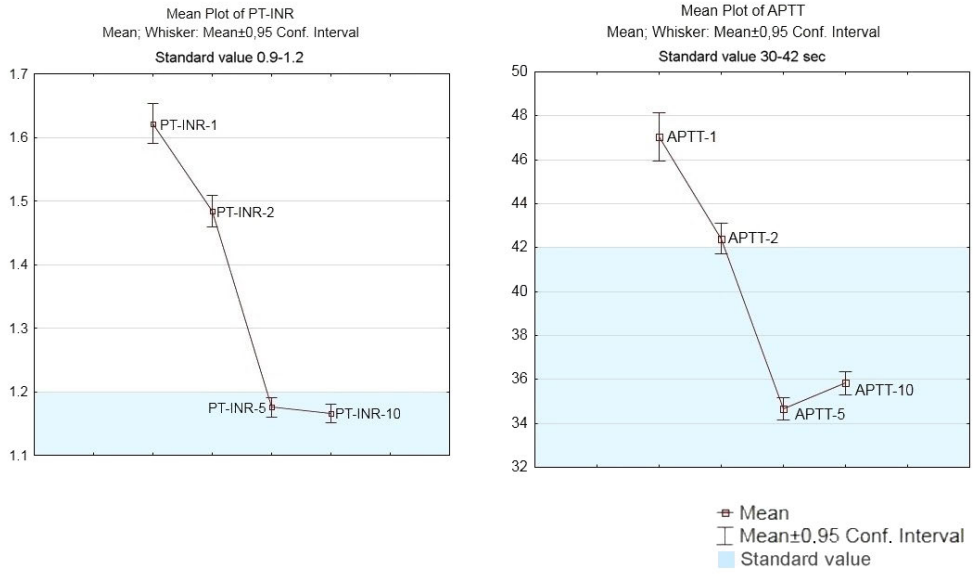


Figure 15 – The dynamics of probleeding coagulation markers in relation to time and standard value. Numbers 1, 2, 5 and 10 refer to the postoperative day on which blood samples were taken.

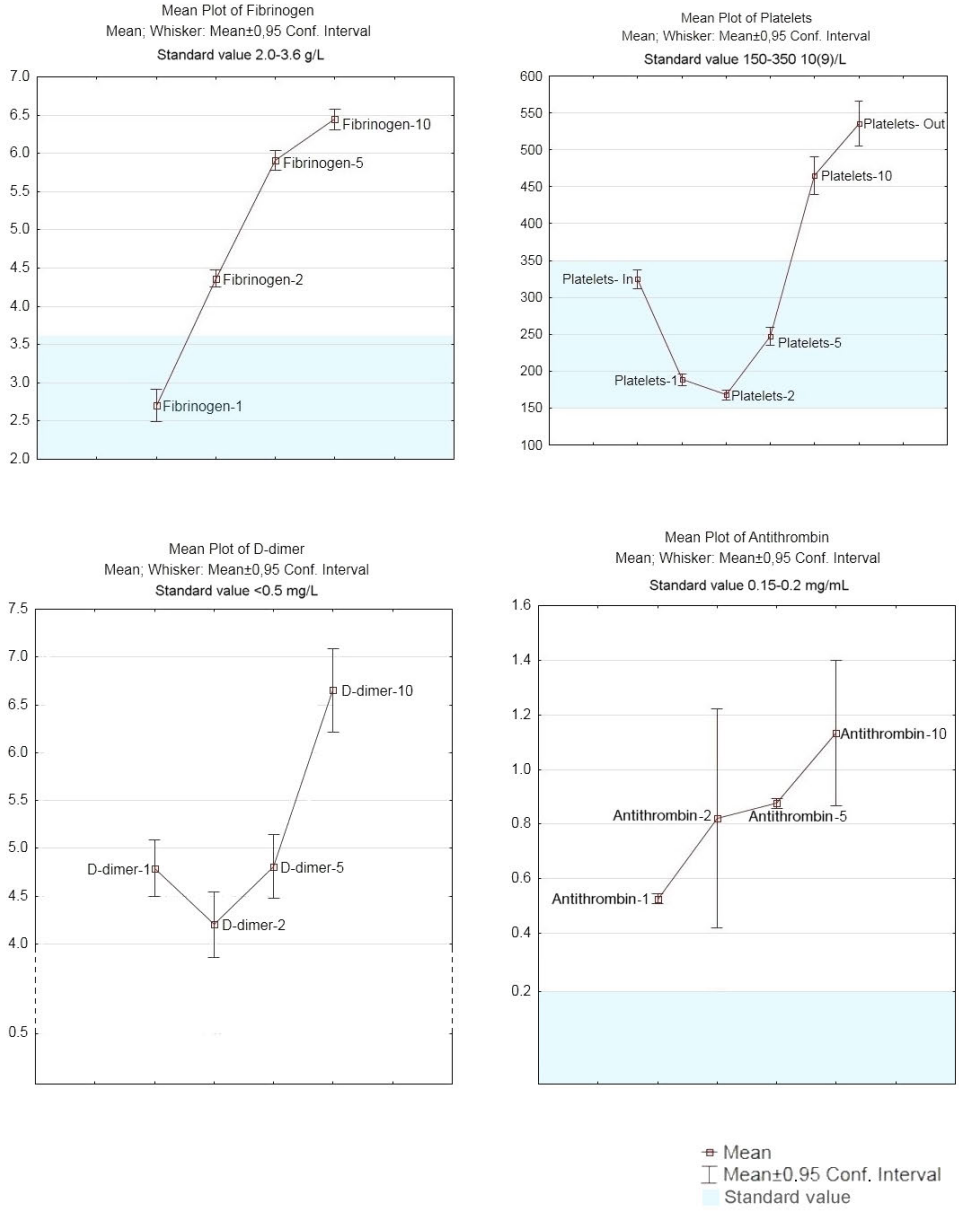


Figure 16 – the dynamics of prothrombotic coagulation markers in relation to time and standard value. Numbers 1, 2, 5 and 10 refer to the postoperative day on which blood samples were taken.

The univariate analysis on coagulation markers on POD 1 showed that an elevated level of D-dimer was a significant risk factor for postoperative VTE (OR 0.88 CL: 0.79-0.98, *p*=0.02) but this was excluded from further analysis due to a large amount of missing data (36%, n=135). Elevated D-dimer on POD 2 indicated an increased risk for VTE (OR 1.12 CI: 1.04-1.22, *p*=0.004).

There was no correlation between biomarkers on POD 5, POD 10 or upon discharge, and the increased risk for VTE. The multivariate logistic regression analysis found incomplete cytoreduction and D-dimer on POD 2 to be independent risk factors for postoperative VTE within six months (Table 6).

Table 6 – Logistic regression of venous thromboembolism events within six months of CRS and HIPEC

	Univariate analysis OR (CI)	***p*-value**	**Multivariate analysis OR (CI)**	***p*-value**
Age at treatment	0.96 (0.93-1.00)	0.055		
Gender: Male vs Female	0.57 (0.24-1.35)	0.20		
BMI (Kg/m^2)	0.96 (0.86-1.07)	0.50		
Active smoker Previous smoker Non-smoker	 0.96 (0.21-4.31) 1.46 (0.58-3.68) Reference	 0.96 0.41		
Cardiovascular comorbidity	1.35 (0.55-3.28)	0.50		
Caprini score	1.26 (0.98-1.61)	0.06		
Primary tumor site* Colorectal Appendix Gynecological Mesothelioma	 *Reference* 1.16 (0.45-2.98) 1.51 (0.18-12.74) 1.24 (0.14-10.52)	 0.92 0.78 0.98		
Preoperative intravenous chemotherapy, within 3 months	1.22 (0.50-2.98)	0.64		
HIPEC: Oxaliplatin	*Reference*			

HIPEC: Cisplatin+Doxorubicin HIPEC: Mitomycin C	1.31 (0.40-4.19) 1.05 (0.40-2.76)	0.66 0.86		
Systemic start temperature High Low	 3.85 (0.49-29.92) 0.25 (0.03-2.01)	 0.19 0.19		
Systemic end temperature High Low	 0.77 (0.26-2.24) 1.29 (0.44-3.75)	 0.63 0.63		
Mean IP temp	1.10 (0.39-3.12)	0.84		
PCI	1.00 (0.96-1.04)	0.98		
CCS: 0-1 2-3	*Reference* 2.87 (1.07-7.73)	 0.03	*Reference* 2.78 (1.01-7.62)	 0.047
Splenectomy	2.11 (0.90-4.95)	0.08		
Liver resection	1.81 (0.74-4.43)	0.18		
HIPEC + EPIC	1.51 (0.62-3.68)	0.36		
Duration of surgery	0.88 (0.76-1.03)	0.12		
Estimated blood loss (ml)	0.99 (0.99-1.00)	0.06		
ASA score: 3 vs. 1-2	1.57 (0.44-5.60)	0.48		
Intra-op erythrocytes infusion (ml)	0.99 (0.99-1.00)	0.20		
Intra-op plasma infusion (ml)	0.99 (0.99-1.00)	0.39		
Intra-op thrombocytes (Yes/No)	1.57 (0.19-12.88)	0.67		
Intra-op crystalloid fluids replacement	0.99 (0.99-1.00)	0.17		
Intra-op colloid fluids replacement	0.99 (0.99-1.00)	0.27		

Postop ICU: ≥ 2 days vs. 0-1	0.59 (0.13-2.63)	0.49		
Erythrocyte count upon admission**	0.36 (0.14-0.94)	0.03	0.39 (0.15-1.05)	0.061
D-dimer post-op day 2	1.12 (1.04-1.22)	0.004	1.12 (1.03-1.21)	0.0082
*Small intestine group was excluded due to the absence of VTEs. Gastric cancer group was excluded due to the insignificant number of patients (n=6). ** Erythrocyte count cut-off value between 4.30-5.70 10(12)/L				

Discussion

Two important risk factors for postoperative VTE were identified in this study – incomplete cytoreduction and elevated D-dimer on postoperative day 2. The latter finding, however, might be considered as a marker of subclinical coagulopathy.

Khan et al. (2019) identified high Caprini score, low serum albumin levels and additional inpatient comorbidity as risk factors for VTE following CRS and HIPEC.[26] However, in our study, the Caprini score showed no significant value in predicting the VTE risk (p=0.06).

The cumulative incidence of VTE within six months after CRS and HIPEC was 6%. Considering all pre-, peri- and post-operative risk factors, this rate is still in the middle range compared to previous studies (3% - 14%).[125-128] Using Falanga et al.'s (2013) classification of thrombotic risk factors in cancer patients[23], our results failed to show that patient-related factors, such as high age at time of treatment, high BMI, history of thrombosis, tobacco use, previous abdominal surgery and previous chemotherapy treatment were related to a significant risk for VTE within six months of CRS and HIPEC (Table 6). On a cellular level, our study results showed no significantly increased risk for VTE when the platelet count was elevated and, although the univariate logistic analysis on erythrocyte count upon admission prior to CRS and HIPEC showed a significant risk (OR 0.36 CI:0.14-0.94, p=0.03), this risk was no longer significant in multivariate analysis (Table 6).

It seems as though an early rise in D-dimer is more closely VTE-related than a later rise in D-dimer, probably because the later rise in D-dimer may be more closely related to the general postoperative inflammatory response.

As for the treatment-related variables, just one was associated with increased VTE, namely an incomplete cytoreduction (CC) score.

The difference lay between CC0-1 and CC2-3. As such, the real increase in risk occurred in patients with remaining bulky peritoneal disease. This is relevant in patients with large pseudomyxoma peritonei tumors.

Multivariate analysis done by Rottenstreich et al. (2017) identified the lack of extended anticoagulation treatment at discharge as the only risk factor for

thrombosis after CRS and HIPEC.[128] However, none of the patients included in our study lacked postoperative anticoagulant treatment and none was treated for less than two weeks. Neither the majority who were treated for four weeks, nor the 4% who received shorter postoperative anticoagulant therapy (2-3 weeks), developed a VTE within six months of CRS and HIPEC.

Paper III: Morbidity Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastases With or Without Early Postoperative Intraperitoneal Chemotherapy: A Propensity Score Matched Study.

Patients and Methods

Our study included all consecutive patients with PM regardless of primary tumor site, being treated with CRS and HIPEC ± EPIC from 2004 to 2014 at Uppsala University Hospital. Even though the use of EPIC ended in 2009, the inclusion period was extended another 5 years to have a sufficient cohort to perform successful propensity score matching (PSM). The cohort was divided into two groups depending on whether EPIC was administered or not.

Surgical radicality was defined according to the completeness of cytoreduction score (CCS).[75, 129] However, the decision to add EPIC was not predefined but mainly taken intraoperatively by the surgical team during a certain time period (2004–2009). EPIC was first initiated in the PMP cohort of patients, primarily for those with large volume PMP. Shortly after, for a short period, it was used more generally in other tumors as our institutional standard. EPIC use was halted after preliminary international reports of increased morbidity. The EPIC drug (5-fluorouracil or Taxol) measured in mg/m^2 was administered according to a standardized treatment protocol via an intraperitoneal catheter. EPIC was given from postoperative day one to day five either in the intensive care unit (ICU) or the surgical ward.

Treatment included the main HIPEC regimen ± perioperative intravenous 5-fluorouracil (IV-5-FU, only to patients treated with oxaliplatin ± irinotecan-based HIPEC regimen) ± EPIC. Mitomycin C (30 mg/m^2) was used with a flow rate of 2 L /min for approximately 90 min at a mean intraabdominal temperature of 41.5°C as the main HIPEC regimen to treat the majority of appendiceal cancers, while the HIPEC regimen with oxaliplatin ± irinotecan (360 mg/m^2 for both drugs) for 30 min at a mean intraabdominal temperature of 42°C was the main treatment for colorectal and gastric cancers. Lastly, cisplatin ± doxorubicin (50±15 mg/m^2) was used as HIPEC regimen for peritoneal mesothelioma or ovarian cancer.

PSM was applied using the covariates: sex, primary tumor site, preoperative chemotherapy, peritoneal cancer index (PCI), completeness of cytoreduction score and HIPEC regimen (Figure 17). PSM was performed 1:1 using the nearest neighbor method with a caliper of 0.2.

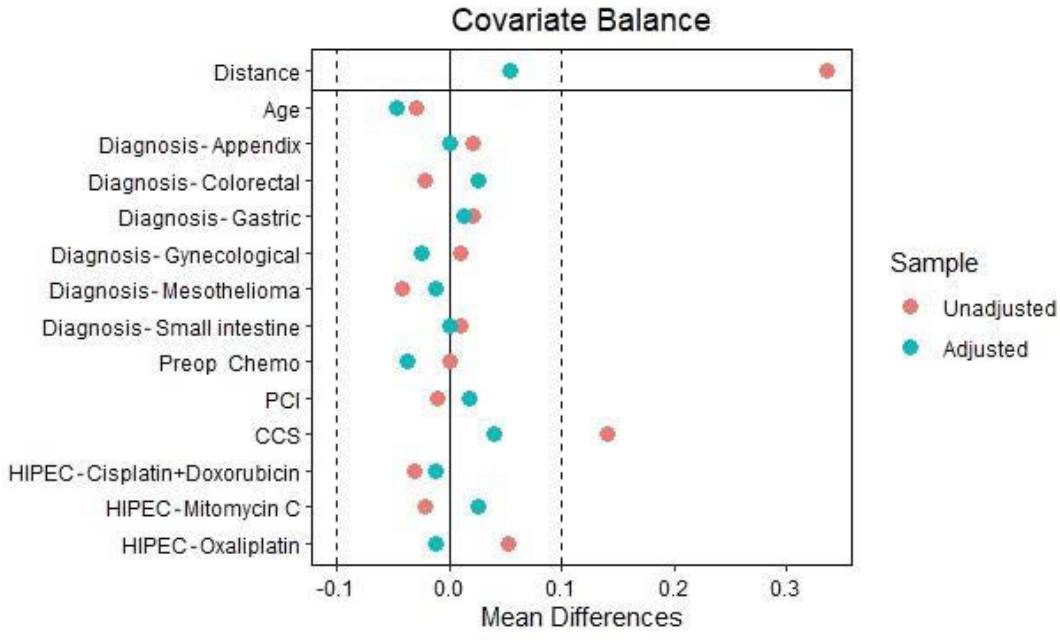


Figure 17 – Love plot demonstrating propensity score matching of 115 HIPEC + EPIC patients to 282 HIPEC alone with a 1:1 nearest neighbor.

Results

Study population and general demographics

A total of 397 patients with PM who underwent CRS and HIPEC ± EPIC were included in the analysis. Seven patients were excluded due to missing data while the rest (n=390) formed the unadjusted cohort (Figure 14). Mean age was 55.2 [range 13-77]. The cohort was divided into two arms, the HIPEC+EPIC arm (n=115) and the HIPEC alone arm (n=275). Six primary tumors were included (appendix, colorectal, gastric, ovarian, mesothelioma and small intestine). The majority of the HIPEC+EPIC group had a PCI ≥ 21 (57%, n=65) while the HIPEC alone group had a PCI ≥21 (36%, n=100). Seventy-eight percent of patients in the HIPEC alone arm reached CCS 0 (n=216) compared to 48% in the HIPEC+EPIC arm (n=55). The mean length of surgery was 540 min [range 240-960] and mean intraoperative blood loss was 908 ml [range 25-8600].

The main EPIC regimen was 5-FU. However, 9% of the cohort were treated with Taxol as the EPIC regimen due to allergic reactions to 5-FU (n=10).

In-hospital length of stay (LOS) in the unadjusted population was longer in the HIPEC+EPIC group (30 vs 24 days, $p<0.001$).

However, LOS lost its statistical significance in the propensity score matched population, but with a trend towards significance (29 vs 25 days, $p=0.062$, Table 7).

Table 7 – Postoperative characteristics of the unadjusted and propensity matched population.

Unadjusted cohort	**Overall**	**HIPEC only**	**HIPEC+EPIC**	***p*-value**	**SMD***
n	**390**	**275**	**115**		
LOS, mean (SD)	25.99 (15.20)	24.22 (13.73)	30.23 (17.61)	<0.001	0.38
Clavien-Dindo, n (%)				0.29	0.24
1	190 (49)	133 (48)	57 (50)		
2	116 (29)	89 (32)	27 (24)		
3a	42 (11)	28 (10)	14 (12)		
3b	30 (8)	18 (7)	12 (10)		
4	12 (3)	7 (3)	5 (4)		
Clavien-Dindo Grades III-IV, n (%)	84 (22)	53 (19)	31 (27)	0.11	0.24
Selected specific morbidity, n (%)					
Fistula within 6 months	13 (3)	8 (3)	5 (4)	0.44	0.229
Ileus	15 (4)	8 (3)	7 (6)	0.13	0.425
Neutropenia	63(16)	49 (18)	14 (12)	0.20	0.246
Disruption of operation wound	9 (2)	7 (3)	2 (2)	0.65	0.214
Anastomotic insufficiency	9 (2)	5 (2)	4 (3)	0.30	0.631
In-hospital reoperation, n (%)	34 (9)	22 (8)	12 (10)	0.39	0.161
Readmission, n (%)	99 (25)	65 (24)	34 (30)	0.39	0.154
Propensity matched Population					
n	**190**	**95**	**95**		
LOS, mean (SD)	27.34 (16.97)	25.04 (16.15)	29.63 (17.53)	0.062	0.27
Clavien-Dindo, n (%)				0.59	0.24
1	93 (49)	46 (48)	47 (49)		
2	55 (29)	31 (33)	24 (25)		
3a	22 (12)	11 (12)	11 (12)		

3b	15 (8)	5 (5)	10 (11)		
4	5 (2)	2 (2)	3 (3)		
Clavien-Dindo Grades III-IV, n (%)	42 (22)	18 (19)	24 (25)	0.38	0.20
Selected specific morbidity, n (%)					
Fistula within 6 months	7 (4)	4 (4)	3 (3)	0.70	0.164
Ileus	11 (6)	4 (4)	7 (7)	0.35	0.327
Neutropenia	29 (15)	15 (16)	14 (15)	0.84	0.044
Disruption of operation wound	3 (2)	1 (1)	2 (2)	0.56	0.388
Anastomotic insufficiency	7 (4)	3 (3)	4 (4)	0.70	0.164
In-hospital reoperation, n (%)	14 (7)	4 (4)	10 (11)	0.30	0.307
Readmission, n (%)	47 (25)	23 (24)	24 (25)	0.86	0.031
*Standardized mean difference					

Overall, 27% of the HIPEC+EPIC population developed morbidity Grades III-IV (n=31).

The rate of in-hospital morbidity in the HIPEC alone population was lower compared with the HIPEC+EPIC population, both for the unadjusted and the PSM population. However, the difference did not reach statistical significance (Table 7). Overall, 19% of the HIPEC alone population developed Clavien-Dindo III-IV (n=53). Two in-hospital deaths (Clavien-Dindo Grade V)[122] occurred in the HIPEC+EPIC population (2%) while three in-hospital deaths (Clavien-Dindo Grade V) occurred in the HIPEC alone population (1%).

As EPIC use did not reach statistical significance in the univariate analysis (Table 8), we undertook a second adjusted analysis for EPIC use including sex, age, primary tumor site, preoperative chemotherapy use, PCI, and CCS. In this multivariable adjusted analysis, the use of EPIC did not increase the risk of Clavien-Dindo morbidity either (adjusted OR 1.22 [95% CI 0.67-2.23], *p*-value 0.49).

Table 8 – Predictive factors for postoperative morbidity Grade III-V assessed by univariate and multivariate logistic regression analysis.

	Univariate analysis		**Multivariate analysis**	
Variables	**OR (95%CI)**	***p*-value**	**OR (95%CI)**	***p*-value**
Sex	1.36 (0.83-2.21)	0.21		
Age at treatment	0.98 (0.96-1.00)	0.12		
BMI	1.01 (0.95-1.08)	0.54		
Primary tumor site				
Mesothelioma	Reference			
Appendix	0.68 (0.41-1.10)	0.12		
Colorectal	3.00 (0.48-18.41)	0.69		
Ovarian	4.43 (0.86-22-84)	0.48		
Small intestine	2.73 (0.52-14.21)	0.40		
Gastric	6.00 (0.42-85.24)	0.57		
KPS				
≥90	0.73 (0.31-1.71)	0.47		
≤80	1.35 (0.58-3.17)	0.47		
Neoadjuvant chemotherapy	1.15 (0.71-1.87)	0.54		
Duration of surgery	0.87 (0.80-0.95)	**0.003**	0.99 (0.87-1.12)	0.90
Intraoperative blood loss				
<2000ml	Reference			
≥2000ml	2.77 (1.62-4.75)	**0.0001**	2.05 (1.11-3.78)	**0.02**
HIPEC regimen				
Cisplatin+Doxorubicin	Reference			
Oxaliplatin	0.63 (0.32-1.26)	0.32		
Mitomycin C		0.54		

	0.67 (0.32-1.40)			
PCI	0.96 (0.93-0.98)	**0.0004**	0.97 (0.94-1.00)	0.09
CCS				
0-1	Reference			
≥2	2.60 (1.36-4.97)	**0.003**	1.29 (0.60-2.77)	0.51
EPIC	1.22 (0.67-2.23)	0.49		

Discussion

This study is one of the few larger studies to compare the outcome of HIPEC+EPIC to that of HIPEC alone. Our study showed no increased risks when adding EPIC to HIPEC, although the LOS increases, which is a natural consequence when adding up to five days of treatment. However, the incidence of morbidity was numerically higher in the HIPEC+EPIC group both in the unadjusted and adjusted analyses and we cannot therefore exclude a slightly increased risk of morbidity when adding EPIC to HIPEC.

Considering the lack of HIPEC efficacy demonstrated in a recent trial (PRODIGE7), we believe our results are of interest in view of the need for intensified intraperitoneal chemotherapy treatment. Despite the possible increase in morbidity, it is still within acceptable limits in the literature after CRS+HIPEC and combining HIPEC with EPIC may be an important way to increase the efficacy of the treatment of residual tumor cells after CRS.[130]

However, the few studies that do exist have been rather small with few EPIC patients included and have shown conflicting results.[35]

Due to the inclusion of different primary tumors in this study, analysis of survival data was not feasible. The reason for including all patients was to have as large group as possible to conduct a proper evaluation of postoperative risks. However, in previous studies from our institution, the addition of EPIC to HIPEC showed no benefit for the PMP patient group, but it did for the colorectal patient group.[131, 132]

Due to the previous conflicting results concerning morbidity, particularly a reportedly increased risk for GI fistulation with the HIPEC+EPIC combination, the EPIC treatment option has fallen from the treatment arsenal. However, our study has evaluated GI fistulation up to six months postoperatively and has shown no increased risk of that specific morbidity. Therefore, it is time to reassess EPIC as a possible treatment alternative in peritoneal surface malignancy.

Based on the last decade´s improvements of PM treatment techniques and chemotherapy regimens, it is clear that further exploration of EPIC use would

be valuable, especially for cases of PM disseminated from colorectal origin, where improvements are needed in the current arsenal of intraperitoneal chemotherapy treatments. In Sweden, we are currently conducting a dose-titration trial for a 1-day EPIC treatment in conjunction with an intensified oxaliplatin/irinotecan HIPEC for colorectal cancer patients. The results from this current safety study have helped in providing a rationale for this treatment intensification.

Paper IV: The Impact of Intraoperative Fluid Management Strategies During Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Postoperative Outcomes.

Patients and Methods

Patients were categorized into two groups according to intraoperative fluid management strategy. The first group included 328 patients (64%) treated with traditional intraoperative fluid administration in the pre-goal directed therapy (pre-GDT) era between November 2004 and December 2012. The second group comprised 181 patients (36%) treated with goal-directed therapy (GDT) between January 2013 and December 2017. Initially, GDT was monitored intraoperatively using an esophageal probe (CardioQ™, Deltex Medical Ltd, Sussex, UK) and since early 2015 with the use of FloTrac/Vigileo (Edwards LifeSciences, Irvine, CA, USA). All surgical characteristics that might have an impact on the risk for postoperative bleeding were registered. These included duration of surgery, volume of intraoperative blood loss, splenectomy, excision of liver capsula or liver resection, peritoneal cancer index (PCI) and completeness of cytoreduction score (CCS) as well as the use of different HIPEC regimens.

During the pre-GDT era of fluid management, fluid administration of 9-12 mL/kg/h was advocated to ensure a satisfactory urinary output of at least 1 mL/kg/h.[82, 133] Urine output, and point-of-care blood gas measurements— lactate, base excess, and hemoglobin levels— were used to guide fluid administration. GDT treatment was monitored by an intraoperative hemodynamic protocol using the FloTrac/Vigileo device or esophageal echo-Doppler to predict the fluid responsiveness by dynamic preload parameters such as stroke volume variation (SVV) or aortic blood flow corrected flow time (FTc)[86] as a measure of intraoperative fluid replacement.

Postoperative morbidity was graded according to the Clavien-Dindo classification.[122] Postoperative hemorrhage was defined as a Clavien-Dindo ≥ Grade IIIa complication due to radiologically or intraoperatively proven intraabdominal hemorrhage. Survival was defined as time between date of surgery and date of death from any cause.

Results

Five hundred and nine patients were included in the analysis. The pre-GDT group constituted 64% of the cohort (n=328) while the GDT group made up 36% of the cohort (n=181). The cardiovascular co-morbidity rate was higher in the GDT group compared to the pre-GDT group (49%, n=88 vs. 34%, n=110). However, it did not reach a significant *p*-value (0.06).

Estimated intraoperative blood loss (≥2000ml) was much higher in the pre-GDT group (22%, n=72) compared to the GDT group (13%, n=24, *p*=0.01). The GDT group had a significantly higher rate of treatment with oxaliplatin ± irinotecan (71%, n=128 vs. 43%, n=141, *p*<0.0001).

The overall risk for postoperative hemorrhage was 7% (n=35) with oxaliplatin-based HIPEC regimens having a bleeding rate of 10% (n=27) vs. other HIPEC regimens with a rate of 3% (n=8), *p*-value=0.006. Most cases with hemorrhage in both groups had a late onset (≥72 h). There was a trend towards more postoperative bleeding in the GDT group (9% vs 5%, *p*-value 0.09, Table 18). The majority of late-onset hemorrhage (83%) received oxaliplatin ± irinotecan as the HIPEC regimen (n=24); 10% received cisplatin + doxorubicin (n=3), and 7% received mitomycin C (n=2). However, the double-drug HIPEC regimens showed no significantly increased risk for postoperative hemorrhage (*p*=0.23).

In-hospital mortality was 0.2% (n=1) and 2% mortality was observed within 90 days (n=9). No difference in 90-day mortality between the groups was detected. No patient died from postoperative hemorrhage. Survival analysis is presented in Figure 18. Median overall survival in Figure 18 was 83 months for the pre-GDT group and 72 months for the GDT group (*p*=0.50).

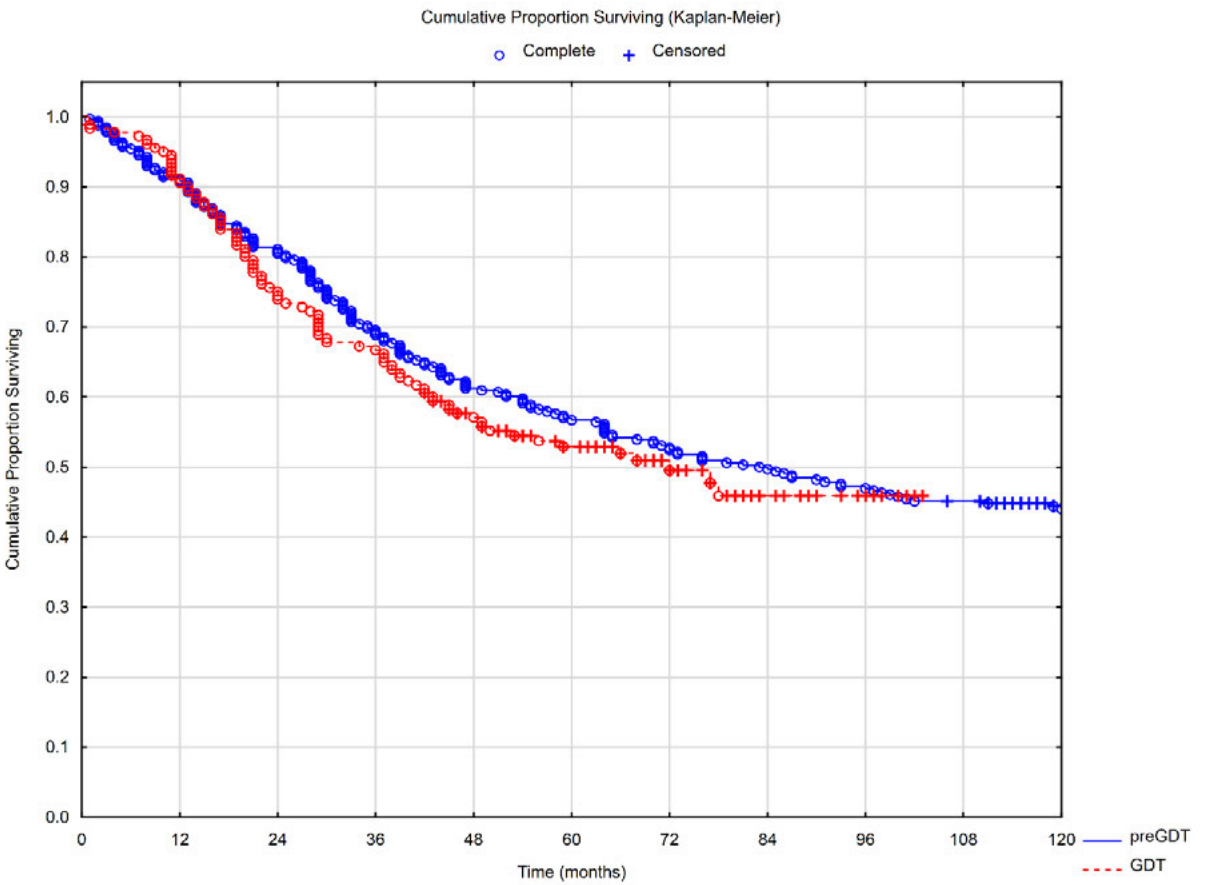


Figure 18 – Overall survival for the pre-GDT group compared to GDT group.

The multivariable adjusted OR for Clavien-Dindo Grades III-V morbidity according to the prespecified covariables [age, ASA score, primary tumor site (small intestine and gastric cancer were excluded due to few cases in both groups), neoadjuvant chemotherapy, PCI, CCS, as well as HIPEC regimen use] was 1.80 (95%CI 1.10-3.10, p=0.02) for the GDT group compared to pre-GDT group (Table 9).

Table 9 – Univariate analysis and multivariate logistic regression with postoperative hemorrhage as the endpoint.

	Univariate analysis OR (CI)	***p*-value**	**Multivariate analysis OR (CI)**	***p*-value**
Age at treatment ≥70	1.00 (0.97-1.03) 1.96 (0.88-4.36)	0.83 0.09	1.77 (0.77-4.06)	0.17
Gender: Female Male	Reference 0.88 (0.44-1.75)	0.72		
BMI (kg/m^2)	1.07 (0.97-1.17)	0.14		
Cardiovascular comorbidity	1.09 (0.53-2.25)	0.80		
ASA score: 1-2 ≥3	 Reference 1.49 (0.62-3.55)	 0.36	 	
Previous abdominal surgery for primary tumor	2.88 (0.86-9.62)	0.08	2.23 (0.65-7.63)	0.19
Preoperative intravenous chemotherapy, within 3 months	0.99 (0.45-2.19)	0.99		
Fluid management: Group 1 (pre-GDT*) Group 2 (GDT)	 Reference 1.78 (0.89-3.55)	 0.09	 1.37 (0.64-2.95)	 0.40
HIPEC regimen: Mitomycin C Oxaliplatin ± Irinotecan Cisplatin ± Doxorubicin	 Reference 3.07 (1.36-6.90) 0.28 (0.09-0.81)	 0.006 0.01	 3.32 (1.11-9.94) 2.20 (0.52-9.30)	 0.03 0.28

HIPEC regimen: Single drug Double drug	 Reference 0.61 (0.27-1.38)	 0.24		
PCI: 1-20 21-39	 Reference 0.92 (0.45-1.87)	 0.81		
CCS: 0-1 2-3	 Reference 0.28 (0.03-2.09)	 0.21		
Splenectomy	1.57 (0.78-3.12)	0.19		
Liver resection	1.21 (0.35-4.16)	0.75		
Extirpation of liver capsule	0.78 (0.26-2.29)	0.65		
HIPEC + EPIC	0.50 (0.17-1.45)	0.20		
Surgery duration (min)	1.00 (0.99-1.00)	0.35		
Estimated blood loss (ml): <2000 ml ≥2000 ml	 Reference 0.70 (0.26-1.85)	 0.47		
Intraoperative erythrocytes infusion (ml) 0 PRBC 1-4 PRBC >4 PRBC	 Reference 1.04 (0.52-2.09) 1.06 (0.39-2.85)	 0.90 0.89		
Intraoperative plasma infusion (ml) 0 FFP 1-4 FFP >4 FFP	 Reference 1.21 (0.53-2.75) 0.60 (0.20-1.76)	 0.64 0.36		
Intraoperative thrombocytes	1.03 (0.13-8.10)	0.97		

Intraoperative crystalloid fluids replacement <7500ml ≥7500ml	Reference 0.66 (0.32-1.33)	0.24		
Intraoperative colloid fluids replacement <2000ml ≥2000ml	Reference 0.58 (0.29-1.16)	0.12		
Total fluid replacement (ml/kg/h)	1.00 (0.95-1.05)	0.85		
* Goal-directed therapy				

Discussion

With over 500 patients, our study is one of the largest to date evaluating goal-directed fluid therapy management in CRS and HIPEC treatment. Unexpectedly, patients in the GDT group had an increased Clavien-Dindo morbidity. Despite these findings, patients were discharged home or to the referring hospitals earlier in the GDT group. To our knowledge, there is only one small, randomized trial investigating GDT in HIPEC patients done by Colantonio et al. (2015) with 38 patients in the GDT arm and 42 in the standard fluid therapy arm.[13] The same study concluded that the use of GDT minimized the incidence of postoperative major abdominal morbidity (10.5% in GDT group, n=4 vs. 38%, n=16, p=0.005) and shortened LOS (19 days in GDT group vs. 29 days, p<0.0001).[87] Likewise, among the few observational studies published, the cohort sizes are relatively small and have demonstrated conflicting results.[85, 88, 89]

The increased morbidity in the GDT group in our study is probably partially explained by broader indications for treatment. As our center has developed its long-standing expertise, it is clear that older and more frail patients have been included for treatment. Both age and ASA score were significantly increased in the GDT period. Despite this increase in age and ASA, the length of stay has decreased, demonstrating that successful treatment in higher age and comorbid groups appears feasible.

The results of our study confirmed that oxaliplatin was an independent prognostic factor for postoperative hemorrhage with a three-fold increased risk compared to non-oxaliplatin HIPEC regimens. While there was a trend towards increased risk of bleeding in the GDT group, the difference disappeared in the multivariable analysis, in part due to more oxaliplatin-based HIPEC treatments in the GDT period.

LOS was significantly shorter in the GDT group compared to the pre-GDT group (17 vs. 26 days, p<0.001) despite the fact that postoperative care in the ICU was longer. The mean intraoperative fluid replacement in the GDT group

with extended ICU (more than 2 days) was 14.3 ml/kg/h [range 8-36] which was lower than the GDT group as a whole. Twenty-nine patients needed more than 2 days in ICU, but only 15 patients had Clavien-Dindo Grade IV morbidity (requiring ICU care). It is possible that an overly restrictive fluid replacement regimen could be behind these other cases and that fluid balance issues have led to prolonged intermediate care needs. Further follow-up analysis is warranted to interpret the differences that have been demonstrated in the morbidity analysis. Nonetheless, the LOS was shortened, and, while we do not possess data on return of bowel function, we hypothesize that GDT may support this effort leading to a shortened overall LOS.

Our study results demonstrated no survival benefits for patients treated with GDT compared to those receiving liberal intraoperative management (Figure 18) in either the Kaplan-Meier analysis or the multivariable analysis. The slight difference in trend is explained by a larger proportion of pseudomyxoma patients in the pre-GDT period and conversely larger proportion of colorectal patients in the GDT period.

General Discussion and Future Perspectives

Although the in-hospital morbidity needing surgical intervention (Clavien-Dindo III-IV) following CRS and HIPEC appeared to be similar to previous studies (11% - 26.8%) [2, 96, 112], it appeared that there was a significant number of readmissions within six months after CRS and HIPEC, higher than expected. Moreover, our national population-based study in Paper I confirmed that gastric resection and high age are independent predictors of morbidity and readmission. Additionally, half of readmission interventions occurred at the referral hospital and, in most cases, were performed without consultation or feedback to the treating HIPEC center. There appear to be some increased long term readmission risks connected to CRS and HIPEC that warrant consideration in future.

One vital postoperative morbidity is coagulopathy and venous thromboembolic events (VTEs). The coagulation biomarkers on postoperative days (POD) 1, 2, 5 and 10 revealed that an elevation in D-Dimer on POD 2 along with residual tumor at completion of surgery were independent risk factors for postoperative VTE. The overall risk for VTE, however, was low (6%) taking into consideration the magnitude of the procedure with CRS and HIPEC and its possible impact on fluid balance and the coagulation cascade.

Adding extra treatment with early postoperative intraperitoneal chemotherapy (EPIC) to CRS and HIPEC on POD 1 – POD 5 was associated with a prolonged hospital stay. Apart from the obvious prolongation caused by the treatment itself, a longer hospital stay might be related to a delay in bowel function caused by gastro-intestinal paralysis as a result of the procedure and chemotherapy. However, when comparing HIPEC alone to treatment with HIPEC+EPIC, the results showed no significant increase in postoperative morbidity, reoperation rate or incidence of readmission. Thus, it would be helpful to evaluate the use of EPIC in future randomized trials.

The intraoperative use of fluid management during CRS and HIPEC using a goal-directed therapy (GDT) increased the risk for postoperative morbidity. Despite this, GDT was associated with shortened hospital stay. Although age and ASA score did not account for the whole difference, it was clear that the increased age and ASA in the later GDT group contributed partially to the increase of postoperative morbidity. Intraoperative fluid management during CRS and HIPEC did not affect the postoperative risk for hemorrhage, while the use of oxaliplatin as the HIPEC regimen did.

Due to the high number of readmissions within six months of CRS and HIPEC, studies focusing on patient-related outcome measures (PROMs) should be prioritized for broader evaluation of CRS and HIPEC. A quality-of-life survey is one way to evaluate patients' own experience of the outcome. Moreover, an extended follow-up with PROMs would be preferable and could provide significant feedback as quality control as well as monitoring the long-term effects of CRS and HIPEC.

In some PM cases, patients undergo an open/close procedure due to widespread high-volume tumor. Even though those patients are not exposed to a major abdominal procedure such as CRS, still they are undergoing a 1-2 hour open/close procedure. Unfortunately, those patients were not included in the study presented in Paper II and thus their postoperative coagulopathy has not been analyzed. However, based on the results of Paper II, a residual tumor at completion of surgery increases the risk of postoperative VTE. Therefore, a prolonged follow-up of this group to study their risk of developing postoperative VTE should be considered.

Based on the last decade´s improvements of peritoneal surface malignancy (PM) treatment techniques and chemotherapy regimens, it is clear that further exploration of EPIC use would be of great value, especially for cases of PM disseminated from a colorectal origin, where improvements are needed in the current arsenal of intraperitoneal chemotherapy treatments. In Sweden, we are currently conducting a dose-titration trial for a 1-day EPIC treatment in conjunction with an intensified oxaliplatin/irinotecan HIPEC procedure for colorectal cancer patients. The results from this current safety study have helped in providing a rationale for this treatment intensification. Thus, further studies are needed to investigate the oncological efficacy of EPIC as adjuvant treatment after CRS and HIPEC.

Although the existing body of knowledge is conflicted regarding intraoperative fluid management using GDT during CRS and HIPEC, our study has shown an increased rate of postoperative morbidity following GDT. Further studies are needed to look at different sub-groups within the GDT group to identify where the risks are greatest. Moreover, a more accurate registration of return of bowel function could be a factor of interest that might improve the postoperative LOS.

Conclusions

Paper I: Morbidity causing HIPEC-related readmission was higher than expected with almost half of the interventions occurring outside the HIPEC center. Gastric resection and high age are independent predictors of morbidity and readmission.

Paper II: Significant postoperative changes in coagulation biomarkers occur with dynamic changes over 10 days postoperatively. The incidence of VTE was low. Residual tumor at completion of surgery and elevated D-dimer on POD 2 were independent risk factors for postoperative VTE.

Paper III: HIPEC+EPIC is associated with a prolonged hospital stay, but with no statistically significant relevant increase in postoperative morbidity, reoperation rate or incidence of readmission.

Paper IV: While GDT management increased the risk for postoperative morbidity, it was associated with a shortened hospital stay. Intraoperative fluid management during CRS and HIPEC did not affect the postoperative risk for hemorrhage, while the use of oxaliplatin regimen did.

Limitations

Paper I: Recently, the coding of comorbidity data has become a phenomenon in Sweden, as it is now partly being used for health-care reimbursement. However, this was not the case earlier in our study period. Therefore, reliable comorbidity data are not available to adjust the risk ratios in this study. Nonetheless, most patients being considered for this treatment did not have extensive comorbidities, and while this is a definite limitation, the authors do not believe it changes the risk factors as identified in this study.

Paper II: Although the study design is prospective, the main limitation of this study is that the endpoint was retrospectively assessed. Even though the study was a prospectively planned one, the retrospective assessment of VTE most probably means that the study might potentially have missed VTE events that did not lead to hospitalization. However, this means that only minor VTE events were possibly missed and the assessment through the National Swedish Inpatient Register means that the study has the same follow-up for all patients. Another limitation is that the study would have been improved if D-dimer was taken at baseline preoperatively. Patients already demonstrating some increase in D-dimer at baseline may correlate with the POD 2 D-dimer, highlighting possible subclinical susceptibility to VTE instead of being related to the surgical treatment. Even so, the D-dimer response to the surgical treatment is still a relevant finding regardless of correlation to underlying preoperative susceptibility since the surgical treatment adds risk to this susceptibility, leading to higher incidences of clinically significant VTEs. Identifying these individuals may be important to prevent late VTE development.

Paper III: The main limitation of this study is the retrospective design and the historical cohort, similar to the few published studies that compare HIPEC+EPIC to HIPEC alone. The main reason for this is that EPIC was used in Sweden from 2004 to 2009 and has not been practiced since then. However, the results remain highly relevant because variations in the EPIC protocol are under consideration in current clinical trials. The size of the EPIC group in our study is one of the largest published and thus provides an important evaluation of the safety of adding EPIC to HIPEC.

Paper IV: The main limitation of this study is the time aspect. There is always a progression of learning and patient selection. With this comes increased confidence in when to discharge patients to referring hospitals for rehabilitation. It is inevitable that intraoperative GDT management is not solely responsible for decreased LOS. Even GDT treatment has evolved over time and with different monitoring techniques. We acknowledge that even though it is difficult to completely separate time-dependent learning improvement from GDT use, this study corroborates the fact that LOS has indeed decreased and that GDT use is probably associated with this improvement. Finally, even though the study is based on a prospective HIPEC register, some of the variables were retrospectively retrieved and, as such, there is always a certain risk of bias in evaluation.

Svensk sammanfattning

Avhandlingen innefattar flera olika aspekter av postoperativa komplikationer efter cytoreduktiv kirurgi (CRS) med hypertermisk intraperitoneal kemoterapi (HIPEC). Denna behandling är behäftad med en hel del komplikationer och biverkningar och syftet har varit att undersöka dessa i detalj.

Återinläggningskomplikationer, tromboemboliska komplikationer, komplikationsrisk efter kombinationsbehandling med HIPEC och tidig postoperativ intraperitoneal kemoterapi jämfört med behandling med enbart HIPEC och till sist analyser av olika strategier for intraoperativ vätsketerapi under CRS och HIPEC.

Återinläggningskomplikationer har undersökts i en stor nationell studie med långtidsuppföljning efter CRS+HIPEC. Studien påvisade 150 HIPEC-relaterade återinläggningar hos 129 patienter (25%). Av dessa krävde 67 patienter invasiva åtgärder (13%). Sammanfattningsvis var sjukligheten som orsakade HIPEC-relaterade återinläggningar högre än förväntat och nästan hälften av interventionerna inträffades utanför HIPEC-centret. Ventrikelresektion och hög ålder var oberoende riskfaktorer för postoperativ morbiditet och återinläggning.

Andra studien fokuserade på koagulationsrubbning och dynamiken av koagulationsbiomarkörer efter CRS och HIPEC. Risken för att utveckla postoperativa tromboemboliska komplikationer av venöst ursprung (VTE) undersöktes. Denna studie baserades på ett prospektiv provtagning dag 1, 2, 5 och 10 postoperativt. Studieresultaten påvisade 23 radiologiskt verifierade fall av VTE inom 6 månader (6%). Analyser av postoperativa koagulationsbiomarkörer visade att PT-INR och APTT stiger direkt efter operation men återgick till normala nivåer efter dag 5, vilket tyder på en ökad blödningsbenägenhet under de första postoperativa dygnen. Fibrinogen, trombocyter, D-dimer och antitrombin började däremot stiga dag 5 och fortsatte att öka fram till dag 10, vilket indikerade en ökad risk för tromboemboliska komplikationer. I multivariata analyser visade studien att inkomplett cytoreduktion samt förhöjd D-dimer dag 2 var oberoende riskfaktorer för postoperativ VTE.

I tredje studien jämfördes CRS och HIPEC-behandling med CRS och HIPEC plus tilläggsbehandling med tidig postoperativ intraperitoneal kemoterapi (EPIC). I Sverige och även i Norden så har denna behandling varit specifikt förknippad med Uppsala HIPEC-center och gjordes enbart under en begränsad period mellan 2004 och 2009. En ”propensity score matching”

gjordes på en kohort av 390 patienter (115 HIPEC+EPIC vs 275 HIPEC) där fick vi 95 patienter i varje grupp. Studieresultaten bekräftade att användningen av EPIC förlängde den postoperativa sjukhusvistelsen. I övrigt var denna behandling inte förknippad med en ökad risk för postoperativa komplikationer, reoperation eller återinläggning.

I sista studien analyserades olika former av intraoperativa vätsketerapier, en restriktiv (goal-directed therapy, GDT) och en mer liberal (pre-GDT) och jämfördes komplikationsrisken efter de båda regimerna med fokus på postoperativ blödning och överlevnad. Studien visade att marginal av intraoperativ vätsketerapi under CRS och HIPEC inte påverkade blödningsrisken. GDT strategin var dessvärre förknippad med förlängning av vårdtid på intensivvårdavdelning och även med högre risk för postoperativa komplikationer. Studieresultaten visade även en ökad risk för postoperativ blödning efter användning av oxaliplatin vid HIPEC-behandling jämfört med andra preparat. GDT gruppen hade trots ökade komplikationsrisker hos en del patienter en signifikant minskad sjukhusvistelse generellt.

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