DOI:10.14753/SE.2023.2775

Multimodal treatment of peritoneal carcinomatosis of various origins

PhD thesis

Miklós Imre Ács, MD

Károly Rácz Clinical Medicine Doctoral School

Semmelweis University

Supervisor: Tamás Ruttkay, MD, Ph.D

Official reviewers: Zsolt Káposztás, MD, Ph.D,
Noémi Csibi, MD, Ph.D

Head of the Complex Examination Committee:

Miklós Tóth, MD, D.Sc

Members of the Complex Examination Committee:

Kinga Lakatos, MD, Ph.D,
Áron Cseh, MD, Ph.D

Budapest

2022

DOI:10.14753/SE.2023.2775

Table of Contents

DOI:10.14753/SE.2023.2775

List of Abbreviations

CC score: Completeness of Cytoreduction score

CC-0: complete cytoreduction, no residual disease

CC-1: residual nodules smaller than 2,5 mm

CC-2: residual nodules between 2,5 mm and 2,5 cm in size

CC-3: residual nodules over 2,5 cm in size

CI: Confidence Interval

CRC: Colorectal Cancer

CRS: Cytoreductive Surgery

DNA: Deoxyribonucleic Acid

FIGO: International Federation of Gynecology and Obstetrics

GOG: Gynecologic Oncology Group

HIPEC: Hyperthermic Intraperitoneal Chemotherapy

IQR: Interquartile Range

IVC: Inferior Vena Cava

LSS: Lesion Size Score

NCCN: National Comprehensive Cancer Network

OS: Overall Survival

PC: Peritoneal Cancer

PCI: Peritoneal Cancer Index

PM: Peritoneal Metastasis

PRODIGE 7 trial: CRS plus HIPEC versus CRS alone for colorectal peritoneal metastases

SB-PCI: Small Bowel Peritoneal Cancer Index

DOI:10.14753/SE.2023.2775

1 Introduction

Peritoneal metastases (PM) encompass primary tumor origins of the serosa along with peritoneal seedings from other sites such as colorectal, gastric, and ovarian carcinoma. As tumor growth ensues from these entities, peritoneal spread of tumor cells can transpire. Peritoneal metastases used to be seen historically as terminal and as the final stage of the condition, therefore, they were treated with palliative intention solely.

With the advance of medical science, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have recently surfaced as treatment possibilities for a select few patients with PM. Their advantages when it comes to survival have been confirmed, too [1]. The objective of this multimodal treatment is to attain complete tumor resection macroscopically via cytoreductive surgery of the disseminated tumor burden and eradication of microscopic residual tumor cells by heated intraperitoneal chemotherapy [2].

The preeminent prognostic factor for survival in the case of CRS + HIPEC is the thoroughness of the performed cytoreduction, which is assessed with the Completeness of Cytoreduction (CC) score [3]. The completeness of cytoreduction was scored as recommended by Sugarbaker [3], namely CC-0: no residual disease; CC-1: residual nodules less than 2,5 mm in size; CC-2: residual nodules between 2,5 mm and 2,5 cm in size; and CC-3: residual nodules over 2,5 cm in size.

Another significant prognostic factor, which is also a crucial aspect in patient selection, is the scope of the peritoneal disease. This is evaluated with the Peritoneal Cancer Index (PCI) [4]. To aid the evaluation of operability and to assess peritoneal carcinomatosis and abdominal tumor burden, score systems have been created. The Peritoneal Cancer Index, which was outlined in 1996 by Jacquet and Sugarbaker [4], is to be used in clinical practice. The PCI redivides the abdomen into 13 different regions: nine regions in a grid of the abdomen, each on the right, middle and left sides in three tiers, namely the upper, mid, and lower abdomen/pelvis, and 4 regions of the small intestine: upper and lower jejunum, upper and lower ileum. Moreover, the tumor burden of these regions is specified, which is then followed by the assignment of a Lesion Size Score (LSS) of 0-3 points. The absence of tumor evidence amounts to 0 points, tumor nodules up to 0,25 cm amount to 1 point, for tumor nodules between the sizes of 0,25 cm and

2,5 cm 2 points are given, and tumor nodules over 2,5 cm in size correspond to 3 points. The LSS is established for each region, starting with the number 0 for the central region, followed by all the other regions, described in a clockwise manner (starting with the upper right field). Since a maximum LSS of 3 can be attached to each of the 13 regions, the peak PCI is 39.

The core of the present thesis was compiled by two studies [5, 6], which examined two different clinicopathological aspects of multimodal therapy for peritoneal carcinomatosis in ovarian and colorectal cancer (CRC) patients.

In modern countries, ovarian cancer is the most prominent cause of gynecological cancer-related fatality. The poor prognosis is associated with the fact that two-thirds of patients do not receive a diagnosis until ovarian cancer reaches an advanced stage [7]. In 2018, there were approximately 300 000 new incidents around the world [8]. In Germany alone, the occurrence is approximately 7500 women/year, furthermore, 5486 women succumbed to this disease in 2016 [9]. It is estimated that during their lifetime, about one in 75 women will develop ovarian cancer. The median age of onset for this disease is 68 years [9]. Most of these women have major intra-abdominal contamination with substantial peritoneal involvement at the time of diagnosis, which engenders low overall survival (OS) rates.

The most important moment in the history of cytoreductive surgery for ovarian cancer arrived in 2002 when the meta-analysis by Bristow et al. was publicized [10]. The study included eighty-one patient cohorts, involving 6885 patients with stage III and IV ovarian cancer. All of the patients were treated with platinum-based chemotherapy between 1989 and 1998. In this study, maximum cytoreduction was found to be the most critical determinant of survival, and this correspondence remained unchanged even after all other variables were accounted for (e.g., the ratio of patients with stage IV, dose intensity of administered platinum therapy, mean age). A simple linear regression analysis displayed an increase in the median survival time. In cohorts in which maximum cytoreductive surgery was achieved in ≤ 25% of patients the median survival time of 23,0 months increased to 36,8 months. This equates to an observed increase of 60%. The results of Bristow's meta-analysis have granted assurance to radical gynecologic oncologists that they were correct when it came to challenging boundaries

of surgical achievements in the case of this disease. Over the past decade, regular publications have been citing the worth of extensive cytoreductive procedures in the upper abdomen, which include liver resection, full-thickness diaphragmatic resection, removal of cardiophrenic lymph nodes, complete parietal and visceral peritonectomy, splenectomy with distal pancreatectomy, and thoracoscopic surgery with video-assistance.

Consequently, after cytoreductive surgery, the most relevant prognostic factor is the residual disease status [10, 11]. Furthermore, up to 40% of patients suffering from advanced-stage ovarian cancer present with bulky metastases in the diaphragmatic peritoneal region, mainly on the right-side [12]. In order to accomplish complete tumor resection, extended surgery is required on varied localisations. Moreover, diaphragmatic peritonectomy and full-thickness resection create an effective practice when it comes to the removal of diaphragmatic carcinomatosis. Diaphragmatic surgery is predominantly restricted to stripping. Nevertheless, when cancer spreads to the diaphragmatic muscle fibers, full-thickness resection becomes unavoidable, and the opening of the pleural cavity is a necessity. These latter interventions regularly provoke pulmonary and intrathoracic complications, although long-term morbidity is infrequent.

As gynecological oncologists have also been carrying out diaphragmatic operations for advanced ovarian cancers lately, the conventional, transperitoneal approach they have been utilizing is comprehensively discussed in the literature. Nonetheless, upper abdominal peritonectomy from the extraperitoneal approach comprises a technique safely implemented in surgical oncology that may provide certain advantages. The gravity of this issue was given by the evaluation of the Gynecologic Oncology Group (GOG) 182 trial, which demonstrated that the diaphragm is the most prevalent localization for residual tumors post-surgery in advanced ovarian cancer cases [13], which accentuates the significance of this topic. Moreover, by expanding the armamentarium of gynecological oncologists and oncological surgeons involved in ovarian cancer treatment, we can accomplish longer survival in these patients through a higher rate of complete tumor resection.

Globally, colorectal cancer ranks as the third most prevalent cancer and it is the fourth most frequent cancer concerning mortality [14, 15]. Aside from the lymphatic and hematogenous avenues of dissemination, colorectal cancer regularly engenders

transcoelomic spread of tumor cells in the peritoneal cavity, which eventually leads to peritoneal carcinomatosis (PC). PC is identified with a reduction in quality of life and poor prognosis for the patients [14]. The seed and soil hypothesis of cancer invasion and metastasis [16] explains how various genes and proteins characterizing the intrinsic properties of these specific cancer cells presumably result in the implantation and settlement of a metastatic focus in the peritoneum [15, 17]. Furthermore, the interaction of the cancer cell microenvironment and cancer cell surface characteristics creates a disposition toward the development of peritoneal metastases [15, 18]. Common occurrence sites of the peritoneal cavity include the pelvis, the mesentery, bowel surfaces, the lesser sac, and the subphrenic region. The sites for peritoneal surface implantation may be influenced by physical principles, for instance, the impacts of gravitational forces and peritoneal fluid circulation [15].

In the case of CRC patients, peritoneal metastases are seen in as many as 5–10% of the cases at the time of primary cancer evaluation (i.e., synchronous peritoneal metastases) This percentage rises to 15–30% of patients in recurrent setting at the time of the follow-up after primary cancer surgery (i.e., metachronous peritoneal metastases) [6] [19, 20]. Over 20 years ago, peritoneal metastasis originating from CRC was seen as a terminal condition and was primarily treated with palliative methods. Over the last two decades, the emergence of the combined approach of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy has bettered survival statistics of CRC peritoneal metastases [21-23]. Cytoreductive surgery intends to clear all visible macroscopic tumor nodules via visceral resections and peritonectomy procedures [1]. Peritoneal carcinomatosis is considered to be chemoresistant, assumably due to the plasma-peritoneal barrier preventing the penetration of intravenous chemotherapeutic agents into the peritoneal cavity [6, 24].

Hyperthermic intraperitoneal chemotherapy serves as an intraoperative adjunct to cytoreductive surgery, which is implemented after completion of CRS by administration under anesthesia at temperatures between 39-43 °C. It merges the theorized cytotoxic effect of heat with the delivery of chemotherapeutic agents at the time of surgery. Enhancement of chemotherapeutic drug potency is suggested by both in vitro and in vivo laboratory studies in case of concurrent delivery with heat [25, 26]. Heat in itself is tumoricidal and boosts the cytotoxicity of several chemotherapeutic agents, for instance,

cisplatin, irinotecan, carboplatin, mitoxantrone, oxaliplatin, doxorubicin, docetaxel, and mitomycin C [27]. There is compelling proof that hyperthermia (39-43 °C) elevates the uptake of chemotherapeutic agents (e.g., doxorubicin, carboplatin, cisplatin, melphalan, and mitoxantrone) in cancer cells elevated adduct formation of deoxyribonucleic acid (DNA) and DNA repair inhibition is caused. In the event of cisplatin administration, inhibition of the nucleotide excision repair pathway and suppression of DNA repair enzymes take place [25, 28]. Hyperthermia has also been shown to hinder homologous recombination, which leads to the sensitization of epithelial ovarian cancer cells to the inhibition of poly(adenosine diphosphate-ribose)polymerase-1 [29].

Utilization of intraperitoneal chemotherapy during CRS allows for target chemotherapeutic active agents to enter cancers even of the lowest, preferably microscopic, volume after multiorgan resection. Additionally, it also grants agents the ability to reach the totality of peritoneal surfaces. This also comes with the added benefits of treating deperitonalized surfaces antecedently to the postoperative inflammatory fibrotic healing process arising after surgery and ensuring a systemic chemotherapeutic penetration of the potential residual foci (microscopic tumor remnants) [30].

When compared to systemic administration, direct intraperitoneal administration of chemotherapy during HIPEC allows for a several-fold elevation in drug concentration in the peritoneum. Regardless of this local advantage, direct penetration into tumor tissue is restricted to a few millimeters. This effect may be strengthened even further by raising the temperature of the intraperitoneal chemotherapy. Nevertheless, this form of treatment is the most effective when it is limited to small-volume diseases. This accentuates the relevance of complete cytoreduction and minimal residual disease (no metastatic deposits over 2 to 2,5 mm).

It has been observed that with this multimodal treatment, the number of patients attaining long-term survival with peritoneal metastasis from CRC has risen over the past decade [31]. Even though CRS and HIPEC are associated with substantial perioperative morbidity, which has been stated to be 33% and is associated with a considerably longer average span of hospital stay [32], there is a limited number of long-term consequences to perioperative morbidity when compared to patients experiencing no complications

[33]. The objective of the multicentric study was to specify key characteristics of long-term survivors from a large cohort of patients with peritoneal metastases from CRC. All of the selected patients underwent curative intent CRS with or without HIPEC.

DOI:10.14753/SE.2023.2775

2 Objectives

When it comes to performing subdiaphragmatic peritonectomy the extraperitoneal approach is seldom implemented for cytoreductive surgeries despite potential advantages. Currently, the procedure has been associated with increased morbidity, as adjacent vital structures make the surgery problematical and technically demanding, hence, gynecological oncologists and oncologic surgeons use the classical transperitoneal method primarily. However, there have been no studies comparing the two approaches before. Nonetheless, once the indicators of long-term survival and cure are identified, these procedures may prove crucial in the future treatment of advanced-stage malignancies with peritoneal metastases.

The author of this thesis intended to examine and compare the two different clinicopathological aspects of the multimodal therapy for peritoneal carcinomatosis, namely the transperitoneal and the extraperitoneal approach, and to improve current surgical therapies and techniques for tumor resection. This research has the potential to shed light to as of yet undiscovered benefits, indicators, and contra indicators for CRS and HIPEC via the examination of long-term survivors' characteristics. The analysis included a larger scale retrospective study about peritoneal metastases from CRC and a descriptive study about advanced ovarian cancer – which often presents with peritoneal involvement, as this tumourous disease has reached stage IIIC or IV in the majority of patients by the time they receive diagnosis [7].

The first, descriptive study spotlights the peritonectomy technique in the right upper abdomen in the framework of the surgical treatment of advanced ovarian cancer [5], while the other, multicentre study aims to analyze the clinicopathology of long-term survivors of peritoneal metastatic colorectal carcinoma [6].

The primary objective of the first study was to evaluate and compare the safety and assets of the surgical technique of right subdiaphragmatic peritonectomy through extraperitoneal access, which is used by surgical oncologists for peritoneal surface malignancies to the traditional and most commonly used peritonectomy procedure carried out by gynecological oncologists at most oncology centers.

Another aim was to review the most relevant and controversial features of the two cytoreductive surgical techniques (extraperitoneal versus transperitoneal), summarizing

the potential benefits of the extraperitoneal surgical technique. Additionally, we retrospectively evaluated and reviewed procedure-specific complications.

The target of our retrospective, international, multicenter study was to present long-term CRC survivors with peritoneal metastases who received a combined treatment of CRS and HIPEC [6] and to describe their characteristics, including effectiveness, overall survival rate, PCI, interquartile range (IQR), CC score, possible drawbacks, and complications. As the largest of its kind in the world, this study aimed to combat some of the above-mentioned constraints of CRS and HIPEC, namely the small available sample sizes and shorter-term studies. Analyzing long-term survivors' data enables us to see possible indicators of prognosis, which then will lead to better patient selection and criteria. Moreover, these data can be implemented in all cancers with peritoneal metastases.

3 Results

Ovarian cancer study

As there had been no comparisons made between the extraperitoneal and transperitoneal approaches in cases of metastases in the right upper abdomen area, the author of the present thesis took part in the conceptualization and conducted a study on the matter. His person was responsible for data collection, documentation, tables, and writing the article. The author has previously published the aforementioned study, including the following results [5].

For this study, only patients who underwent peritonectomy and full-thickness resection of the right upper diaphragm through the extraperitoneal approach with or without liver capsule resection were selected. Patients were separated into two groups: the CRS plus HIPEC group and the CRS-only group. Surgical, pathological, and Intensive Care Unit records were collected from each patient's documentation, which, along with other patient data, were entered into the German national HIPEC registry, initiated by the German Society for General and Visceral Surgery, and retrospectively analyzed for this study. The operations were performed by an ovarian team consisting of a gynecological oncologist and a surgical oncologist. The completeness of cytoreduction was scored as proposed by Sugarbaker [5]. The clinicopathological data were retrospectively analyzed for this study after being prospectively entered in the national HIPEC registry run by the German Society for General and Visceral Surgery (DGAV).

A total number of 64 patients, with the median age of 58, were included in the study [5]. 55 of the 64 patients (86%) received bidirectional HIPEC after the CRS with the closed-abdomen technique. In this case, Cisplatin at 75 mg/m2 and doxorubicin at 15 mg/m2 body surface area were administered at 42˚C for 60 or 90 min. Considering the small number of patients in the CRS-only group (n=9;14%), at the evaluation of the postoperative outcome, the two study groups, i.e., all 64 patients, were analyzed in one block [5].

Overall, 72% of the 64 ovarian cancer patients who underwent peritonectomy and full-thickness resection of the right upper diaphragm, with or without liver capsule resection, received primary CRS. All patients in the primary setting had advanced, International Federation of Obstetrics and Gynecology stage IIIC-IV disease.

The remaining 28% underwent secondary or tertiary CRS (15% and 13%, respectively). Full-thickness diaphragmatic resection was necessary for 44% of the patients with recurrent ovarian carcinoma and in 17% of patients in the primary setting. Full-thickness resection was carried out in 16 patients (25%), while liver capsule resection was performed in 12 (18%). The tumorous involvement of the right upper quadrant was completely resected in all patients [*Table 1*]. Postoperative diaphragmatic surgery-related short-term complications occurred in 30 patients (47%). The most common complication was pleural effusion, which developed in 21 out of 64 patients (32%) in the postoperative period. Postoperative chest tube insertion was necessary for five patients (8%), whereas thoracocentesis was performed in 10 patients (15%). Additionally, in six cases (9%), the pleural effusion was resolved by pharmacological treatment. Intraoperative chest tube insertion was carried out in 34 cases (53%). The fluid discrepancy between the total inflow and the outflow after HIPEC occurred in five cases in our patient group (8%). Major complications of Clavien-Dindo grade III and IV occurred in 34% (n=22) and 3% (n=2) of patients, respectively [5] [35].

Table 1. Frequency of procedures, surgical outcomes, and histological subtypes of patients undergoing peritonectomy in the right upper quadrant following an advanced stage ovarian cancer diagnosis [5]

	Frequency, n (%)
Surgical procedures	
Peritonectomy in the right upper quadrant	64 (100%)
Full-thickness resection	16 (25%)
Primary	8 (12,5%)
Recurrent	8 (12,5%)
Liver capsule resection	12 (18%)
Intraoperative chest tube insertion	34 (53%)
Complete cytoreduction (no residual tumor)	45 (70%)
Residual disease < 1 cm (not diaphragm-related residual disease)	19 (30%)

Histology	
High-grade serous ovarian, fallopian tube, and peritoneal cancer	40 (62,5%)
1st recurrence	8 (12,5%)
2nd recurrence	7 (11%)
Mucinous	2 (3%)
2nd recurrence	1 (1,6%)
Transitional cell cancer	1 (1,6%)
1st recurrence	1 (1,6%)
Yolk-sac tumor	1 (1,6%)
Granulosa cell tumor 1st recurrence	1 (1,6%)
Immature teratoma	1 (1,6%)
Endometrioid	1 (1,6%)
Tumor	
Primary	46 (72%)
Recurrent	18 (28%)
Total	**64 (100%)**

In one patient (1,5%), an infected suprahepatic seroma had developed, which was treated with ultrasonography-guided puncture. A subphrenic abscess was observed in one case (1,5%), requiring computed tomography-guided insertion of an abdominal drain. Subcapsular liver hematoma occurred in one patient (1,5%) and was treated successfully with ultrasonography-guided drain insertion. In one patient, the postoperative course was complicated by pleural effusion, which was managed by thoracocentesis; subsequently, pneumothorax arose and thoracic drainage was applied. In the further course, a septate pleural empyema II˚ evolved, which required surgical intervention with thoracoscopic decortication and the removal of the pleural fluid.

Apart from this, two patients developed postoperative respiratory failure, requiring admission to the Intensive Care Unit and mechanical ventilation. In one of the instances, it occurred in the context of a septic disease resulting from the perforation of a duodenal ulcer. Further respiratory complications included pneumothorax (n=3; 4,6%) requiring chest tube insertion, and pneumonia (n=5; 8%), which was treated with antibiotics and respiratory therapy. Pulmonary embolism occurred in four patients (6%), all of whom received pharmacological treatment. Concerning the mortality rate, in our cohort, the 30-day postoperative mortality rate was 3% (two patients) considering the 64 patients. None of the deaths appear to have been directly related to the diaphragmatic surgery but rather to the consequences of multiorgan resection performed during CRS [5].

When it comes to comparing the two approaches [*Table 2*], the extraperitoneal approach [*Figures 1, 2, 3*] might offer several benefits as compared to the traditional transperitoneal approach in right diaphragmatic surgery. The main features of the two different approaches are the following: in the extraperitoneal approach, liver mobilization and peritonectomy occur simultaneously, thus, mobilization of the liver before peritonectomy is not necessary in contrast to two-step traditional peritonectomy. Another advantage of extraperitoneal peritonectomy is that transperitoneal adhesiolysis can be avoided. Therefore, the upper abdominal peritoneum and the liver capsule can be removed as a single specimen while the important vascular structures can safely be visualized and palpated.

The extraperitoneal approach considers and respects embryology and anatomical layers in contrast to the transperitoneal approach [5].

Table 2. Comparison of the transperitoneal and extraperitoneal approach in surgery [5]

Extraperitoneal approach
• Considers embryology and anatomical layers • The liver is mobilized in conjunction with the peritoneum • Complete extraperitoneal centripetal dissection • Dissection is simplified, no contamination with ascites or tumorous deposits occurs • Dissection is technically easier, facilitated by traction and contra-traction

- Longer learning curve
- Enables *en bloc* resection of the liver capsule

Transperitoneal approach

- Opening of the peritoneal cavity
- Initial liver mobilization
- Initiation of the parietal peritonectomy from posterior to anterior and from caudal to cranial directions
- Dissection is technically more demanding
- Clamps are necessary for dissection
- Short learning curve
- Glissonectomy is only possible as a separate specimen

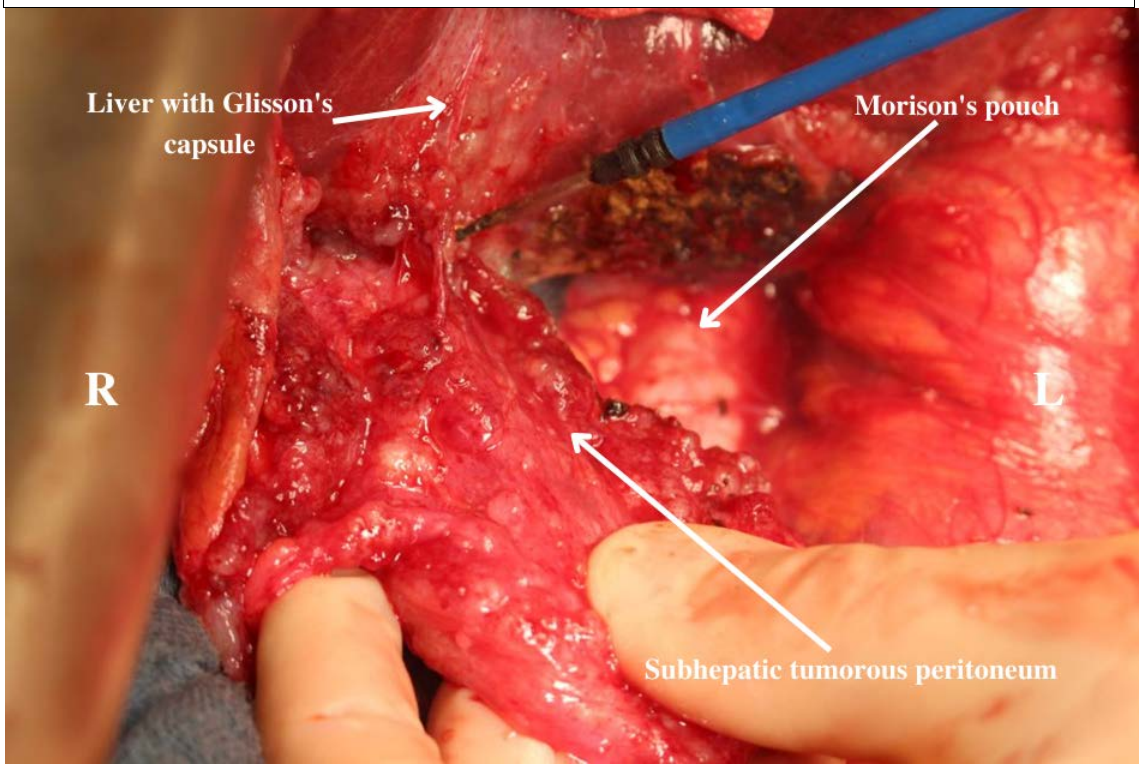

Figure 1. En bloc resection of the subhepatic tumorous peritoneum (Morison's pouch) that has invaded the Glisson's capsule in a metastatic ovarian cancer patient. The affected area is removed through electrocoagulation in the right subphrenic region with a 3mm ball tip electrosurgical handpiece. Own image.

DOI:10.14753/SE.2023.2775

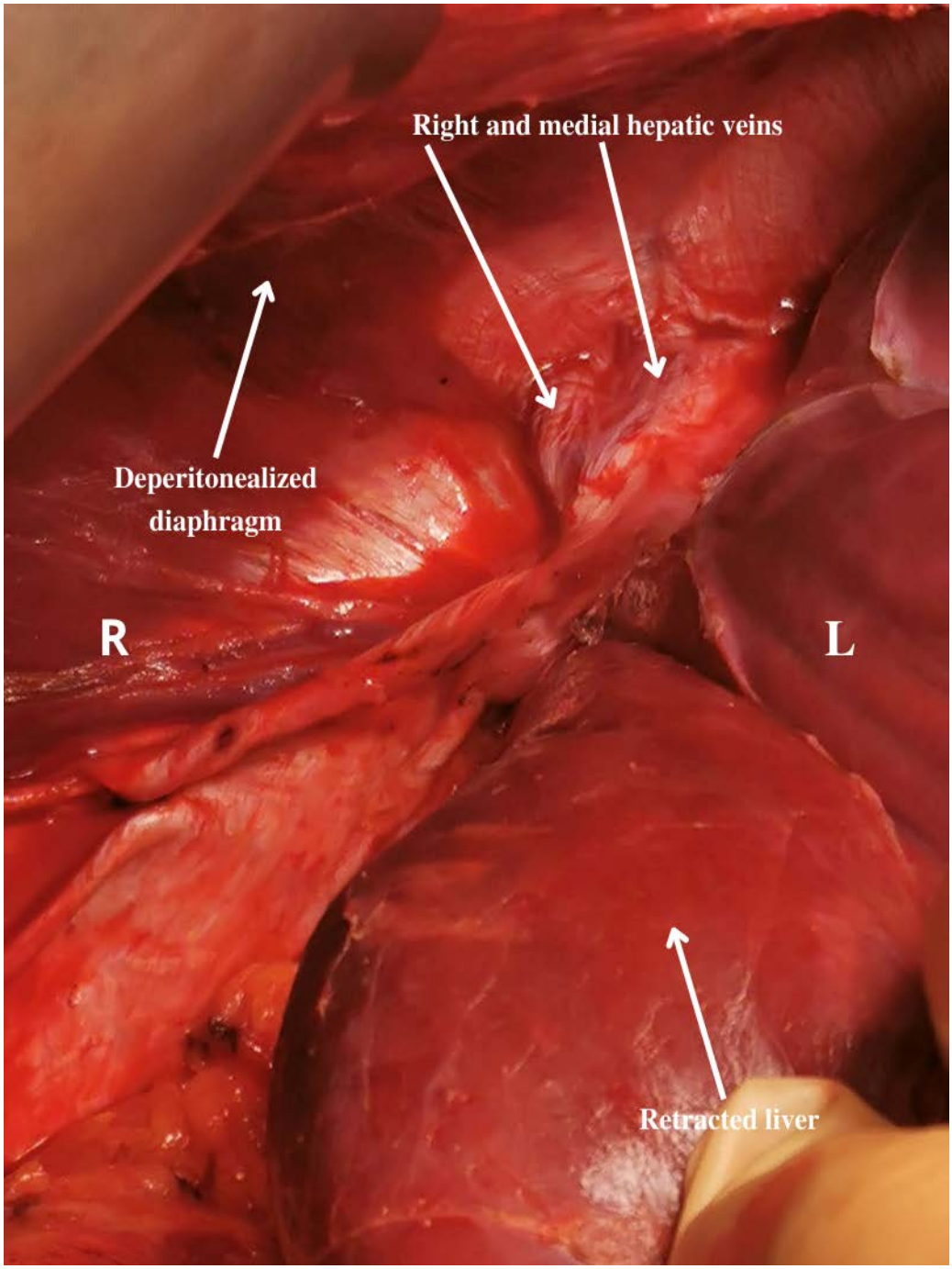

Figure 2. After peritonectomy in a metastatic ovarian cancer patient, the right and medial hepatic veins that drain into the anterior surface of the Inferior Vena Cava (IVC) can be visualized. The liver has been retracted medially. Own image.

DOI:10.14753/SE.2023.2775

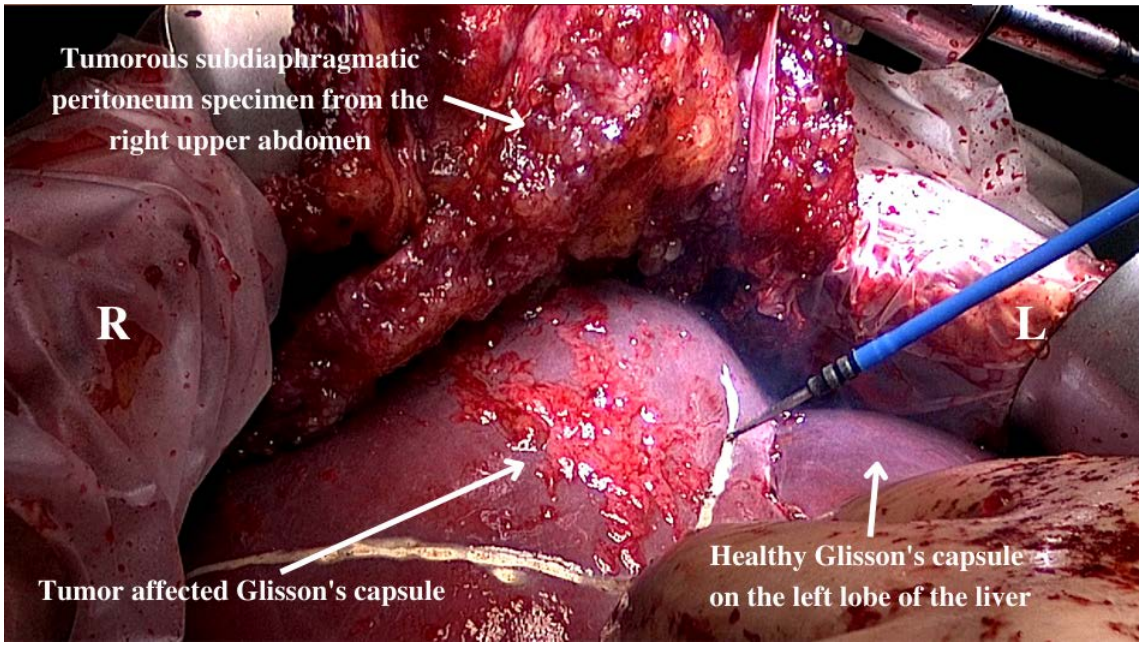

Figure 3. After peritonectomy of the tumorous right upper abdomenin a metastatic ovarian cancer patient, en bloc resection of the Glisson's capsule ensues in one specimen. Device: 3mm ball tip electrosurgical handpiece. Own image.

Colorectal cancer study

The second, multicentric study [6] evaluated clinicopathological features of long-term survivals with CRC and PM. The author of this thesis contributed by solely being responsible for conducting the study, collecting and analyzing data, and selecting patients in one of the 13 research centers.

Upon examining the data, it was discovered a total number of 206 (14,2%) long-term survivors out of the 1455 patients were included in the study [6]. A cure was observed in 84 cases out of 206 patients. The total cohort had a median follow-up time of 6,6 years. Regarding the sex of the patients, a total of 101 male patients (49,0%) and 105 female patients (51,0%) were included in the study, with a median age of 58 years. The primary tumor locations were the right colon in 90 patients (43,7%), the left colon in 101 patients (49,0%), and the rectum in 14 individuals (6,8%). In terms of onset, synchronous metastases were found in 89 individuals (43,2%), while metachronous metastases were found in 93 patients (45,1%).

One hundred forty-nine patients (72,3%) had well-to-moderately differentiated adenocarcinoma, fifty patients (24,3%) had mucinous adenocarcinoma, and six patients (2,9%) had poorly differentiated and/or signet ring cell carcinoma. Pathological evidence of lymph node metastases was found in 123 individuals (59,7%). Peritoneal metastases occurred synchronouslyin 62 (50,4%), metachronously in 56 (54,5%), and unknown in 5 of the long-term survivors with lymph node metastases (4,0%). Liver metastases were discovered and removed in 27 individuals (13,1%).

The 206 long-term survival patients had a median peritoneal cancer index of 4 (IQR 2–7). In this group, 169 patients (82,0%) had PCI less than 10, 23 (11,2%) had PCI 11–20, and 4 (3,1%) had PCI greater than 21. The small bowel regions of the PCI (SB-PCI) had a median score of 0 (IQR, 0–2). One hundred thirty patients (63,6%) had an SB-PCI of 0, 51 patients (24,8%) had 1–4, while 9 patients (4,4%) had 5 [*Table 3*].

Table 3. Baseline characteristics and their frequency as presented in 206 long-term survivors with peritoneal metastases from colorectal cancer [6]

Variable	**Long-Term Survivors**	**Cured Patients**
	(n = 206)	**(n = 84)**
Age, y, median (IQR)	58 (49-66)	55 (44-64)
Gender		
Male	101 (49,0%)	40 (47,6%)
Female	105 (51,0%)	44 (52,4%)
ASA grade		
I	97 (47,1%)	46 (54,8%)
II	84 (40,1%)	30 (35,7%)
III	6 (2,9%)	1 (1,2%)
Missing	19 (9,2%)	7 (8,3%)
Date of CRS		
Before 2001	16 (7,8%)	5 (6,0%)
Between 2001 and 2010	76 (36,9%)	37 (44,0%)
2011 or later	114 (55,3%)	42 (50,0%)

Onset		
Synchronous	96 (46,6%)	42 (50,0%)
Metachronous	96 (46,6%)	35 (41,7%)
Missing	14 (6,8%)	7 (8,3%)
Location of primary tumor		
Right colon	90 (43,7%)	38 (45,2%)
Left colon	101 (49,0%)	42 (50,0%)
Rectum	14 (6,8%)	4 (4,8%)
Missing	1 (0,5%)	0 (0%)
Histology		
Well to moderately	149 (72,3%)	67 (79,8%)
mucinous	50 (24,3%)	15 (17,9%)
Poorly or signet ring cell	6 (2,9%)	2 (2,4%)
Missing	1 (0,5%)	0 (0%)
pT category		
pT ≤ 3	89 (43,2%)	33 (39,3%)
pT4	100 (48,5%)	45 (53,6%)
Missing	17 (8,3%)	6 (7,1%)
pN category		
N0	64 (31,1%)	25 (29,8%)
N1 / 2	123 (59,7%)	51 (60,7%)
Missing	19 (9,2%)	8 (9,5%)
Extraperitoneal metastases		
None	177 (85,9%)	78 (92,9%)
Liver metastases	27 (13,1%)	5 (6,0%)
Lung metastases	2 (1,0%)	1 (1,2%)
PCI, median (IQR)	4 (2-7)	3 (2-5)
0-5	129 (62,6%)	66 (78,6%)
6-10	40 (19,4%)	14 (16,7%)
11-15	15 (7,3%)	2 (2,4%)

16-20	8 (3,9%)	1 (1,2%)
≥ 21	4 (1,9%)	0 (0%)
Missing	10 (4,9%)	1 (1,2%)
SB-PCI, median (IQR)	0 (0-2)	0 (0-1)
0	130 (63,1%)	60 (71,4%)
1-4	50 (24,3%)	15 (17,9%)
≥ 5	9 (4,4%)	2 (2,4%)
Missing	16 (7,8%)	7 (8,3%)

Preoperative systemic chemotherapy was administered to 137 patients (66,5%). 180 patients (87,4%) achieved complete cytoreduction, 22 patients (10,7%) achieved CC-1, and two patients achieved CC-2 (1,0%). HIPEC was delivered to 151 patients (73,3%). HIPEC was performed in the case of 21 patients (87,5%), intraperitoneal chemotherapy in seven individuals (29,2%), postoperative systemic chemotherapies in nine patients (37,5%), and no treatment in eight patients with CC-1/2 (33,3%). Exposure technique (open versus closed), time, and temperatures (40,0 to 43 °C) were all included in the technical variety. 85 patients received mitomycin-based regimens, while 63 received oxaliplatin-based regimens [6].

According to the Clavien-Dindo classification, major complications (grade ≥ IIIA) occurred in 38 patients (18,4%) with CRC: intra-abdominal in 31 patients and extra-abdominal in 7. In 149 patients, postoperative systemic chemotherapy was administered (72,3%) [6].

Tumor recurrence occurred in 122/206 instances (59,2%) during the long-term follow-up, with a median time to recurrence of 2,0 years (95% confidence interval (CI) 1,7–2,1). Isolated peritoneum (n = 43), liver (n = 12), abdominal wall (n = 11), lung (n = 9), lymph nodes (n = 5), bone (n = 1), and multiple sites (n = 41) were among the recurrence locations. 70 patients received treatment with second CRS and/or metastasectomy with or without HIPEC in this group of 122 patients with recurrence [*Table 4*] [6].

DOI:10.14753/SE.2023.2775

Table 4. Site and treatment of recurrence. 122 out of 206 long-term survivors with peritoneal metastases from colorectal cancer were found to have new malignances during the long-term follow-up [6]

Variable	**Total Number (n = 122)**
Site of recurrence	
Isolated	
Peritoneum	43 (35,3%)
Liver	12 (9,8%)
Abdominal wall	11 (9,0%)
Lung	9 (7,4%)
Lymph nodes	5 (4,1%)
Bone	1 (0,8%)
Multiple	
Peritoneum + other site(s)	36 (29,5%)
Others	5 (4,1%)
Treatment of recurrence	
Reoperation + chemotherapy	70 (57,4%)
Chemotherapy	21 (17,2%)
Palliative therapy	5 (4,1%)
Unknown	25 (21,3%)

4 Discussion

Even after several decades have passed since the descriptions of the two distinct methods, namely the conventional transperitoneal approach described by Montz et al. in 1989 [36] and the extraperitoneal approach described by Sugarbaker in 1995 [1], gynecological oncologists along with oncologic surgeons still perform subdiaphragmatic peritonectomy in different ways. Since the dissemination of metastatic tumor nodes takes place in close proximity to the vital structures and the complicated anatomy of the right upper abdomen, peritonectomy in this area is one of the most technically demanding component of CRS.

The extraperitoneal method described in the present thesis [5] might offer significant advantages over the traditional transperitoneal approach in the case of right diaphragmatic surgery. Among these, the most striking contrast between the two operational procedures becomes the most apparent when the tumorous illness is inseparable from the Glisson’s capsule. The two sides of the tumorous plate (which consist of the peritoneum and the liver capsule) are divided in the transperitoneal approach, which is unnecessarily overcomplicating the resection of the tumorous layer by splitting it into two phases. Since orientation in the tumorous environment is rather challenging, in such cases, as advised by Pathiraja et al. [37], the primary vascular structures must be identified cranially, beginning with the liver's hilum. In contrast, cutting into tumorous tissue can be avoided with the extraperitoneal technique since preparation throughout the intervention preserves the embryological anatomical layers while also maintaining constant visualization of the key vascular structures. The dissection in this example proceeds along the upper part of the IVC until it reaches the posterior wall of the right hepatic vein.

Because of the apparent link between optimal cytoreduction and improved survival rates in patients with peritoneal metastases of ovarian cancer above the pelvis, many centers perform upper abdominal oncological surgeries at an increasing rate [38]. Despite the growing numbers, including diaphragmatic operations raises the risk and incidence of postoperative respiratory complications. As part of the present study, all 64 patients received postoperative thorax radiography. However, because 34 patients (53%) had a

chest tube inserted intraoperatively, it is impossible to correctly determine the true occurrence of intrathoracic complications free of bias.

As previously stated, the rate of full-thickness resection in the study was 25%, encompassing 16 patients. Several authors report varying rates for diaphragmatic resection. Examples for this include Cliby et al. [39], representatives of the Mayo Clinic, suggesting that diaphragmatic resection was performed in roughly 10% of the cases, meanwhile Chi et al. [38], researchers from the Memorial Sloan Kettering Cancer Center, described the rate to be 14%. Other authors, like Chèreau et al. [40] from Paris mentioned a rate of 15%, while Ye et al. [41], a group from the Shanghai Cancer Center, reported 17,3%, and Zapardiel et al. [42] from Milan referred to a rate of full-thickness resection in 29,5% of the cases.

The comparatively high percentage of full-thickness resection in the present study could be ascribed to the rather high proportion of patients with recurrent ovarian cancer (representing 28% of the subjects), which predisposed them to require full-thickness resection. The high prevalence of infiltrating diaphragmatic involvement in recurrent cancerous disease indicates that the first surgical resection might have been insufficient to achieve cure. According to a report from the Mayo Clinic, which demonstrated similar results, 85% (namely 35 out of 41 patients) of diaphragmatic resections were performed in patients with recurrent disease [39]. Researchers have also highlighted that pleural effusion incidence is higher whenever HIPEC perfusion is administered [43].

Without HIPEC, small diaphragmatic lesions may be overlooked and untreated, on the downside of HIPEC, the occurrence of drainage-worthy pleural effusion is common. Pleural effusion is also more frequent following full-thickness diaphragmatic resection than after diaphragmatic stripping [44, 45]. Additionally, when a prophylactic chest tube is not inserted following diaphragmatic resection, approximately half of the patients develop pleural effusion [46].

Overall, in patients with ovarian cancer, the prevalence of postoperative thoracocentesis and chest tube insertion after diaphragmatic surgery ranged from 14% to 42,5% [38, 40, 47]. This aligns with literature data, which states that chest drainage establishment during surgery ranges from 0 to 65% [45]. When it comes to a newly published study, where intraoperative chest tube insertion composed an indispensable part of

diaphragmatic surgery during CRS in ovarian cancer patients, no incidences of pleural effusion or pneumothorax were observed. As a result, routine chest drain placement is recommended to limit and reduce the risk of serious respiratory complications [48].

Because several organs are resected throughout the entire abdominal cavity during CRS, an increase in morbidity is to be expected. The patient cohort of the current study had a 3% mortality rate, which was most likely owing to the high tumor load, previous surgeries, and concurrent illnesses. After CRS and HIPEC, the same center reported a mortality rate of 2,1% in over 500 consecutive patients and 2,3% in the German national HIPEC registry, respectively [49, 50].

The primary goal of the descriptive study was to compare the description of extraperitoneal peritonectomy in the upper right abdominal quadrant to the traditional technique in patients suffering from ovarian carcinoma. Following the analysis of the data, it can be concluded that the that procedure-specific postoperative outcomes of this technique are substantially comparable to those of the transperitoneal approach in diaphragmatic surgery while also indicating several benefits as outlined above. However, it should be noted that our tertiary referral institution specializes mainly in the treatment of patients with advanced disease. As a result, the procedures used are of the more complicated kind and may be associated with increased morbidity.

Rodriguez et al. found that tumorous tissue in the diaphragmatic area was a common cause of postoperative residual disease in advanced-stage ovarian cancer patients [13], emphasizing the need of surgeons being familiar with operating in the right upper abdominal region in case of ovarian cancer. As a result, the author's team recommends cytoreductive surgical management of the upper abdomen in the setting of a multidisciplinary team. This team is to include a gynecological oncologist and a surgical oncologist forming an ovarian team, as this scenario may the most beneficial to our patients. Other organizations have also suggested this line-up, and the Memorial Sloan Kettering Cancer Center group and their ovarian team have demonstrated it in an impressive manner, too [51].

The potential merits of including an ovarian team entail less time-consuming parietal peritonectomy, no contamination of the pleural cavity, and improved control over any incidental bleeding from either the liver veins or the IVC, therefore, blood loss can also

be minimized. Furthermore, glissonectomy with simplified peritonectomy of the hepatoduodenal gastrohepatic ligament, including the ligamentum venosum, the subhepatic vena cava, and the floor of the omental bursa, can result in a higher rate of complete cytoreduction of the upper abdomen.

Limitations of the study include its retrospective nature and the inclusion of both primary and recurrent ovarian cancer cases, which resulted in a heterogeneous group. This work is most notable for demonstrating that diaphragm-related tumor tissue can always be retrieved using the extraperitoneal method. As our patients had a significant tumor burden, we observed how this approach can motivate complete tumor reduction in the right upper abdomen, even in advanced metastatic cases.

The first prospective randomized phase III clinical trial of HIPEC therapy in the treatment of epithelial ovarian cancer following neoadjuvant chemotherapy and interval cytoreductive surgery has been published recently [52].

Moreover, several prospective studies are being conducted to determine the additional role of HIPEC in patients with primary and recurrent ovarian cancer [53]. Despite the aforementioned study's favorable findings and the superiority of the HIPEC arm, HIPEC therapy is yet to be incorporated into the German guideline recommendation [9]. This decision can be explained by the fact that only a small portion of the "ovarian cancer population" was chosen for the van Driel trial, namely those who were initially thought inoperable and thus underwent neoadjuvant treatment first. Nonetheless, this research adds a much-needed contribution to the growing body of knowledge on HIPEC therapy for primary ovarian cancer. After the van Driel study was publicized, HIPEC was included in the NCCN (National Comprehensive Cancer Network) only as a treatment option for interval debulking procedures (NCCN clinical practice guidelines version 1. 2019-March 8, 2019 OV-2). Additionally, the French clinical practice guideline recommends using a debulking procedure in cases of initially non-resectable FIGO (International Federation of Gynecology and Obstetrics) stage III ovarian, tubal, and primary peritoneal carcinomas followed by hyperthermic intraperitoneal chemotherapy when a complete or optimal cytoreduction (with tumor residues under 1cm) has been achieved. This is to be performed following three cycles of intravenous chemotherapy [54].

There are also several retrospective studies with lesser evidence strength, whose findings support the superiority of HIPEC therapy. In terms of inclusion criteria (entailing histologic subtypes, phases, and HIPEC), these studies present a fairly large heterogeneity. Primary or interval therapy, cytostatic drugs, and treatment duration). The main concern regarding HIPEC therapy is the possibility of increased toxicity, which would result in higher morbidity and mortality. However, the currently available results of multiple trials suggest that the morbidity and mortality rates linked with hyperthermic intraperitoneal chemotherapy for primary ovarian cancer are not higher than those associated with cytoreductive surgery alone without HIPEC. These generally elevated morbidity rates can be attributed to substantial multivisceral resection [55].

Furthermore, it is expected that approximately 40% of individuals with colorectal cancer may acquire peritoneal metastases at some point throughout the disease's natural course [56]. Studies of necropsies have revealed that the majority of individuals dying of colorectal cancer presented with PM [57, 58].

A cohort of long-term CRC survivors with peritoneal metastases was treated with CRS combined with HIPEC in our retrospective, worldwide, multicenter trial [6]. The goal of this research was to introduce these uncommon patients and define their characteristics. 206 patients survived beyond five years among the 1455 patients who received CRS for peritoneal metastases, and 84 of the 206 patients maintained their recurrence-free status for more than five years following the first CRS. Involving 13 institutions from eight countries and focusing on the clinical, pathological, and oncological characteristics of long-term survivors with colorectal peritoneal metastases, this study is the largest series of its kind in the world.

PM may develop as a result of the main tumor's progression through the serosal lining of the bowel lumen, permitting the exfoliation and shedding of malignant cells intraperitoneally. Furthermore, iatrogenic surgical manipulation, such as the transection of lymphatics or blood arteries, may result in the release of tumor cells into the peritoneal cavity [56].

Although numerous institutions across the world use CRS and HIPEC to treat peritoneal metastases, there is room for debate when it comes to this combined treatment. A point of contention for these treatment options is the uncertainty about the efficacy of HIPEC

for peritoneal metastases following CRC. In our study, 55 patients (26,7%) of the 206 long-term survivors were not administered HIPEC, indicating that HIPEC is not required for long-term survival. That being said, our statistics cannot determine whether CRS and HIPEC improve long-term survival when compared to CRS alone. Another disadvantage is the procedure's high rate of morbidity and mortality. The morbidity rates were reported to range from 23% to 44%, and the fatality rates were reported to range from 0% to 12% [59]. Relating to this, a recent study found that the risk of morbidity and death after CRS/HIPEC get reduced when the surgical process and patient selection are improved [60]. Long-term survival rates may be negatively affected by postoperative complications [61]. In accordance with other existing studies in the literature, our study found a low rate of serious postoperative complications. For better outcomes, patient selection is required to identify candidates for the radical operation.

Patients with peritoneal metastases who receive modern systemic chemotherapy treatment had a median overall survival of at least 22 months, according to studies [62]. CRS/HIPEC, on the other hand, is thought to improve survival for CRC patients with peritoneal metastases; the median OS is 30–43 months [63, 64]. However, investigations on CRS and HIPEC have several drawbacks and limitations, including small sample sizes, duration, heterogeneity of patients and HIPEC compounds, and lack of control groups. The features of long-term survivors who underwent CRS were presented in this thesis. Our study found numerous long-term survivors and cured individuals when CRS was performed among highly selected patients, despite the fact that this does not reveal the survival benefits of CRS and HIPEC when compared to contemporary systemic chemotherapy.

This research yielded further useful information [6]. First, the PCI distribution of long-term survival in peritoneal metastases from CRC was determined. The majority of our patients (169/206, or 8,0%) had a PCI of less than 10 with a median of 4 (IQR, 2–7). Long-term survivors were compared against non-survivors (OS less than 5 years) in a recently published study that included data from patients with peritoneal metastases from CRC in two Japanese hospitals [65]. This study reported that the median PCI was considerably lower among long-term survivors (4 (range, 1–27) versus 9 (range, 0–39), $p < 0,001$), and the cohort presented the following results: the survival rate at 5 years was 14,0%; the median PCI was 8 (IQR, 3–20); the PCI distribution was 0 to 5 in

86 patients, 6 to 10 in 50 individuals, 11 to 15 in 27 people, 16 to 20 in 21 sufferers, and over 21 in 52 subjects. As previously indicated, the PCI gives a quantitative assessment of the amount of peritoneal illness and has been linked to OS [21, 66]. The idea that there is a strong link between PCI and CRS completeness is now widely acknowledged.

According to several researchers, CRS and HIPEC should not be offered in patients with peritoneal carcinomatosis from CRC if the estimated PCI is over 17–20 [21, 67]. In our cohort, 1,9% (4/206) had a PCI over 20, compared to 3,6% (3/84) who presented with a PCI over 10 in the cured patients' subgroup, while no patient displayed a PCI over 20. In addition, nearly 90% of long-term survivors and cured patients (180/206, 87,4% and 77/84, 91,7%) attained CC-0. According to a prior study by Kamada et al. [65], there was a statistically substantial disparity in CC-0 rates between the groups of long-term survivors and non-survivors (33/33 (100%) versus 141/203 (69,8%), $p < 0,001$). As a result, these findings suggest that low PCI and CC-0 levels are linked to long-term survival and cure in CRC patients with peritoneal metastases. Regardless, due to the discrepancies in datasets, a statistical comparison should be avoided. On the other hand, in this study, some of the long-term survivors exhibited high PCI and/or CC-1/2. Patients with these unfavorable prognostic characteristics would not have to be excluded if the curative intent treatments are deemed appropriate.

Furthermore, the median SB-PCI was 0 (IQR, 0–2), and the small bowel-peritoneal cancer indexes were also low. Small intestinal involvement is thought to be associated with a poor prognosis and incomplete cytoreduction, especially when peritoneal tumors are found at the junction between the mesentery and the small bowel [68, 69]. It's worth noting that more than half of the patients (63,1%, 130/206) had an SB-PCI = 0. Kamada et al. earlier's investigation found that [65] the overall cohort's median SB-PCI was 2 (IQR, 0–3). Although the SB-PCI cannot be statistically compared between this study and the previous one, these findings revealed that lower SB-PCIs than in other abdominopelvic regions are required for long-term survival. A future relative contraindication for this treatment could be disease expansion to the small intestinal areas.

Third, some patients with variables linked to poor prognoses lived for more than five years. These include liver metastases [70], signet ring cell carcinoma [71], rectal

primary [72], and incomplete cytoreduction [21, 73]. It is worth noting that patients having lymph node metastases at the time of primary tumor excision accounted for over half of long-term survivors and the subgroup of cured patients (123/206, 59,7% and 51/84, 60,7%, respectively). Previous research has shown lymph node metastases to be predictive of poor outcomes [21, 74]. However, by standardizing complete mesocolic excision, we can remove tumors in their entirety with lymphatic involvement, reducing local recurrence. According to our findings, patients with lymph node metastases may have a good chance of long-term survival and potentially reach a cure.

The vast number of patients mentioned, the number of international institutes involved, and the originality of focusing on long-term survivors' characteristics are all strengths of our study. This work has the potential to produce new research questions and hypotheses in the area of CRC peritoneal metastases with a long-term survival outcome.

There were also other restrictions for various reasons. The first one of these is that long-term survival and cure are not explicitly defined and are dependent solely on prior study survival periods. Second, we have observation and treatment variability due to the inherent nature of a multi-institutional retrospective cohort study. Furthermore, certain data points were missing, which could lead to selection biases. Finally, because this was a retrospective descriptive trial, there was no comparison of control groups for statistical analysis of CRS/HIPEC effectiveness and prognostic variables. We were unable to obtain data on all colorectal peritoneal metastases patients who received CRS/HIPEC at the 13 facilities. As a result, no comparisons were made between long-term survivors and non-survivors. The data obtained from this study, on the other hand, provide for a detailed analysis of long-term survivors' clinical characteristics in patients with CRC peritoneal metastases.

In order to evaluate the treatment of colorectal peritoneal carcinomatosis with CRS and HIPEC, the PRODIGE 7 trial (a trial evaluating the outcomes of CRS plus HIPEC versus CRS alone for colorectal peritoneal metastases) has been recently released [75]. The goal of this study was to determine the particular benefit of combining HIPEC with cytoreductive surgery versus cytoreductive surgery alone. In both therapy arms, 265 individuals were randomized. After a median follow-up of 63,8 months, the cytoreductive surgery combined with the HIPEC group had a median overall survival of

41,7 months (95% CI 36,2-53,8) and the cytoreductive surgery group had a median overall survival of 41,2 months (35,1-49,7) (hazard ratio 1,00 [95,37% CI 0,63-1,58]). Quénet et al. concluded that adding HIPEC did not improve overall survival and that cytoreductive surgery alone should be the cornerstone of therapeutic methods for colorectal peritoneal metastases with curative intent [75]. Nonetheless, many pieces of methodological information were not disclosed and were dubious [76]. At the moment, there are five randomized phases III trials in progress to assist with defining the role of HIPEC.

5 Conclusions

The main sites of manifestation of peritoneal carcinomatosis in primary and recurrent ovarian cancer are frequently constituted by the right upper abdomen and right hemidiaphragm, which makes peritoneal stripping or full-thickness resection of the diaphragm unavoidable to reach complete cytoreduction. The presented extraperitoneal upper quadrant peritonectomy is a feasible procedure and an efficacious approach when it comes to the treatment of peritoneal carcinomatosis of the diaphragm in ovarian cancer patients. It shows various advantages compared to the conventional transperitoneal approach and it provides a high rate of complete cytoreduction with a simplified technical performance. The preparation, in particular, considers the embryological anatomical layers by continuously visualizing the essential structures. Appropriate surgical training is vital for mastering the technically demanding procedure with a long learning curve. Under expert hands, the morbidity rate is comparable to that of the conventional approach. Expanding the surgical toolbox with the extraperitoneal route may help patients with ovarian cancer achieve a higher rate of complete tumor resection [5].

Colorectal cancer long-term survivors tended to show a low Peritoneal Cancer Index/Small Bowel-Peritoneal Cancer Index and to have CC-0. On the other hand, some of the long-term survivors exhibited factors that are considered to have a detrimental impact on survival outcomes. Even if individuals have characteristics associated with poor prognosis, curative intent treatments such as CRS coupled with perioperative chemotherapy should be performed when possible. More research is needed to determine which prognostic markers have a substantial impact on colorectal cancer patients' long-term survival and cure [6].

DOI:10.14753/SE.2023.2775

6 Summary

Primary cancers arising primarily from the lining of the peritoneal cavity (primary peritoneal cancer, mesothelioma) and those that have spread secondarily to the peritoneum from a primary abdominal or pelvic cancer site are referred to as peritoneal malignancies (gastric, colorectal, appendical and ovarian cancer).

The treatment for peritoneal cancers was palliative only. However, with the advancement of surgical science, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy has emerged as an alternative treatment option for selected patients with peritoneal malignancies of diverse origins. A multidisciplinary team approach should be used in the decision-making process to utilize this multimodal treatment, meaning that medical oncologists, radiologists, gastroenterologists, and oncological surgeons should be involved in evaluating the extent of tumor spread and prognostic factors, and the selection of eligible patients to obtain the greatest long-term benefits. Ongoing prospective research will assess the future impact of HIPEC. Until then, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy should be considered only in selected patients outside of clinical trials at specialized centers.

7 References

1. Sugarbaker PH. (1995) Peritonectomy procedures. Ann Surg, 221(1): 29-42.
2. Sugarbaker PH, Van der Speeten K, Stuart OA. (2010) Pharmacologic rationale for treatments of peritoneal surface malignancy from colorectal cancer. World J Gastrointest Oncol, 2(1): 19-30.
3. Sugarbaker PH, Chang D. (1999) Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol, 6(8): 727-731.
4. Jacquet P, Sugarbaker PH. (1996) Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. J Exp Clin Cancer Res, 15: 49-58.
5. Acs M, Leebmann H, Häusler S, Harter P, Piso P. (2022) Extraperitoneal Approach During Peritonectomy in the Right Upper Quadrant for Peritoneal Metastases from Ovarian Malignancies. In Vivo, 36(1): 341-349.
6. Kamada Y, Hida K, Yonemura Y, Sugarbaker PH, Ghabra S, Ishihara S, Nagata H, Murono K, Goi T, Katayama K, Morikawa M, Rau B, Piso P, Acs M, Coccolini F, Canbay E, Hsieh MC, Bhatt A, Bonnott PE, Glehen O. (2021) The Characteristics of 206 Long-Term Survivors with Peritoneal Metastases from Colorectal Cancer Treated with Curative Intent Surgery: A Multi-Center Cohort from PSOGI. Cancers (Basel), 13(12): 2964.
7. Matulonis UA, Sood AK, Fallowfield L, Howitt BE Sehouli J, Karlan BY. (2016) Ovarian cancer. Nat Rev Dis Primers, 2: 16061.
8. Reid F. World Ovarian Cancer Coalition Atlas 2020. World Ovarian Cancer Coalition, Toronto, 2020: 6.
9. Deutsche Krebsgesellschaft. (2020) S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren Langversion 4.0, AWMF online, Registrierungsnummer: 032/035OL 2020.
10. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. (2002) Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol, 20: 1248-1259.

11. du Bois A, Reuss A, Pujade-Lauraine EP, Harter P, Ray-Coquard I, Pfisterer J. (2009) Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer, 115(6): 1234-1244.
12. Zivanovic O, Eisenhauer EL, Zhou Q, Iasonos A, Sabbatini P, Sonoda Y, Abu-Rustum NR, Barakat RR, Chi DS. (2008) The impact of bulky upper abdominal disease cephalad to the greater omentum on surgical outcome for stage IIIC epithelial ovarian, fallopian tube, and primary peritoneal cancer. Gynecol Oncol, 108(2): 287-292.
13. Rodriguez N, Miller A, Richard SD, Rungruang B, Hamilton CA, Bookman MA, Maxwell GL, Horowitz NS, Krivak TC. (2013) Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of Gynecologic Oncology Group (GOG) 182. Gynecol Oncol, 130(3): 487-492.
14. Lemoine L, Sugarbaker P, Van der Speeten K. (2016) Pathophysiology of colorectal peritoneal carcinomatosis: Role of the peritoneum. World J Gastroenterol, 22(34): 7692-7707.
15. Sugarbaker PH. Cytoreductive surgery & perioperative chemotherapy for peritoneal surface malignancy. Textbook and video atlas. CineMed Publishing Inc., Woodbury, 2013
16. Hart IR, Fidler IJ. (1980) Role of organ selectivity in the determination of metastatic patterns of B16 melanoma. Cancer Res, 40(7): 2281-2287.
17. Kawajiri H, Yashiro M, Shinto O, Nakamura K, Tendo M, Takemura S, Node M, Hamashima Y, Kajimoto T, Sawada T, Ohira M, Hirakawa K. (2008) A novel transforming growth factor beta receptor kinase inhibitor, A-77, prevents the peritoneal dissemination of scirrhous gastric carcinoma. Clin Cancer Res, 14(9): 2850-2860.

18. Furuya M, Kato H, Nishimura N, Ishiwata I, Ikeda H, Ito R, Yoshiki T, Ishikura H. (2005) Down-regulation of CD9 in human ovarian carcinoma cell might contribute to peritoneal dissemination: morphologic alteration and reduced expression of beta1 integrin subsets. Cancer Res, 65(7): 2617-2625.
19. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JWW, de Hingh IH. (2011) Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer, 128(11): 2717-2725.
20. Jayne DG, et al. (2002) Peritoneal carcinomatosis from colorectal cancer. Br J Surg, 89(12): 1545-1550.
21. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dubè P, Glehen O. (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol, 28(1): 63-68.
22. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ 3rd . (2010) Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer, 116(16): 3756-3762.
23. Hompes D, D'Hoore A, Van Cutsem E, Fieuws S, Ceelen W, Peeters M, Van der Speeten K, Bertrand C, Legendre H, Kerger J. (2012) The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. Ann Surg Oncol, 19(7): 2186-2194.
24. Jacquet P, Sugarbaker PH. (1996) Peritoneal-plasma barrier. Cancer Treat Res, 82: 53-63.
25. Istomin YP, Zhavrid EA, Alexandrova EN, Sergeyeva OP, Petrovich SV. (2008) Dose enhancement effect of anticaner drugs associated with increased temperature in vitro. Exp Oncol, 30(1): 56-59.
26. Rietbroek RC, van de Vaart PJ, Haveman J, Blommaert FA, Geerdink A, Bakker PJ, Veenhof CH. (1997) Hyperthermia enhances the cytotoxicity and platinum-DNA adduct formation of lobaplatin and oxaliplatin in cultured SW 1573 cells. J Cancer Res Clin Oncol, 123(1): 6-12.

27. Takemoto M, Kuroda M, Urano M, Nishimura Y, Kawasaki S, Kato H, Okumura Y, Akaki S, Kanazawa S, Asaumi J, Joja I, Hiraki Y. (2003) The effect of various chemotherapeutic agents given with mild hyperthermia on different types of tumours. Int J Hyperthermia 19: 193-203.
28. Alberts DS, Peng YM, Chen HS, Moon TE, Cetas TC, Hoeschele JD. (1980) Therapeutic synergism of hyperthermia-cis-platinum in a mouse tumor model. J Natl Cancer Inst, 65(2): 455-461.
29. Krawczyk PM, Eppink B, Essers J, Stap J, Rodermond H, Odijk H, Zelensky A, van Bree C, Stalpers LJ, Buist MR, Soullié T, Rens J, Verhagen HJM, O'Connor MJ, Franken NAP, Ten Hagen TLM, Kanaar R, Aten JA. (2011) Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. Proc Natl Acad Sci U S A, 108(24): 9851-9856.
30. Steller MA, Egorin MJ, Trimble EL, Bartlett DL, Zuhowski EG, Alexander HR, Dedrick RL. (1999) A pilot phase I trial of continous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. Cancer Chemother Pharmacol, 43: 106-114.
31. Kyang LS, Alzahrani NA, Valle SJ, Rahman MK, Arrowaili A, Liauw W, Morris DL. (2019) Long-term survival outcomes of cytoreductive surgery and perioperative intraperitoneal chemotherapy: Single-institutional experience with 1225 cases. J Surg Oncol, 120(4): 794-802.
32. Hamilton TD, Taylor EL, Cannell AJ, McCart JA, Govindarajan A. (2016) Impact of Major Complications on Patients' Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Ann Surg Oncol, 23(9): 2946-2952.
33. Ali YM, Sweeney J, Shen P, Votanopoulos KI, McQuellon R, Duckworth K, Perry KC, Russel G, Levine EA. (2020) Effect of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Quality of Life in Patients with Peritoneal Mesothelioma. Ann Surg Oncol, 27(1): 117-123.

34. Deraco M, Baratti D, Kusamura S, Laterza B, Balestra MR. (2009) Surgical technique of parietal and visceral peritonectomy for peritoneal surface malignancies. J Surg Oncol, 100(4): 321-328.
35. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg, 240(2): 205-213.
36. Montz FJ, Schlaerth JB, Berek JS. (1989) Resection of diaphragmatic peritoneum and muscle: role in cytoreductive surgery for ovarian cancer. Gynecol Oncol, 35(3): 338-340.
37. Pathiraja PNJ, Garruto-Campanile R, Tozzi R. (2013) Diaphragmatic Peritonectomy versus Full Thickness Diaphragmatic Resection and Pleurectomy during Cytoreduction in Patients with Ovarian cancer. Int J Surg Oncol, 2013:876150.
38. Chi DS, Zivanovic O, Levinson KL, Kolev V, Huh J, Dottino J, Gardner GJ, Leitao MM Jr, Levine DA, Sonoda Y, Abu-Rustum NR, Brown CL, Barakat RR. (2010) The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecol Oncol, 119(1): 38-42.
39. Cliby W, Dowdy S, Feitoza SS, Gostout BS, Podratz KC. (2004) Diaphragm resection for ovarian cancer: technique and short-term complications. Gynecol Oncol, 94(3): 655-660.
40. Chèreau E, Rouzier R, Gouy S, Ferron G, Narducci F, Bergzoll C, Huchon C, Lécuru F, Pomel C, Daraï E, Leblanc E, Querleu D, Morice P. (2011) Morbidity of diaphragmatic surgery for advanced ovarian cancer: retrospective study of 148 cases. Eur J Surg Oncol, 37: 175-180.
41. Ye S, He T, Liang S, Chen X, Wu X, Yang H, Xiang L. (2017) Diaphragmatic Surgery and Related Complications In Primary Cytoreduction for Advanced Ovarian, Tubal, and Peritoneal Carcinoma. BMC Cancer, 17(1): 317.

42. Zapardiel I, Peiretti M, Zanagnolo V, Biffi R, Bocciolone L, Landoni F, Aletti G, Colombo N, Maggioni A. (2011) Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. Int J Gynecol Cancer, 21(9): 1698-1703.
43. Lim MC, Kang S, Choi J, Song YJ, Park S, Seo SS, Park SY. (2009) Hyperthermic intraperitoneal chemotherapy after extensive cytoreductive surgery in patients with primary advanced epithelial ovarian cancer: interim analysis of a phase II study. Ann Surg Oncol, 16(4): 993-1000.
44. Soleymani Majd H, Ferrari F, Manek S, Gubbala K, Campanile RG, Hardern K, Tozzi R. (2016) Diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during Visceral-Peritoneal Debulking (VPD) in 100 consecutive patients with stage IIIC-IV ovarian cancer: A surgical-histological analysis. Gynecol Oncol, 140(3): 430-435.
45. Papadia A, Morotti M. (2013) Diaphragmatic surgery during cytoreduction for primary or recurrent epithelial ovarian cancer: a review of the literature. Arch Gynecol Obstet, 287(4): 733-741.
46. Bashir S, Gerardi MA, Giuntoli RL 2nd, Diaz Montes TP, Bristow RE. (2010) Surgical technique of diaphragm full-thickness resection and trans-diaphragmatic decompression of pneumothorax during cytoreductive surgery for ovarian cancer. Gynecol Oncol, 119(2): 255-258.
47. Fanfani F, Fagotti A, Gallotta V, Ercoli A, Pacelli F, Costantini B, Vizzielli G, Margariti PA, Garganese G, Scambia G. (2010) Upper abdominal surgery in advanced and recurrent ovarian cancer: role of diaphragmatic surgery. Gynecol Oncol, 116(3): 497-501.
48. Carboni F, Federici O, Zazza S, Sperduti I, Valle M. (2021) Feasibility of diaphragmatic interventions in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: A 20-year experience. Eur J Surg Oncol, 47(1): 143-147
49. Blaj S, Nedelcut S, Mayr M, Leebman H, Leucuta D, Glockzin G, Piso P. (2019) Re-operations for early postoperative complications after CRS and HIPEC: indication, timing, procedure, and outcome. Langenbecks Arch Surg, 404(5): 541-546.

50. Piso P, Nedelcut SD, Rau B, Königsrainer A, Glockzin G, Ströhlein MA, Hörbelt R, Pelz J. (2019) Morbidity and Mortality Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Data from the DGAV StuDoQ Registry with 2149 Consecutive Patients. Ann Surg Oncol, 26(1): 148-154.
51. Zivanovic O, Aldini A, Carlson JW, Chi DS. (2009) Advanced cytoreductive surgery: American perspective. Gynecol Oncol, 114(2 Suppl): S3-9.
52. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh IHJT, van der Velden J, Arts HJ, Massuger LFAG, Aalbers AGJ, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS. (2018) Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med, 378(3): 230-240.
53. Spiliotis J, Prodromidou A. (2021) Narrative review of hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced ovarian cancer: a critical reappraisal of the current evidence. J Gastrointest Oncol, 12(Suppl 1): S182-S188.
54. Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, Bendifallah S, Bolze PA, Bonnet F, Bourgin C, Chabbert-Buffet N, Collinet P, Courbiere B, De la Motte Rouge T, Devouassoux-Shisheboran M, Falandry C, Ferron G, Fournier L, Gladieff L, Golfier F, Gouy S, Guyon F, Lambaudie E, Leary A, Lecuru F, Lefrere-Belda MA, Leblanc E, Lemoine A, Narducci F, Ouldamer L, Paupatier P, Planchamp F, Pouget N, Ray-Coquard I, Rousset-Jablonski C, Senechal-Davin C, Touboul C, Thomassin-Naggara I, Uzan C, You B, Daraï E. (2019) Management of epithelial cancer of the ovary, fallopian tube, primary peritoneum. Long text of the joint French clinical practice guidelines issued by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY, endorsed by INCa. (Part 2: systemic, intraperitoneal treatment, elderly patients, fertility preservation, follow-up). J Gynecol Obstet Hum Reprod, 48(6): 379-386.
55. Gerestein CG, Damhuis RAM, Burger CW, Kooi GS. (2009) Postoperative mortality after primary cytoreductive surgery for advanced stage ovarian cancer: A systematic review. Gynecol Oncol, 114(3): 523-527.

56. Koppe MJ, Boerman OC, Oyen WJG, Bleichrodt RP. (2006) Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg, 243(2): 212-222.
57. Welch JP, Donaldson GA. (1979) The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg, 189(4): 496-502.
58. Gilbert JM. (1983) Distribution of metastases at necropsy in colorectal cancer. Clin Exp Metastasis, 1(2): 97-101.
59. Yan TD, Black D, Savady R, Sugarbaker PH. (2006) Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol, 24(24): 4011-4019.
60. Foster JM, Sleightholm R, Patel A, Shostrom V, Hall B, Neilsen B, Bartlett D, Smith L. (2019) Morbidity and Mortality Rates Following Cytoreductive Surgery Combined With Hyperthermic Intraperitoneal Chemotherapy Compared With Other High-Risk Surgical Oncology Procedures. JAMA Netw Open, 2(1): e186847.
61. Choudry MHA, Shuai Y, Jones HL, Pai RK, Pingpank JF, Ahrendt SS, Holtzman MP, Zeh HJ, Bartlett DL. (2018) Postoperative Complications Independently Predict Cancer-Related Survival in Peritoneal Malignancies. Ann Surg Oncol, 25(13): 3950-3959.
62. Goéré D, Sourrouille I, Gelli M, Benhaim L, Faron M, Honoré C. (2018) Peritoneal Metastases from Colorectal Cancer: Treatment Principles and Perspectives. Surg Oncol Clin N Am, 27(3): 563-583.
63. Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, Baratti D, Baumgartner JM, Berri R, Bretcha-Boix P, Deraco M, Flores-Ayala G, Glehen O, Gomez-Portilla A, González-Moreno S, Goodman M, Halkia E, Kusamura S, Moller M, Passot G, Pocard M, Salti G, Sardi A, Senthil M, Spilioitis J, Torres-Melero J, Turaga K, Trout R. (2014) The American Society of Peritoneal Surface Malignancies (ASPSM) Multiinstitution Evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 Patients with Colorectal Cancer with Peritoneal Carcinomatosis. Ann Surg Oncol, 21(13): 4195-4201.

64. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D, French Surgical Association. (2010) Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer, 116(24): 5608-5618.

65. Kamada Y, Hida K, Ishibashi H, Sako S, Mizumoto A, Ichinose M, Padmanabhan N, Yoshida S, Yonemura Y. (2021) Thirty-three long-term survivors after cytoreductive surgery in patients with peritoneal metastases from colorectal cancer: a retrospective descriptive study. World J Surg Oncol, 19(1): 31.

66. Faron M, Macovei R, Goéré D, Honoré C, Benhaim L, Elias D. (2016) Linear Relationship of Peritoneal Cancer Index and Survival in Patients with Peritoneal Metastases from Colorectal Cancer. Ann Surg Oncol, 23(1): 114-119.

67. Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, Dumont F, Elias D. (2015) Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. Ann Surg Oncol, 22(9): 2958-2964.

68. Benizri EI, Bernard JL, Rahili A, Benchimol D, Bereder JM. (2012) Small bowel involvement is a prognostic factor in colorectal carcinomatosis treated with complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. World J Surg Oncol, 10: 56.

69. Spiliotis J, Kalles V, Kyriazonos I, Terra A, Prodromidou A, Raptis A, Kopanakis N, Christopoulou A. (2019) CRS and HIPEC in patients with peritoneal metastasis secondary to colorectal cancer: The small-bowel PCI score as a predictor of survival. Pleura Peritoneum, 4(4): 20190018.

70. Thomassen I, van Gestel YR, Lemmens VE, de Hingh IH. (2013) Incidence, prognosis, and treatment options for patients with synchronous peritoneal carcinomatosis and liver metastases from colorectal origin. Dis Colon Rectum, 56(12): 1373-1380.

71. Winer J, Zenati M, Ramalingam L, Jones H, Zureikat A, Holtzman M, Lee K, Ahrendt S, Pingpank J, Zeh HJ, Bartlett DL, Choudry HA. (2014) Impact of aggressive histology and location of primary tumor on the efficacy of surgical therapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol, 21(5): 1456-1462.
72. Tonello M, Ortega-Perez G, Alonso-Casado O, Torres-Mesa P, Guiñez G, Gonzalez-Moreno S. (2018) Peritoneal carcinomatosis arising from rectal or colonic adenocarcinoma treated with cytoreductive surgery (CRS) hyperthermic intraperitoneal chemotherapy (HIPEC): two different diseases. Clin Transl Oncol, 20(10): 1268-1273.
73. Ihemelandu C, Sugarbaker PH. (2017) Management for Peritoneal Metastasis of Colonic Origin: Role of Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy: A Single Institution's Experience During Two Decades. Ann Surg Oncol, 24(4): 898-905.
74. Chua TC, Yan TD, Ng KM, Zhao J, Morris DL. (2009) Significance of lymph node metastasis in patients with colorectal cancer peritoneal carcinomatosis. World J Surg, 33(7): 1488-1494.
75. Quénet F, Elias D, Roca L, Goéré D, Ghouti L, Pocard M, Facy O, Arvieux C, Lorimier G, Pezet D, Marchal F, Loi V, Meeus P, Juzyna B, de Forges H, Paineau J, Glehen O, UNICANCER-GI Group and BIG Renape Group. (2021) Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology, 22(2): 256-266.
76. Auer RC, Sivajohanathan D, Biagi J, Conner J, Kennedy E, May T. (2020) Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery: a systematic review. Eur J Cancer, 127: 76-95.

8 Bibliography of the Candidate's Publications

Publications cited in the present thesis

1. Kamada Y, Hida K, Yonemura Y, Sugarbaker PH, Ghabra S, Ishihara S, Nagata H, Murono K, Goi T, Katayama K, Morikawa M, Rau B, Piso P, **Acs M**, Coccolini F, Canbay E, Hsieh MC, Bhatt A, Bonnot PE, Glehen O. (2021) The Characteristics of 206 Long-Term Survivors with Peritoneal Metastases from Colorectal Cancer Treated with Curative Intent Surgery: A Multi-Center Cohort from PSOGI. Cancers (Basel), 13(12): 2964.

Impact factor: 6,575

2. **Acs M**, Leebmann H, Häusler S, Harter P, Piso P. (2022) Extraperitoneal Approach During Peritonectomy in the Right Upper Quadrant for Peritoneal Metastases from Ovarian Malignancies. In Vivo, 36(1): 341-349.
Impact factor: 2,406

The Candidate's other publications

1. **Acs M**, Häusler S, Lighvani HR, Zustin J, Piso P. (2021) Malignant Struma Ovarii Treated With Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). In Vivo, 35(6): 3591-3596.
Impact factor: 2,155

2. **Acs M**, Piso P, Prader S. (2022) Current Status of Metastatic Cardiophrenic Lymph Nodes (CPLNs) in Patients With Ovarian Cancer: A Review. Anticancer Res, 42(1): 13-24.
Impact factor: 2,435

3. **Acs M**, Halmy L, Isgandarova S, Blaj S, Gerken M, Hormann B, Piso P. (2022) Hyperthermic Intraperitoneal Chemotherapy With Cisplatin and Doxorubicin for 90 Minutes Versus 60 Minutes After Cytoreductive Surgery (CRS). Does the 30-Minute Difference Matter? A Comparative Study in a High Volume Centre. Anticancer Res, 42(2): 1019-1029.
Impact factor: 2,435

4. **Acs M**, Dadras A, Blaj S, Leebman H, Piso P. (2022) Selection Criteria for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy With Special Emphasis on Laparoscopy as an Efficient Tool. In Vivo, 36(3): 1367-1374.

Impact factor: 2,406

5. **Acs M**, Gerken M, Gajic I, Mayr M, Zustin J, Piso P. (2022) Ten-year single-center experience with treatment of primary diffuse malignant peritoneal mesothelioma (DMPM) by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Langenbecks Arch Surg, in print. Available from: https://europepmc.org/article/med/35732846

Impact factor: 2,895

6. Rajha A, Piso P, Halmy L, Panczel I, Nedelcut D-S, Herold Z, Szasz AM, **Acs M**. (2022) Rare Histologies and Infrequent Indications for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Anticancer Res, 42(7): 3681-3692.

Impact factor: 2,345

Cumulative Impact Factor: 23,993

DOI:10.14753/SE.2023.2775

9 Acknowledgements

At this point, I would like to thank Prof. Dr. med. Dr. h. c. P. Piso for his professional support and mentorship. Furthermore, I would like to thank my supervisor Dr. Tamás Ruttkay for his daily help and review of my work. My thanks are due to all of those who have supported and accompanied me on my way so far. With two exceptions, I will not list their names here. Dr. Dora Novotny and Dr. Lajos Patonay, I am grateful to you! Thank you from the bottom of my heart to my parents for making this life possible and starting me on this path.

Above all, I thank my wife, Dora, and my children, Mark and Hanna, for their love and patience, and for helping me to understand what moments in life are true and meaningful.