Management of Peritoneal Metastases-Cytoreductive Surgery, HIPEC and Beyond

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Foreword

During the last two decades, the management of peritoneal metastasis is probably one field for which most progresses have been performed in oncology. In the 1980s, this condition was considered as the terminal stage of the disease and the therapies were only palliative, especially for peritoneal metastasis from digestive primary tumor. Today, some patients accurately selected and treated in specialized institutions involved in the management of peritoneal surface malignancies may be cured; 20 years before, they had no escape or no hope. How could we tailor therapeutic strategy for the same patient for the same disease?

Firstly, we have to thank the following pioneers, "evangelists," who believed that curative treatment could be applied for this difficult disease, despite the great skepticism of the oncologic community: Paul H. Sugarbaker from Washington, who developed and taught the techniques of peritonectomies and defended the concept of cytoreductive surgery that allows to treat the macroscopic disease; François N. Gilly from Lyon and Dominique Elias from Villejuif who developed in France the "open" and "closed" techniques of hyperthermic intraperitoneal chemotherapy (HIPEC) to treat the microscopic disease following cytoreductive surgery; and Franz Zoetmulder from the Netherlands who conducted the first randomized trial on peritoneal metastasis from colorectal cancers that evaluated the combination of cytoreductive surgery and HIPEC and who demonstrated the benefit of this combined treatment over systemic palliative chemotherapy. Of course other contributors and defenders of this combined procedure participated all over the world in the development of this locoregional management for a locoregional disease.

Secondly, other than these pioneer surgeons, all disciplines have increased their interest to this difficult medical condition that requires not only surgery and HIPEC but a real multidisciplinary management: the radiologists to better detect or evaluate the extent of disease which represents one of the principal prognostic factors whatever the etiology; the anesthetists and resuscitators to take in charge of a delicate postoperative period, to better control postoperative complications of extensive and at-risk procedures; the oncologists to better select good candidate for a curative treatment and to delay the extraperitoneal recurrence by an adapted perioperative management; the psychologists to help patients face bad prognosis condition and complex therapies; the pathologists and biologists to define new classification of rare peritoneal disease or identify new biologic or molecular markers; the pharmacologists

to optimize intraperitoneal administration of anticancer drugs; and the nurses and physiotherapists to help physicians to facilitate the recovery of patients following extensive procedures.

This book is of course principally dedicated to surgical or medical oncologists who are or will be involved in the management of peritoneal surface malignancies. It describes the rationale, treatment, and results already obtained for rare diseases such as pseudomyxoma peritonei and peritoneal mesothelioma but also for more frequent peritoneal metastasis from colorectal, appendiceal, ovarian, gastric, or other digestive and gynecologic cancers. A lot of internationally renowned peritoneal surface oncology teams have authored the chapter.

What will be the future? Even if there are many progresses and changes in the prognosis of many peritoneal surface malignancies, too many patients still remain nonamenable to a curative treatment and a lot of improvement could be done. One direction that was already taken is prevention. The use of proactive treatment (second-look surgery with prophylactic HIPEC) may prevent the occurrence of peritoneal metastasis for patients who are at risk and are currently evaluated in prospective randomized studies in colorectal or gastric cancers. The development of new intraperitoneal techniques may also provide better palliative results in a neoadjuvant setting: pressurized intraperitoneal aerosol chemotherapy (PIPAC), intraperitoneal targeted therapy, and laparoscopic HIPEC.

Finally, each country should help the establishment of specialized centers involved in peritoneal surface malignancies that represents today a medical discipline, a specific field that teaches the younger generation in order to offer new and reliable hope to patients suffering from this past terminal condition. Peritoneum should be considered as an organ, and peritoneal metastasis should be treated with the same conviction and ambition as with other metastases.

25 March 2017

Prof. Olivier Glehen
Centre Hospitalier Lyon Sud
Lyon, France

Preface

The curative approach to the management of peritoneal metastases involves a complex surgical procedure that aims at complete tumor removal with or without the use of various forms of intraperitoneal chemotherapy of which hyperthermic intraperitoneal chemotherapy (HIPEC) is the most commonly used form. For most disease processes, systemic treatments are needed along with aggressive locoregional therapy to provide a maximum benefit in survival and quality of life to the patients. Proficiency in the surgical management needs to be coupled with an understanding of the disease biology to best administer and sequence various treatment modalities. The widespread acceptance of cytoreductive surgery and HIPEC, though after a prolonged initial resistance by the oncology community at large, has paved the way for new innovative therapies that can benefit a larger proportion of patients. Much has been and continues to be published on this subject.

This book has been written with the goal of providing comprehensive reviews on various aspects of management of peritoneal metastases. The authors try to raise important practical issues that surgical oncologists encounter in their practice and provide evidence-based answers to these. Experts in this field have authored/reviewed most of the chapters.

I wholeheartedly thank all the authors for their contribution and kind and effective collaboration in bringing this book together.

I would also like to thank Dr. Naren Agarwal, Associate Editorial Director of Springer India, for conceiving this book and his prompt help at various stages of the publication process.

Bangalore, India
31 July 2017

Aditi Bhatt

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Part I

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1 Evolving Role of CRS and HIPEC: Current Indications

Firoz Rajan and Aditi Bhatt

1.1 Introduction

The term "peritoneal carcinomatosis" has been euphemistically replaced by "peritoneal metastases" in the last decade by surgical oncologists whose efforts have helped to dismiss the nihilistic approach of the oncologic community, in general, toward this condition and improve the survival and quality of life in patients with peritoneal cancer spread. Peritoneal metastases (PM) have a poorer prognosis compared to other metastatic sites and are comparatively less responsive to systemic therapies [1]. Patients are more often symptomatic from PM than other metastatic sites, and these symptoms severely impair the quality of life [2].

Surgical oncologists are often faced with the challenge of alleviating these symptoms and have worked to introduce innovative therapies for treating PM [3]. As a result, development in this field has largely focused on the disease site rather than histology [3]. Surgical removal of peritoneal deposits was first performed for ovarian cancer and subsequently other primary sites with PM [4]. Cytoreductive surgery (CRS), that is, complete removal of all macroscopic disease, and (hyperthermic intraperitoneal chemotherapy) HIPEC, in which a heated chemotherapy solution is circulated in the peritoneal cavity at a fixed flow rate of 30–120 min maintaining an intra-abdominal temperature of 42–43 °C, comprise an aggressive locoregional therapy that was introduced in the 1980s. The rationale of an aggressive locoregional strategy is the propensity of metastases from certain primary sites to remain confined to the peritoneal cavity for prolonged periods without the development of other metastases. The surgical technique of peritonectomy and associated visceral resections was developed and described by Paul Sugarbaker in the 1990s [5]. HIPEC drug regimens and methods were developed by various investigators during the same period [6–8]. The basic principle is to intraoperatively affect tumor cell kill by the process of diffusion of chemotherapeutic drugs into the residual tumor cell deposits after the CRS, using heat to potentiate their cytotoxicity [9–11]. There is a critical residual tumor size (ideally less than 2.5 mm in size), above which the HIPEC treatment is not effective. With this treatment, selected patients experience a significant prolongation in survival and an improvement in the quality of life [12]. Selected patients who remain disease-free for prolonged periods are considered to be cured [13, 14].

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Other forms of intraperitoneal chemotherapy like early postoperative intraperitoneal chemotherapy (EPIC) given on postoperative days 1–5 and sequential intraperitoneal chemotherapy (SIPC) given through an intraperitoneal catheter in multiple cycles are used less commonly. This treatment was initially instituted to treat PM from various primary sites or tumors arising de novo from the peritoneum, provided there was no metastatic disease elsewhere and the patient was in a condition to withstand the procedure. The prognostic and predictive factors were established irrespective of the site of origin. Some of the common prognostic indicators that are used to select patients for this treatment are Sugarbaker's peritoneal carcinomatosis index (PCI) that determines the extent of the disease, completeness of cytoreduction score (CC score), and the histologic tumor grade [15]. The main concern was the high morbidity and mortality of this procedure. It has been associated with a prolonged learning curve that peaks at 120 procedures which is not just for the surgeon but also for the institute [16]. Over time, with the increasing experience of the surgical community and the development of some high volume centers, there has been a reduction in the morbidity and mortality, and now in experienced centers, it is similar to that of other major gastrointestinal surgeries [17]. With the increase in experience, level 2 and 3 evidence is available for its use for various indications, and clinical trials are underway to determine its role in other situations [18]. Each disease site is now being dealt with separately. Various aspects of treatment like the right time for instituting this therapy, the prognostic factors for patient selection, the drug regimens and HIPEC methodology, and the correct sequencing with other therapies are being studied to standardize various aspects of treatment. Over the years, the indications have become better defined, and there are specific indications and contraindications for each disease site. An overview of the same is provided here.

1.2 Current Indications for CRS and HIPEC

Based on the existing evidence, a synopsis of the disease-specific indications and prognostic factors is listed in Table 1.1.

Table 1.1 Synopsis of the current indications for CRS and HIPEC

Primary site	Indications	Prognostic factors	Systemic therapy	Level of evidence
Colorectal cancer	PCI < 20, complete CRS possible, no systemic disease except <3 *easily* resectable liver metastases, no ascites	PCI < 12, CC-0 resection, good response to chemotherapy, mucinous tumors, non-signet ring cell tumors	Neoadjuvant/ adjuvant	3
Recurrent colorectal PM	Complete CRS possible, limited disease, no systemic spread	PCI < 10, CC-0 resections, no grade 3–5 morbidity	Neoadjuvant/ adjuvant	3
Gastric cancer	PCI < 13, complete CRS possible, no systemic disease	PCI < 6, peritoneal fluid cytology negative, non-signet ring cell tumors, good response to neoadjuvant therapies	Neoadjuvant preferred	1
Gastric cancer	As adjuvant therapy in patients with T3/4 tumors, N2 disease and positive peritoneal fluid cytology		Neoadjuvant/ adjuvant	experimental
Ovarian cancer (frontline therapy)	Complete CRS is possible	Complete cytoreduction	Neoadjuvant therapy for unresectable disease	1 (for CRS alone)
	HIPEC in the setting of a clinical trial			HIPEC-currently under trial

Table 1.1 (continued)

Primary site	Indications	Prognostic factors	Systemic therapy	Level of evidence
Ovarian cancer (second-line therapy)	For platinum-sensitive recurrence if complete cytoreduction is possible	PCI < 8, CC-0/1 resections	Neoadjuvant/ adjuvant	2/3
	For platinum-resistant disease if first surgery was incomplete and a complete CRS is possible			
	For platinum-resistant disease if there is a response to chemotherapy and the disease is resectable			
PMP arising from epithelial appendiceal tumors	Complete CRS possible, irrespective of PCI or tumor grade	Low PCI, CC-0/1 resection, low-grade PMP, no prior surgery or chemotherapy, lymph nodes negative, prior surgical score 0–1	Neoadjuvant/ adjuvant for high grade tumors	3
Recurrent PMP	Complete CRS possible	CC-0/1 resection, low-grade tumors, disease-free interval > 1 year, localized recurrence		3
Peritoneal mesothelioma	Epithelioid histology, complete cytoreduction is possible	PCI < 17, no lymph node involvement, CC-0/1 resection		3
Rare indications	Mucinous ovarian tumors, neuroendocrine tumors. For other indications, decisions need to be individualized	PCI < 15, CC-0/1 resection	Neoadjuvant/ adjuvant depending on the histology	3

The three main criticisms of CRS and HIPEC have been the high rate of morbidity, the lack of level 1 evidence, and the heterogeneity of HIPEC regimens. It must be kept in mind that in most situation PM represent stage 4 disease with a substantially poorer prognosis compared to other patients and conducting clinical trials in these patients is fraught with difficulties as pointed out by David Bartlett [3]. Phase I dose escalation studies may need to be terminated because of surgical complications/morbidity rather than the toxicity of the drug itself which could make interpretation difficult [3]. In phase II trials, as there is no residual tumor/disease, the clinical end points have to be disease-free and overall survival [3]. The outcomes need to be compared to systemic chemotherapy which represents a moving target due to the constant introduction of new drugs and regimens. Moreover, the chemotherapy data is not available for patients with PM alone but is mixed with other sites of metastatic cancer spread which makes a comparison even more difficult. Phase III trials are difficult to conduct for similar reasons.

Any surgical intervention requires multiple parameters to be considered while reporting the outcomes of a clinical trial and, CRS and HIPEC is a relatively more complex procedure [19].

Though there are nine trials pertaining to CRS and HIPEC that have been published so far, there are deficiencies in the design and reporting of most of them [20–23]. The evidence on which the current indications for CRS and HIPEC are based comes from single or multi-institutional case series and case-controlled studies. Though most of the studies are retrospective, they represent the experience of the pioneering centers of the procedure across the world and comprise of consecutive patients treated in a systematic fashion. The studies would be categorized as level 3 evidence

Table 1.2 Levels of evidence according to the National Cancer Institute's guidelines [24]

Levels of evidence	Studies included
Level 1	Well-designed double-blinded[a] randomized controlled trials or a meta-analysis of these trials
Level 2	Non-randomized, controlled, clinical trials. Includes subset analysis performed in randomized controlled trials
Level 3	Population-based, consecutive series
	Consecutive cases (not population based)
	Nonconsecutive cases or other observational study designs (e.g., cohort or case-control studies)

[a]Double blinding is not possible in most oncology trials due to the toxicity of therapies involved

according to the National Cancer Institute's guidelines for stratification of clinical studies (Table 1.2) [24].

The studies that fall into the third category have the weakest study designs, but may be the only available or practical information in support of a therapeutic strategy, especially in the case of rare diseases or when the evolution of the therapy predates the common use of randomized study designs in medical practice [23]. They may also provide the only practical design when treatments in study arms are radically different (e.g., amputation vs limb-sparing surgery). Thus, in rare diseases like pseudomyxoma peritonei where there is a clear benefit in survival over other therapies and conducting randomized trials is difficult and may be considered unethical, evidence from large retrospective studies is considered adequate.

1.2.1 Pseudomyxoma Peritonei Arising from Epithelial Appendiceal Tumors

Pseudomyxoma peritonei (PMP) also called jelly belly is characterized by presence of a gelatinous material sometimes amounting to a few liters within the abdominal cavity with mucinous implants on the visceral and peritoneal surfaces. The usual site of primary is the appendix and sometimes the ovary. In a biologically heterogeneous group of diseases, the spectrum ranges from the low-grade diffuse peritoneal adenomucinosis (DPAM) where there is abundant extracellular mucin with scanty simple to focally proliferative mucinous epithelium without any atypia (60% of cases) with/without an appendicular mucinous adenoma to a frank adenocarcinoma condition called peritoneal mucinous carcinoma (PMCA) constituting 28% of PMP cases [25]. An intermediate variety with discordant features constituted the rest. The standard of care for PMP is aggressive locoregional therapy comprising of complete cytoreductive surgery and HIPEC [12, 26, 27]. The conventional treatment used to be repeated drainage of mucin or debulking surgery comprising of removal of the primary tumor and the omentum. With this treatment, the reported 10-year survival was 32% in one series and 5-year survival 6% in another [28, 29]. Contrary to this, Sugarbaker reported a 5-year survival of 86% in patients with low-grade tumors undergoing a complete cytoreduction in a series of 385 consecutive patients [30]. Subsequently, a retrospective study of 2298 patients from 16 specialized institutions around the world treated with cytoreductive surgery and HIPEC reported a median survival rate of 196 months (16.3 years) and the median progression-free survival rate of 98 months (8.2 years), with 10- and 15-year survival rates of 63 and 59%, respectively [31]. In the largest single institution series of 1000 patients, Moran et al. reported a 5- and 10-year overall survival (OS) was 87.4 and 70.3%, respectively, in the 738 patients who had CC-0/1 compared with 39.2 and 8.1%, respectively, in patients who had a CC-2/3 resection [32]. CRS and HIPEC is now the standard of care for treating PM arising from epithelial appendiceal tumors. The most important prognostic factors for PMP are the completeness of cytoreduction, a low PCI, and low-grade PMP. Patients who have no regional nodal metastases and have not had prior non-definitive surgery or chemotherapy have a better outcome [32].

Approximately one in four patients develops recurrence after complete CRS and HIPEC for PMP of appendiceal origin [33]. Recurrence can be diffused or localized. A diffuse recurrence

represents an aggressive disease biology or insensitivity of the tumor to intraperitoneal chemotherapy especially if the recurrence-free interval is short. This type of recurrence is associated with a poorer survival. Localized recurrence is probably due to tumor cell entrapment at the suture line or in adhesions and has a better prognosis [34]. CRS and HIPEC can be performed in patients with localized recurrence and in selected cases of diffuse recurrence if there is a prolonged recurrence-free interval and a complete cytoreduction is possible [35]. Some of the factors to be considered are the performance status, the extent of the peritoneal disease, recurrence-free interval from the first surgery, the completeness of primary surgery, and the grade of the PMP [36]. Selected patients with a second and third recurrence can also be treated with CRS and HIPEC resulting in a prolonged survival [37].

1.2.2 Colorectal Cancer

Peritoneal metastases are the second most common cause of death in colorectal cancer patients after liver metastases [20]. Around 10% of CRC have PM at presentation, while another 25% will develop PM after treatment of the primary. There is a single randomized trial comparing use of CRS and HIPEC versus palliative chemotherapy with 5FU/leucovorin in colorectal PM, and updates of the trial show that few of these treated patients can survive up to 8 years [20, 38]. A number of comparative studies and retrospective analytical studies have shown that the median survival is close to 3 years in most of them and 5-year survival is close to 30% [38–40]. In the largest retrospective multi-institutional study from French centers, in comparison to only systemic therapy, patients with PM are treated with CRS and HIPEC. Elias et al. reported a median overall survival of 30.1 months, 5-year overall survival of 27%, and a 5-year disease-free survival of 10% [41]. Patients who have complete cytoreduction (CC-0) experience a survival benefit with a 5-year survival of 30%. Data from randomized trials involving chemotherapy with or without targeted therapy include all metastatic site; an analysis of patients with PM alone has shown an inferior survival compared to other disease sites [39, 42, 43]. It can be inferred that systemic therapy alone in patients with colorectal PM produces poorer results as compared to patients without (12.7 months vs 17.6 months) [43]. CRS and HIPEC for CRC is performed for limited peritoneal metastases (PCI < 20) and in patients with up to three synchronous easily resectable liver metastases [44]. It is essential to take up this procedure only when complete tumor removal is possible. Elias et al. showed a significant difference in 5-year survival of 29% vs 14% in patients with CC-0 (no macroscopic residual disease) and CC-1 (residual disease < 2.5 mm) resections, respectively [42]. Some patients experience a prolonged disease-free survival, and patients who are disease-free for 5 years after CRS and HIPEC are considered cured [13]. Whereas the role of CRS is established, that of HIPEC is being evaluated in a randomized trial, the results of which are expected at the end of 2017. Its role as a prophylactic procedure in those cases where there is high risk of dissemination in the peritoneum (T4 disease, perforated tumors, ovarian metastases) is being evaluated in clinical trials [45]. One clinical trial is evaluating a systematic second-look strategy for patients at high risk for peritoneal dissemination (NCT01226394). Patients with a PCI < 12, those who have complete tumor resection CC-0, and those who have a good response to systemic chemotherapy experience a prolonged survival [46–48]. The value of systemic chemotherapy in addition to CRS and HIPEC has been debated though most centers prefer to use chemotherapy in addition to CRS and HIPEC.

Though CRS and HIPEC are performed with the intent of cure, around 70–80% of the patients will develop recurrent disease and about half of these recurrences are confined to the peritoneal cavity [49, 50]. Over the years, evidence has accumulated showing the feasibility and survival benefit of a repeat CRS and HIPEC in selected patients [51, 52]. In the largest multi-institutional study from 11 institutions across the world comprising of 189 patients, the reported median survival was 26.4 months, disease-free survival

10.1 months, and 5-year overall survival 20% following a repeat CRS and HIPEC [53]. The median PCI was 6.9, and 81% of the patients had a complete cytoreduction. A PCI of <10 during the second procedure, a complete cytoreduction, and absence of grade 3–5 morbidity were associated with a favorable prognosis.

1.2.3 Ovarian Cancer

In 75% of the cases, ovarian cancer is diagnosed in either the third of fourth stage. In ovarian cancer, PM are classified as stage III as compared to other cancers where it is stage IV. Stage IV is the involvement of the pleura and pleural space and other distant organs. The standard treatment of advanced ovarian cancer comprises of CRS followed by systemic chemotherapy. Despite radical surgery and chemotherapy, there is a high probability of recurrence leading to a poor 5-year overall survival rate of only 30% [54]. Recurrent ovarian cancer itself has a poor long-term outcome. The conventional treatment is multiple lines of chemotherapy with or without targeted therapy.

There is level 1 evidence to support the use of SIPC in patients with advanced ovarian cancer undergoing "optimal debulking" [55, 56]. This led to a NCI alert advocating the use of adjuvant intraperitoneal chemotherapy in 2008 [57]. However, intraperitoneal chemotherapy is not widely used mainly due to the concerns of catheter-related morbidity which occurs in 1/3 of patients [56]. HIPEC has the advantages of being administered directly after surgery in the operation theater, thus having a more even distribution. Moreover, the use of heat potentiates the action of cisplatin and helps in overcoming platinum resistance [58, 59]. HIPEC is used at the time of first-line therapy or second-line therapy. The nomenclature depends on the timing of the intervention in relation to systemic chemotherapy and was described by Mulier et al. It is called upfront/primary CRS and HIPEC when performed before chemotherapy and interval CRS and HIPEC when performed after it [60]. In patients who undergo a second-look surgery, it is consolidation CRS and HIPEC if the procedure is performed. For patients who have recurrence after a complete primary CRS, the surgery performed is termed "salvage CRS and HIPEC," and for patients who had suboptimal first surgery, it is termed "secondary CRS and HIPEC" [60]. In frontline therapy, the addition of HIPEC to CRS has not shown any benefit over CRS alone. The evidence comes mainly from retrospective single and multi-institutional studies [61–65]. The results of randomized controlled trials that are evaluating its role in this setting are awaited pending which is not recommended outside the setting of clinical trial. A benefit of CRS and HIPEC has been shown for recurrent ovarian cancer in retrospective and case-control studies. In a multi-centric study of 474 patients from France, the median overall survival was 45.7 months. More importantly, in patients who have a complete cytoreduction, the survival in the platinum-sensitive and platinum-resistant groups was similar (47.2 and 51.6 months, respectively, $p < 0.05$) [65]. There are case-controlled studies comparing CRS and HIPEC with CRS alone, but they are all retrospective in nature with small numbers [66–73]. The recurrent setting is different from the frontline setting as there is no standard treatment. Based on the above evidence, CRS and HIPEC can be used for patients with platinum-sensitive recurrence that is completely resectable. For platinum-resistant disease, if the patients had an incomplete CRS in the first sitting or have a good response to chemotherapy, secondary CRS can be performed with HIPEC. However, complete CRS should be possible in all these cases. It is best that such treatment is undertaken in the setting of a clinical trial or as a study approved by the institutional review board. On the other hand, there is substantial evidence for performing CRS in patients with platinum-sensitive recurrence, provided a complete cytoreduction can be obtained.

1.2.4 Gastric Cancer

PM occur synchronously in 14–43% and metachronously in 10–46% of the patients with gastric cancer [74, 75]. The peritoneum is the sole

site of disease in 35% of the patients with synchronous metastases [76].

HIPEC has been used for prevention of gastric PM in patients at high risk, to treat patients with PM in combination with CRS, and as a palliative treatment for the management of intractable ascites [77]. HIPEC has been used as a prophylaxis treatment to prevent peritoneal dissemination in patients at high risk (serosal invasion or nodal metastasis). Several prospective and retrospective studies, randomized controlled trials, and a meta-analysis have shown that when performed with curative gastric cancer surgery, HIPEC is safe, significantly improves the survival, and reduces the risk of peritoneal recurrence [78–83]. There is level 1 evidence for the use of adjuvant HIPEC. However, the caveat is that this evidence comes from Japan where the outcomes of gastric cancer are superior to those reported from the rest of the world which has in part been attributed to the disease biology.

CRS and HIPEC has shown benefit in patients with PM from gastric cancer as well and is the only treatment modality that can produce a long-term survival in these patients. A multi-institutional series of 159 patients treated with CRS and HIPEC reported 1-, 2-, and 5-year survival rates of 43, 18, and 13%, respectively [21, 84]. A randomized controlled trial from China comparing CRS and HIPEC with CRS alone reported a 3-year survival in the CRS with HIPEC arm was 5.9% compared to 0% in the CRS alone arm. CRS with HIPEC was associated with a significantly higher median survival compared to CRS alone (11 months vs 6.5 months, $p = 0.04$) [21]. CRS and HIPEC is currently recommended for gastric PM with limited peritoneal spread (PCI < 13) and patients who can have a complete cytoreduction. A small percentage of patients who are disease free at 10 years are considered cured. Neoadjuvant strategies like neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) to reduce the disease burden and intraperitoneal free cancer cells have shown good results, and patients who are downstaged subsequently undergo CRS and HIPEC [85]. In 69% of the patients, a positive peritoneal cytology was converted to negative after NIPS as reported by Yonemura et al. The role of PIPAC is being evaluated for advanced unresectable PM from gastric cancer.

The PIPAC EstoK 01 is a prospective, multicenter, randomized, open-label, controlled, parallel-group, phase II trial designed to evaluate the effect of PIPAC with oxaliplatin combined with systemic chemotherapy in patients with gastric PM with a PCI > 8. The primary end point of this trial is the progression-free survival at 24 months. The secondary end points are the 24-month OS, safety, tolerability, and quality of life. It will also evaluate the feasibility of three successive PIPAC procedure and secondary resectability rate in these patients.

1.2.5 Mesothelioma

As a rare clinical entity and linked to asbestos exposure, mesotheliomas can affect any of the serosal surfaces – pleura, pericardium, peritoneum, or tunica vaginalis. Systemic chemotherapy and radiation have failed in altering the disease course [86]. In a pooled study of 401 cases from eight institutions from across the globe, CRS and HIPEC has shown that in selected cases, durable control of ascites in >90% cases and survival (median survival of up to 60 months and a 5-year survival of 50% in selected patients) can be achieved [87]. Epithelial subtype, lymph node negative status, CC 0/CC1 completeness of cytoreduction scores, and use of HIPEC were found to be independent prognostic factors on multivariate analysis.

1.2.6 Rare Indications

There are some rare primary and secondary tumors involving the peritoneum that have been treated with CRS and HIPEC [88–92]. Some common cancers metastasize to the peritoneum like hepatobiliary, pancreatic, cervical, and breast cancers and are generally treated with systemic chemotherapy alone. However, in rare situation when there is limited disease confined to the peritoneal cavity alone, patients with PM from these

primary sites have been treated with CRS and HIPEC. These form rare indications for CRS and HIPEC. CRS and HIPEC in these situations is used on the basis of logic rather than evidence with the hope of providing a survival benefit to these patients. The only other treatment for such patients would be systemic chemotherapy that is largely ineffective. In a recent multi-institutional study by the PSOGI and BIG-RENAPE groups, the results of CRS and HIPEC for rare indications and rare tumors in 850 patients were reported [93]. The three most common indications were rare ovarian primary tumors, neuroendocrine tumors, and sarcomas. The median OS was 39.45 months (33.18–44.05 months), and the 1-year, 3-year, and 5-year OS were, respectively, 77.8, 52.2, and 38.7%. A low PCI was associated with an improved OS, and ovarian and neuroendocrine had a longer survival compared to patients with sarcomas. This study showed a benefit of CRS and HIPEC in mucinous ovarian tumors comparable to that obtained in patients with PMP of appendiceal origin [93]. A significant benefit was also observed in patients with neuroendocrine tumors. For other histologies, there was a benefit of the combined strategy, but the roles of CRS and HIPEC, respectively, need further evaluation. Based on the above evidence, for mucinous ovarian tumor and neuroendocrine tumor, CRS and HIPEC can be offered to patients. The most significant prognostic factors are the PCI and the completeness of cytoreduction. For other histologies, CRS and HIPEC may be performed for limited disease, provided complete tumor removal is possible; the treatment needs to be individualized. Newer therapies like pressurized intraperitoneal chemotherapy (PIPAC) may be considered for extensive disease as an alternative in patients where the benefit is not clear and the risk of morbidity is high.

Conclusions

CRS and HIPEC is an aggressive treatment strategy that has the potential to cure certain patients with peritoneal metastases. There are disease-specific indications and contraindications based on existing evidence that should be followed to yield the best results. CRS and HIPEC has been evaluated as a combined modality, and given the high morbidity, the respective roles of CRS and HIPEC have been questioned. The existing evidence shows that surgical resection of PM leads to a survival benefit in selected patients and is a potentially curative treatment in these patients. The role of this combined modality is established in PMP and malignant mesothelioma. The added benefit of HIPEC in certain diseases like colorectal and ovarian cancer will be determined by the results of the ongoing randomized trials. Reiterative procedures also have a survival benefit in selected patients with recurrent disease. The role of HIPEC in prevention of peritoneal metastases is under evaluation. The results of clinical trials will further expand and modify the indications of CRS and HIPEC and integration with other therapies. The introduction of newer therapies like pressurized intraperitoneal aerosol chemotherapy (PIPAC) that are also being evaluated in clinical trials could further modify the timing and indications for CRS and HIPEC.

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2 Role of HIPEC in the Prevention of Peritoneal Metastasis from Colorectal, Gastric and Appendiceal Cancer

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2.1 Introduction

Colorectal cancer is the third most common cancer in men and second in women, while gastric cancer is the third leading cause of cancer death in both sexes worldwide and accounts for 8.8% of cancer deaths every year [1]. Both these malignancies metastasise by lymphatic, haematogenous and transcoelomic dissemination. Synchronous colorectal peritoneal metastases (CPM) occur in approximately 7% of patients, while a further 10–20% develop metachronous CPM [2, 3].

The most common cause of death in patients with gastric cancer is peritoneal metastasis (PM). At the time of diagnosis, nearly 15–40% of patients with gastric cancer will have peritoneal spread [4]. After curative surgery for gastric cancer, distant metastasis is seen in 25–50% of patients [5–7], with PM accounting for 35–45% of all recurrences [6]. While the survival after curative surgery in gastric cancer is marginally improved by adjuvant or perioperative therapies [5, 7–9], these strategies have not been successful in significantly lowering the rate of distant metastases, including PM [10, 11].

2.2 Current Standard of Care for Colorectal/Gastric Peritoneal Metastases

Traditionally, patients with CPM were considered incurable and underwent palliative chemotherapy. Although systemic therapy for metastatic colorectal cancer has greatly evolved over recent years, particularly with the development of biological agents, the survival benefit achieved with modern systemic therapy remains limited. A subgroup analysis of the Dutch CAIRO2 study showed that patients with CPM treated with modern systemic chemotherapy (capecitabine with oxaliplatin) combined with biological agents (bevacizumab and, in selected patients, cetuximab) had a limited median overall survival of 15 months and a median progression-free survival of just 6 months; moreover, these survival outcomes were significantly worse than those achieved in patients with non-peritoneal metastatic disease, as shown in Fig. 2.1 [12]. A pooled analysis of two US trials comparing various chemotherapy regimens for metastatic colorectal cancer showed that, in all chemotherapy arms, patients with peritoneal metastatic disease had a significantly worse survival outcome than those

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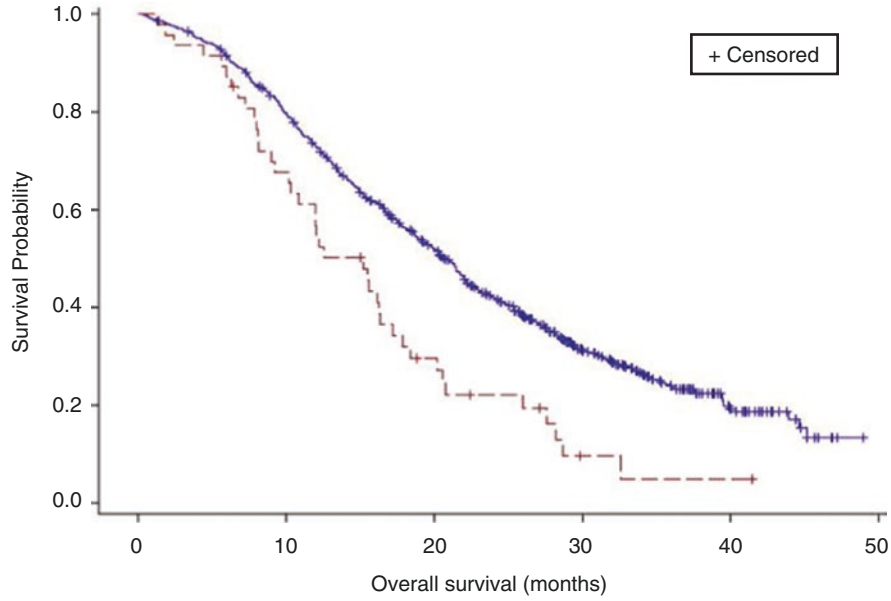

Fig. 2.1 Kaplan-Meier curves showing differences in survival between patients with non-peritoneal (blue) and peritoneal metastatic disease, treated with modern systemic chemotherapy + biological agents (reproduced with permission from [12])

with non-peritoneal sites of disease, with a median overall survival of just 12.7 months [13].

Similarly, the prognosis of gastric cancer-associated PM (GPM) is worse than that of other metastatic sites, with a median survival of only 3–7 months and a 5-year survival of 0% [4, 14]. The median survival of patients with GPM with systemic chemotherapy ranges from 9 to 12 months, and even in the 40–56% of the patients who respond to drugs like S1 and paclitaxel, the median survival is only 18 months [14–17].

2.3 Role of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Since the 1990s, a growing body of evidence has emerged indicating that a proportion of patients with PM from colorectal and gastric cancers can be offered long-term survival and some can be cured, using a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [18]. The mainstay of this multimodality treatment is complete macroscopic tumour removal (defined as a completeness of cytoreduction score CC0), which is achieved by a combination of various peritonectomy procedures and visceral resections. After CRS, the abdominal cavity is perfused with a hyperthermic solution containing a suitable chemotherapeutic agent; the most widely used for CPM are mitomycin C (MMC) and oxaliplatin.

The evidence base for CRS and HIPEC to treat patients with CPM is robust. A prospective randomised controlled trial, conducted at the Netherlands Cancer Institute, showed 5-year survival rates of 45% with a median survival of 48% in patients undergoing a complete cytoreduction and HIPEC, followed by systemic chemotherapy (Fig. 2.2) [19, 20]. A large retrospective French study demonstrated 5-year survival rates of 51% with a median survival of 62.7 months in patients undergoing complete CRS and HIPEC following neoadjuvant systemic chemotherapy [21]. It is estimated that around 16% of patients with CPM can be cured by CRS and HIPEC [22].

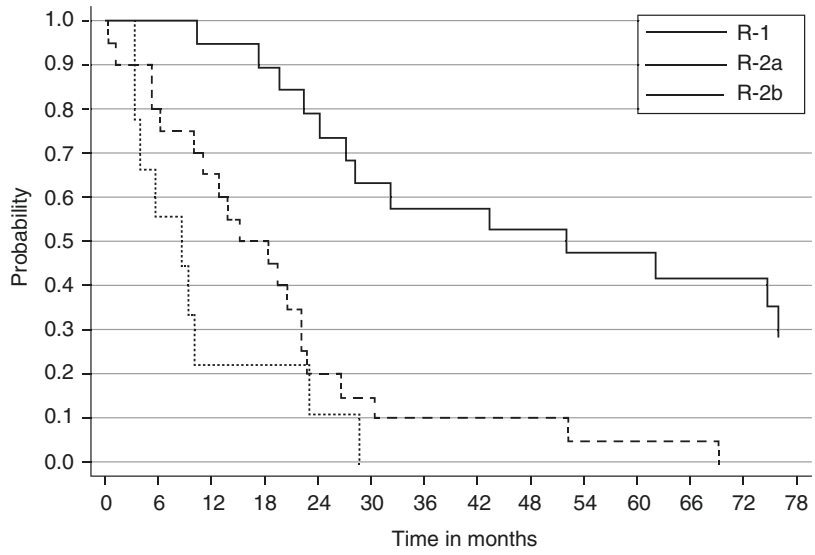

Fig. 2.2 Kaplan-Meier curves showing survival outcomes after CRS and HIPEC in the only prospective, randomised controlled trial for treatment of CPM (R-1 denotes CC0 cytoreduction) (reproduced with permission from [19])

A number of studies have reported the results of CRS and HIPEC in patients with GPM since 1988 [23]. A systematic review of 17 studies of CRS and HIPEC in GPM reported a median survival of 11–43 months and a 5-year survival of 13–23% in patients who underwent a complete cytoreduction [24]. Chia et al., in an analysis of 81 GPM patients from five French institutions who underwent CRS and HIPEC, observed a cure rate (defined as a 5-year disease-free survival) of 11% [25].

However, in spite of such excellent results, a large subset of patients with CPM or GPM will not benefit from CRS and HIPEC due to the extent and/or distribution of their peritoneal disease. The outcome of CRS and HIPEC depends on various factors, the most important of which are initial disease extent and completeness of cytoreduction [26–28]. A complete cytoreduction (CC0) and HIPEC in patients with CPM is associated with 5-year survival rates of 40–60% in a highly selected patient population [19, 21, 29]. Unfortunately, a complete cytoreduction is not achievable in a significant proportion (estimated at approximately 20%) of patients undergoing surgery for established CPM, due to either disease volume or distribution [30]. For patients in whom a complete cytoreduction is possible, the extent of peritoneal disease (quantified by the peritoneal cancer index or PCI) is an independent predictor for long-term survival [21, 27, 31, 32]. A retrospective study of 523 patients undergoing CRS and HIPEC for CPM showed that 5-year overall survival rates differed significantly according to PCI: 44% for PCI 1–6, 22% for PCI 7–12, 29% for PCI 13–19 and 7% for PCI > 19 [28]. Moreover, postoperative morbidity and mortality were significantly associated with PCI [28].

The results of CRS and HIPEC in GPM are significantly inferior to those obtained for tumours from other primary sites, in particular CPM. Recurrence following CRS and HIPEC is seen in nearly half of the patients [33, 34], and 10–79% patients die due to peritoneal recurrence [33, 35]. One of the most important prognostic factors following CRS and HIPEC in GPM is the completeness of cytoreduction [24, 33, 36], which in turn depends on the PCI, another important prognostic factor [34, 37, 38]. A meta-analysis reported a risk ratio of 6.38 for survival benefit in patients who underwent a CC0 cytoreduction when compared to those who underwent a CC1 cytoreduction. The 5-year survival was also significantly different for patients who had a PCI score above or below 12 [39]. However, a complete cytoreduction is possible only in 10–56% of patients even in the most experienced hands [24, 40]. Further, the procedure may be associated with a high morbidity (12–47%) and mortality (0–7%) [36, 37, 40].

Although a CT scan is often used to stage the extent of PM preoperatively, its sensitivity in identifying peritoneal nodules smaller than 0.5 cm and detecting small bowel involvement is low, and there is a considerable discordance between CT scan-estimated PCI and intraoperative PCI [41, 42]. Hence, during posttreatment surveillance for colorectal or gastric cancers, it is difficult to identify patients with PM who have a low PCI score. For patients with extensive, unresectable peritoneal involvement, no curative treatment options exist; as has been discussed, systemic chemotherapy, even combined with biological agents, is palliative at best with only very limited survival benefit. Therefore, strategies aimed at preventing the development of CPM or early identification and treatment of low-PCI peritoneal disease will yield higher cure rates with lower postoperative morbidity and mortality rates and are preferable to strategies aimed solely at treatment of already established PM.

2.4 Pathogenesis of Peritoneal Metastasis

In order to understand the rationale of strategies to prevent PM, it is important to know its pathogenesis. Various hypotheses exist regarding the pathogenesis of peritoneal metastases, some suggesting direct transcoelomic spread, while others support subperitoneal lymphatic dissemination pathways. The predisposing factor for GPM is intraperitoneal free cancer cells (IPFC) which result from the exfoliation of tumour cells from advanced tumours that have invaded the serosa or during surgical handling of the tumour at the time of curative resection [43]. IPFC may be seen in around 25–40% patients with stage I and stage II/III gastric cancer, respectively [44]. Advanced tumours that involve the serosal surface tend to shed cells in the peritoneal cavity. During surgery, blood and lymph containing tumour cells leak in the peritoneal cavity, and contamination also occurs from the margins of resection if they are close [43, 45]. Once the cancer cells gain access to the peritoneal cavity, they spread to various areas aided by gravity, intestinal peristalsis and negative pressure due to diaphragmatic contractions.

According to the "tumour cell entrapment hypothesis", the IPFC adhere to the raw area created during the surgery in a short time. Fibrin entrapment that occurs as a part of the wound healing process promotes trapping of cancer cells in a hypoxic environment, and these trapped cells cannot be destroyed by systemic chemotherapy [43]. Intraperitoneal chemotherapy (IPC) is therefore intended to clear these IPFC which persist after a curative resection.

When cytotoxic agents are administered in the perioperative period intraperitoneally, these free cells are destroyed before they get incorporated into the scar tissue. A delay in the administration of intraperitoneal chemotherapy leads to formation of scars and also adhesions which limit the effectiveness of intraperitoneal chemotherapy [46].

Regardless of the specific pathway, peritoneal dissemination of free-floating peritoneal tumour cells may occur via the redistribution phenomenon and will follow predictable patterns of disease spread, as in pseudomyxoma peritonei (PMP) [47]. However, there are some crucial differences when compared to PMP. Firstly, due to the invasive nature of tumour deposits, small bowel serosal or mesenteric involvement is more common, which has clear implications for treatment and prognosis. Additionally, as a significant proportion of PM are metachronous and occur in patients who have already undergone surgical resection, tumour deposits often develop along previously opened surgical planes.

2.5 The Role of HIPEC in Prevention of Peritoneal Recurrence in Colorectal Cancers

The development and appropriate implementation of prevention and early treatment strategies are highly dependent on the identification of those patients with colorectal cancer who are at high risk of developing peritoneal metastases.

This is comparable to current strategies aimed at preventing the formation of distant, haematogenous metastatic disease, by adjuvant administration of systemic therapy to patients who, based on clinical, surgical and/or pathological characteristics, are at high risk of systemic dissemination.

The overall risk of development of metachronous CPM after curative treatment of colorectal cancer has been estimated at 10–20%. However, this risk is substantially higher in selected subsets of patients, based on various clinicopathological parameters, as listed in Table 2.1.

As shown, the risk factors most strongly associated with development of metachronous CPM are:

- Limited, synchronous peritoneal metastases completely resected at primary tumour surgery: synchronous CPM are encountered in 4.3–7.8% of colorectal cancer resections. Peritoneal recurrence occurs in 54–75% of these patients and is mostly limited in extent (mean PCI at 1 year 8–10) [48–50].
- Isolated synchronous ovarian metastases: macroscopic ovarian metastases, without associated peritoneal disease, are encountered in 0.8–7.4% of colorectal cancer patients; the incidence of subsequent metachronous CPM ranges between 62 and 71% [49, 50].
- Primary tumour perforation: the incidence of true tumour perforations is unknown, as most studies include diastatic perforation proximal to an obstructing tumour in their analysis. Estimates range between 1.6 and 5.4% of all colorectal cancers. Approximately 27% of patients with a perforation at or proximal to the primary tumour will develop CPM [48].
- pT4 primary tumour: one prospective study has shown that 15.6% of patients with a pT4 tumour will develop CPM 1 year after primary tumour surgery [51].
- Mucinous primary tumour: approximately 3–15% of all patients have a mucinous colorectal primary tumour. A relatively high proportion of these patients have synchronous CPM at the time of primary surgery, bearing similarities to mucinous appendiceal neoplasms; the incidence of metachronous CPM in patients without synchronous peritoneal disease is estimated at 22% [55].

Although CRS and HIPEC is currently firmly established as a modality for treatment of CPM, the first data regarding the benefit of intraperitoneal chemotherapy in colorectal cancer actually did not involve treatment of established peritoneal disease but reducing the risk of developing peritoneal disease. Three early phase III trials focused on adjuvant intraperitoneal chemotherapy in patients with advanced, "high-risk" primary colorectal tumours [56–58]. A meta-analysis of these three early studies showed that the 286 patients who received adjuvant intraperitoneal chemotherapy, compared to 283 patients who had had standard treatment, had significantly improved 5-year overall survival rates (62% vs 41%; $P < 0.001$) and had significantly lower rates of development of metachronous CPM (5% vs 11%; $P = 0.025$) [59].

Table 2.1 Risk factors for development of metachronous CPM

Risk category	Risk factor	CPM risk	Reference
Very high	Resected synchronous peritoneal metastases	27–71% at 1 year	[48–50]
	Ovarian metastases		
	Perforated primary tumour		
High	pT4 primary tumour	16–22% at 1 year	[49, 51]
	Mucinous histology		
Standard	Emergency presentation (bleeding/obstruction)	3.4–6.3%	[52, 53]
	Lymph node involvement		
	Laparoscopic resection		
Low	Rectal cancer	<3%	[54]

By 2000, a robust evidence base had been established supporting the role of intraperitoneal chemotherapy in the adjuvant treatment of colorectal cancers at high risk of peritoneal dissemination. Nevertheless, partly due to the Dutch randomised trial on CRS and HIPEC in treatment of CPM, focus shifted away from adjuvant and prophylactic strategies [19, 20]. It would be approximately a decade before a series of nonrandomised, prospective studies were published regarding the value of adjuvant intraperitoneal chemotherapy in high-risk patients [60–62]. These studies showed that, in selected patients, intraperitoneal chemotherapy was associated with increased long-term survival and/or lower peritoneal recurrence rates, as compared to patients who did not receive intraperitoneal chemotherapy [63]. Table 2.2 provides an overview of the results of the various prospective, comparative studies investigating adjuvant intraperitoneal chemotherapy in patients with colorectal cancer.

Though differing in their patient selection and their intraperitoneal treatment strategies, all these trials showed that it was possible to select patients at high risk of developing peritoneal recurrence and that early intraperitoneal intervention could mitigate this risk and, ultimately, increase survival. Based on these principles, various approaches have been developed to either prevent CPM development or treat CPM at the earliest possible stage.

Three distinct approaches are currently employed: a proactive approach, where patients considered to be at high risk of microscopic peritoneal dissemination undergo CRS (including resection of the primary tumour combined with resection of organs at high risk of involvement, e.g. omentectomy, BSO) and HIPEC; an adjuvant approach, where selected patients undergo HIPEC in the immediate or delayed postoperative period after primary resection; and a second-look approach, where selected patients undergo a systematic second-look operation approximately 1 year after primary resection, with cytoreduction of any observed peritoneal disease and HIPEC.

Proactive CRS and HIPEC are currently being investigated in the Italian Promenade trial. Patients with high-risk T3/T4N0 colonic cancer (defined as ≥5 mm invasion beyond the muscularis propria on preoperative imaging) are randomised to either standard surgical resection or proactive cytoreduction (resection of the primary tumour combined with omentectomy, appendicectomy and BSO) with oxaliplatin-based HIPEC, followed in both arms by systemic chemotherapy for patients with poor prognostic factors (Fig. 2.3). The primary endpoint for this trial is the rate of intraperitoneal recurrence at 36 months [62, 64].

A similar trial, the Spanish HIPECT4 study, is randomising patients with T4a/b colorectal cancers to either standard surgical resection or proactive CRS and mitomycin C-based HIPEC (Fig. 2.4). Primary endpoint will be locoregional control rate.

Adjuvant HIPEC is currently being investigated in the Dutch COLOPEC trial, which randomises patients undergoing curative surgery for T4 or perforated colon cancer without systemic metastases to either adjuvant systemic chemotherapy or adjuvant HIPEC (either laparoscopically or open) at the time of or within 10 days after primary resection or 5–8 weeks later, followed by adjuvant systemic chemotherapy (Fig. 2.5). Primary endpoint for this study is peritoneal recurrence-free survival at 18 months after resection, determined by CT and, if negative, by diagnostic laparoscopy [52].

The second-look strategy was investigated in a seminal cohort study by Elias et al. [48], in which 41 patients without any sign of recurrence on imaging studies underwent second-look surgery 1 year after resection of their primary tumour; these patients were selected based on three tumour-associated criteria: resected minimal synchronous macroscopic CPM, synchronous ovarian metastases and perforation. All 41 patients received oxaliplatin-based HIPEC of whom 23 patients (56%) were found to have peritoneal metastases at second-look laparotomy and underwent a complete cytoreduction. The 5-year overall and disease-free survival rates following second-look surgery were 90 and 44%, respectively. Based on this study, the French ProphyloChip trial was designed and initiated. In this study, all patients with colorectal cancer and at

Table 2.2 Phase III trials investigating adjuvant intraperitoneal chemotherapy in high-risk colorectal cancer

Authors (year)	Reference	Inclusion criteria	Adjuvant treatment arms	*n*	5-year overall survival (%)	CPM risk (%)	*P*-value for CPM risk
Sugarbaker et al. (1985)	[56]	T4	EPIC 5FU	36	43	20	0.003
		N+					
		Obstruction					
		Perforation	iv 5FU	30	46	91	
		Age < 30 years					
Scheithauer et al. (1998)	[57]	T3/4	EPIC + iv 5FU/LV	117	85	8	0.005
		N+	iv 5FU + levamisole	119	66	21	
Vaillant et al. (2000)	[58]	T3/4	EPIC + iv 5FU	133	74	8	Not reported
		N+	No adjuvant treatment	134	69	10	
Noura et al. (2011)	[60]	Positive peritoneal cytology	IPEC MMC + iv 5FU/Ox	31	54	12	0.0003
			iv 5FU + Ox	22	10	60	
Tentes et al. (2011)	[61]	T3/4	HIPEC MMC or Ox + iv 5FU/LV	40	100[a]	Not reported	Not reported
			EPIC 5FU + iv 5FU/LV	67	69[a]		
Sammartino et al. (2014)	[62]	T3/4	HIPEC Ox + iv 5FU/LV	25	Not reported	4	<0.03
		Perforation					
		Signet ring cell	iv 5FU + Ox	50		28	
		Mucinous					

ip intraperitoneal, *iv* intravenous, *EPIC* early postoperative intraperitoneal chemotherapy, *(H)IPEC* (hyperthermic) intraperitoneal chemotherapy, *5FU* 5-fluorouracil, *LV* leucovorin, *MMC* mitomycin C, *Ox* oxaliplatin

[a]3-year overall survival

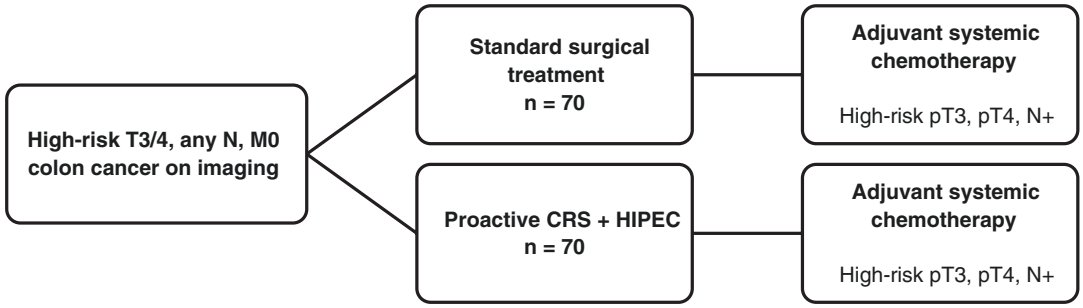

Fig. 2.3 The Italian Promenade trial investigating proactive CRS and HIPEC in high-risk patients

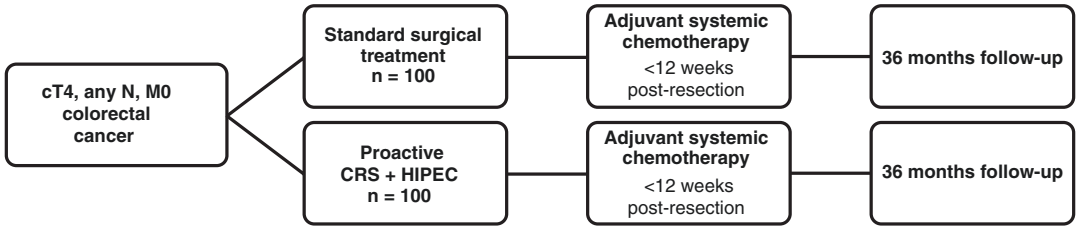

Fig. 2.4 The Spanish HIPECT4 trial investigating proactive CRS and HIPEC in high-risk patients

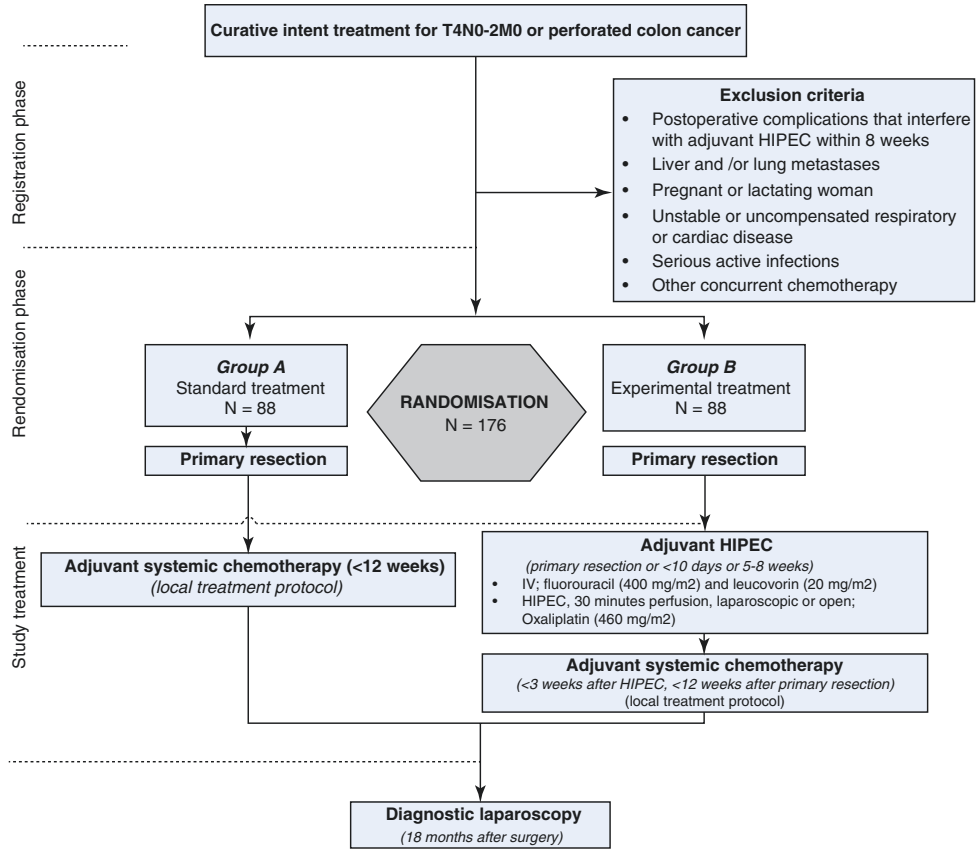

Fig. 2.5 The Dutch COLOPEC trial investigating adjuvant HIPEC in high-risk patients (reproduced with permission from [52])

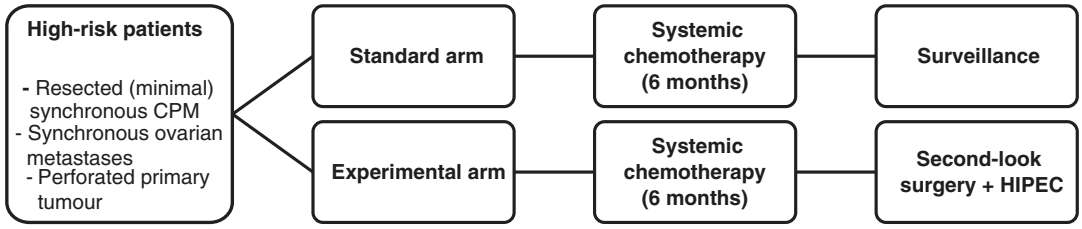

Fig. 2.6 The French ProphyloChip trial, investigating systematic second-look + HIPEC

high risk of developing CPM (minimal CPM resected simultaneously with the primary tumour, ovarian metastases, perforation of the primary tumour, iatrogenic rupture of the primary tumour during surgery) will receive standard adjuvant chemotherapy; those patients without any signs of recurrence will then be randomised to either surveillance or a second-look laparotomy and HIPEC (Fig. 2.6). The primary endpoint for this trial will be a 3-year disease-free survival.

Despite the enormous progress which has been achieved using CRS and HIPEC for treatment of patients with colorectal peritoneal metastases, a significant proportion of patients with CPM will either not have a complete cytoreduction or a very limited survival benefit due to the disease being too extensive at the time of diagnosis. Therefore, strategies aimed at prevention and/or early treatment of CPM are hoped to increase survival and offer cure in a larger proportion of patients. Considerable progress has been made in identifying and classifying risk factors associated with development of metachronous CPM. Based on these factors, and building on evidence dating from the "early days" of intraperitoneal chemotherapy, several trials are currently underway investigating the role of CRS and HIPEC in either an adjuvant or second-look setting. Based on the outcomes of these trials, CRS and HIPEC are expected to evolve from a purely curative modality to a measure to prevent the development of CPM in high-risk patients.

2.6 The Role of HIPEC in Prevention of Peritoneal Recurrence in Gastric Cancer

Gastric cancer is more aggressive as compared to colorectal cancer; PM once established have a poorer prognosis and survival outcome with CRS and HIPEC, and only those with very limited PM (PCI < 6) benefit from a curative approach. Given this scenario, prevention of PM appears to be better strategy in patients who are at high risk for developing PM. The factors predisposing to the development of GPM include advanced T stage (especially serosal involvement), advanced nodal stage, tumour size, young age, female gender, signet ring cell and diffuse-mixed histology [4, 6, 65]. HIPEC has several theoretic benefits in this situation—the large volume of fluid used for HIPEC washes out the IPFC, and in addition, the synergistic effect of heat and chemotherapy destroys the tumour cells. The rationale of HIPEC is further strengthened by the poor 5-year survival of 2% in patients with positive peritoneal cytology without macroscopic PM (Cy+/P0), this survival being similar to that of patients with overt PM [66–68]. Nearly 80% of Cy+/P0 patients recur in the peritoneum after a curative gastrectomy compared to 45% of patients with a negative cytology (Cy−/P0) [34].

Koga et al. in 1988 first reported a survival benefit of adding HIPEC to curative gastric cancer surgery (3-year survival of 74% with HIPEC and 53% without HIPEC, $p < 0.04$). The incidence of peritoneal recurrences was also reduced [69]. Since then, a number of randomised controlled evaluating the role of adjuvant HIPEC were conducted in China and Japan (Table 2.3) [69–76]. In spite of heterogeneity in these trials with respect to the drugs used, their dosage, duration of HIPEC, etc., these trials provide level I evidence of the efficacy of adjuvant HIPEC in reducing peritoneal recurrence and improving survival. A low rate of complications after prophylactic HIPEC in these studies is noteworthy. Most of these trials included patients with a high risk of developing PM—the presence of serosal invasion and/or lymph nodal metastasis with no

macroscopic peritoneal disease. Patients with a positive peritoneal cytology were not included in these trials, and there is one study only that reported a 5-year survival of 42% in 15 patients with Cy+/P0 disease after gastrectomy plus HIPEC [77].

A recent development is the combined use of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). In this bidirectional strategy, oral S-1 is administered for 21 days at a dose of 60 mg/m^2 followed by docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) as an intraperitoneal infusion on days 1–3 every 4 weeks followed by a 1-week rest period. This sequence is repeated twice. Although NIPS is currently used for patients with established PM, it has also shown to be effective in eradicating the IPFCs. In a recent report, Yonemura et al. observed that in patients with GPM, 69% of the patients who initially had a positive peritoneal cytology had a negative cytology after NIPS [78]. This method therefore holds promise in preventing peritoneal recurrence in patents with gastric cancer.

Other variants of intraperitoneal chemotherapy have been shown to improve survival when used in the adjuvant treatment of gastric cancer, like normothermic intraoperative intraperitoneal chemotherapy (NIIC) [79] and early postoperative intraperitoneal chemotherapy (EPIC) [80]. However, two studies comparing NIIC with HIPEC showed a significant advantage of HIPEC over NIIC in terms of survival and reducing the peritoneal recurrence, especially in patients with serosal invasion and nodal metastasis [71, 75].

In a meta-analysis of ten RCTs of prophylactic HIPEC in gastric cancer, HIPEC showed benefit in overall survival, and this was irrespective of the use of drug used for HIPEC and the use of systemic chemotherapy [81]. The prophylactic use of HIPEC results in a nearly 50% reduction in the peritoneal recurrence rates. Another pooled analysis of 16 RCTs reported a significant reduction in the peritoneal recurrence at 3 and 5 years and an improvement in the 3- and 5-year survival in patients who received HIPEC compared to those who did not [82]. Both of them did not show any significant increase in the rate of postoperative morbidity.

However, the data on prophylactic HIPEC in gastric cancers from the Western world is scarce. An ongoing European multicentre study, the GASTRICHIP study, is evaluating the role of HIPEC with oxaliplatin in patients with gastric cancer treated by a curative gastrectomy with risk factors for developing PM (serosal infiltration and/or lymph nodal involvement and/or positive peritoneal cytology) [83]. The primary aim of the study is the 5-year overall survival. Another trial is being conducted by the European Network of Excellence (EUNE) in which patients with high-risk gastric cancer will receive 3 cycles of neoadjuvant systemic chemotherapy followed by a D2 gastrectomy and then randomised to receive HIPEC or no HIPEC [84]. The Dutch PERISCOPE study is examining the safety and feasibility of gastrectomy combined with CRS and HIPEC after neoadjuvant systemic chemotherapy as primary treatment option for advanced gastric cancer with tumour positive peritoneal cytology and/or limited peritoneal carcinomatosis.

There are still some unresolved issues in the use of HIPEC as an adjuvant treatment in gastric cancer—the choice of drug, the dosage, the duration of treatment, the addition of EPIC, etc. for which there is no consensus yet. The role of prophylactic HIPEC in patients with Cy+/P0 is not yet established. Since this is an important risk factor for peritoneal recurrence, a preoperative laparoscopy with wash for cytology needs to be done if such patients are to be considered for prophylactic treatment. This may entail additional costs.

The surgeon may occasionally be faced with a situation when peritoneal metastases are detected incidentally during laparoscopy or laparotomy for a gastric or colorectal cancer. In this situation, non-definitive procedures should be avoided except in an emergency setting like a perforated or obstructed tumour, since it can have negative implications for a subsequent CRS and HIPEC. A palliative resection can result in the implantation of tumour cells in the raw surfaces along the planes of dissection [85]. The tumour cells which get entrapped in this avascular scar tissue cannot be effectively treated with chemotherapy. Retroperitoneal implantation of tumour cells can involve tubular structures like the ureters leading

Table 2.3 HIPEC for prevention of peritoneal metastasis in gastric cancer: summary of comparative studies

Author	Type of study	Inclusion criteria	Treatment arms (no. of pts)	Curative surgery	Drugs used for IPC	Complications	Post-op mortality	Survival	Peritoneal recurrence
Koga et al. [69]	Randomised controlled	Serosal invasion	Surgery + HIPEC (26) vs surgery alone (21)	100% vs 100%	Mitomycin C	Leak 3.1% vs 7.1%	NA	30-month survival: 83% vs 67% (NS)	NA
Hamazoe et al. [70]	Randomised controlled	Serosal invasion	Surgery + HIPEC (42) vs surgery alone (40)	95% vs 88%	Mitomycin C	Leak 4.8% vs 7.5%	0% vs 0%	5-year survival: 64% vs 52% ($p = 0.24$) Median survival: 77 vs 66 months	39% vs 59% ($p = 0.084$)[a]
Fujimura et al. [71]	Randomised controlled	Serosal invasion	Surgery + HIPEC (22) vs surgery + CNPP (18) vs surgery alone (18)	NA	Mitomycin C Cisplatin	30% vs 0%[b]	NA	3-year survival: 68% vs 51% vs 23% ($p < 0.01$)	9% vs 22% vs 22%[a]
Ikeguchi et al. [72]	Randomised controlled	Serosal invasion	Surgery + HIPEC (78) vs surgery alone (96)	100% vs 100%	Mitomycin C	1.2% vs 2.08%	NA	5-year survival: 51% vs 46%	35% vs 40%[a]
Fujimoto et al. [73]	Randomised controlled	Serosal invasion[c]	Surgery + HIPEC (71) vs surgery alone (70)	94.3% vs 92.8%	Mitomycin C	2.8% vs 2.8%	0% vs 0%	4-year survival: 76% vs 58% 8-year survival: 62% vs 49% ($p = 0.03$)	1.4% vs 23% ($p = 0.00008$)
Hirose et al. [74]	Prospective case control	Serosal invasion	Surgery + HIPEC (15) vs surgery alone (40)	NA	Mitomycin C Cisplatin Etoposide	60% vs 42.5%	0% vs 12.5%	5-year survival: 39% vs 17% Median survival: 33 vs 22 months ($p = 0.01$)	26% vs 45%
Yonemura et al. [75]	Randomised controlled	Serosal invasion	Surgery + HIPEC (48) vs surgery + CNPP (44) vs surgery alone (47)	100% vs 100% vs 100%	Mitomycin C Cisplatin	19% vs 14% vs 19%	4% vs 0% vs 4%	5-year survival: 61% vs 43% vs 42%	13% vs 15% (HIPEC vs surgery)
Kim et al. [76]	Prospective controlled study	Serosal invasion	Surgery + HIPEC (52) vs surgery alone (51)	NA	Mitomycin C	36.5% vs 33.3%	NA	5-year survival: 33% vs 27%[d] (NS) 5-year survival: 59% vs 44%[d] (in stage IIIB)	7.6% vs 25% (isolated PM)

NA not available, *NS* not significant, *PM* peritoneal metastasis

[a]Death due to PM

[b]Perfusion vs surgery 40 pts. vs 18

[c]Intraperitoneal free cancer cells identified in 18% and 11% patients in the surgery + HIPEC and surgery alone arms, respectively

[d]All patients

[e]Patients with serosal invasion

to obstruction. Hence, when peritoneal metastasis is encountered during laparotomy or laparoscopy, further surgical intervention should cease, and the patients should be referred to a centre experienced in treating peritoneal metastases [85].

2.7 The Role of HIPEC in Prevention of Peritoneal Dissemination from Mucinous Appendiceal Tumours

Most epithelial tumours of the appendix are mucinous in nature and begin as a mucocele of the appendix [86]. It has been estimated that over 90% of PMP originate from rupture of a mucinous appendiceal tumour [87, 88]. Due to the mostly superficial, non-infiltrative nature of mucinous disease in PMP, a complete cytoreduction is often achieved even in patients with extensive small bowel involvement or with large volumes of disease; high PCI in PMP therefore may not have the same prognostic implications as in colorectal and gastric malignancies [89]. However, more extensive resections may be required in patients with high PCI, which is a risk factor for increased postoperative morbidity and mortality [90]. A majority of patients with appendiceal tumours present with acute appendicitis or as an incidental finding during exploration performed for other indications [91, 92]. This provides an opportunity to intervene in patients with risk of peritoneal dissemination and prevent the subsequent development of PMP.

Not all mucinous appendiceal tumours go on to develop peritoneal dissemination. Misdraji et al. found in a retrospective analysis of 49 patients with low-grade mucinous neoplasms that tumours confined to the appendix behaved in a benign manner with no recurrence after 6 years of follow-up, while the low-grade tumours that had breached the wall of the appendix had a 5-year survival of 45% [93]. Macdonald et al. identified two subtypes of low-grade mucinous appendiceal tumours (LAMN)—LAMN I (disease confined to the appendiceal lumen) and LAMN II (mucin or neoplastic epithelium or both in the appendiceal submucosa, wall or periappendiceal tissue or both, with or without perforation). Patients with LAMN II lesions were found to have an increased risk of developing peritoneal dissemination [94]. The reported incidence of peritoneal spread in patients with appendiceal neoplasms on surveillance after the initial surgery ranges from 23 to 52% of [95, 96]. In a French series of 25 patients with perforated mucinous tumours, 52% developed PMP at a median follow-up of 60 months [95].

When an appendiceal mucocele is found during laparoscopic or open surgery, every effort should be made to remove it intact, since rupture can lead to peritoneal dissemination [86, 92, 97]. Plastic bags for tumour removal during laparoscopy can avoid contamination [98]. Surgeons need to have a low threshold for converting to open surgery when they are not confident of removing the tumour laparoscopically without causing rupture [97, 98]. When conversion to an open procedure is done, a midline laparotomy rather than a McBurney's incision is preferred [95]. Careful examination of the peritoneum around the appendix should be carried out [86]. The ovaries must be examined for presence of cystic tumours, and any fluid or mucus near the appendix must be aspirated and subjected to cytologic examination [86]. In case of a perforated mucocele without evidence of peritoneal dissemination, the following strategy has been proposed—if the tumour is benign, the patient should be placed on an active surveillance schedule with tumour marker evaluation and a CT scan every 6–12 months for 5–10 years [86, 92]. In one study, only 64% of patients who had a prior removal of a mucinous appendiceal tumour and subsequently developed PMP could undergo a complete cytoreductive surgery [95]. In contrast, another small study showed that patients with incidental LAMN who were followed up with CT scans and laparoscopy and subsequently developed peritoneal metastasis had a low median PCI of 7, and the rate of R0/R1 resections in these patients was 100% [96]. Hence, all efforts should be made to detect disease progression at the earliest. If the perforated specimen shows a mucinous adenocarcinoma of the appendix, a second-look open surgery

is recommended 6 months after the appendicectomy with a thorough exploration of all the peritoneal surfaces [86]. If no peritoneal spread is found, a prophylactic surgery comprising of greater and lesser omentectomy, sampling of the appendiceal nodes (and a right hemicolectomy if they are positive), bilateral oophorectomy with HIPEC should be performed. The rationale for such treatment is that for adenocarcinomas of the appendix, the long-term outcome depends on the extent of the disease, and early disease could be missed by CT scans and tumour marker surveillance (CEA and CA-19-9) [99]. A recent overview of patients referred with an incidental finding of a high-grade appendix tumour and/or appendiceal adenocarcinoma without any surgical or radiological signs of dissemination found that, upon second-look laparotomy, 56.5% of patients had peritoneal metastases versus 15% nodal involvement; 37% had peritoneal disease beyond the confines of a standard right hemicolectomy (Mehta AM, personal communication).

In conclusion, there is an emerging role for HIPEC in the prevention of peritoneal metastasis from colorectal, gastric and appendicular cancers. Identification of the patients at high risk of developing peritoneal metastasis, standardisation of the drugs and their dosage and positive results from ongoing trials will strengthen the case to adopt it as a standard of care.

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3 Cytoreductive Surgery for Peritoneal Metastases: Principles and Techniques

Aditi Bhatt and Sanket Mehta

3.1 Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a locoregional therapy for peritoneal metastases (PM) that has resulted in a significant increase in the survival of patients as compared to other treatments [1]. The goal of CRS is complete tumor removal. This involves performing one or more peritonectomy procedures and resection of contiguous visceral where required. These techniques were first described by Paul Sugarbaker. The surgery can be extensive depending on the extent and distribution of the disease. Most surgeons remove only diseased peritoneum and not the normal-looking areas. However, this is a complex treatment that is difficult to implement. The surgeon should be not only adept at operating all areas of the peritoneal cavity but should be able to predict and prevent complications and deal with them when they occur. The benefit of performing a radical procedure has to be balanced against the ensuing morbidity and its impact on the quality of life. Multidisciplinary management is required for selecting the appropriate patients, delivering perioperative care and subsequent treatment and rehabilitation of patients. The biology of the underlying disease that has an impact on both the short- and long-term outcomes in these patients should be kept in mind while making treatment decision and disease-specific indications, and prognostic factors that have been extensively described and defined should be used to select patients for the procedure. An understanding of the normal anatomy and physiology of the peritoneum as well as the pathophysiology of peritoneal dissemination is essential. This knowledge forms basis of developing new innovative therapies.

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3.2 The Peritoneum as an Organ

The peritoneum is an organ with its own structural framework and plays a protective role in the physiology of the abdominal cavity [2].

3.2.1 Anatomy of the Peritoneal Cavity

The peritoneum is a serous membrane that lines the visceral and peritoneal surfaces. The peritoneal cavity is a space enclosed by the parietal peritoneum that lines the abdominal wall and the visceral peritoneum that lines the organs/viscera.

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Underneath is the subperitoneal space or the retroperitoneum [3]. The peritoneal cavity is incompletely divided into spaces and fossae (or recesses), which play an important role in the circulation of the intraperitoneal fluid and therefore tumor dissemination (Fig. 3.1).

Peritoneal ligaments are double layers or folds of the peritoneum that support a structure within the peritoneal cavity; the omentum and mesentery are specifically named peritoneal ligaments [4].

The falciform and triangular ligaments are the suspensory ligaments of the liver that bind the bare area:

- The hepatoduodenal ligament (containing the common bile duct, hepatic artery, and portal vein) and the gastrohepatic ligament (which contains the left gastric artery and the coronary vein) together form the lesser omentum.
- The gastrosplenic ligament that connects the greater curve of the stomach to the spleen and contains the short gastric vessels.
- The splenorenal ligament that contains the pancreatic tail.
- The transverse mesocolon which attaches the transverse colon to the retroperitoneum and contains the middle colic vessels.

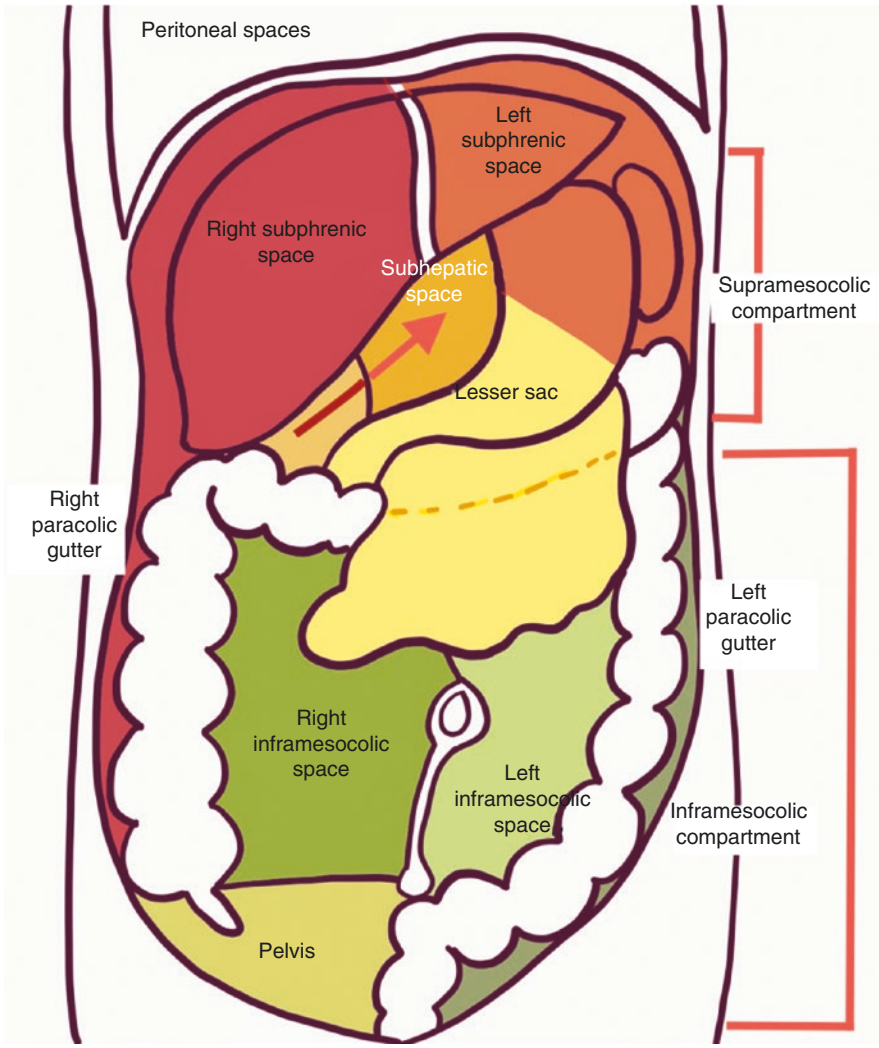

Fig. 3.1 The peritoneal spaces (From ref [7] with permission)

- The small bowel mesentery that extends from the ligament of Treitz to the ileocecal valve, attaches the small bowel to the retroperitoneum, and contains the superior mesenteric vessels and their branches.
- The sigmoid mesocolon that is a peritoneal ligament that attaches the sigmoid colon to the posterior pelvic wall and contains the hemorrhoidal and sigmoid vessels.
- The greater omentum or gastrocolic ligament extends from the stomach to the transverse colon and has a redundant portion that hangs freely in the peritoneal cavity [5, 6].

The transverse colon and mesocolon are the major landmarks dividing the peritoneal cavity into supramesocolic and inframesocolic compartments (Fig. 3.1). On the anterior aspect of the liver, the supramesocolic compartment is divided into the left and tight subphrenic spaces by the falciform ligament. The subhepatic space, including the lesser sac, is located under the liver. The inframesocolic compartment is subdivided by the root of the small intestine mesentery into the right and the left inframesocolic space and into the pelvis [7].

The right subphrenic space is located under the right diaphragm; it communicates with the right paracolic space inferiorly and is separated from the left subphrenic space by the falciform ligament [8].

The right subhepatic space continues medially through the foramen of Winslow (epiploic foramen) to the lesser sac (bursa omentalis) [8].

The lesser sac is a potentially large cavity with various recesses that communicate with the left subphrenic space cranially and into the greater omentum caudally. The lesser sac contains a superior recess (located above the peritoneal reflection of the left gastric artery) that is in close proximity to the caudate lobe and a larger inferior recess that lies between the stomach and the pancreatic body. The superior and inferior recesses are separated by a peritoneal fold that accompanies the left gastric artery. Sometimes, the inferior recess communicates with a potential space between the leaves of the greater omentum [8].

The right and left inframesocolic spaces are separated from the supramesocolic spaces by the transverse mesocolon and from the paracolic gutters laterally by the ascending or descending colon. The right space is smaller than the left and the left communicates with the pelvis; the right does not as it is bounded by the root of mesentery inferiorly [9].

The paracolic spaces (gutters) are located lateral to the peritoneal reflections of the left and right sides of the colon. The right paracolic gutter is larger than the left and communicates freely with the right subphrenic space. The connection between the left paracolic gutter and the left subphrenic space is partially limited by the phrenicocolic ligament. Both the right and left paracolic gutters communicate with the pelvic spaces [9].

In men, the most gravity-dependent site is the rectovesical space. In women, it is the retrouterine space (the pouch of Douglas). The pelvic space is divided into right and left halves by the medial umbilical folds containing the obliterated umbilical arteries and further into the medial and lateral inguinal fossae by the inferior epigastric artery on each side [9].

3.2.2 Structural Anatomy of the Peritoneum

The total surface area of the peritoneum in adults approximates the surface area of the skin (1.5–2 m^2) [10]. Only a fraction of this total area remains exposed and is further limited by prior adhesions and abdominal surgery [11, 12]. The visceral peritoneum represents about 70% of the total peritoneal surface [13, 14]. The anterior abdominal wall of humans comprises less than 4% of the peritoneal surface [15]. The ultrastructure was described in detail by Baron who observed that a layer of mesothelial cells rests on five layers of connective tissue [16]. The total thickness of this membrane is 90 μm. The connective tissue adjacent to the mesothelial layer has few blood vessels, and most of them are found at a distance of 40 μm or more from the surface. The underlying basement membrane is a thin

laminar network containing type I and IV collagen, proteoglycans and glycoproteins [17]. The submesothelium consists of extracellular matrix (ECM) made up of different types of collagen, glycoproteins, glycosaminoglycans, and proteoglycans. Blood vessels, lymphatics, and various cell types (fibroblasts, resident tissue macrophages, and mast cells) are also found in this layer [18]. The mesothelial cells are either flattened stretched, squamous-like, or cuboidal cells. Cuboidal cells are found in various areas including the liver, the spleen, the "milky spots" of the omentum, and the peritoneal side of the diaphragm overlying the lymphatic lacunae. Milky spots play an important role in peritoneal tumor dissemination [19]. Milky spots are composed of macrophages, lymphocytes, and some plasma cells that aggregate in the perivascular region. They are not secondary lymphoid organs [20]. Experimental in vivo studies have shown that tumor cells rapidly and specifically attach, invade, and proliferate within the milky spots after intraperitoneal injection [21–23].

Tumor growth is not prevented by the resident immune cells in the milky spots [24]. Proinflammatory cytokines secreted from cancer, stromal, mesothelial, and immune cells, more specifically, the macrophages, contribute to an inflammatory environment that promotes peritoneal metastasis [25–27]. There are adipocytes surrounding the milky spots which help the tumor cells meet their energy demands through the metabolism of lipids contained within them and thus promote tumor growth [28]. These milky spots are important promoters of tumor growth that convert micrometastatic tumor deposits to disseminated peritoneal disease [29, 30].

3.2.3 Blood Supply of the Peritoneum

The common belief is that only a fraction of the cardiac output reaches the peritoneum and that the peritoneal metastatic deposits are poorly vascularized. Hence, when chemotherapy is administered systemically to treat peritoneal metastases, it does not reach the target tissue adequately [31]. However, studies have shown that the blood supply of the peritoneum is proportional to that of other tissues when the minute volume is normalized to the weight [31]. This blood supply like that of other organs is regulated by physical, chemical, neurological, and hormonal factors and drugs. Neoangiogenesis in the submesothelial tissue has been described [32]. However, the neoangiogenic vessels are defective and do not increase the blood supply proportionally [31].

The peritoneum has several important functions:

- The mesothelial cells secrete fluid that lubricates the surfaces of the organs and facilitates their movement against each other.
- The peritoneum regulates the transfer of fluid, solutes, and macromolecules from the peritoneal cavity to the blood forming what is not as known as the "plasma-peritoneal barrier" [33].
- The peritoneum acts as a first line of defense in host resistance [2].
- The peritoneum aids tissue repair by releasing growth factors [2].

3.3 The Peritoneal Metastatic Cascade

This term was coined by Lemoine et al. in a recent publication and describes an orderly sequence of event that takes place in peritoneal cancer spread [2].

3.3.1 Pathways of Peritoneal Cancer Spread

There are four pathways of peritoneal cancer spread [34].

3.3.1.1 Direct Spread

This is seen in high-grade malignancies like cancers of the stomach, colon, and pancreas. Tumor deposits are seen in the vicinity of the primary tumor as well as at distant sites [35]. There is

contiguous and noncontiguous spread in both. The predisposing factors are full-thickness bowel wall involvement and iatrogenic spillage caused during surgery [36].

Lymphatic Spread Cancer cells also spread along the subperitoneal lymphatics seen in the ligaments, mesenteries, and omenta. Lymphatic spread is an uncommon mode of peritoneal cancer spread and is seen in lymphomas, most commonly, non-Hodgkin's lymphoma [37].

Along the Flow of Ascitic Fluid (Redistribution Phenomenon) This is characteristic of pseudomyxoma peritonei and ovarian cancer (Fig. 3.2) [38, 39]. Peritoneal fluid collects in the pelvis due

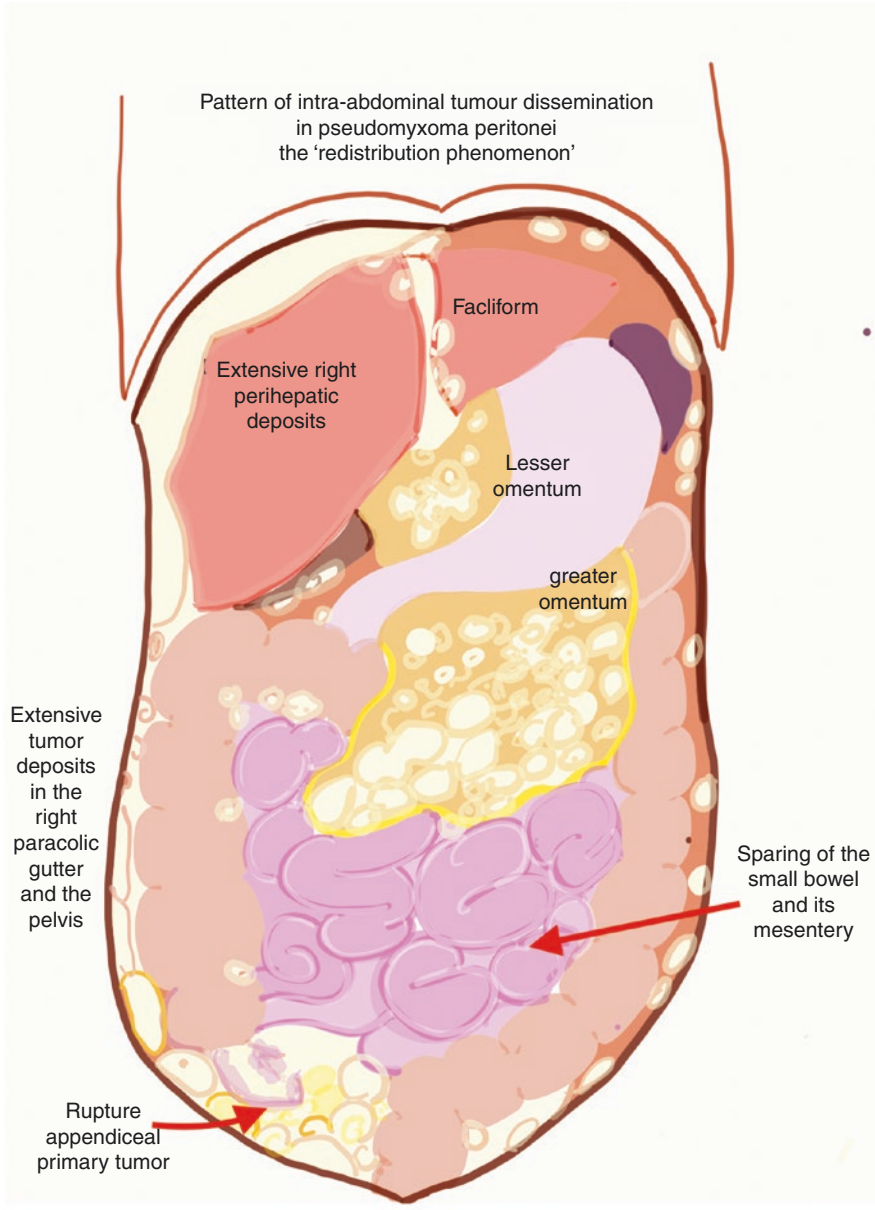

Fig. 3.2 The "redistribution phenomenon"

to the effect of gravity. It is also directed upward toward the undersurfaces of the diaphragm by the negative intra-intrathoracic pressure during respiration; hence, there are heavy deposits in the paracolic regions. Tumor seeding is extensive on the right undersurface of the diaphragm as compared to the left due to the splenocolic ligament which restricts the spread on the left side. Disease spread occurs to the falciform ligament and the omenta also. The small bowel is spared due to constant peristalsis. There are three sites of extensive PM—these are the areas where the bowel is relatively fixed—the pylorus, the ileocecal junction, and the small bowel proximal to it.

Hematogenous Route This is a common mode of spread mainly in extra-abdominal cancers like lung cancer, breast cancer, and malignant melanoma and some intra-abdominal tumors like hepatobiliary and pancreatic tumors [40].

3.3.2 Intraperitoneal Dissemination of Free Cancer Cells

3.3.2.1 Detachment and/or Release of Free Intraperitoneal Cancer Cells

The initiation of peritoneal metastases is caused by exfoliation of single or clumps of tumor cells from the primary tumor [41]. The presence of viable tumor cells in the peritoneal cavity could also occur by iatrogenic or spontaneous perforation of the primary cancer or from transected lymphatics and blood vessels which occurs during surgery for the primary tumor [42].

Spontaneous exfoliation of malignant cells can be promoted by the downregulation of intracellular adhesion molecules on the tumor cell surfaces, more specifically E (epithelial)-cadherin [43]. E-Cadherin connects through α- and β-catenin to the actin microfilaments within the cytoplasm, thereby anchoring epithelial cells to each other. In general, loss of E-cadherin in epithelial cancer correlates with epithelial mesenchymal transition (EMT) and the acquisition of an invasive phenotype.

Once the cells are released in the peritoneal cavity, they undergo epithelial to mesenchymal transition which is brought on by the loss of E-cadherin and the upregulation of mesenchymal N (neural)-cadherin [44]. It is characterized by reduction of cell-cell adherence, loss of polarity of epithelial cells, resistance to apoptosis, and reversal to a mesenchymal phenotype with enhanced motility [45]. This is believed to play a major role in the invasion and metastasis of tumor cells [45]. The first step in malignant transformation is epithelial mesenchymal transition (EMT) in which the tumor cells lose E-cadherin-mediated cell-cell interactions and upregulate other cadherins (e.g., N-cadherin, P-cadherin) as part of a global "cadherin switch." The transformed cells, which now look more like fibroblasts, acquire an invasive phenotype and proliferate. EMT allows the tumor cells to survive in hypoxic conditions and enables mesenchymal signaling through interactions with surrounding stromal cells [46, 47].

3.3.2.2 Transport Through the Peritoneal Cavity

Once the cancer cells are seeded in the peritoneal cavity, they spread to different anatomical regions of the abdomen governed by three basic forces: gravity, peristaltic movement of the gastrointestinal tract, and negative pressure exerted by diaphragm muscle movements [48]. The successive localization of intraperitoneal dissemination depends on the biology not only of free cancer cells but also of the tissue that will harbor the metastatic implantation. In general aggressive malignancies like colorectal and gastric cancer, tumor cells implant in the vicinity of the primary tumor, whereas in the less aggressive tumors like pseudomyxoma peritonei and ovarian carcinomas, the tumors follow the flow of peritoneal fluid and a "redistributed" throughout the peritoneal cavity. Sugarbaker et al. explained this phenomenon through their study of 129 patients with peritoneal metastases [49]. Based on their findings, they inferred that the presence of intraperitoneal free fluid or mucin acted as a transport vehicle for tumor cells leading to widespread dissemination in all areas of the peritoneal cavity.

The tumor cells do not immediately adhere to the peritoneal surface after being shed. They follow the flow of the fluid and are kept away from the peritoneal surface by forces generated by peristaltic activity. The cells implant on the surfaces that absorb peritoneal fluid like the peritoneum covering the diaphragmatic surfaces and lymphoid aggregates of the greater and lesser omenta and omental appendages. There is implantation in the pouch of Douglas due to the effect of gravity. Though the small bowel and its mesentery are exposed to a larger proportion of cancer cells as compared to the ileocecal region, the implantation in these regions does not occur till a very late stage in the course of the disease due to peristaltic activity [49].

Mucinous adenocarcinoma of the colon though more aggressive than pseudomyxoma peritonei had a similar pattern of spread due to the presence of intraperitoneal mucin. This peritoneal dissemination was not dependent on the tumor grade. Contrary to this, peritoneal dissemination of non-mucinous adenocarcinoma of the colon frequently involves the colon, greater omentum, and small bowel; these are tissues close to the primary site of cancer. Distant sites, such as Treitz ligament and lesser omentum, are often involved when a fluid vehicle is present but are spared when fluid is absent. The same concept is supported by the analysis of peritoneal sarcomatosis. Other gastrointestinal malignancies, like pancreatic cancer and gastric cancer, should have a seeding directly adjacent to the primary cancer when ascites is absent but generalized dissemination when ascites is present [49].

3.3.2.3 Attachment to and Invasion of the Peritoneal Surface

Once a viable, free tumor cell is present in the peritoneal cavity, adhesion to the peritoneal surface is required in order to ultimately invade the peritoneum, proliferate, and produce peritoneal deposits. The process takes place through either the transmesothelial or the translymphatic route. During transmesothelial spread, the free tumor cells directly attach to the distant mesothelium, a process that is mediated by adhesion molecules such as CD44, lymphocyte homing molecules, members of integrin superfamily, the selectins, and a variety of other leukocyte-associated adhesion molecules [50]. The most important of these are the β1 integrins. The cancer cells must then breach the mesothelial barrier and reach the submesothelial tissue. One hypothesis is that the production of cytokines (interleukins, EGF, HGF, VEGF-C) induces the contraction of mesothelial cells exposing the submesothelial basement membrane. The other being that the mesothelial cells do not contract but undergo apoptosis [51]. This process of mesothelial retraction includes cell shrinkage, nuclear fragmentation, and membrane blebbing. The existence of functional mesothelial Fas receptors, and the ability to inhibit tumor-induced apoptosis by the use of blocking anti-FasL proteins, suggests a role for these death ligands and receptors as the mediators of mesothelial apoptosis [52].

Invasion of the submesothelial tissues is largely mediated by matrix metalloproteinases (MMPs). This phenomenon has been studied extensively in ovarian cancer models. When ovarian carcinoma cells attach to mesothelial cells, the cancer cells upregulate MMP-2, which then cleaves the extracellular matrix proteins fibronectin and vitronectin into smaller fragments. The cancer cells then adhere much more strongly to these smaller fragments, using the fibronectin ($\alpha_5\beta_1$-integrin) and vitronectin ($\alpha_v\beta_3$-integrin) receptors [39].

In the translymphatic route, tumor cells enter the subperitoneal lymphatic spaces through lymphatic stomata. The regions of the peritoneal cavity that have a high concentration of lymphatic stomata and milky spots are the greater omentum, appendices epiploicae of the colon, inferior surface of the diaphragm, falciform ligament, Douglas pouch, and small bowel mesentery [53]. Once the subperitoneal lymphatics are invaded, the stromal cells and tumor cells both produce growth factors that promote the growth and proliferation of tumor cells. Epidermal growth factor and insulin-like growth factor both are known to enhance the invasive potential of tumor cells [54]. Subsequent to this, neoangiogenesis takes place which is mediated by the production of VEGF-A and VEGF-C.

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis which drives endothelial cell survival, proliferation, and migration while increasing vascular permeability. The neoangiogenesis and increased vascular permeability lead to the formation of malignant ascites. In both experimental and clinical studies, VEGF levels have been inversely correlated with survival [55].

3.4 Omental Metastases

There is preferential involvement of the omentum in patients with PM. The first step in the development of omental deposits is the lodging of tumor cells in the milky spots [56, 57]. The abundant blood supply around the milky spots permits early survival of cancer cells, and the production of growth factors, including VEGF, by the surrounding mesothelial cells, increases the angiogenesis necessary for continued tumor growth. This process is further stimulated by the adipose cells in the omentum which also secrete various growth factors, including VEGF, thereby increasing the formation of blood vessels [28, 58, 59]. In addition, the omental adipocytes also serve as a source of nutrition to the cancer cells. This proposition is supported by the fact that in patients with an "omental cake," the omental fat is completely replaced by tumor [60].

Just as the omentum plays a role in mitigating intra-abdominal infection, it also restricts the development of PM at other sites in the peritoneal cavity by scavenging the tumor cells and limiting their release in the systemic circulation [60].

3.5 Ascites

The formation of malignant ascites is multifactorial. There is increased fluid production due to increased vascular permeability and impaired drainage due to lymphatic blockage by the tumor cells, the combination of which leads to ascites formation [61]. VEGF is overexpressed by the tumor cells and contributes to the formation of ascites fluid [62]. High levels of VEGF are found in the malignant effusions of ovarian, colorectal, and breast cancer patients. In preclinical models, the administration of malignant ascitic fluid to animals without malignant ascites can cause malignant ascites [62]. Patients with colorectal and appendiceal tumors with increased VEGF expression have a poorer prognosis compared to those that don't [63].

The VEGF family constitutes five structurally related proteins, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. VEGF-C and VEGF-D are important in the process of lymphangiogenesis, while VEGF-A, VEGF-B, and placental growth factor are important in neovascularization [64–66]. The most potent proangiogenic growth factor, VEGF-A, binds to its receptors VEGFR-1 and VEGFR-2 and thereby increases endothelial cell survival, proliferation, migration, and differentiation [67, 68].

3.6 Difference Between Peritoneal Metastases and Other Sites of Metastases

The difference between peritoneal metastases and other sites of metastases has been described in the setting of colorectal cancer. In colorectal cancer, though liver metastases are more common compared to PM, they are less aggressive. Sugarbaker and collaborators studied the growth of peritoneal and liver metastases and pointed out several differences in the biology of CPM and colorectal liver metastases (Table 3.1). [69]. Liver metastases arise as a result of portal dissemination and have a lower metastatic potential as compared to PM which spread more rapidly. Single cells or small clusters of cancer cells then lodge within the venous sinusoids of the liver and derive their blood supply from the hepatic artery. These tumor masses grow and remain confined to the liver till there is necrosis of the mass leading to disruption of capillaries within it and a consequent release of cells into the systemic circulation. This results in metastases at other sites particularly the lung.

Table 3.1 Difference between peritoneal metastases and liver metastases from colorectal cancer [Adapted from reference [69] with permission]

PERITONECTOMY PROCEDURES	Involved regions	RESECTIONS
Anterior parietal peritonectomy	Peritoneum lining of the anterior abdominal wall bilaterally extending laterally to the line of Toldt. Lower boundary at the pelvic brim (false pelvis) Superiorly up to the costal margins merging with the subphrenic peritoneum	Old abdominal incisions, umbilicus, epigastric fat pad
Left upper quadrant peritonectomy	Peritoneum lining undersurface of the left hemidiaphragm extending medially up to the falciform ligament inferiorly merging with the parietal peritoneum at the costal margin	Greater omentum and spleen
Right upper quadrant peritnectomy	Peritoneum lining the undersurface of the right hemi-diaphragm extending medially up to the falciform ligament antero-inferiorly up to the costal margin and postero-inferiorly, the peritoneum overlying the gerota's fascia, medially extending up to the lateral edge of the hepatoduodenal ligament	Glisson's capsule deposits
Pelvic peritonectomy	From the brim of the false pelvis, the upper margin is at the origin of the inferior mesenteric artery, laterally to the peritoneal reflection over the psoas and internal opening of the inguinal canal, inferiorly the peritoneal reflection in the recto uterine or recto-vesical pouches	Uterus, ovaries and rectosigmoid colon
Omental bursectomy	The peritoneum overlying the gall bladder, the hepatoduodenal and hepatogastric ligaments and the tissue overlying the caudate lobe and between the caudate and inferior vena cava extending up to the superior border of the pancreas behind the stomach	Gall bladder and lesser omentum

Liver metastases have a doubling time of approximately 3 months and become substantially large (generally over 10 cm) before satellite nodules are formed [70]. This process of metastases in the liver resulting in metastases in the lungs and other systemic sites may take many months and even years. It may not occur at all with a response to chemotherapy or if a liver resection is successful [71].

However, PM have an alternative and more aggressive mechanism of abdominal and pelvic progression. The cells exfoliate from the primary tumor to produce PM and this represents a more aggressive phenotype [72]. Even small tumor nodules can shed cancerous cells that form new implants. This exfoliation process causes a far more rapid disease progression, and all quadrants of the abdominal cavity are involved in the disease process within a few months (Fig. 3.3).

3.7 The Surgeon and Peritoneal Tumor Dissemination

The surgeons play an important role not just in the treatment of peritoneal metastases but also in their development. A surgeon's role in peritoneal tumor dissemination was first described by

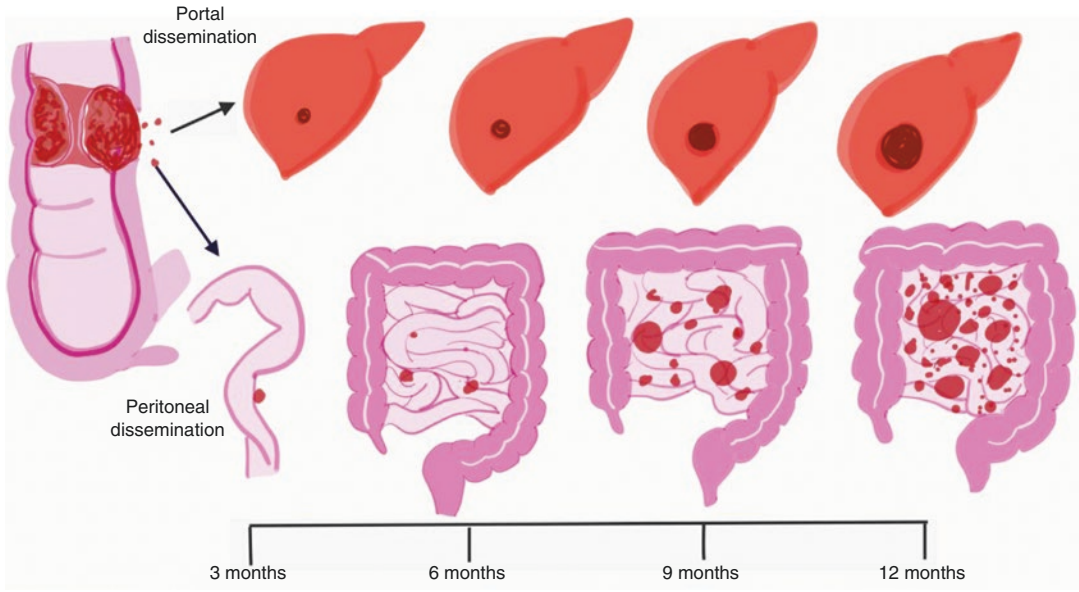

Fig. 3.3 A diagram representing the theoretical model comparing progression of liver and peritoneal metastases. A solitary liver metastases has a doubling time of 3 months in the liver parenchyma. A solitary peritoneal metastases grows at the same rate but also exfoliates free cancer cells into the peritoneal cavity. This produces metastasis of various sizes disseminated throughout the abdomen and pelvis during the same period. Adapted from [70] with permission

Paul Sugarbaker. Cancer spread following resection of the primary can occur in the following ways: through portal dissemination, lymph nodal recurrence, recurrence at the operative site, and peritoneal spread [73]. Whereas portal dissemination cannot be prevented, other recurrences could be minimized by proper surgical technique. This has been demonstrated in colorectal cancer patients where there is a decreased local recurrence and a longer disease-free survival when the resection of the primary tumor is performed by experienced surgeons at high-volume centers [74].

Sugarbaker suggested that proper surgical technique can prevent peritoneal dissemination to a certain extent. In order to limit peritoneal spread, "containment" should be one of the main goals of the gastrointestinal cancer surgeon. He described a technique called "centripetal surgery" in which one must move around the tumor mass with perfect hemostasis, adequate margins of dissection, and sufficient visualization so that the vital structures are not damaged. If all of these requirements are not met, the surgeon must approach the malignant disease from another anatomic site [75, 76].

Laparoscopic surgery minimizes surgical trauma and, compared with open surgery, has been associated with less peritoneal as well as metastatic tumor growth in several animal models [77]. The technique has raised concerns regarding the potential effect of a CO_2 pneumoperitoneum on peritoneal cancer spread [78]. However, large clinical trials comparing open surgery with laparoscopic colectomy for colorectal cancer did not identify an increased risk of peritoneal recurrence associated with the laparoscopic approach [79]. The minimally invasive approach requires considerable amount of skill and should not be performed at the risk of compromising other oncological requirements like adequate margins and lymph node yield and avoiding intraoperative tumor rupture and spill.

The other important aspect of prevention is surgical handling of patients with positive peritoneal fluid cytology or with peritoneal nodules at presentation. Non-definitive procedures except those needed in the emergency setting, i.e., for perforated or obstructed tumors, should be avoided. Sugarbaker pointed out that the peritoneum itself acts as a first line of defense against carcinomatosis, and in its absence, cells become implanted wherever a raw surface is created [80].

Non-definitive surgery in these situations has some adverse consequences. These patients become poor candidates for subsequent curative approach using CRS and HIPEC, the lymph nodal clearance becomes more difficult, and there is tumor cell entrapment in avascular scar tissue which cannot be treated with chemotherapy. Retroperitoneal implantation of tumor cells can involve tubular structures like the ureters leading to obstruction. When such a situation is encountered during laparotomy or laparoscopy, further surgical intervention should be stopped, and the patients should be referred to a center experience in treating peritoneal metastases [80]. Sugarbaker and colleagues also hypothesized that surgery alone as a treatment of PM may have adverse consequences. They proposed the "tumor cell entrapment" hypothesis to explain the rapid progression of peritoneal-surface malignancy in patients who undergo treatment using surgery alone [81]. This theory relates the high incidence and rapid progression of peritoneal-surface implantation to (1) free intraperitoneal tumor emboli as a result of serosal penetration by cancer, (2) leakage of malignant cells from transected lymphatics, (3) dissemination of malignant cells directly from the cancer specimen as a result of surgical trauma and backflow of venous blood, (4) fibrin entrapment of intra-abdominal tumor emboli on traumatized peritoneal surfaces, and (5) progression of these entrapped tumor cells through growth factors involved in the wound-healing process.

One of the most important prognostic factors determining the treatment outcomes in patients with PM is the disease extent determined by the peritoneal cancer index (PCI). In general patients with less extensive disease have better outcomes, and one of the first treatment goals is to detect PM early in the course of disease evolution. At the time of treatment of the primary malignancy, imaging modalities may fail to pick up low-volume disease, and during an open or laparoscopic resection, PM should be searched for and the extent documented in detail, especially in patients with known risk factors for peritoneal dissemination. For patients on surveillance also, the index of suspicion should be high. An elevation in tumor markers without evidence of disease on imaging should prompt the use of diagnostic laparoscopy for detection of early peritoneal cancer spread.

3.8 Cytoreductive Surgery: Principles and Techniques

Cytoreductive surgery deals with macroscopic disease, and intraperitoneal chemotherapy acts on microscopic disease. Since intraperitoneal chemotherapy acts only on tumor deposits measuring 2.5 mm or less, the goal of CRS is to remove all tumor deposits >2.5 mm in size [82]. Whereas this may be adequate for low-grade tumors like pseudomyxoma peritonei and peritoneal mesothelioma, for other high-grade malignancies like colorectal cancer, there should be no visible residual disease.

The various peritonectomy procedures required to achieve complete tumor removal are listed in Table 3.2 [84]. There are no distinct boundaries for each of the peritonectomies, and often two or more peritonectomies are performed in continuity. This knowledge is important however; for any tumor spread in particular area of the peritoneum, not just a segment of the peritoneum but the peritonectomy corresponding to that region should be performed.

Complete tumor removal may necessitate removal of adjacent viscera. Some of the examples are performing a panhysterectomy with or without resection of the rectosigmoid colon along with a pelvic peritonectomy, subtotal or total gastrectomy with total omentectomy, resection of the terminal ileum and proximal right colon, and resection of segments of the small bowel and its mesentery [49, 85, 86].

3.8.1 Technique of Dissection

Sugarbaker hypothesized that using conventional surgical methods like scissors and or knife dissection leads to increased blood loss and promotes intraperitoneal tumor dissemination. Using high-voltage electrocautery creates a zone of necrosis along the line of resection and thus

Table 3.2 Peritonectomy procedures and resections that are combined to achieve a complete cytoreduction [14]

Peritonectomy procedures	Involved regions	Resections
Anterior parietal peritonectomy	Peritoneum lining of the anterior abdominal wall bilaterally extending laterally to the line of Toldt Lower boundary at the pelvic brim (false pelvis) superiorly up to the costal margins merging with the subphrenic peritoneum	Old abdominal incisions, umbilicus, epigastric fat pad
Left upper quadrant peritonectomy	Peritoneum lining undersurface of the left hemidiaphragm extending medially up to the falciform ligament inferiorly merging with the parietal peritoneum at the costal margin	Greater omentum and spleen
Right upper quadrant peritonectomy	Peritoneum lining the undersurface of the right hemidiaphragm extending medially up to the falciform ligament anteroinferiorly up to the costal margin and posteroinferiorly, the peritoneum overlying the Gerota's fascia, medially extending up to the lateral edge of the hepatoduodenal ligament	Glisson's capsule deposits
Pelvic peritonectomy	From the brim of the false pelvis, the upper margin is at the origin of the inferior mesenteric artery, laterally to the peritoneal reflection over the psoas and internal opening of the inguinal canal, inferiorly to the peritoneal reflection in the rectouterine or rectovesical pouches	Uterus, ovaries, and rectosigmoid colon
Omental bursectomy	The peritoneum overlying the gall bladder, the hepatoduodenal and hepatogastric ligaments, and the tissue overlying the caudate lobe and between the caudate and inferior vena cava extending up to the superior border of the pancreas behind the stomach	Gall bladder and lesser omentum

prevents tumor dissemination [87, 88]. Hence, he advocates the use of high-voltage electrocautery for performing CRS. A 3 mm ball tip is most suited for this purpose [87]. Contrary to this, other surgeons use combination of blunt and sharp dissection with cautery, bipolar scissors, and an ultrasonic scalpel.

3.8.2 Preparing the Patient

Patient is placed in a supine position with the gluteal fold at the end of the table to allow full access to the perineum. The limbs should be supported properly using stirrups to prevent pressure sores and myonecrosis of calf muscles [89]. Skin preparation is from the mid-chest to mid-thigh with preparation of the genitalia and catheterization.

To perform a thorough exploration of the abdominal cavity, a midline laparotomy incision from the xiphoid to the pubis is essential. The old scars and umbilicus are excised. The dissection proceeds carefully avoiding injury to the bowel that may be densely adherent to the scar due to presence of tumor or postsurgical adhesions [90].

3.8.2.1 Where to Begin

Some surgeons prefer the extraperitoneal approach which facilitates faster dissection and saves time. This is possible if the disease is limited and the surgeon is confident of proceeding with the surgery. Others prefer the intraperitoneal approach irrespective of the disease extent that allows a more thorough evaluation. One of the main regions to be evaluated in the small bowel and its mesentery as preoperative investigations may grossly underestimate the extent of disease in that area. It may be

prudent to deal with the difficult areas early in the course of the surgery when the surgical team is not fatigued. However, many surgeons proceed in a systematic fashion, e.g., in a clockwise manner starting with the right upper quadrant peritonectomy and then left upper quadrant peritonectomy [86]. This is followed by a greater omentectomy and splenectomy. These dissections are followed by a pelvic peritonectomy with hysterectomy, salpingo-oophorectomy, and rectosigmoidectomy if necessary. This is followed by a cholecystectomy, lesser omentectomy, and omental bursectomy. In patients with limited disease, all the peritonectomies may not be required [86].

3.8.3 Lysis of Adhesions

Before proceeding with peritonectomies or visceral resections, all adhesions are separated. As far as is possible, these adhesions are resected and submitted as a pathological specimen [86]. This is to clear any tumor cells that may be trapped in the scar tissue in accordance with the "tumor cell entrapment hypothesis" [86].

3.8.4 Xiphoidectomy

If the preoperative radiologic studies suggest the need for right or left subdiaphragmatic peritonectomy, a xiphoidectomy should be performed [86]. The midline abdominal incision is extended to approximately 4 cm above the xiphoid-sternal junction, and the epigastric fat pad is released from the posterior rectus sheath. The xiphoid is adequately exposed and divided using high-voltage electrocautery at its attachment to the sternum.

The electrosurgical current denatures the protein within the bone at the base of the xiphoid, so the bone is fractured precisely with minimal downward pressure at this line.

The xiphoid is released from the sternum, and the diaphragm muscles attached to it are divided to free it completely. The dissection should be carried out superficial to the diaphragmatic muscles to avoid inadvertent entry into the pleural or pericardial space [86].

3.9 Peritonectomy Procedures

3.9.1 Anterolateral Parietal Peritonectomy

This may be the first peritonectomy that is performed especially if the extraperitoneal approach is employed. In the extraperitoneal approach, the peritoneum is not opened, and the various peritonectomies are performed in continuity; the dissection is extended to the subphrenic region keeping the peritoneum intact [91]. The advantage of this approach is that it is fast and saves time. A small window may be made in the peritoneum to confirm the presence of PM on the parietal peritoneum. The abdominal wall needs to be kept under constant tension by retraction to facilitate the dissection.

The dissection continues to the paracolic region till the line of Toldt is reached. Superiorly, this dissection can blend into the right and left subphrenic peritonectomy, and inferiorly it can continue into the complete pelvic peritonectomy (Fig. 3.4) [92]. On the other hand, when the disease on the parietal peritoneum is minimal and it is not thickened, it may be difficult to dissect off the sheath. In such cases, dissection can begin inferiorly by dividing the line of Toldt and proceeding upward using both blunt and sharp dissection. This makes identification of the plane and preservation of the sheath easier.

3.9.2 Right Upper Quadrant Peritonectomy

The falciform ligament is divided off its superior attachment from the abdominal wall till the xiphoid is reached. A xiphoidectomy can be performed at this stage if it has not been performed before. The falciform ligament is divided off its hepatic attachment till the posterior peritoneal reflection on the liver is reached. Anteriorly, the division of the hepatic bridge (pont hepatique) can be performed at this stage or done later (described below). The dissection then proceeds to the right in continuity stripping the peritoneum off the underlying diaphragmatic muscle.

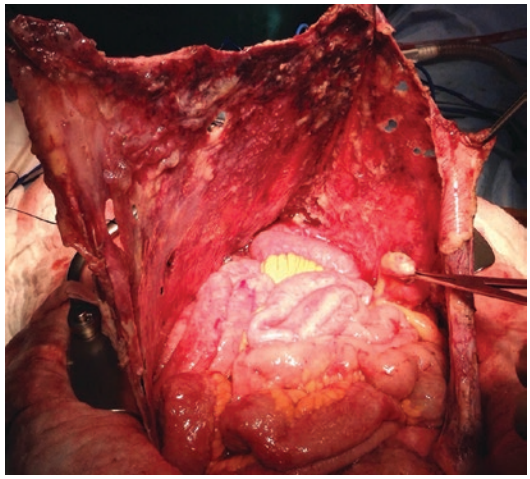

Fig. 3.4 Anterolateral parietal peritonectomy

Maintaining constant traction on the specimen helps in exposing the plane of dissection between the diaphragmatic muscle and the peritoneum. As the peritoneum is taken off the central portion of the diaphragm, the fold between the liver and the diaphragm is reached. The peritoneum is divided where it attaches to the superior surface of the liver exposing the inferior vena cava and right hepatic vein (Fig. 3.5). The dissection on the superior surface continues laterally till the right triangular ligament is reached. The peritoneum is stripped off the right dome. At this point dividing the right triangular ligament facilitates retraction of the liver to expose the lateral surface of the diaphragm. There are several small vessels from the diaphragmatic muscles to the peritoneum which should be cauterized. The diaphragmatic vessels will be encountered just before the tendinous portion of the diaphragm, and if possible, they should be preserved. This part of the procedure can be performed by blunt dissection or by electrocautery depending on the preference of the surgeon. If the peritoneum is not thickened, care should be taken while stripping it off the tendinous portion of the diaphragm so as to avoid a full-thickness excision/breach. In invasive diseases, the tumor deposits may be infiltrative and involve the diaphragmatic muscle, especially in the region of the tendinous portion. This may require resection of a part of the diaphragm. Some surgeons suture such defects immediately with absorbable or nonabsorbable sutures, whereas others prefer to leave them open till after the HIPEC is performed. This allows perfusion of the pleural space as well.

The subphrenic peritoneum at the level of the bare area of the liver gets reflected onto the liver becoming continuous with the Glisson's capsule. Tumor deposits on the Glisson's capsule are not uncommon, and in PMP, they may be extensive.

Conventionally, the tumor is destroyed using high-voltage pure cut electro-evaporation. But complete tumor removal like that of a peritoneal resection may not be achieved by this method. Glehen and his collaborators have described the technique of digital glissonectomy using blunt finger dissection and bipolar scissors by which a fast and bloodless Glisson's capsulectomy can be performed [93]. After complete mobilization of the liver, a glissonectomy can be performed when the liver parenchyma is not invaded by the tumor, irrespective of how widespread it is around the liver parenchyma. When there is extensive tumor on the subphrenic peritoneum, the capsulectomy is performed en bloc with the peritonectomy. Glissonectomy starts 1–2 cm away from the disease, within normal peritoneum [94]. The capsule is incised and stripped long enough to ensure a complete resection of the disease; this must also be large enough to allow at least one finger to fit between liver parenchyma and Glisson's capsule to allow for efficient blunt dissection (Fig. 3.6). The most important step is to find the right plane between the Glisson's capsule and the liver parenchyma. For this the capsule is lifted with a forceps, and blunt scissors or bipolar scissors is used to separate the capsule from the parenchyma in an avascular plane. Once the right plane has been identified, the capsule is stripped away with digital dissection and removed. Maintaining the specimen intact facilitates the dissection. The digital dissection should be easy to perform, and if resistance is encountered, it indicates either an entry into a "false plane" or parenchymal infiltration by the tumor. Involvement of the liver parenchyma by the tumor requires a formal liver resection for complete tumor clearance. The capsulectomy is performed in areas of disease typical in the right superior and lateral surfaces of the liver to the right of the falciform, the left superior surface to the left of the falciform, and the inferior surfaces as well. Isolated deposits of tumor can be electro-

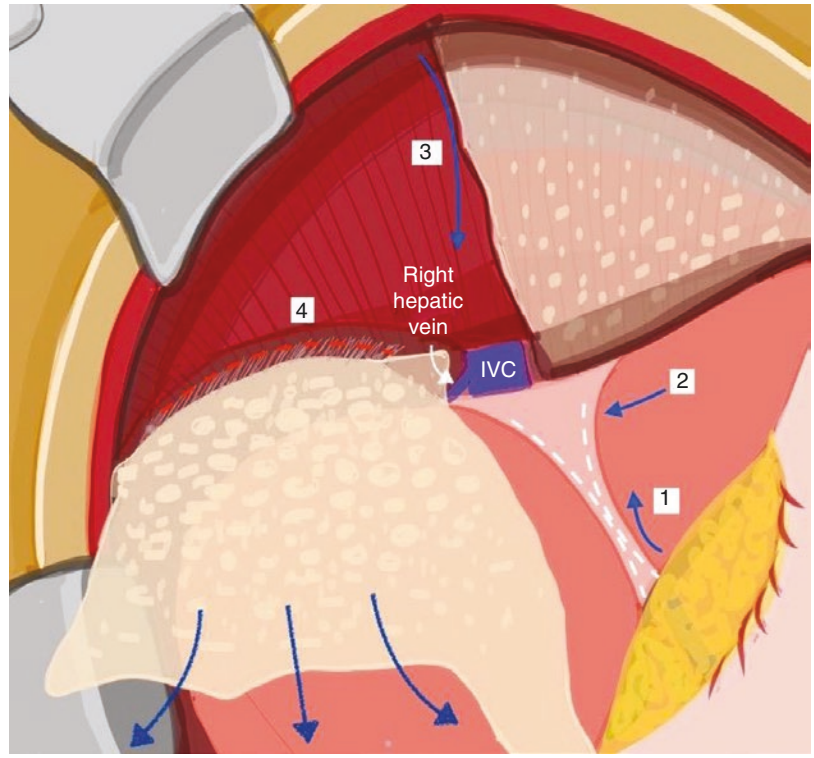

Fig. 3.5 Right subphrenic peritonectomy: (**1**) The falciform ligament is divided at its attachment to the superior surface of the liver till (**2**) its reflection on the the diaphragm; (**3**) The dissection is then carried onto the diaphragm moving from below upwards or coming down from the edge of the abdominal incision stripping the peritoneum in the central region. The inferior vena cava and right hepatic vein are exposed in the process and safeguarded; (**4**) The dissection continues laterally

vaporated or dissected off. Once all diseased capsule is released from liver parenchyma, the specimen can be removed and sent to pathology. The liver is packed using a large sponge, and this is left in place for the remainder of the procedure. When required, the glissonectomy is always performed at the beginning of the surgical procedure in order to provide the longest delay before closure to ensure hemostasis and biliostasis. At the end of the CRS, a second look is performed to achieve thorough hemostasis and biliostasis. Before abdominal closure, a silicon drain is placed in the perihepatic space [94] (Fig. 3.6).

Posterolaterally, the dissection proceeds over the upper part of the Gerota's fascia and the adrenal, which constitute the base of the dissection. Medially, the peritoneum is divided off its attachment on the posterior surface of the liver retracting segments 6 and 7 medially to expose the inferior vena cava (Fig. 3.7). Care should be taken while retracing the liver to avoid lacerations/tears that may cause unwanted bleeding.

As the peritoneal reflection is divided, there is a risk of traumatizing the vena cava or the caudate lobe veins that pass between the vena cava and the segment 1 of the liver. Care should be exercised to avoid injury to these structures, which can cause significant bleeding.

The dissection then proceeds onto the inferior surface of the right lobe lateral to the gall bladder and the peritoneum overlying the anterior surface of the right kidney. The Glisson's capsule in this region may be removed if a glissonectomy is performed or left intact if it is not involved by tumor. The medial limit of dissection is the lateral edge of the hepatoduodenal ligament.

Complete mobilization of the right lobe should be done to look for minimal disease. Sometimes there is no visible disease on the area of the diaphragm that are exposed and not covered by the liver. Flimsy adhesions between the liver and the diaphragm may be indicative of disease in the unexposed areas of the diaphragm. Palpation of the liver surface and diaphragm may not be adequate in all cases to rule out presence of disease.

In cases of extensive infiltrative disease, there is contiguous involvement of the Glisson's capsule with infiltration of the underlying hepatic parenchyma. In such cases, the peritonectomy should be performed on all sides of the involved

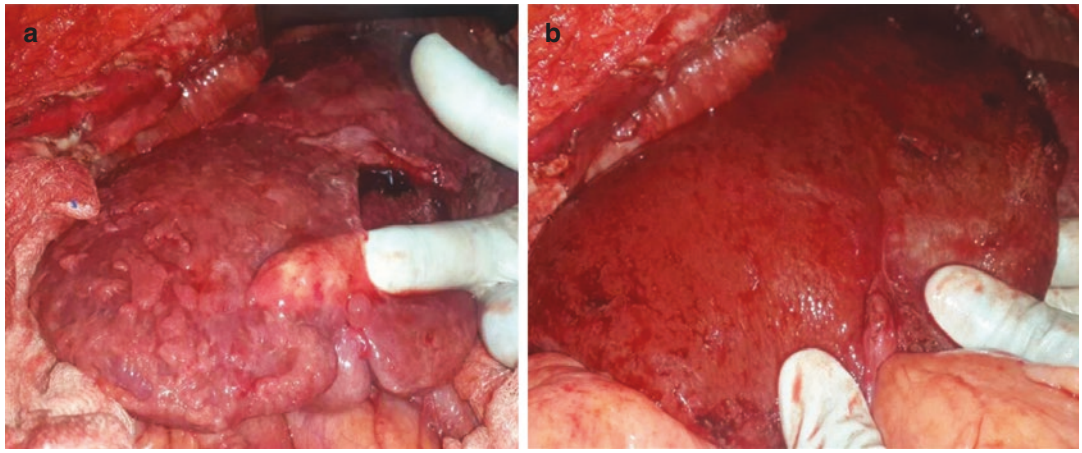

Fig. 3.6 Digital glissonectomy. (**a**) The capsule is incised at one point to allow insertion of a finger and is then stripped off the liver surface. (**b**) The liver surface after removal of the tumor bearing Glission's capsule

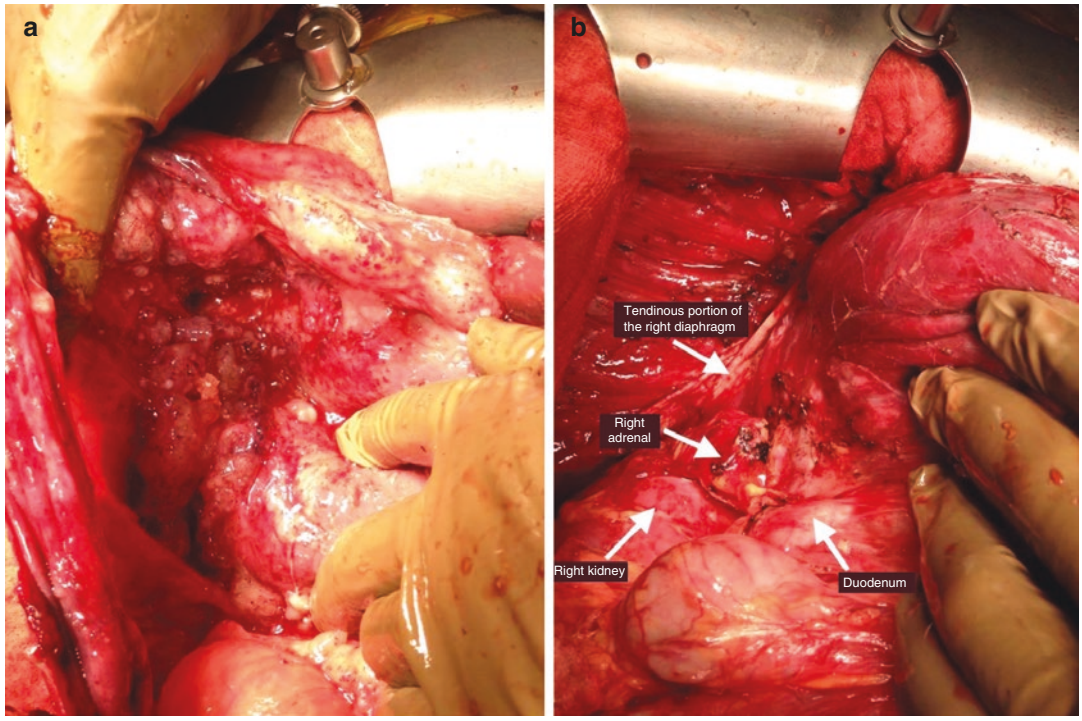

Fig. 3.7 Right subphrenic peritonectomy. (**a**) Extensive tumor deposits over the right subphrenic peritoneum in a patient with low grade pseudomyxoma peritonei. (**b**) Complete tumor clearance in the region exposing the right kidney, adrenal, and duodenum. The right lobe of the liver has been completely mobilized and retracted

liver and the nonanatomic liver resection performed at the end to obtain complete tumor clearance. When the disease is close to the vascular structures, a vascular control should be obtained. The control of the porta hepatis is secured, and the infrahepatic vena cava is exposed. Dissection proceeds along the superior aspect of the vena cava till the posterior surface of the right hepatic vein is reached and the vein is looped and secured. Then the peritonectomy is commenced [95].

3.9.3 Left Subphrenic Peritonectomy

The dissection begins at the edge of the abdominal incision dissecting the epigastric fat and peritoneum

off the posterior sheath. It is then carried on to the undersurface of the left hemidiaphragm. One should be cautious in the central region where the peritoneum overlying the tendinous portion of the diaphragm is usually thin and the pericardial cavity is in close proximity. If the pericardium is opened, it needs to be repaired. Medially the dissection is carried out till the falciform ligament and the left lobe of the liver are mobilized during the process. The left hepatic vein can have a tortuous course in some patients and needs to be safeguarded. Moving more laterally, the abdominal esophagus and greater curvature of the stomach and spleen are encountered. If a splenectomy is planned, performing it before the left upper quadrant peritonectomy provides better exposure. Moreover, retraction of the spleen can be avoided which can lead to capsular tears that may cause unwanted bleeding. The dissection proceeds posterolaterally to separate the peritoneum off the entire diaphragmatic surface, the left adrenal, and the superior half of the perirenal fat. The splenic flexure of the colon is then mobilized, and the colon retracted inferiorly and medially. Once the peritonectomy is complete, the left adrenal, pancreas, and perinephric fat are clearly exposed. The anterior leaf of the transverse mesocolon is exposed [91].

3.9.4 Greater Omentectomy and Splenectomy

The infracolic portion of the greater omentum is dissected off the transverse colon, and the dissection then proceeds to remove the anterior layer of the peritoneum covering the transverse mesocolon. This layer may be thin and very flimsy especially when the tumor deposits are not extensive. The pancreatic capsule is removed in continuity. It may, however, be left behind in the absence of disease (Fig. 3.8). Once the pancreatic capsule is dissected off, the posterior layer of the lesser sac

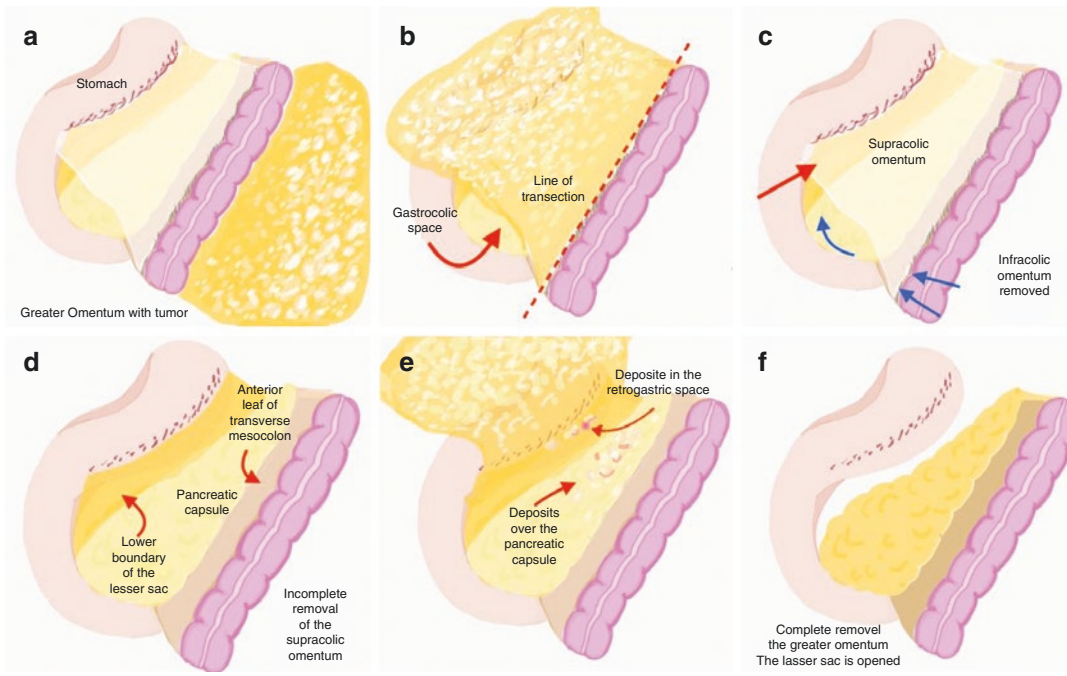

Fig. 3.8 Greater omentectomy. (**a**) Deposits in the infracolic omentum with a normal looking supracolic portion; (**b**) Line of transection for starting a complete supracolic omentectomy; (**c**) An infracolic omentectomy has been performed—the dissection should commence at the attachment of the remaining omentum to the transverse colon and should follow the blue arrows to remove the anterior leaf of the. Directly dividing the omentum along the gastroepiploic arcade leads to incomplete removal; (**d**) Incomplete supracolic omentectomy—anterior layer of the transverse mesocolon should be removed in all patients. The pancreatic capsule may be left behind if there is no tumor involvement. However, the lasser sac should be opened and the retrogastric space examined for the presence of tumor deposits; (**e**) Tumor deposits over the pancreatic capsule and in the retrogastric space; (**f**) Complete removal of the greater omentum

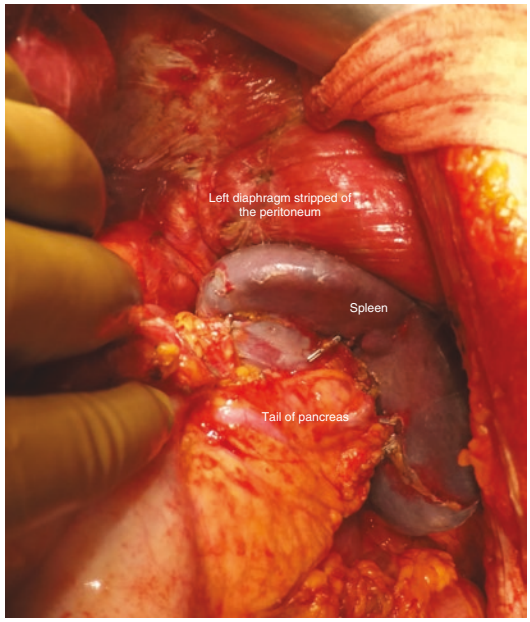

Fig. 3.9 Greater omentectomy with preservation of the spleen: complete removal of the omentum results in infarction of the lower pole of the spleen as is seen in th e picture

is reached. This layer should be divided to expose the retrogastric area, and unless this is done, deposits in this region may be missed. The greater omentectomy is completed by dividing the branches of the gastroepiploic arcade to the greater curvature. If the omental disease isn't significant, the gastroepiploic arcade may be preserved. The short gastric vessels are divided next. A splenectomy is not performed unless it is involved (Fig. 3.9). During this process, the spleen should be manipulated carefully to avoid injury and damage to the pancreatic tail and splenic vessels. The heavy tumor seeding at the splenic hilum, posterior approach dividing the splenic vessels first, is employed. This prevents injury to the pancreatic tail [96]. Some authors have reported that splenectomy ameliorates the hematologic toxicity of HIPEC and reduces the requirement of growth factors and platelets [97].

3.9.4.1 Partial or Total Omentectomy?

The rationale for omentectomy and its extent have been elaborated by Celeen et al. According to them, in case of gross involvement of the greater omentum, omentectomy is warranted. The high risk of omental recurrence favors complete omentectomy as opposed to partial omentectomy, especially in colorectal carcinomatosis, where systemic chemotherapy is less efficacious as compared to ovarian cancer. When there is absence of macroscopic disease involving the omentum, the benefit of a complete as opposed to a partial omentectomy can be determined only by a randomized trial [60]. However, even in such a trial, it would be difficult to determine the extent of benefit due to the high incidence of recurrence in both colorectal and ovarian cancers. These investigators are of the opinion that such trail would require recruiting a large number of patients and have a non-inferiority design making it impossible to conduct, and hence, it is unlikely that some definite conclusion will be drawn in the future on this matter [60].

3.9.5 Lesser Omentectomy and Hepatoduodenal Ligament Clearance

The clearance of the hepatoduodenal ligament begins with a cholecystectomy. The gall bladder is approached by the fundus first method dissecting the cystic artery and the cystic duct and dividing them. The peritoneum over the gall bladder is maintained intact and then retracted over the portal structures which are carefully dissected using blunt or bipolar dissection (Figs. 3.10 and 3.11) [91]. When there is extensive disease, the cystic duct can be used to identify the correct plane. Medially, the lesser omentum is reached. The right gastric artery should be preserved as far as possible. The hepatogastric ligament is then divided at its attachment on the caudate lobe. An accessory or aberrant left hepatic artery may be present in this area which needs to be identified and preserved. If the artery is embedded in the tumor and or its preservation prevents clear exposure if the omental bursa, the artery can be divided close to the liver [91].

Superior clearance of the hepatogastric ligament requires mobilization of the left lateral segment of the liver by dividing the left triangular ligament. It is retracted to the right to expose the ligament completely. Along the lesser curve, blunt and sharp dissection is performed. The

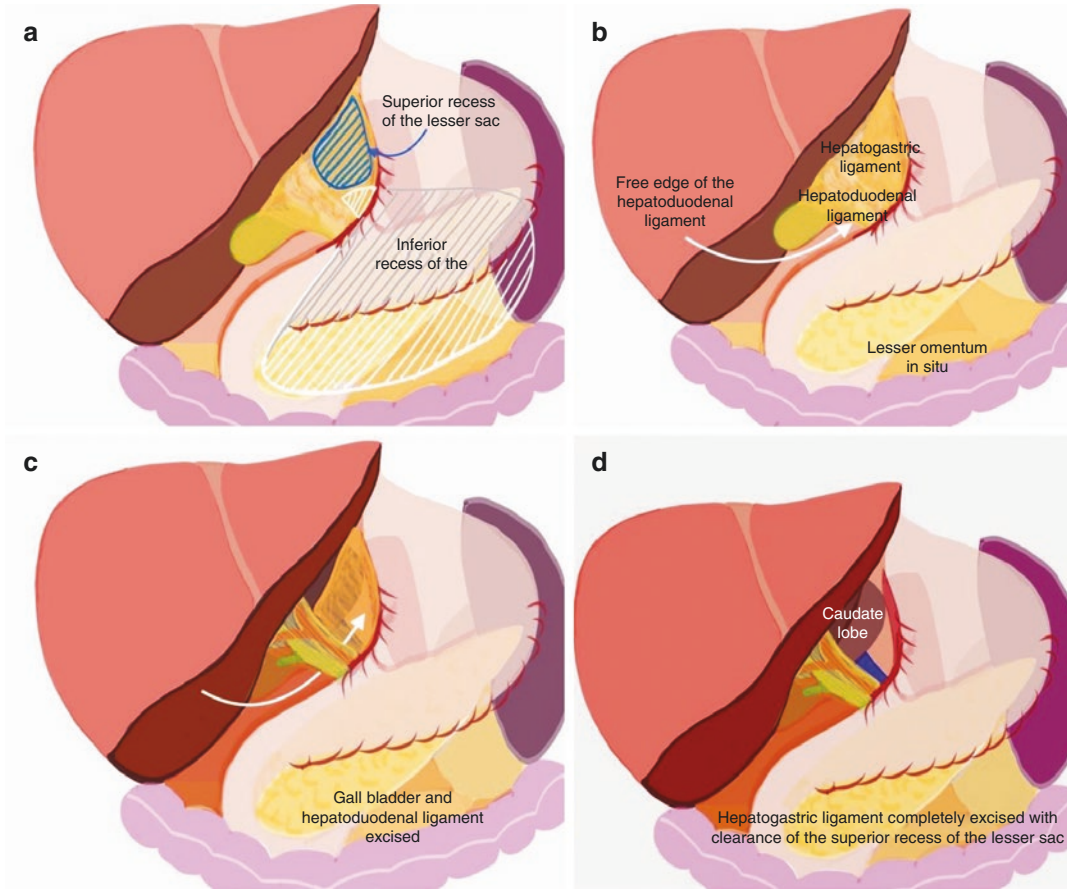

Fig. 3.10 Lesser omentectomy and clearance of the lesser sac (omental bursa): (**a**) The lesser omentum in situ. (**b**) The smaller superior and larger inferior recess of the lesser sac. (**c**) Removal of the gall bladder and hepatoduodenal ligament; the arrow shows the foramen of Winslow which has been cleared. (**d**) Removal of the gastrohepatic ligament opens up the superior recess of the lesser sac that is completely cleared. This needs mobilization of the left lobe of the liver to completely resect the gastrohepatic ligament (not shown in the figure). The inferior recess needs to be approached superiorly and through the gastrocolic space from below as well

vagus and left gastric vein should be preserved. This is important if the gastroepiploic arch has been divided. The tumor over the surface of the caudate lobe may be electroevaporated [91].

Once this dissection is completed, the caudate lobe is retracted to expose the floor of the omental bursa. Tumor deposits on the posterior surface of the caudate lobe and anterior surface of the inferior vena cava are removed. Medially the crus of the diaphragm is cleared off the tumor. A combination of blunt and bipolar dissection is used for the same. At this point the involvement of the subpyloric space is performed, and if required, a subtotal or distal gastrectomy is performed [91].

The umbilical ligament needs to be removed completely. It may be surrounded by a variable amount of hepatic parenchyma in the umbilical fissure. Sugarbaker has referred to this bridge as "pont hepatique"; in some cases the liver tissue is absent i.e. an absent or open hepatic bridge (Fig. 3.12) [98]. To clear deposits in the peritoneum surrounding the umbilical ligament, the hepatic bridge needs to be divided to expose the full length of the ligament. The left hepatic artery or one of its branches may be at risk of injury during the stripping of the peritoneum in the umbilical fissure, and special care needs to be taken to avoid it (Figs. 3.12 and 3.13).

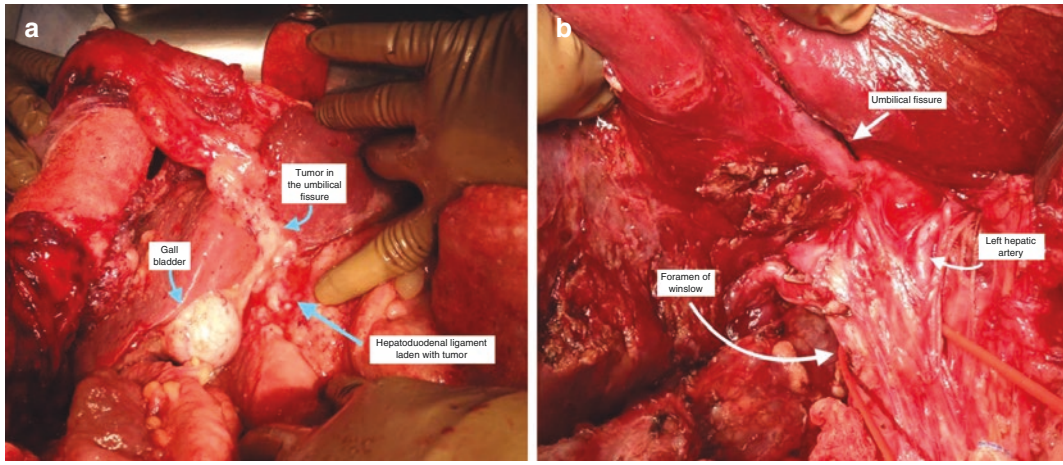

Fig. 3.11 Clearance of the hepatoduodenal ligament – (**a**) Hepatoduodenal ligament laden with tumor in a patient with low grade pseudomyxoma peritonei; (**b**) Complete clearance of the tumour

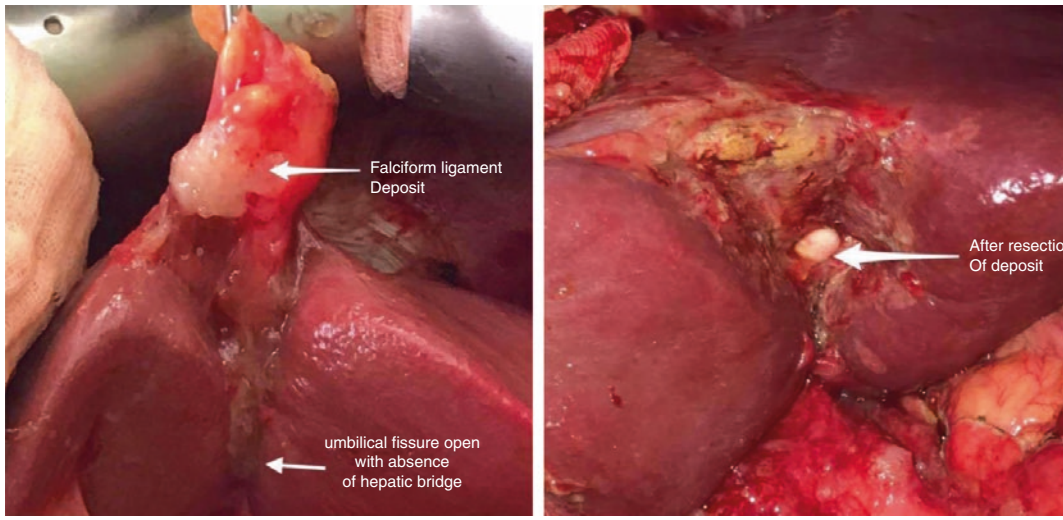

Fig. 3.12 Absent hepatic bridge

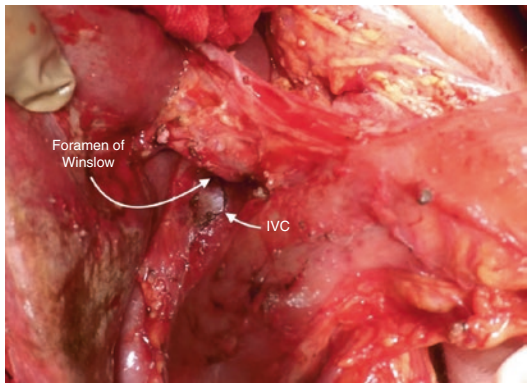

Fig. 3.13 Foramen of Winslow exposed after complete tumor clearance in the region

3.9.6 Clearance of the Foramen of Winslow

A potential site for incomplete cytoreduction is the foramen of Winslow, especially the posterior aspect of the hepatoduodenal ligament. Residual tumor at this site is a prominent cause of unnecessary treatment failure in the management of patients with mucinous appendiceal neoplasms [99]. The foramen of Winslow is bounded posteriorly by the peritoneum covering the inferior vena cava, anteriorly by the peritoneum that covers the posterior surface of the portal triad, superiorly by the junction of the right and left

caudate lobes of the liver, and inferiorly by the peritoneum covering the first portion of the duodenum. Peritonectomy of both the anterior and posterior aspects of the hepatoduodenal ligament can be performed comfortably for small-volume disease and low-grade tumors like PMP and cystic mesothelioma. The peritoneum is loosely attached to the portal structures, and detachment of the peritoneum from the liver may allow complete stripping of the peritoneum. However, more invasive large volume pseudomyxoma peritonei or mucinous neoplasms may be more adherent to portal triad structures, and there is a risk of injury to these structures [99].

Sugarbaker has described the Kocher maneuver can be used to rotate the duodenum, head of pancreas, and portal structures by 180°. By doing this, the foramen of Winslow is clearly exposed for peritonectomy. The peritoneum and natural adhesions securing the second portion of the duodenum to the perirenal fat are divided and elevated. Complete division of the adhesions at the superior aspect of this dissection will cause the foramen of Winslow to open completely (Fig. 3.13). Further right to left rotation of the duodenum and the head of the pancreas exposes the posterior aspect of the hepatoduodenal ligament. This also leads to complete opening of the most dependent part of the omental bursa, the subpyloric space [99].

Sugarbaker does not recommend this procedure for all patients as it opens up the retroperitoneal areas with the risk of tumor implantation in these areas. Rotation of the pancreas can lead to acute pancreatitis in rare cases. There is a risk of capsular injury which can also lead to pancreatitis that is a slow resolving process. He recommends that this procedure should be undertaken only after all the other peritonectomies are complete and the abdomen has been thoroughly irrigated with saline [99].

3.9.7 Pelvic Peritonectomy

Pelvic peritonectomy begins with the stripping of the peritoneum from the posterior surface of the lower anterior abdominal wall muscles in the midline to expose the rectus abdomens muscles. The dissection proceeds laterally till the psoas muscles are reached. The urachus is identified and held, and the peritoneum is stripped off the surface of the urinary bladder [91]. At the bladder dome, the peritoneum is relatively thin and adherent to the muscle. The correct plane needs to be identified to avoid inadvertent opening of the bladder. The peritoneum is loosely attached over the trigonal area and in absence of disease can be dissected off by blunt or sharp dissection. The inferior limit in females is the cervix at the level of the vesicouterine fold, and in males it is the seminal vesicles at the level of the rectovesical fold. Laterally, the dissection proceeds centripetally once more where the peritoneum dissected off the psoas and off the external iliac vessels and ureter. The connective tissue around the ureter should be preserved to prevent ischemic injury (Fig. 3.14).

The round ligaments of the uterus are divided extraperitoneally on either side, and the ureters are dissected away from the peritoneum. The ovarian vessels are ligated at the lower pole of the kidney on either side.

In females, the deeper dissection in the pelvis proceeds extraperitoneally to expose the uterine vessels that are ligated at the point where they cross the ureters [58]. The bladder is dissected away from the cervix and the vagina. The vaginal cuff is divided circumferentially and the rectovaginal septum is exposed. The perirectal fat is divided beneath the pelvic peritoneal reflection in the pouch of Douglas (POD) so that all the tumor in this region is removed intact with the specimen [100].

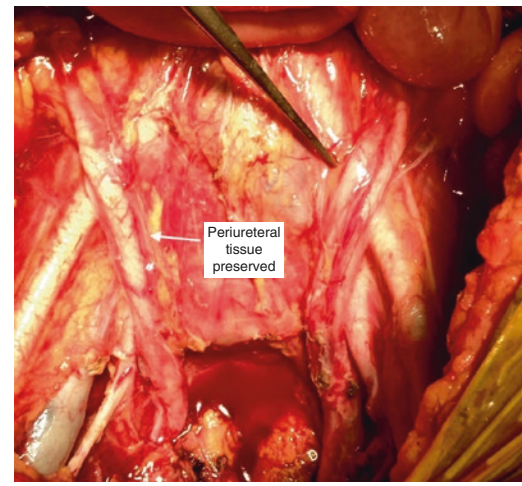

Fig. 3.14 Pelvic peritonectomy completed. Preservation of the connective tissue around the ureters avoid ischemic damage to the ureters

An evaluation of the involvement of the rectosigmoid is now performed, and if it is to be resected, the rectum is mobilized by dividing the mesorectal fascia. The inferior mesenteric artery is ligated and divided, and the sigmoid colon can be stapled off at the required level. When there is involvement of the wall of the rectosigmoid, the removal of the mesentery should also be performed as the nodes may harbor metastatic disease as well [91].

The rectal musculature is skeletonized, and the rectum is transected at the desired level using a stapler, thus completing the pelvic peritonectomy. If the rectal wall and serosa is spared of metastases, the pelvic peritoneum can be divided along the lateral border of the mesorectum and along the reflection onto the anterior surface of the rectum to complete the pelvic peritonectomy.

Though bowel anastomoses are generally performed after HIPEC, the vaginal stump needs to be repaired before HIPEC to prevent leakage of the chemotherapy solution through the vaginal opening [91].

3.9.8 Small Bowel and Mesentery

Tumor deposits over the small bowel and its mesentery are removed by electrovaporization or using scissors. The underlying vessels need to be safeguarded. Electroevaporation of bowel surface nodules can lead to fistula formation, and the same must be used cautiously. Sugarbaker et al. have classified small bowel involvement into five types based on the extent of invasion, the size of the tumor nodule, and its anatomic location on the bowel wall (Figs. 3.15 and 3.16) [101].

Type 1: Noninvasive nodules that can be removed with a curved Mayo scissors. These nodules can be seen in aggressive tumors where the nodules are very small and have not invaded past the peritoneum because of their small size. Large nodules arising from low-grade PMP and low-grade mesothelioma also fall into this category due to their noninvasive nature. These can be electroevaporated as well.

Type 2: Small invasive nodules on the antimesenteric portion of the small bowel. These involve only the seromuscular layer and require partial-thickness bowel wall resection. The seromuscular layer should be repaired in these cases.

Type 3: Moderately sized invasive nodules on the antimesenteric portion of the small bowel which require a full-thickness elliptical resection of the bowel wall.

Type 4: Small invasive nodules at the junction of the small bowel and its mesentery, if possible, can be removed without damaging the vascular supply, and segmental bowel resection could be avoided. Others require a segmental resection.

Type 5: Large invasive nodules which require a segmental resection with a generous margin of bowel and mesentery on either side.

3.10 Resection of Contiguous Structures and Viscera

In some cases, though the disease is extensive, a complete cytoreduction is warranted, and these patients usually require resection of multiple viscera and one or more segments of the bowel.

Sacrificing large segments of the small bowel that leads to a remnant of 2 m is often the limiting factor for achieving a complete CRS. When the remnant is smaller than 2 m, patients require total parenteral nutrition. When the total colectomy is required, at least 3 m of small bowel needs to be preserved, and if the colonic remnant is less than 30–50 cm, at least 2.5 m should be preserved [102].

3.10.1 Full-Thickness Diaphragm Resection

There may be superficial or full-thickness infiltration of the diaphragmatic muscle necessitating resection of the full thickness of the muscle. The resection is performed with electrocautery of Mayo scissors, and the defects are repaired with absorbable or nonabsorbable interrupted sutures.

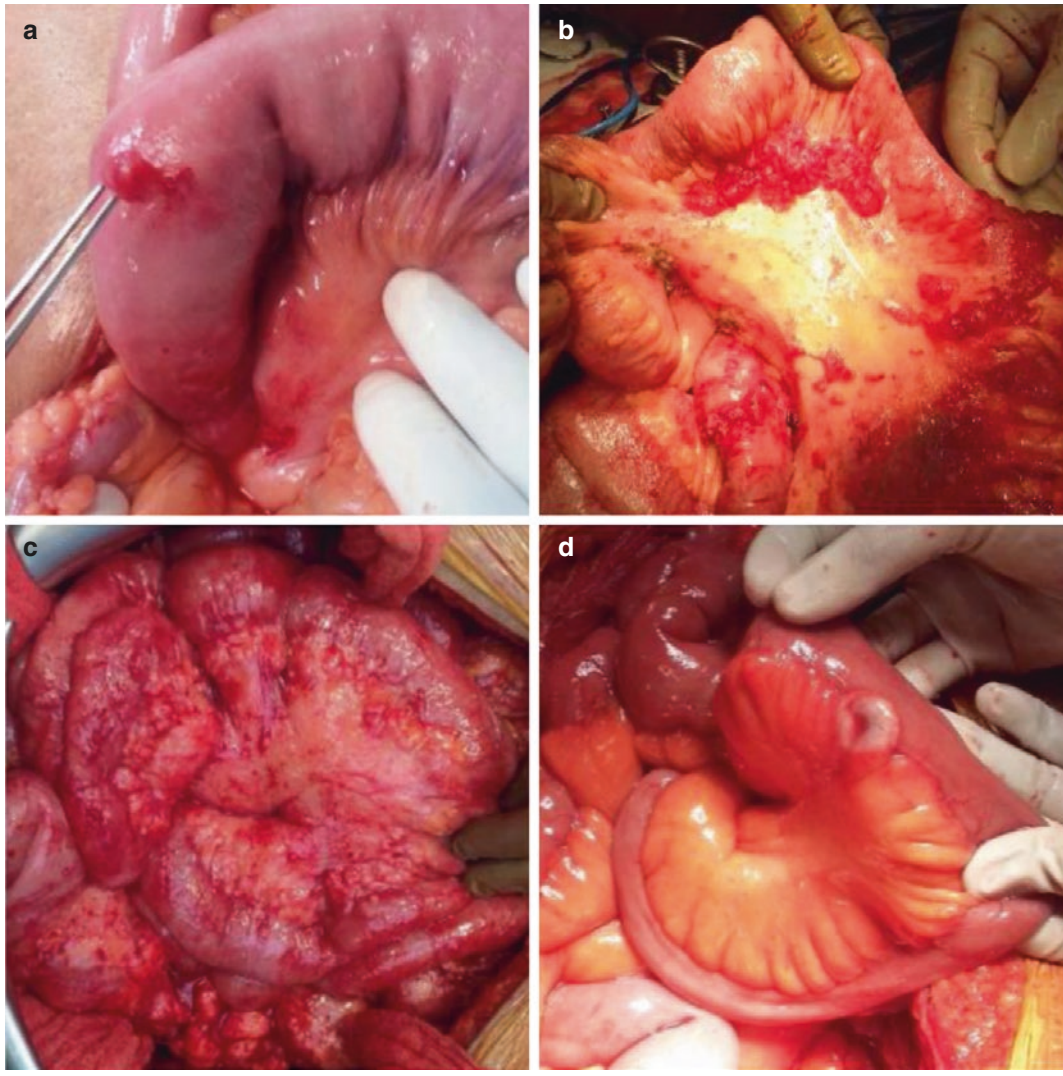

Fig. 3.15 Bowel and mesenteric deposits. (**a**) Type 1 deposit that can be excised with Mayo scissors or electrocautery; (**b**) Multiple noninvasive deposits (Type 1) that can be completely excised; (**c**) Extensive infiltrative deposits (Type 4), complete cytoreduction is unlikely; (**d**) Single infiltrative deposit (Type 4), requires segmental bowel resection

[95]. The use of prosthetic materials is usually not required. A chest tube should be used in case of large rents or multiple rents.

3.10.2 Partial/Total Gastrectomy

The presence of tumor around the stomach/and or involvement of the left gastric artery may necessitate a total or a partial gastrectomy.

Mucinous tumor that enters the lesser sac through the foramen of Winslow will accumulate by gravity in the subpyloric space which is a cul-de-sac beneath the pylorus [85]. For complete cytoreduction mucinous tumor accumulation in the subpyloric space must be cleared.

If there is tumor accumulation in the subpyloric space and the left gastric artery can be preserved, a complete cytoreduction can be achieved without gastrectomy. In other cases, complete

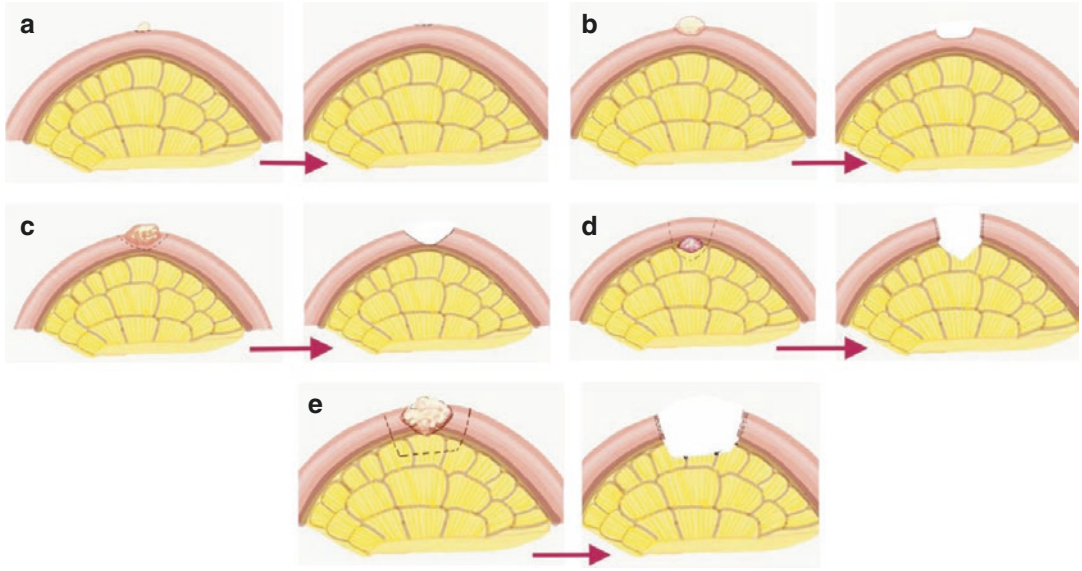

Fig. 3.16 Classification of bowel surface deposits as proposed by Sugarbaker (adapted from reference 101). (**a**) Noninvasive deposits (Type 1) that can be excised with Mayo scissors or electrocautery; (**b**) Small invasive deposits (Type 2) on the antimesenteric surface that require resection for the seromuscular layer. It is repaired before or after HIPEC; (**c**) Moderate-sized invasive deposits (Type 3) on the antimesenteric surface that require full-thickness resection of a portion of the circumference of the bowel wall; (**d**) Small invasive deposits (Type 4) on the mesenteric side that require segmental bowel resection; (**e**) Large invasive deposits (Type 5) on the mesenteric side that require segmental bowel resection

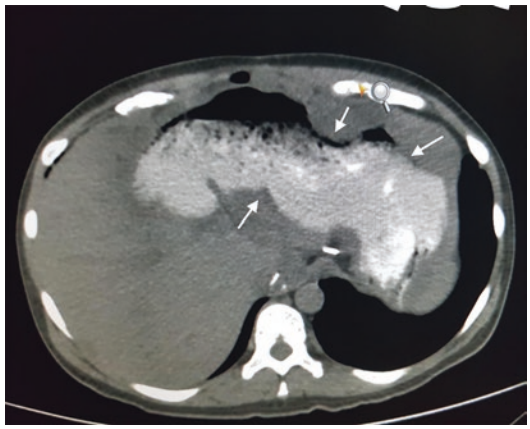

Fig. 3.17 CT scan showing extensive infiltrative deposits encasing the body of the stomach that will require a total gastrectomy for complete cytoreduction in that region

tumor clearance requires a partial or total gastrectomy [102] (Fig. 3.17).

Sugarbaker initially used a staged procedure performing a high jejunostomy to drain the enteric secretions followed by a Roux-en-Y anastomosis few months later [95]. Recent studies have shown that in experienced centers, immediate restoration of gastrointestinal continuity is feasible and safe [103, 104].

In a review of 1014 patients of PMP by Moran et al., 12% of the patients received a total or partial gastrectomy. The morbidity was significantly higher in patients undergoing a gastrectomy (31% vs. 13%; $p = 0.001$), but there was no difference in the mortality. Patients requiring a gastrectomy experienced a good long-term survival (5-year DFS 48% and 5-year OS OF 77%) though this was significantly inferior to that in patients not requiring a gastrectomy.

Yonemura et al. reported the results of performing a total gastrectomy and total colectomy in 48 patients with a median PCI of 33. Grade 3–5 complications were seen in 18 (37.5%) patients, and the mortality was 2.1% [105]. Patients who had staged resections had an acceptable quality of life.

A total gastrectomy should not be performed in patients who have undergone extensive small bowel resection.

A Roux-en-Y jejunal loop should be used for reconstruction performing an end-side esophago-jejunal and jejuno-jejunal anastomoses.

Contrary to these reports, Elias et al. do not recommend a total gastrectomy for patients with PMP stating that these patients require extensive small bowel resection that precludes maintaining a good nutritional status and quality of life [102].

They recommend the following strategy to deal with high-volume disease in patients with PMP requiring gastric resection:

- Preservation of the proximal one-third of the stomach
- Preservation of at least 3 m of the small bowel if a total colectomy is required
- Preservation of at least 2.5 of the small bowel if the length of the remnant colon is <30–50 cm

Their three step approach is as follows:

Step 1—To ensure an adequate length of the small bowel is preserved. Clearance of the bowel of tumor deposits is performed as described above.
Step 2—Preserving the proximal one-third of the stomach.

When a tumor mass encasing the antrum and involving the subpyloric space is found, the left gastric vessels should be dissected off the mass. Prior to preservation of the left gastric vessels, the gastroepiploic arcade should not be excised. In case of inadvertent injury to the left gastric artery, the stomach can still be preserved. The mucinous mass in the omental bursa is transected exposing the posterior wall of the stomach. Careful dissection along the lesser curve dividing the branches of the left gastric vessels supplying the tumor and preserving those supplying the normal stomach is performed till the vessels are dissected off the tumor completely [102].

Step 3—To ensure complete clearance of the hepatic pedicle and the caudate lobe.

The retropancreatic portion of the IVC is dissected off the tumor for 10–12 cm. The mass encasing the hepatoduodenal ligament is transected horizontally exposing the surfaces of the bile duct and hepatic artery. Thirdly, a vertical incision is performed splitting the tumor in two parts like we would open a book. This incision follows the anterior surface of the bile duct and the hepatic artery. The cystic artery and the cystic duct are divided to separate the tumor that surround the gall bladder from the hepatic pedicle. The hepatic artery, the bile duct, and then the vena porta are looped and gently retracted, and the tumor is dissected off these structures. The tumor mass that has already been separated from the left gastric vessels is now dissected off the caudate lobe [102].

3.10.3 Colectomy

Resection of the right or transverse colon is often required in patients with extensive omental deposits or bowel surface/mesenteric deposits. In cases of more extensive disease, a total or subtotal colectomy may be required. A right hemicolectomy may not be necessary for dealing with an appendiceal primary in patients with pseudomyxoma peritonei [107].

3.10.4 Resection of the Rectosigmoid Colon

Resection of the rectosigmoid colon is often necessary to achieve a complete cytoreduction. Hertel et al. showed that in patients with advanced ovarian cancer, with suspected rectal serosal involvement, 73% of the patients had residual disease when a rectosigmoid resection was not performed with a pelvic peritonectomy [108]. A stapled end-to-end tension-free anastomosis is performed. When the anastomosis is above the peritoneal reflection, a temporary ileostomy can

be avoided. Sugarbaker has described the technique of inverting the stapled anastomosis with a layer of interrupted silk sutures, and avoiding a temporary ileostomy that provided 10–15 cm of the rectum is preserved [109].

Several studies have shown that it does not increase the morbidity of CRS and not all cases require a diverting ileostomy [109–113]. Care should be taken to avoid the left ureter and the vaginal stump in females while performing a stapled anastomosis. In a series of 958 patients undergoing CRS and HIPEC from Basingstoke, 34.5% of the patients required a stoma for achieving complete CRS of which 25% of the patients had a permanent stoma. All temporary stomas in this series were subsequently reversed [114]. In some patients, the authors performed an end ileostomy with a low Hartmann's procedure to achieve a complete cytoreduction or maximal tumor debulking. Such stomas were permanent. The indication for a permanent stoma was generally due to the extent of the disease; the other factors that were taken into consideration were the age, general health, comorbidities, and impaired sphincter function.

3.10.5 Diverting Stoma: Pros and Cons

A diverting stoma is performed after rectal resection to protect the rectal anastomosis. Though in most cases this anastomosis is at the level of the mid-rectum, a stoma is still performed considering the extensive nature of the surgery and the use of HIPEC. Performing a stoma in these cases can have technical difficulties due to bowel edema that sets in toward the end of the procedure and in obese patients [109]. Stoma reversal itself can have complications as is seen in patients with rectal cancer. A complication rate of 7–20% has been reported for stoma reversal surgery that includes anastomotic leaks [115, 116]. De Cuba et al. reported a morbidity rate of 67% in 21 patients undergoing stoma reversal following CRS and HIPEC though there were no life-threatening complications or mortality [117]. On the contrary, the morbidity in the series from Basingstoke was low. In an interim analysis of the PRODIGE 7, the rate of gastrointestinal fistulas was higher in the HIPEC group as compared to the non-HIPEC group. Though this difference did not reach statistical significance, fistulas occurred even in the presence of a diverting ostomy. The presence of a stoma did not prevent fistulas but reduced the incidence of peritonitis. Hence, the authors recommend that a protective ostomy should be performed in case of more than two areas of intestinal stiches, in case of more than two bowel anastomoses, or in case of rectal resection (unpublished data; personal communication with Francois Quenet). This highlights the benefits of performing a diverting stoma which cannot be offset by the risk of complications that may arise from subsequent procedures.

3.10.6 Distal Pancreatectomy

A distal pancreatectomy may be required in patients with involvement of the distal pancreas with or without splenic hilar involvement and pancreatic capsule involvement or due to iatrogenic injuries [118]. Such a procedure may increase the morbidity and fistula formation but it does not increase the morbidity rate. Such procedures are best performed in expert centers [119, 120]. In patients with ovarian cancer, morbidity caused by pancreatic fistula may cause a delay in starting adjuvant chemotherapy [121].

3.10.7 Hepatic Resection

Liver involvement can occur synchronously with peritoneal involvement. Intraparenchymal metastases must be distinguished from surface deposits that are infiltrative and require non-anatomical liver resections. Intraparenchymal metastases are surrounded by a rim of normal liver tissue on all sides. When the involvement of the liver and peritoneum is both limited, a synchronous resection of the PM and LM can be carried out. The two common conditions in which synchronous resection of peritoneal and liver metastases is performed are colorectal cancer and ovarian cancer.

In patients with ovarian cancer, synchronous resection of intraparenchymal liver metastases

has been performed with CRS, especially in patients with solitary liver metastases [122, 123]. In patients with both advanced and recurrent ovarian cancers, resection of one or more liver metastases has been performed with CRS with good long-term survival [124–132]. The goal of such resections should be to resect the liver lesions with a negative margin. Several retrospective studies have reported an acceptable morbidity and mortality for such combined resections. The common prognostic factors reported in these studies were optimal CRS <1 cm residual disease, negative resection margins, disease-free interval >12 months, fewer number of liver metastases, and fewer sites of disease. Major hepatic resections have also been performed with acceptable morbidity and a benefit in survival [133, 134].

Colorectal on the other hand represents a more aggressive disease, and the presence of simultaneous liver and peritoneal metastases from colorectal cancer has been considered a contraindication for aggressive treatment of either [135–138]. However several studies have shown that when synchronous resection of PM and LM with HIPEC is performed, a survival similar to patients undergoing CRS and HIPEC for PM alone can be achieved [138–141]. A PCI of <12 and up to 3 easily resectable metastases are the limiting criteria for such procedures. The patients should have a good performance status, a CC-0 resection of the peritoneal metastases should be possible, and there should be no invasion of the hepatic hilum, vena cava, or hepatic veins. In such procedures, the CRS is performed first. Once a complete removal of the peritoneal tumor deposits is obtained, the liver resection is performed.

Techniques for safe resection like the selective use of portal triad clamping, an emphasis on maintaining low intravascular volumes during parenchymal transection, and meticulous hemostasis and biliostasis should be employed [142].

3.10.8 Urological Procedures

Direct metastasis to the urogenital tract is rare and has only been described in case reports or small case series [143]. In contrast, primary tumor in-growth or locoregional or peritoneal metastases is more frequent [144]. Ureteric involvement in particular is higher in patients with recurrent disease and prior non-definitive surgeries due to implantation of tumor in the retroperitoneum which subsequently encases the ureter [145]. It has been reported in patients with less invasive disease like low-grade PMP as well. However, in these patients it is the prior surgery that creates a breach in the peritoneal lining and subsequent involvement of structures like the distal ureters, the dome of the bladder, and the vesicorectal space. At times, the involvement of these structures is detected on preoperative imaging, and such a procedure is planned preoperatively. In other cases, the tumor could be adherent to these structures, and it's difficult to distinguish malignant involvement from inflammatory adhesions [146]. A frozen section may not be of much help in such cases [146].

Some patients with limited disease may require a resection of kidneys, ureters, or bladder, like nephrectomy, partial cystectomy, and resection of a segment of the ureter, to attain a complete cytoreduction [144, 147]. A total cystectomy in this context is not recommended as it offers no oncological benefit. One small study reported increase morbidity with such procedures—the incidence of bowel fistulas and intra-abdominal abscesses was reported to be significantly higher though it was attributed to the extent of bowel resection rather than the urological procedure itself. The reported incidence of urinary fistulas ranges from 5 to 71%. In one study, a PCI > 30 and severe preoperative malnutrition were the factors associated with a high rate of fistula formation. Several other studies do not report an increased morbidity with such procedures [147–149].

3.10.9 Resection of Ovaries

A pelvic peritonectomy entails removal of the uterus and the ovaries. It is impossible to completely strip the peritoneum off the ovaries, and hence removal is essential to attain a complete

cytoreduction. Ovarian metastases are common in patients with colorectal PM. Synchronous ovarian metastases (OM) are reported in 1–9% of the women undergoing surgical resection of a primary CRC, and metachronous OM occur in 1–7% [150, 151]. Verwaal et al. recommended that a bilateral oophorectomy should be performed for all patients undergoing CRS and HIPEC [151]. Patients with OM and PM have a similar OS and DFS when treated with CRS and HIPEC [152]. Women undergoing this treatment may not have completed their families and may be desirous of a future pregnancy. Of interest is the fact that in colorectal cancer, stromal involvement as opposed to capsular involvement is seen in majority of the patients indicative to hematogenous spread [152]. Elias et al. evaluated the feasibility of ovarian preservation in 106 women aged less than 41 years undergoing CRS and HIPEC for PM [153]. Oophorectomy was done:

1. When the ovary was macroscopically involved with tumor
2. In case of clinical suspicion for tumor involvement based on intraoperative macroscopic inspection (presence of superficial tiny granulations or cysts)
3. Systematically (contralateral oophorectomy) in patients who had previous unilateral oophorectomy at the time of initial surgery due to macroscopic involvement of one ovary, while the other macroscopically normal-appearing ovary was left in place
4. When hysterectomy was needed due to tumor extent
5. In women who clearly did not want future pregnancy

Based on their findings, they recommend that a bilateral oophorectomy should be performed in all women who have suspicious involvement of both ovaries, when a hysterectomy is needed, and in women who do not wish to have any more children. In women who have metastases in one ovary, the risk of contralateral ovarian metastases is 46%, and a bilateral oophorectomy is recommended in these women as well. In women with grossly normal ovaries, the risk of occult metastases is 17%, and the risk of future metastases to the ovary is over 50%. They recommend conservation of ovaries in some of these patients though pregnancy following CRS and HIPEC in patients with CPM has not been reported in literature [146, 154].

The team from Basingstoke have devised a new strategy for young women with low-grade PMP with pelvic involvement who are desirous of preserving fertility. [158]. This involves a laparoscopic procedure aimed at staging of disease extent; in cases with relatively limited mucinous disease (pelvic mucin with limited or no extrapelvic disease), an appendicectomy is performed, and the abdominal and pelvic cavity is irrigated and copiously washed out with water, with stripping of disease off the peritoneal surface of the pelvis and the surface of the ovaries, till both the pelvis and the ovaries are macroscopically free of disease. In their experience, many of these women present with infertility. During a 12-year period, 884 women were referred to their center, of which 21 (2.5%) were under 45 years old, childless, potentially capable of having children, but highly likely to be rendered infertile due to CRS and HIPEC (unpublished data) [155].

Of the four women who were treated in this manner, a histological examination of the appendix demonstrated a low-grade appendiceal mucinous neoplasm (LAMN) in all patients; the pelvic disease consisted of acellular mucin in two patients and low-grade mucinous carcinoma peritonei in the remaining two. All four patients successfully conceived subsequently and gave birth to full-term healthy babies with only one requiring in vitro fertilization. One patient underwent a cesarean section, at which time no pelvic disease was found. One patient underwent a repeat laparoscopy to evaluate a trace amount of pelvic fluid demonstrated on follow-up imaging; during this procedure, no intra-abdominal or pelvic mucinous disease was identified. At the last follow-up (12–29 months postsurgery), all women were well with no radiological or (in one case) laparoscopic evidence of disease recurrence and normal tumor markers. These patients are under active surveillance, and CRS and HIPEC will be performed on disease progression [155].

3.10.10 Pelvic Exenteration

Provided the peritoneum has not been breached, even with heavy tumor burden in the pelvis, it is possible to preserve the lower rectum and the bladder trigone and thus the need for sacrificing either of these structures does not arise. In recurrence form gynecological malignancies, there may be vaginal vault deposits or deposits in the pouch of Douglas which infiltrate the bladder and/or the rectum and necessitate resection of either of these structures. A total pelvic exenteration is associated with a significant morbidity and negative impact on the quality of life, and some investigators do not recommend performing CRS and HIPEC when a pelvic exenteration is required. There are no studies evaluating the role of such a procedure probably because many consider it to be an exclusion criterion. There are reports in which cystectomy with urinary diversion has been performed as a part of CRS, and HIPEC has been performed as well. These procedures have a significant morbidity. In some patients who have had one or more attempts at debulking, the pelvic peritoneum may be breached leading to implantation of tumor in the mesorectum/perirectal fat and on the wall of the mid and lower rectum. It may be impossible to perform a low rectal anastomosis in these patients, and they require an abdominoperineal resection or Hartmann's procedure with an end ileostomy/colostomy.

3.11 Morbidity of Multivisceral Resection

The impact of the extent of surgery on morbidity has been studied by several investigators. The number of organs resected, the number of peritonectomies, and the number of bowel anastomosis are some of the parameters used to evaluate the extent of the surgery. An increasing number of peritonectomies and two or more bowel anastomosis both increased the morbidity, whereas the number of organs resected did not. Several studies have shown that two or more bowel anastomoses have a significant impact on morbidity of patients undergoing CRS and HIPEC [156–158]. An increasing number of peritonectomies also increase the morbidity [159, 160]. Only the number of anastomoses seems to have an impact on morbidity, not the number of organs resected [160].

3.12 Patient Selection for CRS and HIPEC/Prognostic Indicators

Over the years, there has been a reduction in the morbidity of CRS and HIPEC, and this has been attributed largely to better patient selection. There is a risk of inflicting excessive morbidity without a survival benefit if appropriate patients are not selected for the procedure [161]. Rapid recurrence can occur in the peritoneum itself or at other sites when such procedures are undertaken in patients with extensive disease thus, putting them at an increased risk of morbidity without a benefit in survival. Quantitative prognostic indicators have been defined that can predict the likely benefit of CRS and HIPEC in a given patients, and these should be employed for patient selection [162]. These indicators are histopathology, imaging findings, peritoneal cancer index (PCI), and the completeness of cytoreduction score (CCR) [162, 163]. All patients need evaluation by a multidisciplinary team comprising of surgeon, medical oncologist, anesthesiologist, intensivist, radiologist, and pathologist.

3.12.1 Histopathology

There are two important aspects—the histological subtype and the tumor grade.

3.12.1.1 Tumor Grade

In PMP arising from appendiceal tumors, low-grade tumors have a better long-term outcome as compared to high-grade tumors with or without signet ring cells [162, 163]. The same is not seen in high-grade malignancies like colorectal cancer and gastric cancer where the grade does not have an impact on survival [164]. But even in these tumors, the presence of signet ring cells is a poor prognostic factor.

3.12.1.2 Histological Subtype

In peritoneal mesotheliomas, histopathology has a strong impact on survival results, and the epithelioid subtype do better than the biphasic or sarcomatoid subtype [165]. The outcomes seem to be better for mucinous adenocarcinoma than for the other types. In a retrospective analysis of the Netherlands Cancer Registry, PM of mucinous adenocarcinoma had a median survival of 10.9 months vs. 7.4 months for adenocarcinoma vs. 6.6 months for signet ring histology ($p < 0.0001$) [166]. Multiple retrospective analyses have shown that the overall survival in signet ring histology PM patients undergoing CS/HIPEC is dramatically worse than other subtypes, with median survival ranging 12–14 months and 5-year survival rates of 0–7% [135, 167]. In fact, in both the PSDSS and the colorectal peritoneal metastases prognostic surgical score (COMPASS), signet ring cell histology has been given special consideration signifying poorer outcomes [168].

3.12.2 Imaging

Imaging studies for the cornerstone of evaluating patients for CRS and HIPEC.

There are three main goals of performing an imaging study:

- To rule out distant metastases
- To look of signs of inoperability and exclude such patients from surgery
- To quantify the extent of disease in terms of a "predicted PCI"

The commonly used modalities are a contrast-enhanced CT scan of the thorax, abdomen, and pelvis, a contrast-enhanced MRI with diffusion-weighted imaging, and a PET-CT scan. The common limitations of all imaging modalities are:

- Limited sensitivity in detecting small tumor nodules
- Inaccuracy in detecting disease at certain anatomical sites, like the small bowel and its mesentery
- Lack of radiological expertise for interpreting the findings [169]

A contrast-enhanced CT scan of the thorax abdomen and pelvis is the standard investigation used for evaluating patients prior to surgery, both for evaluating the disease extent and excluding metastatic spread [170, 171]. The sensitivity of helical CT for peritoneal tumors < 1 cm was found to be only 25–50% compared with 85–95% for larger tumor deposits [172]. The preoperative CT scan can underestimate the extent of disease in up to 33% of the patients [173]. In recent studies MRI has been reported to be more accurate for detecting <1 cm nodules by some authors, while others have found no difference [174, 175]. MRI also has the advantage of providing a combination of functional and morphological imaging and provides a better contrast resolution. MRI requires up to 6 h of fasting and a stringent protocol. The results are also dependent on the expertise of the interpreter [175]. PET or PET-CT scans may add some more information in this direction by detecting extra-abdominal (mediastinal or supraclavicular) lymphadenopathy, predicting the pathology grade and informing on the probability of complete CRS in patients with pseudomyxoma peritonei [176].

However, a PET-CT does not add to the information provided by a good-quality CT regarding the disease extent [177]. For PM from mucinous tumors, there are two CT scan findings predictive of an incomplete cytoreduction-segmental obstruction of the small bowel and presence of tumor nodules greater than 5 cm in diameter on small bowel surfaces or directly adjacent to small bowel mesentery. The greatest limitation of a CT scan is in detecting tumor nodules smaller than 5 mm in size, especially on the bowel surfaces [178]. Carcinomatosis with implants less than 5 mm would not be imaged or would be underestimated in their distribution, especially in patients with postoperative changes [179]. All 533 eligible patients underwent a CT. A total of 449 patients also underwent FDG-PET/CT, and 510

Table 3.3 Radiological features associated with an increased likelihood of incomplete cytoreduction (Adapted from reference [83] with permission)

Small bowel and its mesentery
Bowel obstruction of partial obstruction at more than one site
Mesentery drawn together by tumor (clumped bowel)
Infiltrative tumor deposits between the folds of the mesentery
Tumor >4 cm in the jejunal region
CT PCI >20 (excluding PMP, cystic mesothelioma, and low malignant potential ovarian tumors)
Retroperitoneum
Mesenteric or para-aortic lymphadenopathy
Hydroureter
Psoas muscle invasion
Pelvis
Pelvic side wall involvement
Seminal vesicle involvement
Hepatoduodenal and hepatogastric ligaments
Tumor involving the porta hepatis and/or bile duct obstruction
Tumor >5 cm in the gastrohepatic ligament or subpyloric space
Gastric outlet obstruction
Ascites
Hemorrhagic ascites
Serous ascites in a patients with a gastrointestinal primary tumor

patients underwent an abdominal-pelvic MRI. Despite our imaging protocol, imaging reports failed to alert the surgeon to the presence of unresectable peritoneal lesions in 16% of patients.

Sugarbaker et al. have described 15 radiological features on CT scan that may be associated with an increasing incidence of incomplete CRS (Table 3.3) [83].

Several imaging-based scores have been developed to predict complete resectability for different disease sites.

3.12.3 Peritoneal Cancer Index (PCI)

The peritoneal cancer index (PCI) provides a quantitative assessment of the extent of peritoneal disease in the abdomen and pelvis [180]. It integrates the size of peritoneal implants and distribution of nodules on the peritoneal surface (Fig. 3.18). The abdomen and pelvis are divided into 13 regions, and for each of these 13 regions, a lesion size (LS) score is determined. The LS score grades lesions as LS-0 score when there are no malignant deposits, LS-1 for tumor nodules <0.5 cm, LS-2 for tumor nodules between 0.5 and 5.0 cm, and an LS-3 score that signifies

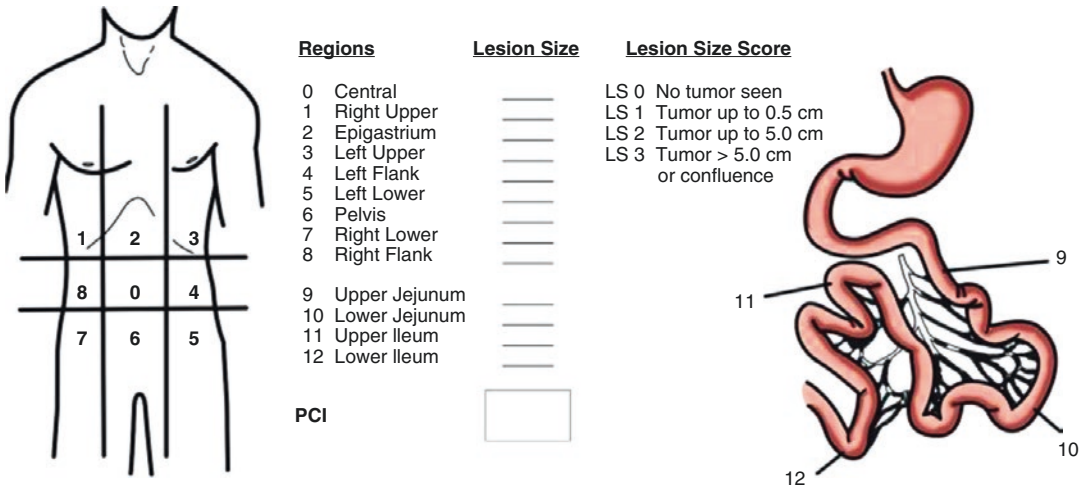

Fig. 3.18 Sugarbaker's peritoneal cancer index (PCI)

tumor nodules >5.0 cm in any dimension or confluent nodules or layering of tumor. It is the size of the largest nodule and not the number of nodules that is considered. The scores of all the regions are summed up in the PCI. Thus, a minimum score of 1 and a maximum of 39 (3 × 13) is possible [180].

The PCI is an independent predictor of both morbidity and overall survival—a higher PCI has a negative impact on both. This has been demonstrated in patients with colorectal, ovarian, and gastric peritoneal metastases [180–182]. In patients with colorectal PM when the predicted PCI is >17–20, CRS and HIPEC should not be offered; similarly for gastric cancer, this cutoff is a predicted PCI of 12 [180, 181]. For recurrent ovarian cancer, a PCI > 8 was associated with an inferior survival though this is not used as an absolute contraindication. Even in low-grade disease like PMP and mesothelioma where CRS and HIPEC are performed irrespective of the extent of disease so long as a complete cytoreduction can be obtained, a higher PCI is a predictor of a poorer long-term outcome. Though the prognostic impact is less and can be offset by complete CRS, PCI is an independent predictor of overall survival even in these patients [182]. There are certain situations in which the PCI is low, but there is presence of invasive tumor deposits at crucial anatomic sites like the common bile duct, the base of the bladder, or the pelvic side wall. The presence of residual unresectable disease at crucial anatomic sites overrides the favorable effect on the prognosis of low PCI score [91].

The BIG-RENAPE and RENAPE working groups have developed the PeRitOneal MalIgnancy Stage Evaluation (PROMISE) internet application (www.e-promise.org) to facilitate tabulation and automatically calculate the peritoneal cancer index (PCI). This application offers computer assistance to produce simple, quick but precise, and standardized pre-, intra-, and postoperative reports of the extent of peritoneal metastases. Not only the peritoneal metastases but other aspects like peritoneal thickening, involvement of adipose tissue, and fluid density are taken into consideration in this application. It can be used by less experienced centers as well and can help in research and multicentric studies related to peritoneal metastases [183]. Radiologists have dedicated screens for each imaging modality. Each screen is designed with the same presentation as the surgical fields but also with specific radiological fields taking into account the different imaging modality parameters (apparent diffusion coefficient (ADC) for diffusion MRI, standard uptake value (SUV) for 18 FDG PET-CT).

Because the PROMISE application has also been designed to allow translational approaches, very precise PCI correlations between radiological, surgical, and pathological findings can be performed. Taking into account the spatial and contrast resolutions of each radiological modality, and the etiology of the peritoneal disease, surgical correlations including the quadrant but also the involved structure and the type of peritoneal lesion (peritoneal implants, peritoneal thickening, fat infiltration) can be performed to assess the accuracy of each imaging modality and help to determine the best imaging modality to accurately calculate the radiological PCI and improve detection of nonresectable lesions. Histopathological findings such as post-therapeutic fibrotic tissue and residual cellularity can be correlated with surgical findings as well as functional imaging to better assess response to treatment [183].

3.12.4 Completeness of Cytoreduction Score (CC Score)

The completeness of cytoreduction score is used for classifying the completeness of cytoreduction [184]. A CC-0 score indicates that no visible peritoneal seeding exists following the cytoreduction; a CC-1 score indicates that tumor nodules persisting after cytoreduction are <2.5 mm. Tumor nodules that are smaller than 2.5 mm can be dealt with intraperitoneal chemotherapy, and hence CC-1 is also classified as a complete cytoreduction. A CC-2 score refers to residual tumor measuring 2.5 mm–2.5 cm; and a CC-3 score refers to residual tumor nodules >2.5 cm or a

confluence of unresectable tumor nodules at any site within the abdomen or pelvis. CC-2 and CC-3 cytoreductions are considered incomplete. Stricter criteria for complete cytoreduction are required for high-grade non-mucinous neoplasms; a complete cytoreduction is restricted to resection to absolutely no visible evidence of disease. The CC score is a major prognostic indicator for PM from colorectal cancer, ovarian cancer, gastric cancer, pseudomyxoma peritonei, and peritoneal mesotheliomas as shown by several large multi-institutional studies [181, 185, 186].

The drawback of this score is that it is available only after completion of the surgery. A surgeon must be able to predict the possibility of a complete cytoreduction with reasonable accuracy based on the preoperative evaluation [180]. This is important in both counseling patients about the procedure and excluding patients who are unlikely to have a CC-0/CC-1 resection. There is no benefit of CC-2/CC-3 resections in most patients, and such procedures should be avoided. There are selected patients in whom a palliative debulking can be done to provide symptomatic relief and/or prolong survival; the goal needs to be defined before undertaking the procedure [187, 188].

3.13 Other Prognostic Factors

3.13.1 Response to NACT: Clinical and Pathological Response

The improved survival in patients with PM can be attributed not just to CRS and HIPEC but also to the availability and use of more effective systemic therapies. Neoadjuvant systemic chemotherapy has been administered to patients with PM for the following possible benefits:

- To identify nonresponders who may not benefit from CRS as well
- To control the systemic disease
- To downstage the disease and increase the probability of a complete CRS

Passot et al. evaluated the prognostic impact of response to chemotherapy in 115 patients with colorectal PM [189]. The pathological response evaluation was based on the criteria used to evaluate the response in patients with colorectal LM receiving NACT and was based on the determination of the percentage of viable tumor cells with respect to the area of each nodule, independent of the presence of chemotherapy-related tissue injury, fibrosis, or necrosis. Three groups were created for statistical analysis: no residual cancer cells in all specimens (complete response), 1–49% residual cancer cells (major response), and 50% residual cancer cells (minor or no response; Fig. 3.1) [190, 191]. In patients with multiple specimens, a mean of values was used to define the pathological response. The complete response rate was 9.7%, close to the 10% reported for CLM. However, the major response rate was lower (20% vs. 36%) than for CLM, illustrating the lower response of peritoneal lesions to systemic chemotherapy compared with extraperitoneal metastases from colorectal cancers [192, 193].

The prognostic impact of pathological complete or near complete response was also seen in a Japanese study comprising of 142 patients, though it was not an independent predictor of survival. The classification used by the authors classified the response into four categories:

- Ef-0—No pathological response or response less than one-third of the tumor tissue.
- Ef-1—Cancer is detected in 1/3 to 2/3 of the tumor tissue.
- Ef-2—Absence of tumor cells in more than two-thirds of the tumor tissue.
- Ef-3—Complete disappearance of the cancer cells.

Eleven (7.9%) patients had a complete response (Ef-3), 13 (8.8%) patients had Ef-2 response, and 36 (25.7%) showed Ef-1 response. The other 82 (57.5%) had no response to preoperative systemic chemotherapy. These authors used this classification to evaluate the response to chemotherapy in patients with gastric cancer as well. In a study of 96 patients receiving multimodality neoadjuvant treatment comprising of systemic and intraperitoneal chemotherapy, com-

Table 3.4 The peritoneal regression grading score (From ref [196] with permission)

	Peritoneal regression grading score (PRGS)	
Grade	Tumor cells	Regression features
PRGS-1	No tumor cells	Abundant fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS-2	Regressive changes predominant over tumor cells	Fibrosis and/or acellular mucin pools and/or infarct-like necrosis predominant over tumor cells
PRGS-3	Predominance of tumor cells	Tumor cells predominant over fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS-4	Solid growth of tumor cells (visible at lowest magnification)	No regressive changes

plete pathological response was seen in 30 (36.8%) patients, and pathological response to chemotherapy was an independent predictor of survival [194].

In a series of 34 patients with PM arising from appendiceal adenocarcinoma who received neoadjuvant systemic chemotherapy, 10 (29%) had a complete or near complete histological response, and patients showing complete response had a better overall survival [195]. Given the prognostic value of the pathological response to chemotherapy, Bibeau et al. proposed a generic score for the assessment of histological tumor response to chemotherapy in PM arising from various primary sites [196]. This four-tiered classification is described in Table 3.4.

They have also made recommendations for performing peritoneal biopsies.

According to their recommendations, at least four biopsies should be taken at suspect localizations (typically in the right upper quadrant, right lower quadrant, left upper quadrant, and left under quadrant), typically from tumor nodules. Peritoneal biopsies should have a diameter of at least 3 mm, ideally 5 mm. The use of a punch biopsy device is recommended to generate standardized samples. Additionally, a local peritonectomy of several square centimeters should be taken.

When CRS is performed, representative samples should be taken from surgical specimen.

In the cases a negative peritoneal histology is suspected, a peritoneal cytology is recommended.

3.13.2 Staging Laparoscopy/ Laparoscopic Score

Laparoscopy allows direct visualization of the peritoneal surfaces, small bowel, and its mesentery, and small tumor nodules missed on imaging can be detected on laparoscopy. The disadvantages are its inability to evaluate retroperitoneal structures like the ureters and pancreas, the omental bursa near the celiac axis, hepatic and splenic parenchymal metastases, and the depth of involvement of the hepatic pedicle and the diaphragm [197]. Fagotti et al. evaluated the role of laparoscopy in addition of a clinical and radiological evaluation in 65 patients undergoing laparotomy for advanced ovarian cancer. Optimal debulking was achieved in 34 of the 39 patients (87%) whose disease was judged completely resectable on the basis of laparoscopic findings. The overall accuracy rate of laparoscopy in predicting optimal cytoreduction was 90%. The same investigators came up with a predictive index value (PIV) based on objective parameters determined at pre-cytoreduction laparoscopy, the "Fagotti score" [198]. The score is a sum of the individual score of seven sites of disease. Patients with a score of ≥8 had a 100% chance of having a suboptimal/incomplete CRS. Each laparoscopic parameter used in the model was chosen not on the basis of a direct correlation with the chances of optimal cytoreduction, but rather to describe the intra-abdominal distribution of disease [198]. The score has been prospectively validated—at a PIV of ≥8, the probability of optimal cytoreduction

(residual tumor ≤1 cm) at laparotomy is 0 [199, 200]. While its sensitivity in detecting PC is approximately 100%, its accuracy in estimating PC resectability is lower. In a study of 533 patients by Mohkam et al., approximately half of the patients in both the resectable and unresectable groups had undergone staging laparoscopy, thus indicating that it did not help in patient selection [169]. Laparoscopy has its limitations and may not detect diffuse bowel involvement, mesentery retraction, and the extent of the disease in some anatomical areas, such as the retroperitoneal structures, the cardiophrenic angle, or the bladder neck [169]. Adhesions further limit the laparoscopic assessment. Some of the limitations can be overcome by hand-assisted laparoscopy and the use of laparoscopic ultrasound if it's available [197, 201].

3.13.3 Prior Non-definitive Surgical Procedures

3.13.3.1 Prior Surgical Score

The prior surgical score quantifies the extent of non-definitive surgery that was performed prior to CRS and HIPEC. Prior surgical score (PSS) ranged from 0 to 3 and looks at abdominal regions 0–8. PSS-0 indicates no prior surgery or only a biopsy, PSS-1 for surgery in one abdominal region only, PSS-2 for surgery in two to five regions, and PSS-3 for surgery in more than five regions [202]. The biopsy could be an open or laparoscopic biopsy, a CT-guided biopsy, or a paracentesis with cytology. The number of abdominopelvic regions is additive for all prior surgical procedures; hence, the PSS is a composite of all prior surgeries [91].

Sugarbaker has demonstrated that in most areas the peritoneum serves the first line of defense against peritoneal metastases and cancer does not spread to the connective tissue below the peritoneum at least in early stages of the disease [80]. The exceptions are the milky spots in the omenta, at the junction of the small bowel and its mesentery, the lacuna in the diaphragm, and naturally occurring raw areas on the surface of the ovary due to corpus hemorrhagic. The most common cause of breach in the peritoneum is prior debulking surgery that leads to the implantation of intraperitoneal tumor cells at the surgical resection sites, deep to the peritoneum. Tumor implanted in the scar tissue deep to the peritoneum may be impossible or difficult to remove by peritonectomy or eradicate by intraperitoneal chemotherapy [80]. Moreover there is formation of intra-abdominal adhesions that makes subsequent cytoreduction technically challenging. In a retrospective study of 83 patients, Chua et al. demonstrated that upfront treatment conferred a superior 5-year recurrence-free survival rate (77% *vs.* 37%; $p = 0.011$) and 10-year overall survival benefit (67% *vs.* 35%; $p = 0.054$) [11]. A prior surgical score of >2 has a negative impact on both DFS and OS [186].

3.14 Contraindications to CRS and HIPEC

CRS and HIPEC is a major surgery for which the patient needs to have a good performance status and all other systemic illness should be under control. Uncontrolled chronic diseases are a contraindication to the procedure [203]. Age is not an absolute contraindication provided the patient is medically fit to undergo the procedure—the chemotherapy doses may need to be altered in some cases [203]. Apart from these, patient selection also depends on the disease extent (PCI) and the primary tumor site, e.g., a predicted PCI of >17–20 for colorectal cancer and >12 for gastric cancer would preclude a survival benefit, and CRS and HIPEC are not recommended for these patients [189, 190]. For patients with colorectal cancer and ovarian cancer, progression on neoadjuvant chemotherapy is not always a contraindication to CRS and HIPEC [204]. If complete cytoreduction can be obtained and disease extent is limited, the procedure may be of benefit. Involvement of the kidneys, ureter, and bladder is also not an absolutely contraindication provided complete tumor clearance can be attained and does not enhance the morbidity from the

procedure. However, a total cystectomy is not performed in the setting of CRS and HIPEC as it is not of oncological benefit. Multiple extra-abdominal metastasis or massive suprarenal retroperitoneal lymph node involvement are absolute contraindications [205, 206]. Liver metastases may be a contraindication except in patients with colorectal and ovarian PM: for colorectal PM, up to three completely resectable metastases, and for ovarian cancer, the probability of complete cytoreduction and resection of liver metastases with a negative margin are the criteria used for patient selection [138, 139]. For conditions where there is no cutoff for PCI, the contraindications are:

- Extensive bowel resection that is likely to compromise the future quality of life, e.g., two or more sites of segmental small bowel obstruction, patients requiring a total gastrectomy with a total colectomy
- Involvement of the pancreas head, bladder trigone, and porta hepatis
- Massive or diffuse involvement of the pleural space [207]

3.15 Reiterative Procedures

Recurrence following initial CRS with HIPEC is not uncommon [208–210]. Recurrence can be localized or diffused and early (within 1 year) or late. A diffuse recurrence represents an aggressive disease biology or insensitivity of the tumor to intraperitoneal chemotherapy especially if the recurrence-free interval is short. This type of recurrence is associated with a poorer survival. Localized recurrence is probably due to tumor cell entrapment at the suture line or in adhesions and has a better prognosis [209]. There is no standard treatment for patients who recur following CRS and HIPEC [211]. In the recent years, repeat CRS and HIPEC have been performed in selected patients with an acceptable morbidity and mortality and favorable survival outcomes.

Recurrence can be diffused or localized. In some cases, the cause of recurrence is technical failure as in the subhepatic region which is a very difficult area to clear [212]. The rationale of a repeat CRS and HIPEC is the probability infrequent metastasis outside the peritoneal cavity, compressive rather than invasive behavior of the recurrent disease, relative sparing of small bowel, and a good response to intraperitoneal chemotherapy as shown by Sugarbaker et al. in one of the first published series of second-look surgery [213].

Considering each disease site specifically, reiterative procedures have shown benefit in patients with colorectal cancer, appendiceal pseudomyxoma peritonei, ovarian cancer, and peritoneal mesothelioma. The most important prognostic factors across all histologies are time to recurrence >1 year, limited PCI, and complete cytoreduction [214].

Patients must be carefully selected, based on the following criteria: origin of carcinomatosis, magnitude of first procedure, length of RFS, physiological age, comorbidity, and possibility of complete cytoreduction. Most publications of iterative procedures are monocentric studies from high-volume centers, and the grade 3–5 morbidity rates range from 33% to 42.7%, although it did not seem to increase the in-hospital mortality rates [215–217].

Before performing a repeat procedure, the prior surgical details should be studied in detail. The surgeon should be aware of the peritonectomies and visceral resections that were performed. Any postoperative anastomotic leaks, fistulas, and wound dehiscence should be noted. These areas are more difficult to deal with especially after CRS and HIPEC. The retroperitoneal areas should be examined on imaging studies to rule out tumor involvement of these areas. If recurrence develops in areas that were not operated upon previously, it is comparatively easy to deal with those areas. When recurrence develops in operated areas, it is difficult to perform a complete adhesiolysis and evaluate the true extent of disease to begin with. The adhesions that form following a peritonectomy tend to be more dense. The bowel adheres to the exposed sheath muscles, and serosal tears are common while lysing these adhesions (Fig. 3.19). Bowel surface disease tends to be infiltrative requiring

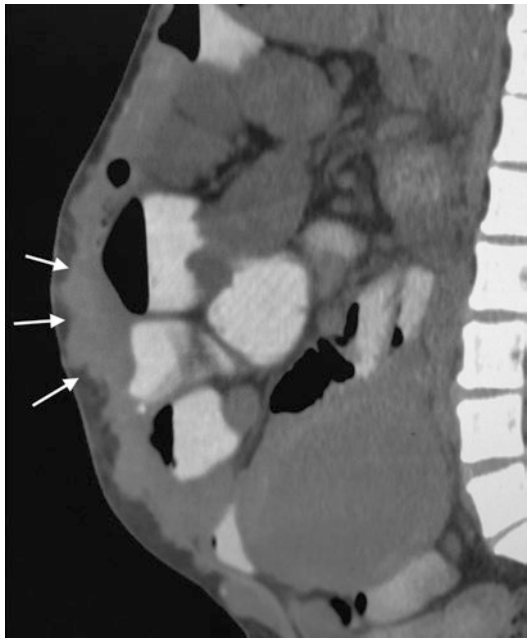

Fig. 3.19 CT image showing diffuse recurrence in a patient with pseudomyxoma peritonei post-cytoreductive surgery and HIPEC. Tumor is infiltrating the anterior abdominal wall as well as the bowel wall

full-thickness resection of the bowel wall. Even low-grade tumor deposits could be surrounded by adhesions making it difficult to approach and completely resect them. The incision should extend from the xiphoid to the pubic symphysis, and all areas should be explored for presence of disease.

Though retroperitoneal tumor spread can be cleared completely, some microscopic disease is always left behind in these areas, resulting in a high probability of future recurrence in the same areas. This should be kept in mind while performing extensive resections.

3.16 Laparoscopic CRS and HIPEC

With each passing day there have been further advancements not only in the surgical skills but also the expectations of the patient. Laparoscopy can be used for diagnosis, triage, and debulking of peritoneal disease. For discussion, role of laparoscopy can be divided into three parts, viz.:

1. Staging laparoscopy.
2. Laparoscopic risk-reduction surgery.
3. Laparoscopic debulking/CRS.
   (a) Staging laparoscopy is used to assess the PCI status and operability. Further definitive treatment is planned based on this triage. Staging laparoscopy has been discussed in detail in further chapters
   (b) Laparoscopic risk-reducing surgery—Low-grade appendiceal mucinous neoplasm (LAMN) is recognized as a precursor to disseminated pseudomyxoma peritonei (PMP). LAMN I consists of disease confined to appendiceal lumen, while LAMN II is characterized by disease or even mucin involving the wall of appendix or periappendicial tissue. LAMN I needs surveillance only. In patients with LAMN II, there is a role for risk-reducing debulking surgery [218]. There is upcoming evidence to suggest that minimal access laparoscopic cytoreductive surgery with HIPEC is a safe alternative to open procedure however, with a smaller abdominal wound and comparable morbidity and inpatient stay. In a case series by Fish et al., ten patients with LAMN II underwent laparoscopic CRS, while seven open procedure. The umbilicus was excised, and a 10 mm balloon port was placed, and five other ports were placed. A complete adhesiolysis, bilateral oophorectomy, excision of the ligamentum teres, division of the hepatophrenic ligament, greater and lesser omentectomy, and cholecystectomy were done. A retrieval bag was used to get the specimen out of the umbilical defect. This was followed up with HIPEC. There were no conversions to open surgery; median procedure length, median length of stay, and complication rates were similar between groups; and there were no 30-day deaths. After 3 and 11 months median follow-up, respectively, no patients have evidence of disease progression. However, a longer follow-up is required to validate this as treatment of choice.

(c) For selected patients with limited disease extent (PCI < 10) and low PMP, laparoscopic CRS and HIPEC have been used with the goal of reducing the morbidity and hospital stay [219–221]. The reported conversion rates were low and improved with experience. Patient selection is important. In patients with recurrent ovarian cancer with limited peritoneal spread, laparoscopic CRS has been used with similar outcomes [222–225]. The drawbacks of this approach are difficulty in properly assessing certain areas like the small bowel mesentery, technical difficulty in obese patients and those with extensive prior surgery, the potential for dissemination of malignant cells (debatable), and prolonged operative times [221]. With growing experience, the utility of such procedures could increase specifically in patients with more extensive disease.

The minimally invasive approach has an important limitation; the evaluation of the disease extent is not as accurate as a conventional laparotomy. A preoperative CT scan combined with a staging laparoscopy should be used to determine the extent of disease, though the extent of disease is usually underestimated. Moreover, the laparoscopic assessment is often limited by the presence of adhesions, and this should be kept in mind when taking up patients for such procedures. Esquivel et al. used five to six ports for the procedure which was performed in conjunction with an experienced laparoscopic surgeon. Adhesiolysis was performed. A detailed exploration of both the parietal and visceral peritoneum was carried out in order to determine the laparoscopic PCI. This was facilitated by instrument retraction and positioning the operating room table for gravity-assisted retraction in order to maximize exposure of dependent areas. Once the diagnostic laparoscopy was completed, a decision to continue with the cytoreduction via the laparoscopic route was made based on two factors: the PCI had to be ten or less, and the amount of disease present had to be able to be removed laparoscopically. The port sites were used for inserting tubes for performing HIPEC [220].

Conclusions

CRS is a complex procedure associated with a prolonged learning curve. A surgeon performing CRS must be comfortable in operating on all areas of the abdominal cavity and should be able to predict the possibility of a complete cytoreduction before undertaking the procedure. Patient selection is as important as the technical skill required for performing this procedure. The quantitative prognostic indicators defined for each disease should be used for this. The best results are obtained in specialized centers where such patients are managed by a multidisciplinary team of experts. Procedures performed with the intent of cure should have a controlled morbidity and mortality and significant impact on the long-term quality of life. It is equally important to employ preventive strategies while performing curative to avoid tumor rupture and peritoneal dissemination. In situation when unexpected peritoneal metastases are discovered intraoperatively, minimal dissection should be performed, and the patient should be evaluated for a curative procedure subsequently or referred to a center offering such treatment.

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4 HIPEC Methodology, Comparison of Techniques, and Drug Regimens: Is There a Need for Standardization?

K. Van der Speeten and L. Lemoine

Abbreviations

5-FU	5-Fluorouracil
AUC	Area under the curve
BIC	Bidirectional intraoperative chemotherapy
BSA	Body surface area
CRS	Cytoreductive surgery
EPIC	Early postoperative intraperitoneal chemotherapy
HIPEC	Hyperthermic intraperitoneal peroperative chemotherapy
IP	Intraperitoneal
IV	Intravenous
MTC	Mass transfer coefficient
NIPS	Neoadjuvant intraperitoneal and systemic chemotherapy
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
PM	Peritoneal metastases
SPIC	Sequenced postoperative intraperitoneal chemotherapy

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4.1 Introduction

The peritoneum is a common site of metastatic disease, specifically from intra-abdominal malignancies of gastrointestinal and gynecological origin. The commonest route of peritoneal dissemination is contiguous spread through exfoliation of tumor cells, and lymphatic and hematogenous spread is less common.

4.2 Pathophysiology of Peritoneal Carcinomatosis

Tumor cells may exfoliate from primary tumors that infiltrate full thickness of the bowel wall and have reached the serosal surface. Several authors established transserosal growth of a colon tumor as a consistent predictor of subsequent intraperitoneal recurrence [1, 2]. It is also an important independent pathological prognostic parameter [3–6]. In addition to this, handling of the tumor during surgery and surgical dissection itself leads to a leakage to tumor cells from the blood vessels and lymphatic channels that are transected during the process [7, 8]. Once released into the peritoneal cavity, loose cancer cells become subject to the physiological peritoneal lymph flow. These cells follow the flow of peritoneal fluid and accumulate in the dependent areas of the peritoneal cavity—the pelvis and various recesses. The negative intrathoracic pressure generated during res-

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piration directs the fluid to the subphrenic regions along the paracolic gutters. The spread to the left subphrenic region is limited by the splenocolic ligament. In low-grade malignancies, there is sparing of the small bowel due to peristalsis [9]. Under experimental conditions, direct passage from the right to left subphrenic space is prevented by the falciform ligament. The flow is predominantly oriented in a clockwise direction [10, 11]. Intraperitoneal fluid dynamics are influencing the distribution of peritoneal cancer nodules in PC patients [12].

Viability studies have suggested that, in contrast to circulating tumor cells in the blood, bone marrow, or liver, the metastatic efficiency of loose intraperitoneal cells is outspoken [13–16]. Also, the acute inflammatory response and healing processes observed at the site of surgical injury are important not only in relation to the formation of postoperative adhesions but also in the enhancement of tumor growth [17–19]. The molecular mechanisms underlying this pathological sequence of peritoneal transport of free tumor cells, mesothelial adhesion, mesothelial invasion, stromal invasion, and eventually proliferation are well documented [20, 21]. Eventually, this will result in the development of clinical PC.

4.3 Revised Hypothesis Regarding Peritoneal Carcinomatosis

Peritoneal metastases (PM) which were not very long ago treated only with systemic chemotherapy and/or supportive care are now approached more aggressively in selected patients, largely due to the efforts of a group of oncologists who have demonstrated that a prolonged survival is possible in these patients. One of the main reasons for a change in the approach was the understanding that PM constitute locoregional spread in some patients, and aggressive locoregional therapies can improve the survival in these patients. The use of heated intraperitoneal triethylenethiophophoramide (thiotepa) was first reported by John Spratt in a patient with pseudomyxoma peritonei [22]. Koga et al. reported the use of normothermic intraperitoneal chemotherapy in 23 gastric cancer patients with PM, and Speyer first reported the use of normothermic intraperitoneal 5-fluorouracil (5-FU) and methotrexate in 16 patients with PM [23, 24]. Intraperitoneal chemotherapy is used in combination with cytoreductive surgery (CRS) that is performed with the goal of removing all visible macroscopic disease with various peritonectomy procedures and resection of contiguous viscera. Once all the visible disease is removed, intraperitoneal chemotherapy deals with the residual microscopic disease [25]. The perioperative intraperitoneal chemotherapy includes hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC). One of the commonly used regimens that combined the intravenous and intraperitoneal routes was developed by Elias et al. in 2002 [26]. HIPEC is performed with oxaliplatin administered intraperitoneally and an intravenous infusion of 5-FU and leucovorin performed just prior to it. Most recent protocols advocate this bidirectional (simultaneous intraperitoneal and intravenous chemotherapy) intraoperative chemohyperthermia (BIC). The timing of the intravenous chemotherapy in relation to the surgery is crucial. In Elias protocol, intravenous 5-FU is used to potentiate the action of oxaliplatin which also undergoes augmentation in cytotoxicity with the use of heat. This strategy could in part be responsible for the favorable outcomes of IPC reported in the recent years.

4.4 Clinical Results in Treating Peritoneal Carcinomatosis

This radical treatment has demonstrated a survival benefit in one randomized controlled trial and other retrospective and phase II studies [26–39]. Verwall et al. reported a 5-year survival of 45% in 103 patients of colorectal PM treated with CRS and HIPEC (using mitomycin C) in a randomized controlled trial that compared this treatment to systemic chemotherapy alone [28]. Similarly, Glehen et al. reported a

5-year overall survival of 37% in a multi-institutional study comprising of 1290 patients of PM from various primary sites treated with CRS and HIPEC [39].

While these studies point to potential benefit of this strategy over chemotherapy alone, further evidence is needed, and the role of CRS and HIPEC needs to be defined individually for which data from phase II and III trials is awaited. At the same time, an optimization of IPC protocols and regimens is needed. There is a limited understanding of the pharmacological aspects of IPC, and a better knowledge of pharmacology could translate into increased safety of the procedure and improved clinical outcomes from more efficacious treatment regimens.

4.5 Rationale for Intraperitoneal Chemotherapy

The two technical terms that must be understood are pharmacokinetics and pharmacodynamics. Pharmacokinetics is what the body does to the chemotherapeutic agent, and pharmacodynamics is what the drug does to the body. The administration of IPC is not only technically more difficult; it has also been associated with an increased morbidity, and hence the pharmacokinetic advantage of employing this route needs to be clearly demonstrated.

4.5.1 The Peritoneal-Plasma Barrier

The ultrastructure of the peritoneum was described by Baron in 1941 [40]. The peritoneum consists of a single layer of mesothelial cells resting on a basement membrane under which is a 90 μm thick layer of connective tissue. The connective tissue comprises of a matrix of collagen, hyaluron, proteoglycans, and interstitial cells that include pericytes, parenchymal cells, and blood vessels. This whole complex is referred to as the peritoneal membrane. The peritoneum is now considered an organ; it is a large and complex organ that covers the abdominal organs and abdominal wall and encloses within its reflections and folds a large space—the peritoneal cavity. The peritoneal membrane itself acts as a barrier between the peritoneal cavity and the systemic circulation, and this is the rationale employed for administering intraperitoneal chemotherapy.

The peritoneum serves several important functions. It acts as a lubricant, reducing the friction between the intra-abdominal organs and the abdominal wall, it plays a role in host defense through the lymphoid aggregates (milky spots) in various regions of the visceral and parietal peritoneum, and it acts as a barrier against peritoneal cancer spread [41, 42]. The role of the peritoneum in preventing PM was described by Paul Sugarbaker [43]. The peritoneum is considered to be the first line of defense against PM, and a disruption of the peritoneal lining facilitates the adhesion and invasion of tumor resulting in the development of PM [43].

It may be presumed that if the peritoneal lining is removed, transport of agents from the peritoneal cavity to the systemic circulation could be affected, especially that of chemotherapeutic agents—this is important since IPC is administered after peritonectomy has been performed. However, Flessnar demonstrated in an experimental study that removal of the mesothelial lining had no impact on the transport across the membrane [44]. Removal of the peritoneum has no impact on the mass transfer coefficient (MTC) over the barrier; this was further demonstrated in a clinical study involving administration of mitomycin C or 5-FU after CRS [45, 46]. And it has been demonstrated that the plasma-peritoneal barrier is formed not by the mesothelial cell layer and basement membrane but by the blood vessel and the surrounding interstitial matrix which form the main barrier for the transport of solutes and molecules from the peritoneal cavity to the systemic circulation [47]. Fluid enters the systemic circulation either by diffusion or by absorption by the peritoneal lymphatics that are abundant on the diaphragmatic undersurfaces [48, 49]. Fluid absorbed by the parietal peritoneum enters the systemic circulation, and that drained by the visceral peritoneum enters the portal circulation [50].

4.5.2 Dedrick Diffusion Model

Dedrick et al. in 1978 discovered that hydrophilic chemotherapeutic drugs had a slow rate of clearance from the peritoneal cavity, whereas the plasma clearance of the same drugs was comparatively higher [51]. The peritoneal clearance of a drug was found to be inversely proportional to the square root of its molecular weight leading to a significantly higher concentration in the peritoneal cavity as compared to the plasma after intraperitoneal administration [52, 53]. This dose intensification that occurs due to the plasma-peritoneal barrier forms the pharmacokinetic rationale for intraperitoneal chemotherapy. According to a simplified mathematical model, there are two compartments—the plasma and the peritoneal cavity—that are separated from each other by an effective membrane (Fig. 4.1).

This results in the following equation:

$$\text{Rate of mass transfer} = \text{PA}(\text{CP} - \text{CB})$$

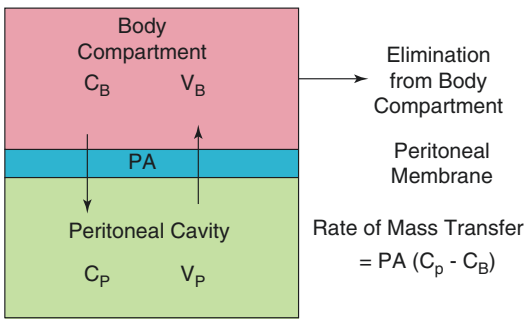

Fig. 4.1 The traditional two-compartment model of peritoneal transport, transfer of a drug from the peritoneal cavity to the blood occurs across the "peritoneal membrane." The permeability-area product (*PA*) governs this transfer. *PA* is calculated by measuring the rate of drug disappearance from the cavity, which is divided by the overall concentration difference between the peritoneal cavity and the blood (or plasma). C_B = the free drug concentration in the blood (or plasma), V_B = volume of distribution of the drug in the body, C_p = the free drug concentration in the peritoneal fluid, and V_p = volume of the peritoneal cavity. (Adapted from Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: Tissue penetration and surface exposure. J Natl Cancer Inst. 1997; 89(7), 480–7) [97]

where PA = permeability area (PA = effective contact area A × permeability P), CP = concentration in peritoneal cavity, and CB = concentration in the blood [54]. This model highlights the importance of the effective contact area, but does not determine its value in the actual transfer across the membrane. Similarly, it has no bearing on the amount of drug that reaches the tumor tissue. Increasing the drug concentration does not necessarily lead to an increased uptake and concentration into the tumor tissue [55]. Hence, this equation just describes a transfer across two compartments.

This does intensification which leads to increased drug concentration in the peritoneal cavity in comparison to plasma after intraperitoneal administration (Fig. 4.2) is expressed as the area under the curve (AUC) ratios of intraperitoneal (IP) versus plasma (IV) concentration. And as mentioned above, though the residual tumor cells are exposed to increased drug levels, it does not necessarily lead to increased uptake and therapeutic effect. It has been shown that even when the intraperitoneal drug concentration is high, penetration into the tumor nodules is limited. Hence, the ideal drug for intraperitoneal administration should not only be retained in the peritoneal cavity for a prolonged period but should get concentration in tumor nodules as well. Once the drug enters the systemic circulation, it undergoes rapid metabolism, thus maintaining the concentration gradient between the two compartments and limiting the systemic toxicity of the drug.

4.6 Pharmacologic Variables

There are a number of pharmacokinetic and pharmacodynamic variables that influence the efficacy of IPC, and these are listed in Table 4.1. Pharmacokinetic data is expressed as a concentration × time graph [55]. Pharmacodynamics evaluated the effect of the chemotherapeutic agent on the tumor nodules taking into consideration the size of the nodules, density, vascularity, interstitial pressure, binding, and temperature. Pharmacodynamic data are depicted in a concentrations × effect graph.

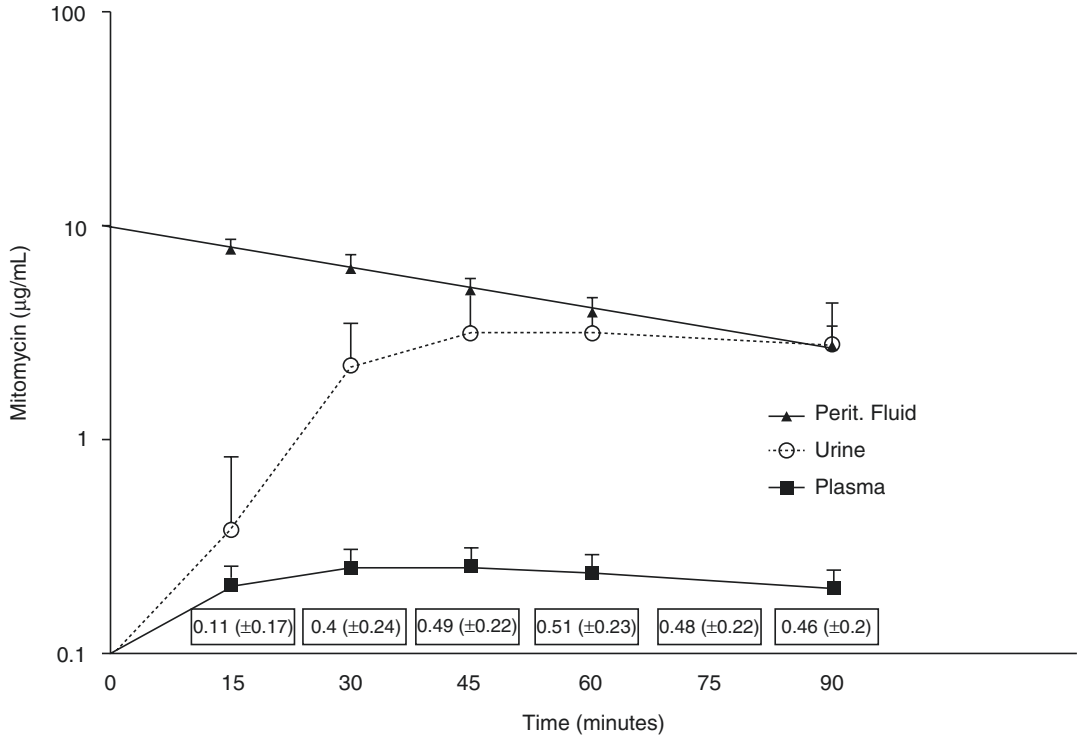

Fig. 4.2 Concentration times time graph of mitomycin C in peritoneal fluid, plasma, and urine in 145 patients during HIPEC. The area under the curve ratio of peritoneal fluid to plasma was 26.6 (±7.1). Peak plasma concentration was 0.25 (±0.06) µg/mL at 30 min. Also shown are the total milligrams of mitomycin C excreted in the urine at 15 min intervals

Table 4.1 Pharmacokinetic and pharmacodynamic variables of intraperitoneal chemotherapy

Pharmacokinetic VR	Pharmacodynamic VR
Dose	Tumor nodule size
Volume	Density
Duration	Vascularity
Carrier solution	Interstitial fluid pressure
Pressure	Binding
Molecular weight	Temperature

4.6.1 Timing of Cancer Chemotherapy in Relation to Timing of Surgical Intervention

In patients with PM, IPC can be used at four different time points. In patients with extensive disease, IPC is used for reducing the tumor burden in addition to systemic chemotherapy. This approach, which is called "neoadjuvant intraperitoneal and systemic chemotherapy" (NIPS), works against small tumor nodules and can facilitate subsequent CRS and HIPEC in patients who respond to therapy [56]. Radiologic and clinical responses have been reported by several groups [56–58]. NIPS has certain limitations as well. Adhesions may limit the distribution of the drug, and its efficacy and complete responses are seldom seen; the use of NIPS increases the morbidity and mortality of a subsequent CRS and HIPEC [59]. Fibrosis which develops in patients who respond to therapy can limit the evaluation of the disease extent on subsequent laparoscopy/laparotomy.

Perhaps the most commonly employed method is hyperthermic intraperitoneal chemotherapy (HIPEC) that is administered intraoperatively, immediately after performing CRS. HIPEC has been combined with CRS and has shown a clinical benefit in many phase II and some phase III trials [27–39].

Chemotherapy is administered for 3–5 days after surgery from postoperative day 1; this is termed as early postoperative intraperitoneal chemotherapy (EPIC). Since it is performed immediately after surgery, adhesions have not formed, thereby reducing the uneven distribution, and the residual disease is at its minimum. The selection of drugs for EPIC is important, and cell cycle-specific drugs like 5-FU and taxanes are most suited for this form of IPC. It is administered through drains placed during surgery and often performed in addition to HIPEC. EPIC has been discussed in greater detail in Chap. 5 of this book.

Long-term combined intraperitoneal and systemic chemotherapy also known as sequential postoperative intraperitoneal chemotherapy (SPIC) seeks to consolidate the surgical effort of CRS by adding long-term cycles of postoperative intraperitoneal chemotherapy. This form of IPC has been evaluated as adjuvant therapy for ovarian cancer, and several large randomized trials have shown a benefit of SIPC with systemic chemotherapy as compared to systemic chemotherapy alone in patients with advanced ovarian cancer who have had an optimal CRS [60–62]. Strictly speaking, this strategy may be termed as "postoperative adjuvant therapy" rather than perioperative chemotherapy. It may also be used as a "chemotherapeutic bridge" in patients who have had an incomplete CRS and are being considered for a secondary CRS. This approach may be used as "chemotherapeutic bridging" between incomplete initial surgery and definitive cytoreduction or second-look surgery.

In patients with PM, recurrence in the peritoneal cavity is common, and these may occur in the absence of systemic disease. An optimized treatment strategy using a combination of one or more of these approaches should be employed to treat patients to provide the maximal benefit in both recurrence-free and overall survival.

4.6.2 Duration

When a drug is administered intraperitoneally, it needs to remain in the peritoneal cavity for a specific period of time to obtain maximal cell kill. This effect increases with time to an extent and then it plateaus. The dependency of dose-response curves on exposure time was demonstrated by Gardner [63]. Moreover, the benefit of the prolonged exposure time needs to be weighed against the risk of systemic toxicity. Based on this rationale and understanding, the duration of HIPEC ranges from 30 to 120 min depending on the drug used. The duration of perioperative chemotherapy regimens should be pharmacology-driven and not arbitrary.

4.6.3 Carrier Solution

The carrier solution used also has an impact on the efficacy of IPC. An ideal carrier solution should lead to increased exposure of the peritoneal surface to the drug and maintain a high intraperitoneal volume for a prolonged period and should be cleared slowly and not have a detrimental effect on the peritoneum itself [64]. The solution used can be hypotonic, isotonic, or hypertonic. It has been used to deliver both low and high molecular weight drugs.

The choice of carrier solution is important when performing EPIC where maintenance of a high volume of chemotherapy solution over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment [65]. Mohamed et al. showed that the use of an isotonic solution comprising of high molecular weight dextrose prolongs the duration of artificial ascites [66]. Some experimental studies have shown that the use of hypotonic carrier solution for HIPEC may be advantageous pharmacokinetically [67, 68]. Elias et al. used a hypotonic solution for performing HIPEC with oxaliplatin in patients with colorectal PM and reported no difference in absorption or intratumoral accumulation of oxaliplatin but an increased incidence of hemorrhage (50%) in the postoperative period and severe thrombocytopenia, both of which could not be explained [69]. More information is needed before hypotonic carrier solutions are recommended for routine use.

4.6.4 Pressure

Dedrick et al. postulated that the depth of drug penetration is equal to the square root of the ratio of the tissue diffusivity and the rate constant for drug removal from the tissue: (D/k)1/2 [70]. Unpublished data by Flessner showed a doubling to the extracellular space in the anterior abdominal wall of rats when the intra-abdominal pressure was raised from 0 to 4 cm of H_2O [44]. Several experimental studies have shown that an increased intra-abdominal pressure during IPC can increase the intratumoral concentration and cytotoxicity of drugs like cisplatin, oxaliplatin, and doxorubicin [70–73]. However, these proposed advantages have failed to translate into a clinical benefit, and the pressure cannot be increased beyond a point due to respiratory and hemodynamic intolerance. The two clinical applications of a raised intra-abdominal pressure are laparoscopic HIPEC at 12–15 mmHg [74–78] that is used for palliating refractory malignant ascites and pressurized intraperitoneal aerosol chemotherapy (PIPAC). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new method of intraperitoneal drug delivery [79]. During PIPAC, laparoscopic access is obtained to create a pneumoperitoneum of 12 mm of Hg at normal temperature (37 °C), and a nebulized chemotherapy solution is then applied to create a "therapeutic capnoperitoneum" which is maintained in a steady state for 30 min [80]. The combined effect of using aerosolized chemotherapy which leads to a more homogenous drug distribution over the peritoneal surfaces and raised intra-abdominal pressure which increases the tissue drug concentration is expected to lead to increased drug in tumor tissue at low doses with limited systemic toxicity. This hypothesis has been tested in several experimental and clinical studies [80–85]. The first report of clinical efficacy was published in 2014 by Solass et al. in which two out of three patients with end-stage peritoneal disease arising from gastric appendiceal and ovarian primary sites experienced a clinical response and prolongation of survival with PIPAC. The dose was only 1/10 the dose of cisplatin and doxorubicin used for HIPEC and produced a higher tumor drug concentration as compared to HIPEC. The depth of penetration of drug was also increased, and the nuclear presence was demonstrated in the retroperitoneum as well. The systemic concentration was low and the tolerance was good [83]. Repeated applications of PIPAC are possible at intervals of 6–8 weeks. No cumulative hepatic or renal toxicity has been reported after multiple applications of PIPAC [85, 86]. Another report showed that the drug concentration was higher in tissues directly exposed to the aerosol jet as compared to those at a distance in an ex vivo model [87]. In a phase II study of 64 patients with recurrent ovarian cancer who underwent three applications of PIPAC using cisplatin and doxorubicin, there was a good tolerance with no grade 4 toxicity and an improvement in quality of life compared to systemic chemotherapy [89]. Similarly, a good tolerance to repeated PIPAC with oxaliplatin was shown in 17 patients of colorectal PM, most of whom had several lines of therapy before undergoing PIPAC [88]. These reports are of patients who have been treated with multiple lines of chemotherapy, and many of them had undergone extensive surgical procedures as well. PIPAC cannot be performed if the adhesions are extensive. Laparoscopic nonaccess is a limitation. The responses are seldom complete and its current use is only in the palliative setting. The other drawback is the high rate of bowel complications reported when it is combined with CRS [89]. Hence, in the current scenario, PIPAC should not be performed with CRS. Another strategy for increasing the drug concentration and penetration is applying an electric current during PIPAC, what is termed as electrostatic PIPAC (ePIPAC) [90]. An experimental study showed that charging the aerosolized particles led to an increased drug uptake and a further reduction in the dose and application time to achieve the same therapeutic effect.

Currently, several phase II trials are evaluating the role of PIPAC in the palliative and neoadjuvant setting for downstaging the disease in patients with extensive PM. PIPAC is often used in combination with systemic chemotherapy. These trials will evaluate its safety, feasibility, and efficacy in different settings. Till then PIPAC remains a palliative option for selected patients with PM.

4.6.5 Temperature

There are several theoretical benefits of using heat with IPC. Exposing tumor cells to heat leads to impaired DNA repair, increased protein denaturation, increased acidity, lysosomal activation, and increased apoptotic cell death [91]. This should lead to enhanced cytotoxicity using heat alone. However, the extent of temperature elevation in the core of tumor tissue is extremely limited. Heat also increases the cytotoxicity of several chemotherapeutic agents. The drugs whose cytotoxicity is enhanced by hyperthermia include cisplatin, mitomycin C, doxorubicin, melphalan, oxaliplatin, and gemcitabine [92]. Hyperthermia can also increase the depth of penetration of chemotherapeutic drugs in tumor nodules. Increased concentration of intraperitoneal doxorubicin in tumor nodules at 43 °C has been demonstrated; the use of heat does not undermine the other pharmacokinetic benefits of IPC [93]. Another benefit of hyperthermia is the reduction in the interstitial fluid pressure which is a major barrier to intratumoral drug penetration [94, 95]. The extent of heat enhancement is different for different drugs, and the level of heat required for maximal enhancement of cytotoxicity also varies. Cisplatin undergoes constant enhancement of cytotoxicity as the temperature increases. Some drugs like mitomycin C and gemcitabine that function as prodrugs do not experience this enhancement beyond a temperature of 41–42 °C [96]. Thus, these drugs are enhanced by moderate hyperthermia at 41 °C. Other drugs like cisplatin, melphalan, ifosfamide, and cyclophosphamide are called "super drugs" for hyperthermia as they undergo thermal enhancement at 43–44 °C as well [97]. However, cyclophosphamide and ifosfamide are not suitable for intraperitoneal use.

As hyperthermia is the main logistic reason complicating widespread use of IP chemotherapy, the suggested increased cytotoxicity of adding hyperthermia to IP chemotherapy suggested by basic science needs urgent validation in clinical trials.

4.7 Modes of Perfusion

Different methodologies for performing HIPEC have been developed at centers experienced in the management of peritoneal surface malignancy.

4.7.1 Open Abdomen Technique

The open abdomen technique with a vapor barrier created by smoke evacuators has been used extensively at the MedStar Washington Hospital Center (Fig. 4.3) [98]. During the open coliseum technique (Fig. 4.4), the abdominal cavity is expanded after CRS by applying traction sutures on the skin, which elevates the skin edge and provides the so-called coliseum [25]. This technique assures chemotherapy solution reaches all abdominal recesses. A heater circulator is used to maintain moderate hyperthermia (41–43 °C) within the abdomen and pelvis. Most treatment centers use a single inflow catheter that is moved in a clockwise direction from the right upper quadrant to beneath the left hemidiaphragm, to the left paracolic sulcus, to the pelvis, to the right paracolic sulcus, and then back to the right upper quadrant. Direct inflow within the small bowel regions is avoided. To remove the chemotherapy solution from the peritoneal space, one or more

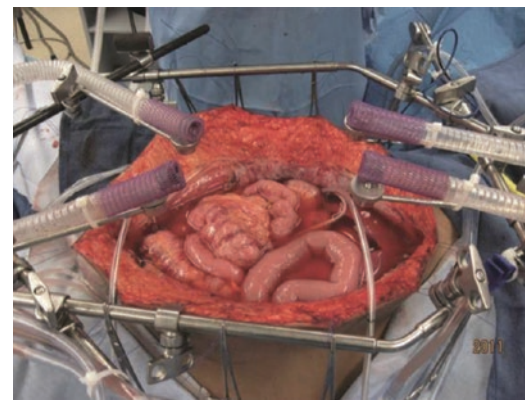

Fig. 4.3 The open abdomen technique to administer hyperthermic intraperitoneal peroperative chemotherapy (HIPEC). A vapor barrier is created by smoke evacuator [98]

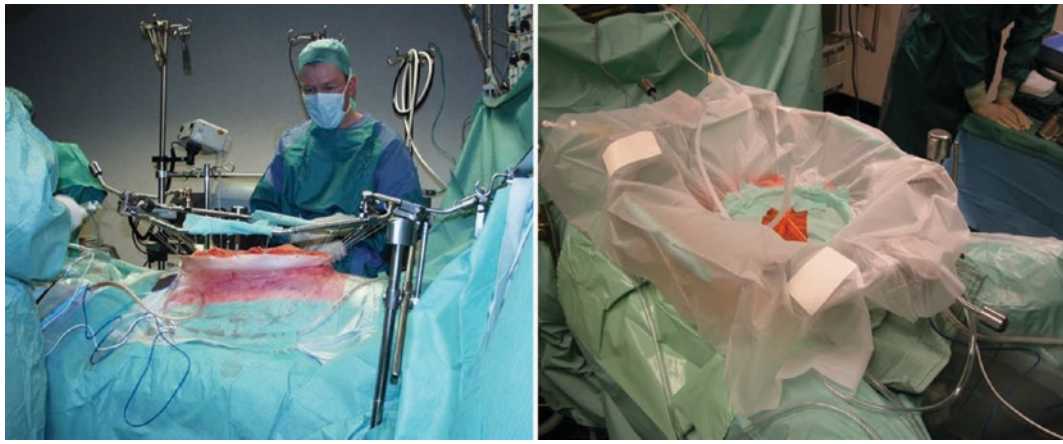

Fig. 4.4 During the open coliseum technique, the abdominal cavity is expanded after CRS by applying traction sutures on the skin, which elevates the skin edge and provides the so-called coliseum. The abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdominal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure

outflow catheters are placed in separate abdominal areas. The flow of the chemotherapy solution is usually set between 1 and 1.5 L/min. During the open abdomen technique, the abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdominal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure.

The concern with the open abdomen technique is the potential hazardous occupational exposure, i.e., exposing the operating room staff, to the chemotherapy solution in liquid or vaporized form. Several studies have been performed to address this issue by measuring platinum levels in the blood and urine of healthcare workers and environmental (air and surfaces) samples during HIPEC [99–101]. They report that there is no risk of platinum exposure during the open coliseum technique when safety considerations are followed. Capron et al. reported that double gloving can be used safely during HIPEC, as there was no detectable permeation of chemotherapy drugs during tests performed at 43 °C [102]. These studies emphasize the need for a standardized protocol concerning HIPEC procedures with specific recommendations regarding environmental contamination risk management, personal protective equipment, and occupational health supervision [103].

4.7.2 Closed Abdomen Technique

Some groups close the abdomen before performing HIPEC and then open the abdomen again to perform the anastomoses and repair the seromuscular tears, finally performing closure of the abdomen once again. During HIPEC (Fig. 4.5a), only the skin is closed tightly to prevent leakage of the chemotherapy solution, and the other layers of the anterior abdominal wall remain in contact with the chemotherapy solution during the procedure [104]. In the totally closed technique, the bowel anastomoses and seromuscular repairs are performed prior to HIPEC, drains are inserted, and a formal closure of the abdominal wall is done before performing HIPEC [105, 106].

Advantages associated with the closed abdomen technique are the ability to rapidly achieve and to maintain hyperthermia and increased safety of operating staff. Another advantage believed to be associated with the closed HIPEC

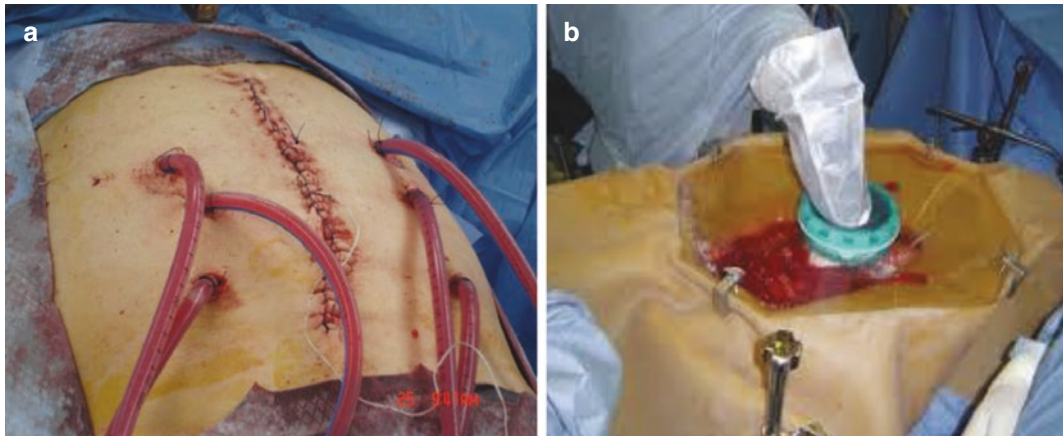

Fig. 4.5 (**a**) In this closed technique, the skin is closed in a water fashion so that all of the structures of the anterior abdominal wall are thoroughly treated by the chemotherapy solution. Tubes and drains are positioned prior to the definitive closure of the abdomen. After closure of the abdomen, the perfusion of the heated chemotherapy solution is started [104]. (**b**) The abdominal cavity expander, also referred to as the Landager technique, is a closed abdomen technique with open abdomen. The skin edges are watertightly stapled with a soft "abdominal cavity expander," supported by a Thompson self-retaining retractor positioned over the abdomen [130]

technique is that increased intra-abdominal pressure may increase the chemotherapy penetration into tissue. However, Ortega-Deballon et al. reported in an experimental study that the open technique had higher systemic absorption and abdominal tissue penetration of oxaliplatin than the closed technique [107]. Facy and colleagues used a pig model to demonstrate that tissue concentration of oxaliplatin was higher in the open technique even when high pressure was used in the closed abdomen technique. They concluded that the use of high pressure during the closed abdomen technique does not counterbalance the drawbacks [108]. These drawbacks include the risk of recurrence in the abdominal incision and suture lines and lack of uniform distribution of the heated solution [109, 110]. Preferential flow circuits exist, and some peritoneal surfaces are underexposed, which increases the risk of recurrence in these undertreated recesses. An attempt to better distribution of the chemotherapy can be made by manually agitating the abdominal wall during the perfusion.

In a clinical study including patients diagnosed with PC of different origins, Halkia et al. evaluated the differences in intraoperative parameters in patients receiving either the closed or open HIPEC technique. They concluded that both methods are safe and efficient in the treatment of PC with equal morbidity and mortality. They recommended the closed technique to be the method of choice for frail patients due to more stable hemodynamic parameters [111].

4.7.3 Semi-Open/Semi-Closed Abdomen Techniques

The peritoneal cavity expander (PCE) was first described by Fujimura et al. [112]. During this technique, an acrylic cylinder is secured over the wound. This cylinder contains inflow and outflow catheters, is large enough to allow the small intestine to float in the heated perfusate, and allows manual manipulation of the perfusate. When compared with the closed perfusion technique, a more uniform drug distribution is achieved by temporarily increasing the volume of the peritoneal cavity. This method was mostly used for the treatment of gastric PC [113, 114].

The abdominal cavity expander, also referred to as the Landager technique, is a semi-closed abdomen technique with open abdomen which ensures protection against potential hazardous occupational exposure and allows permanent access to the whole abdomen cavity ensuring uni-

form drug distribution (Fig. 4.5b) [115]. During this method, the skin edges are watertightly stapled with a soft "abdominal cavity expander," supported by a Thompson self-retaining retractor positioned over the abdomen. In this way, the level of the liquid can be widely raised above the level of the skin edges. The anterior wall peritoneum and the wall edges are constantly exposed to the liquid [116]. The abdominal cavity expander has been recently used by Frøysnes et al. in the treatment of colorectal PC [117].

4.8 Ideal IP Chemotherapy Regimens

The ideal IP chemotherapy regimen should fulfill two important requirements:

Firstly, the pharmacokinetics should be optimized—from the time of administration till the drug enters the tumor cell. Secondly, the drug that is cytotoxic to the specific cancer cell should be used [118]. This underlines the need for a personalized approach, while using IPC and chemosensitivity testing is one way of doing it. In experimental studies, such testing has been performed using patient-derived tumor cell lines [119, 120]. However, though a simulation of the pharmacokinetic aspects is possible in these studies, the pharmacodynamic impact cannot be duplicated, and extrapolation of these results to the clinical setting is inaccurate. Moreover, drug metabolism does not occur and hence the systemic toxicity is not evaluated. When tumor cells are implanted subcutaneously in an experimental animal, the microenvironment and thus the tumor growth and metastasis are different from the situation in the human body. Therefore, xenografts, orthotopic animal models, and other assays all need to be validated and pharmacodynamic variables accounted before drawing conclusions from these studies. Another aspect that needs to be taken into consideration while selecting the drug regimen is the genetic profile of the tumor. Low-grade and high-grade appendiceal tumor have different genotypes, and this has been demonstrated by Levine et al. [121]. Another example is patients with colorectal cancer who express MUC-2. These patients have a significantly inferior survival compared to patients who don't express MUC-2 [122]. Thus, future strategies will be needed to take into consideration genomic factors in selecting drug regimens as well.

4.8.1 IP Cancer Chemotherapy Regimens for Colorectal or Appendiceal PC

Table 4.2 summarizes the most frequently used IP cancer chemotherapy regimens in colorectal and appendiceal PM. The two dominant cancer drugs that form the backbone of these regimens are oxaliplatin and mitomycin C.

4.8.1.1 Oxaliplatin

Oxaliplatin (oxalato-1,2-diaminocyclohexane-platinum(II)) is a third-generation platinum complex and one of the most active agents against colorectal and appendiceal tumors [123]. The first and most commonly used regimen was developed by Elias et al. who concluded that a dose of 460 mg/m^2 in 2 L/m^2 of chemotherapy solution over 30 min produced the maximum therapeutic effect [26, 124]. Though the AUC ratio is low for oxaliplatin, it is rapidly taken up by tumor tissue, and thus the application time of 30 min is sufficient. However, this regimen has been associated with certain complications. In a phase I study, Elias demonstrated no benefit of using a hypotonic solution on the rate of absorption of the drug and clearance from the peritoneal cavity but an increased risk of hemorrhage and thrombocytopenia [69]. Pomel et al. initiated a multicentric study with a lower dose of 350 mg/m^2 but found no reduction in hemorrhage (29%), and this study had to be closed prematurely [125]. In another study of 75 patients, the incidence of grade 3/4 thrombocytopenia was 14%, and the authors concluded that a higher initial concentration of oxaliplatin led to increased absorption and more severe thrombocytopenia [126]. In another recent report from France that studied the incidence of hemorrhage following oxaliplatin-based HIPEC compared to other

Table 4.2 Hyperthermic intraperitoneal chemotherapy (HIPEC) and bidirectional intraoperative chemotherapy (BIC) regimens

Oxaliplatin-based regimens
Elias High-Dose Oxaliplatin Regimen
1. Add oxaliplatin to 2 L/m^2 5% dextrose solution
2. Dose of oxaliplatin is 460 mg/m^2
3. 30-min HIPEC treatment
Intravenous Component
4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs 1 h before intraperitoneal chemotherapy
Glehen Medium-Dose Oxaliplatin Regimen
1. Add oxaliplatin to 2 L/m^2 5% dextrose solution
2. Dose of oxaliplatin is 360 mg/m^2
3. 30-min HIPEC treatment
Intravenous component
4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs 1 h before intraperitoneal chemotherapy
Wake Forest University Oxaliplatin Regimen
1. Add oxaliplatin to 3 L 5% dextrose solution
2. Dose of oxaliplatin is 200 mg/m^2
3. 2 h HIPEC treatment
Mitomycin C-based regimens
Sugarbaker Regimen
1. Add mitomycin C to 2 L 1.5% dextrose peritoneal dialysis solution
2. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution
3. Dose of mitomycin C and doxorubicin is 15 mg/m^2 for each chemotherapy agent
4. Add 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs simultaneous with intraperitoneal chemotherapy
Dutch High-Dose Mitomycin C Regimen: "Triple-Dosing Regimen"
1. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution
2. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 17.5 mg/m^2 followed by 8.8 mg/m^2 at 30 min and 8.8 mg/m^2 at 60 min
3. Total dose of mitomycin C 35 mg/m^2 for 90-min HIPEC treatment
American Society of Peritoneal Surface Malignancy Low-Dose Mitomycin C Regimen: "Concentration-Based Regimen"
1. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution
2. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 30 mg/3 L followed by 10 mg at 60 min
3. Dose of mitomycin C 40 mg/3 L for 90 min HIPEC treatment

drugs in 701 patients, there was an increase in hemorrhage when oxaliplatin was used [127]. Another problem with the drug is that it is not stable in chloride-containing solutions, and using a dextrose-based carrier solution can result in serious electrolyte disturbances and hyperglycemia [128]. Unknown to most, this degradation of oxaliplatin in normal saline only accounts for less than 10% of the total amount at 30 min, as when applied during HIPEC. Moreover, oxaliplatin degradation was associated with the formation of its active drug form Pt(dach)Cl2 [129, 130]. Different oxaliplatin-based HIPEC regimens are used in current clinical practice: "Elias High-Dose Oxaliplatin Regimen" [26], "Glehen Medium-Dose Oxaliplatin Regimen," and the "Wake Forest University Oxaliplatin Regimen" [123].

4.8.1.2 Mitomycin C

Mitomycin C is an alkylating tumor antibiotic extracted from *Streptomyces* species. It causes DNA cross-linking, apoptosis, and cell death. The AUC ration of 23.5 makes it an ideal drug for IP use [46]. Mitomycin C has been one of the first and most commonly used drugs for HIPEC for PM from various sites like colorectal, appendiceal, gastric, and ovarian cancer and malignant mesothelioma [46, 131]. It is also used for performing EPIC. Mitomycin undergoes moderate thermal enhancement and is cleared slowly from the peritoneal cavity; over 50% of the drug is retained at 90 min, and hence HIPEC regimens using this drug have a long application time of 90 min [132]. Some surgeons use a body surface area-based regimen in which the entire dose is added at the beginning, whereas others use a concentration-based regimen or administer the

dose in two fractions, one at the beginning and one midway during the procedure [133, 134]. Triple-dosing regimen may result in more stable peritoneal levels of the drug throughout the time of IP chemotherapy. Current applied HIPEC dosing regimens are the "Sugarbaker Regimen" [132], the "Duth High-Dose Mitomycin C Regimen: Triple-Dosing Regimen" [135, 136], and the "American Society of Peritoneal Surface Malignancy Low-Dose Mitomycin C Regimen: Concentration-Based Regimen" [137].

4.8.1.3 Body Surface Area-Based or Concentration-Based IP Chemotherapy

IPC protocols use either a concentration-based method for determining the drug dose or calculate it based on body surface area (BSA) as is done in the IV regimens. In the BSA method which is in common use, the BSA is used as a substitute for the effective peritoneal surface area in contact with the chemotherapy solution [51]. However, it has been shown that the BSA is an inaccurate method for determining the peritoneal surface contact area, and due to uneven distribution, the actual amount of drug absorbed in tumor nodules depends on its concentration in the carrier solution [51, 138]. The effective peritoneal surface area is also influenced by the body composition of the patient and the method of performing HIPEC—open versus closed. It has been demonstrated that the use of a higher volume of perfusate/carrier solution retards systemic absorption and reduces toxicity [139, 140]. At the same time, it may be concluded from the above evidence that when the concentration of the drug is low, the absorption into tumor nodules is proportionately less.

Contrary to this, concentration-based regimens lead to a more predictable exposure of the tumor nodules to the IP chemotherapy and thus efficacy [141]. The caveat is the unpredictable increase in systemic absorption and toxicity. Currently, a randomized controlled trial is being conducted at our hospital that will compare the pharmacological benefit and morbidity of these two dosing methods. The trial is called "concentration-based versus body surface area-based peroperative intraperitoneal chemotherapy after optimal cytoreductive surgery in colorectal peritoneal carcinomatosis treatment: randomized non-blinded phase III clinical trial (COBOXtrial)" (https://clinicaltrials.gov/ct2/show/NCT03028155).

4.8.1.4 Clinical Results

There is no clear evidence supporting the superiority of either mitomycin C-based regimens or oxaliplatin-based regimens though there is a trend favoring the use of oxaliplatin.

Table 4.3 summarizes the clinical trials comparing oxaliplatin-based and mitomycin C-based HIPEC [142–145]. All of these reports, however, have serious methodological issues (selection bias, historical bias). A randomized controlled trial (https://clinicaltrials.gov/ct2/show/NCT01580410), that is, a multicenter, open-label, randomized phase II trial, has been conducted to evaluate hematologic toxicities after HIPEC with oxaliplatin and mitomycin C in patients with appendiceal tumors. The time to progression for each drug will also be compared. This trial has completed accrual and the results are awaited.

Table 4.3 Clinical studies of oxaliplatin-based versus mitomycin C-based HIPEC (Adapted from Reference [178] with permission)

Year	Author	N	Type	Uni-/Multicentric	Result
2010	Elias	523	Retrospective	Multicentric (23)	MMC = oxali
2014	Hompes	95	Retrospective	Bicentric	MMC = oxali
2014	Prata-Villaverde	539	Retrospective	Multicentric (>15)	MMC = oxali except PSDSS I/II (MMC 54,3 versus 28,2 months)
2016	Leung	201	Retrospective	Unicentric	Oxali (OS 56 versus 29 months)

4.8.2 IP Cancer Chemotherapy for PM of Gastric Cancer, Ovarian Cancer, Mesothelioma, and Sarcoma

The predominant IP regimens in this setting are cisplatin-based.

4.8.2.1 Cisplatin

Cisplatin (cis-diamminedichloroplatinum-III, CDDP) is an alkylating agent that causes apoptotic cell death by the formation of DNA adducts [146]. Normothermic and hyperthermic methods of IPC have used cisplatin-based regimens for the treatment of ovarian cancer, gastric cancer, and peritoneal mesothelioma [60, 62, 147–150]. Cisplatin is considered a "super drug" for hyperthermia and undergoes thermal enhancement at temperatures 42–44 °C as well. Hyperthermia is known not just to enhance the cytotoxicity but reverse the platinum resistance as well which is important in ovarian cancer [97]. The main toxicity is nephrotoxicity, and it has been found to be dose limiting by certain investigators [151]. Currently applied cisplatin-based HIPEC regimens are the "Sugarbaker Regimen" [152] and the "National Cancer Institute Milan Regimen" [153] (Table 4.4).

4.8.2.2 Doxorubicin

Doxorubicin or hydroxyldaunorubicin (Adriamycin) is an anthracycline antibiotic that is seldomly used alone for IPC. It is used in combination with either cisplatin or mitomycin C. Though initially categorized as a DNA-intercalating drug, the actual mechanism of action is a temperature-dependent interaction of doxorubicin with the cell surface membrane [154–156]. The advantages of IP doxorubicin are its favorable AUC ratio of IP to IV concentration times of 230 and its clinical activity in a large number of malignancies [157–161]. More recently PEGylated liposomal doxorubicin has generated interest for HIPEC application due to its favorable pharmacokinetics [162, 163].

Table 4.4 Cisplatin-based HIPEC regimens (Adapted from reference [178] with permission)

Cisplatin-based regimens
Sugarbaker regimen
1. Add cisplatin to 2 L 1.5% dextrose peritoneal dialysis solution
2. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution
3. Dose of cisplatin is 50 mg/m^2, and doxorubicin is 15 mg/m^2 for 90-min HIPEC treatment
Intravenous chemotherapy
4. Add ifosfamide 1300 mg/m^2 to 1 L 0.9% sodium chloride. Begin continuous IV infusion over 90 min simultaneous with intraperitoneal chemotherapy
5. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 15 min prior to ifosfamide infusion
6. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 4 h after ifosfamide infusion
7. Add mesna disulfide 260 mg/m^2 in 100 mL 0.9% sodium chloride to be given IV as a bolus 8 h after ifosfamide infusion
National Cancer Institute Milan Regimen
1. 15.25 mg/L of doxorubicin and 43 mg/L of cisplatin for 90-min HIPEC treatment
2. Chemotherapy solution 4–6 L based on capacity of the peritoneal space

4.8.3 Bidirectional Intraoperative Chemotherapy (BIC)

Most current protocols advocate bidirectional intraoperative chemotherapy (BIC). By combining intraoperative IV and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer containing the cancer nodules. The IV drug is administered as single of multiple boluses or as an infusion during the HIPEC procedure or just before it. This strategy was first used by Elias who demonstrated augmentation of the cytotoxicity of IP oxaliplatin by administering a 5-FU infusion over 1 h just prior to starting HIPEC. We also reported a clear pharmacokinetic advantage for the intraoperative IV administration of 5-fluorouracil [164]. A similar pharmacokinetic advantage and heat targeting of intraoperative IV

ifosfamide were demonstrated [152]. Ifosfamide undergoes thermal enhancement but needs cytochrome P450 to get converted to its active metabolite, thus eliminating the potential for IP use. However, it can augment the cytotoxicity of HIPEC and is used in conjunction with IP cisplatin and doxorubicin in ovarian cancer, gastric cancer, sarcomas, and mesothelioma. The bidirectional approach offers the possibility of optimizing cancer chemotherapy delivery to the target peritoneal tumor nodules. Further pharmacologic studies are needed to clarify the most efficient method of administration (continuous, bolus, or repeated bolus), doses, and choice of cancer chemotherapy drugs for this bidirectional approach.

4.8.4 Early Postoperative Intraperitoneal Chemotherapy (EPIC)

EPIC is administered postoperatively (typically from day 1 to day 4/5) through both an inflow catheter and outflow drains inserted at the time of CRS. It can be used as the sole method of IPC or performed following CRS and HIPEC.

EPIC has theoretical advantages of being administered when the disease burden is minimal and when adhesions have not formed, thus enabling a more even drug distribution. It has also been associated with a higher risk of postoperative complications [29, 165–167]. Cell cycle-specific drugs like 5-FU and taxanes are most suited for EPIC (Table 4.5). Multiple cycles are given, each of which stays in the peritoneal cavity for 23 h. The drains are left open to drain for an hour before the next cycle is administered. This ensures that all residual cells get exposed to the drug.

4.8.4.1 5-Fluorouracil

5-Fluorouracil is an essential component of chemotherapeutic regimens for treating gastrointestinal cancers. 5-FU is an inhibitor of the enzyme thymidylate synthetase that catalyzes the methylation of thymine in the synthesis of thymidine, which is a precursor of DNA [168, 169]. It enters the cell directly and is then metabolized to its active metabolite.

Table 4.5 Early postoperative intraperitoneal chemotherapy (EPIC) regimen

Early postoperative intraperitoneal chemotherapy with 5-fluorouracil on postoperative days 1–4 for adenocarcinoma from appendiceal, colonic, and gastric cancer
1. 5-Fluorouracil _____ mg (400 mg/m^2 for females and 600 mg/m^2 for males, maximum dose = 1400 mg) and 50 meq sodium bicarbonate in _____mL 1.5% dextrose peritoneal dialysis solution via the Tenckhoff catheter daily for 4 days: start date _____, stop date _____
2. The intraperitoneal fluid volume is 1 L for patients ≤2.0 m^2 and 1.5 L for those >2.0 m^2
3. Drain all fluid from the abdominal cavity prior to instillation, and then clamp abdominal drains
4. Run the chemotherapy solution into the abdominal cavity through the Tenckhoff catheter as rapidly as possible. Dwell for 23 h and drain for 1 h prior to next instillation
5. Use gravity to maximize intraperitoneal distribution of the 5-fluorouracil. Instill the chemotherapy with the patient in a full right lateral position. After 30 min, direct the patient to turn to the full left lateral position. Change position from right to left every 30 min. Continue turning for the first 6 h after instillation of chemotherapy solution
6. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy
7. Continue to drain abdominal cavity after final dwell until Tenckhoff catheter is removed
Early postoperative intraperitoneal chemotherapy with paclitaxel on postoperative days 1–5 for peritoneal mesothelioma and ovarian cancer
1. Paclitaxel _____ mg (20–40 mg/m^2 × _____m^2) (maximum dose = 80 mg) in 1000 mL 6% Hespan® (B. Braun, Irvine, CA) via Tenckhoff catheter daily: start date _____, stop date _____
2. Instill as rapidly as possible via Tenckhoff catheter. Dwell for 23 h. Drain from Jackson-Pratt drains for 1 h prior to next instillation
3. During the initial 6 h after chemotherapy infusion, the patient's bed should be kept flat. The patient should be on the right side during instillation. Turn at 30 min post instillation onto the left side and continue to change sides at 30-min intervals for 6 h
4. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy
5. Continue to drain abdominal cavity by Jackson-Pratt drains after the last dose of intraperitoneal chemotherapy

Also, 5-FU by its metabolites 5-fluoro-uridine diphosphate and 5-fluoro-uridine triphosphate gets incorporated in RNA, resulting in a second cytotoxic pathway. The action of 5-fluorouracil is therefore cell cycle specific.

Although a small molecular weight molecule (130.08 Dalton), 5-FU has an AUC ratio > 400 which makes it a favorable drug for intraperitoneal administration (Table 4.2). The plasma concentration is significantly lower than the intraperitoneal concentration due to inactivation of the drug in the systemic circulation by dihydropyrimidine dehydrogenase, an enzyme that is present in the liver in abundance and in the mucosa of the gastrointestinal tract and peripheral lymphocytes. 5-FU is not chemically compatible with other drugs in a mixed solution for infusion or instillation which limits its intravenous and intraperitoneal use along with other agents. These characteristics limit the use of IP 5-fluorouracil to EPIC [170–173].

4.8.4.2 Taxanes

Paclitaxel and docetaxel are drugs with a high molecular weight that have high AUC ratios of 853 and 861, respectively, which make them ideal for IP administration [174]. One of the main mechanisms of action is stabilization of the microtubule against depolymerization, thereby disrupting normal microtubule dynamics [175–177]. Though they do not undergo significant thermal enhancement, their activity against a broad range of tumors adds to their favorable profile for IP use [176, 177]. Taxanes have been used in a neoadjuvant intraperitoneal (NIPS) setting as well as intraoperatively and postoperatively. Their cell cycle-specific mechanism of action makes them a better candidate for repetitive application such as in EPIC, NIPS, or normothermic adjuvant postoperative IP chemotherapy.

4.8.5 Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS)

Neoadjuvant bidirectional chemotherapy combined the intravenous and intraperitoneal routes of delivering chemotherapy prior to definitive CRS. The main benefits of this approach are the prevention of extraperitoneal spread, an opportunity to test the sensitivity to chemotherapeutic agents, and a reduction in the extent of small peritoneal tumor nodules. Table 4.6 lists the most commonly used NIPS regimens [82–88].

Table 4.6 Neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) regimen (Adapted from reference [178] with permission)

Yonemura regimen (2016)
1. Oral S-1 is administered for 14 days at a dose of 60 mg/m^2/day, followed by 7 days rest prior to intraperitoneal chemotherapy administration
2. On day 1 docetaxel (30 mg/m^2) and cisplatin (30 mg/m^2) are administered by IP infusion
3. On day 8 (30 mg/m^2) and cisplatin (30 mg/m^2) are administered IV
Ishigami regimen
1. Oral S-140 mg/m^2 twice daily for 14 consecutive days followed by 7 days rest oral S1 40 mg/m^2
2. Paclitaxel 50 mg/m^2 IV simultaneously with 20 mg/m^2 IP in 1 L normal saline over 1 h on day 1 and day 8
3. Regimen repeated every 3 weeks
Fujiwara regimen
1. Oral S-140 mg/m^2 twice daily for 14 consecutive days
2. Docetaxel 40–60 mg/m^2 IP in 1 L normal saline
3. Regimen repeated every 3 weeks
Sugarbaker regimen
1. Paclitaxel 20 mg/m^2 in 1 L 6% Hespan (B. Braun, Irvine, CA, USA) via IP port or Tenckhoff catheter
2. Instill by gravity flow as rapidly as possible 5 days in a row
3. On day 3 of 5-day cycle, instill oxaliplatin 100–150 mg/m^2 IV in 250 mL D5W over 120 min. Start 30 min after IP paclitaxel

Conclusion

The combination of CRS and IP chemotherapy should now be considered a standard of care for PSM from appendiceal epithelial cancers, colorectal cancer, and peritoneal mesothelioma.

There is a clear pharmacokinetic and pharmacodynamic rationale for this treatment approach. This has resulted in promising clinical results in the treatment of PC, in contrast with uniform failure before. A wide variety of

variables needs to be considered. Though the technique and variables involved in cytoreductive surgery have been standardized, there is an urgent need to standardize the various intraperitoneal chemotherapy methods and protocols. This manuscript reviewed the most commonly used IP regimens for HIPEC, EPIC, and NIPS. Although today, trends in the IP protocols, such as the reduced dosing of oxaliplatin and the triple-dosing regimen of mitomycin C, are observed, more pharmacologic and clinical evidence should be generated to answer important questions raised by the myriad of variables associated with IP chemotherapy.

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Conflict of Interest Statement No potential conflicts of interest.

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5 Early Postoperative Intraperitoneal Chemotherapy: Current Role and Future Perspectives

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Abbreviations

AUC	Area under the curve
BIC	Bidirectional intraoperative chemotherapy
CCR	Completeness of cytoreduction
CRC	Colorectal carcinoma
CRS	Cytoreductive surgery
DMPM	Diffuse malignant peritoneal mesothelioma
EPIC	Early postoperative intraperitoneal chemotherapy
FU	Fluorouracil
HIPEC	Hyperthermic intraperitoneal perioperative chemotherapy
IPC	Intraperitoneal chemotherapy
LV	Leucovorin
MMC	Mitomycin C
NA	Not available
NIPS	Neoadjuvant intraperitoneal and systemic chemotherapy
OS	Overall survival
PCI	Peritoneal carcinomatosis index
PFS	Progression-free survival
PM	Peritoneal metastases
SIPC	Sequenced intraperitoneal chemotherapy

5.1 Introduction

Peritoneal metastases (PM) are a common manifestation of various gastrointestinal and gynaecologic malignancies, as well as the primary location for some tumours [1]. It originates from preoperative or intraoperative intracavitary dissemination of tumour cells, as explained in the 'tumour cell entrapment' hypothesis [2–9]. The median survival in patients with PC from non-gynaecologic cancers, untreated or with palliative surgery alone, is very poor: 7 months in colorectal carcinoma (CRC), 7 months in breast cancer and 12 months in sarcoma [10–12]. Clinical studies on isolated PC from CRC, treated

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with systemic chemotherapy (5-fluorouracil (FU)-leucovorin (LV)), report a median survival of 12.6 months [13, 14]. Despite the development of new, more effective chemotherapeutic agents and their combinations, the results remain disappointing [15–21]. Interesting survival results were obtained with the use of irinotecan or oxaliplatin for metastatic CRC, but a majority of patients had liver metastasis without PC [22, 23]. Unfortunately, in most studies reporting on systemic chemotherapy for metastatic disease, PM is not differentiated from systemic metastases. Subgroup analysis of patients with isolated PM of CRC, selected from several trials with oxaliplatin and irinotecan, reveals a median survival between 10 and 15 months [18, 21, 24]. In PM of gynaecologic origin, the median survival after treatment with chemotherapy alone is 20 months in patients with stage III disease and 8 months in those with stage IV disease [25]. Recent treatment regimens for PM, consisting of optimal cytoreductive surgery (CRS) and combination chemotherapy increased the median survival to 68 months [26–28]. The presence of PM not only has a major impact on survival but also significantly diminishes quality of life due to obstruction, pain, or malignant ascites [10, 29, 30].

Sugarbaker has suggested that PM should probably not be equated with systemic disease, but rather be seen as locoregional dissemination [31, 32]. As such, a locoregional disease warrants a locoregional treatment approach. Based on this idea, the use of CRS to eradicate macroscopic disease and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) as treatment of remaining microscopic disease has been propagated as curative intent treatment of PC [33–35]. The treatment of PM from CRC with CRS and HIPEC was evaluated in 12 phase II studies. These studies reveal a strikingly similar long median survival and, more importantly, a 20–30% 5-year overall survival (OS) rate [33, 36–48]. Currently, one phase III trial supports these retrospective data with a 5-year OS in PM from CRC of 40% [49].

Compared to palliative treatment, curative intent treatment with CRS and HIPEC in patients with PM demonstrates great improvement in OS [50]. However, despite improving progression-free survival (PFS) and OS, recurrence remains the rule and the majority of patients still die of disease progression [51]. In light of these remarks, it is paramount to keep searching for ways to improve this promising treatment strategy. The aim of this manuscript is to evaluate early postoperative intraperitoneal chemotherapy (EPIC) as a possible leverage point to further improve multimodal therapy of PM.

5.2 Potential Strategies for Improving Results of CRS and HIPEC

First, we can identify patients who are likely to have subclinical or low-volume PM and implement CRS and HIPEC earlier in disease progression. The extent of disease, measured by the peritoneal carcinomatosis index (PCI), is a statistically significant predictor of completeness of cytoreduction (CCR) in turn reflecting OS, PFS and morbidity [13, 49, 52–56]. Several risk factors for developing PM after primary resection have been identified: the presence of solitary PM at primary resection, the presence of solitary ovarian metastasis, tumour perforation and T4 status [6, 57–62]. In a prospective case series, Elias et al. reported that in 55% of these high-risk patients, PM was discovered at laparotomy 1 year after primary resection in spite of adjuvant chemotherapy and no indication of PM on imaging [61]. Thus performing HIPEC at the time of primary surgery in patients at high risk of developing subsequent PM might improve survival by eliminating microscopic tumour implants. This hypothesis has been studied by Sammartino et al. They reported that OS was longer in the proactive group than in the control group (59.5 vs. 52 months) [63]. The prophylactic use of HIPEC is currently under investigation in three randomized controlled trials (ProphyloCHIP, NCT01226394; COLOPEC, NCT02231086; NCT01095523).

Secondly, the presence of PM, although a local occurrence, remains a sign of unfavourable tumour biology. As such, these patients are also at increased risk of systemic metastases. The use

Table 5.1 Pharmacokinetic and pharmacodynamic variables of perioperative intraperitoneal chemotherapy

Pharmacokinetic variables	Pharmacodynamic variables
Dose	Tumour nodule size
Molecular weight	Density
Volume	Vascularity
Duration	Interstitial fluid pressure
Carrier solution	Binding
Pressure	Temperature
Timing	

of adjuvant intravenous chemotherapy is becoming an essential part of treatment in patients undergoing CRS and HIPEC [64–66]. The modalities of adjuvant intravenous chemotherapy currently used are diverse [50, 65]. More research will hopefully identify the best treatment protocols and unify them.

Thirdly, the use of intraoperative intravenous chemotherapy can augment the effects of HIPEC. By combining intraoperative intravenous chemotherapy and HIPEC, a bidirectional diffusion gradient is created through the intermediate tissue layer which contains the cancer nodules. This concept called bidirectional intraoperative chemotherapy (BIC) has demonstrated a clear pharmacologic advantage for 5-FU and ifosfamide [67–69].

Lastly from a conceptual point of view, several pharmacologic variables in the IPC concept can be modified in an attempt to improve results. These variables can be divided in pharmacokinetic and pharmacodynamics variables (Table 5.1). Pharmacokinetics describe what the body does to the drug, whereas pharmacodynamics describe what the drug does to the body [70, 71]. Of these variables, the duration and timing of IPC are important factors influencing its effectivity.

5.3 Timing of Intraperitoneal Chemotherapy in Relation to Surgery

In the clinical application of IPC in PM patients, intervention can occur at four points in the timeline. First, induction intraperitoneal and/or intravenous chemotherapy is a therapeutic strategy for reducing extra-abdominal disease progression, assessing the tumour biology based on the response to therapy and for reducing the extent of PM, specifically, the small tumour nodules. Theoretically, this approach, called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), can make it possible for some patients with extensive disease on initial open or laparoscopic evaluation to undergo definitive cytoreductive surgery [72]. Radiologic and clinical responses with NIPS have been reported by several groups [72–76]. NIPS has limitations like uneven drug distribution due to adhesions from previous surgeries, a low incidence of complete responses and an increased incidence of morbidity and mortality from the subsequent surgical interventions. Extensive fibrosis that can result from a response to chemotherapy may make it extremely difficult to evaluate the extent of PM [77].

Second, the use of HIPEC is the most widely explored modality that has shown consistent clinically improved outcomes in many phase II trials and several phase III trials [13, 14, 19, 49, 78, 79].

Third, several phase III trials of long-term combined intraperitoneal and systemic chemotherapy (sequenced intraperitoneal chemotherapy, SIPC) have demonstrated that intravenous plus intraperitoneal chemotherapy improves survival in patients with optimally debulked stage III ovarian cancer, compared to intravenous chemotherapy alone [80–82]. This approach may also be used as chemotherapeutic bridging between incomplete initial surgery and definitive CRS or second-look surgery. In contrast, patients with gastric cancer PM did not benefit from SPIC with cisplatin compared to adjuvant intravenous chemotherapy [83]. This type of chemotherapy is an adjuvant and not a perioperative intraperitoneal use of chemotherapy. The good results in ovarian cancer come at the cost of higher morbidity and catheter-related complications leading to a limited number of planned cycles of SPIC completed [84].

Finally, the administration of IPC during the early postoperative period, EPIC, has some important conceptual advantages. EPIC regimens are administered postoperatively (days 1–4/5) through both an inflow catheter and outflow

drains inserted at the time of CRS and can be applied with or without prior HIPEC. It is initiated after CRS at the time of minimal residual tumour burden. Intraperitoneal drug instillation is initiated before wound healing, and intraperitoneal adhesions can occur and as such can minimize non-uniform drug distribution and eliminate residual cancer cells entrapped in postoperative fibrin deposits. Cell cycle-specific drugs like 5-fluorouracil and taxanes are preferred for EPIC based on principles of pharmacology. EPIC, its rationale and influence on survival will be the subject of the rest of this chapter.

5.4 Rationale for EPIC

From a pharmacologic point of view, dose intensification between the peritoneal compartment and the body compartment is the basic underlying rationale for all IPC [70, 85, 86]. Secondly, hepatic metabolism and first-pass effect can improve the therapeutic ratio, ratio of intraperitoneal drug concentration to plasma drug concentration, for intraperitoneally infused drugs by partially metabolizing them before reaching the systemic circulation. This mechanism also leads to high drug concentrations in the liver, the primary site of systemic metastases for many tumours causing PC [11, 87]. These advantages apply to all types of IPC, but the use of EPIC during the early postoperative period has some additional specific advantages.

The prerequisite for effective IPC is that the administered drug reaches its target, the cancer cell. Unfortunately during HIPEC, the cancer chemotherapy solution does not contact the complete peritoneal surface. Peritoneal dialysis data reveals that only 30–40% of the peritoneum is covered by an intraperitoneal fluid administered during a short period of time [88–90]. On the other hand, a solution instilled in the peritoneal cavity of normal mice and rats for longer time (24 h) succeeds in completely covering the peritoneum [88, 91]. Rosenshein examined the distribution of intraperitoneally infused fluids in rhesus monkeys using a Ringer's lactate solution containing ^{99m}Tc-labeled human serum albumin. There was a good distribution when high intra-abdominal volumes, 250 mL in a 5 kg subject, were used [92]. Graf et al. confirmed, by single photon emission computed tomography, that an intraperitoneal infused volume of 500 mL was not sufficient to obtain a uniform distribution in human subjects [93]. In a study comparing open to closed HIPEC techniques, Elias et al. reported a superior exposure of the peritoneal surfaces by the open 'colosseum' technique, probably due to stirring of the fluid during the procedure and the expanded abdomen [94]. The longer dwell time of chemotherapeutic agents during EPIC might increase the peritoneal surface area that comes in contact with the drug in spite of it being a closed abdomen technique.

Once the drug has reached the tumour surface, it needs to penetrate the tumour to reach the individual cells. The penetration of different drugs after intraperitoneal instillation is only between 2–3 mm and 6–8 cell layers [85, 86, 95–97] (Table 5.2). Notable exception is the penetration of more than 60 cell layers by paclitaxel [98, 99]. Increased intra-abdominal pressure during EPIC might further increase tissue penetration.

Most drugs don't immediately institute absolute cell kill. They depend on some duration of exposure to transfer enough drug to effect a change in the tissue. For example, for cisplatin, the molecule must first enter the cell. Uptake is variable and can be modulated by decreased uptake or increased efflux. Secondly, prior to cisplatin binding to genomic or mitochondrial DNA, the loss of a chloride group is required. Lastly after cisplatin binds to DNA, initially monofunctional DNA adducts are formed, but most of them further react to produce interstrand or intrastrand cross-links, which then block replication and/or prevent transcription [100]. This need for prolonged exposure is evidently true for the potent cell cycle-specific drugs: 5-FU and taxanes. Little data exists concerning the exact exposure time chemotherapeutic drugs require to institute cell kill [101]. During HIPEC, contact time is limited to 30–90 min, while during EPIC, the drug lingers in the abdominal cavity during the first 5 postoperative days. This longer contact time potentially improves cell kill.

Table 5.2 Properties of cytotoxic agents used during intraoperative or early postoperative intraperitoneal chemotherapy

Drug	Molecular weight (Dalton)	AUC ratio	Drug penetration distance
5-fluorouracil	130.08	250	0.2 mm
Carboplatin	371.25	10	0.5 mm
Cisplatin	300.1	7.8	1–3 mm
Oxaliplatin	397.3	16	1–2 mm
Paclitaxel	853.9	1000	>80 cell layers
Docetaxel	861.9	552	NA
Doxorubicin	579.99	230	4–6 cell layers
Mitoxantrone	517.41	115–225	5–6 cell layers
Etoposide	588.58	65	NA
Floxuridine	246.2	75	NA
Gemcitabine	299.5	500	NA
Irinotecan	677.19	NA	NA
Mephalan	305.2	93	NA
Mitomycin C	334.3	23.5	2 mm
Pemetrexed	597.49	40.8	NA

HIPEC and EPIC have some additional advantages over NIPS. Extensive resections and adhesiolysis during CRS maximally expose the peritoneal surface to chemotherapeutic drugs during subsequent HIPEC or EPIC [7, 35]. In addition, CRS reduces the already present peritoneal tumour burden to a microscopic level.

The perioperative period appears crucial regarding the host's defences against the growth of tumour cells, leaving the resection sites and abraded peritoneal surfaces at high risk for tumour cell implantation [102, 103]. This was demonstrated by the development of detectable liver metastases from 'dormant' metastatic cells after liver resection in a rat model [104]. Laparotomy per se enhances the growth of intraperitoneal tumour implants in mice [105]. These implants are then trapped by formation of adhesions and fibrin deposits during the postoperative period [2–7, 9, 106]. The washout effect with large volumes of fluid, such as during EPIC, may decrease fibrin accumulation and adhesions, particularly if the fluid is left in the cavity, or eliminate tumour cells before they fix within scar tissues. The elimination of platelets, white blood cells and monocytes may also diminish the production of tumour growth factors associated with the wound healing process [107].

EPIC can be used as 'adjuvant' therapy to HIPEC to consolidate and further improve its results. HIPEC does not alter the pharmacokinetics of intraperitoneal 5-FU during the early postoperative period [108].

Lastly the implementation of HIPEC in an operating theatre requires specialized organization due to risk of hospital staff exposure to chemotherapeutic agents. Multiple institutes have published guidelines on the handling of intraoperative chemotherapeutic drugs [109, 110]. Additionally heating intraperitoneal drugs requires specific perioperative logistics and materials. EPIC on the other hand is more easily administered. A closed abdomen technique is used limiting the environmental risks for medical personal. The chemotherapeutic agents don't need to be heated. Surgeons at non-specialized centres diagnosing limited PC could use this method to administer IPC after CRS. The additional cost in terms of time and money is minimal since the therapy is instituted and completed within a normal postoperative time frame.

5.5 Surgical Technical Procedure

After completing CRS and prior to closing the abdominal incision, abdominal catheters are placed to administer the intraperitoneal drugs. In most studies, a Tenckhoff catheter is placed

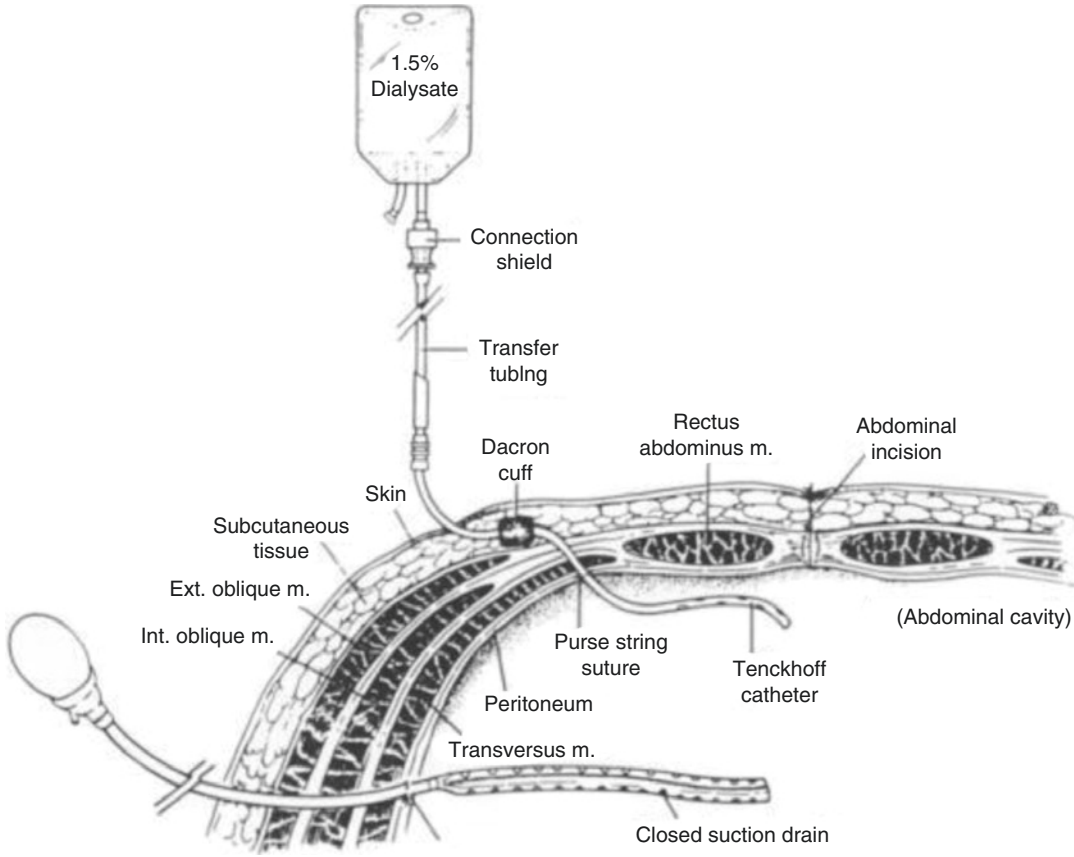

Fig. 5.1 Technical aspects of maintaining abdominal access during EPIC [87]

(Fig. 5.1), but a subcutaneous port or regular drainage catheters can also be used and are potentially cheaper [111, 112]. A purse string suture might be used at the peritoneal level in order to minimize leakage of peritoneal fluid and chemotherapy. After closure of the abdomen, abdominal lavage is instituted to remove blood clots and tissue debris that resulted from surgery. One litre of fluid, either glucose-based dialysis fluid or Ringer lactate solution, is infused into the abdominal cavity as rapid as possible. This lavage fluid is immediately drained by simple gravity. This procedure is repeated on an hourly basis until the effluent is clear. Abdominal lavage is then repeated every 4 h until EPIC begins. The chemotherapeutic solution is instilled as fast as possible after clamping all drainage catheters and left to linger in the abdomen for 23 h after which it is drained and another instillation cycle begins. In most cases, the fluids are infused as fast as possible by gravity, but an infusion pump may also be used [87]. One study infused the drugs during a 3-h period [107].

5.6 Chemotherapy Schedules for EPIC

There are many different drug schedules used for EPIC, although the majority is based either on MMC and 5-FU or taxanes (Tables 5.3, 5.4 and 5.5). The first schedule uses intraperitoneal MMC and 5-FU and was introduced by Sugarbaker (Table 5.6) [87, 131]. After CRS, a single dose of intraperitoneal MMC, 10–12 mg/m^2, is administered on day 1. These concentrations are much higher than those required to reliably kill CRC cell lines in vitro [132, 133]. In case of reduced

Table 5.3 Clinical studies: EPIC in colorectal carcinoma

Clinical studies		*N*	Chemotherapeutic regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 3 J (%)
Sugarbaker [87]	EPIC	25	EPIC: MMC (12 mg/m^2 (7 pt) or 10 mg/m^2 (16 pt), day 0) + 5-FU (20 mg/kg (7 patients) max 2 g or 15 mg/kg (16 patients) max 1800 mg, day 1–5) (1 L peritoneal dialysis solution)	NA	NA	NA	NA	NA	NA
Sugarbaker [113]	EPIC/SPIC	51	SPIC: 12 cycles of intraperitoneal 5-FU (20 mg/kg over 5 days) + IV: MMC (10 mg/m^2)	NA	BA	36	NA	NA	NA
			EPIC + SIPC: MMC (10 mg/m^2) (day1) and 5-FU (15 mg/kg) (day 2–5) + 5 cycles of 5-FU (20 mg/kg over 5 days) + IV: MMC (10 mg/m^2)						
			EPIC: MMC (10 mg/m^2) (day 1) and 5-FU (15 mg/kg) (day 2–5) (1 L peritoneal dialysis solution)						
Pestieau [114]	HIPEC + EPIC	5	HIPEC: MMC (drug dose not reported)	NA	61.4	NS	100	NA	NA
		99	EPIC: 5-FU (drug dose not reported)						
Vaillant [107]	EPIC	133	IV: 5-FU (1 g, intraoperative) EPIC: 5-FU (600 mg/m^2, 6 days, start day 4–14) (1.5 L peritoneal dialysis fluid)	NA	NA	NA	74	NA	NA
	Control	134	No adjuvant therapy	NA	NA	NA	69	NA	NA
Cavalieri [39]	HIPEC	40	(CRC) HIPEC: Cisplatin (25 mg/m^2/L) (90 min) (ovarian) HIPEC: MMC (3.3 mg/m^2/L) and cisplatin (25 mg/m^2/L) (90 min)	NA	NA	NA	NA	NA	NA
	EPIC		(CRC) EPIC: 5-FU (13.5 mg/kg) + lederfolin (125 mg/m^2) (day1–5) (ovarian) EPIC: Cisplatin (25 mg/m^2) (day1–5) (1 L peritoneal dialysis solution)						
Elias [40]	HIPEC	27	HIPEC: MMC (21 pt) (5, 8, or 10 mg/L) and MMC (6 pt) (20 mg/m^2) + cisplatin (200 mg/m^2) (60 min)	29	18	11	1	NA	NA
	EPIC	37	EPIC: MMC (10 g/m^2, day 1) + 5-FU (500 mg/m^2, day 2–6) (1 L/m^2 ringer lactate)	20	13	8	3	NA	NA

(continued)

Table 5.3 (continued)

Clinical studies		*N*	Chemotherapeutic regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 3 J (%)
Mahteme [112]	EPIC + SPIC	18	EPIC: 5-FU (550 mg/m^2 day1–6), IV: LV (60 mg/m^2), 4–6 weeks intervals (500 mL saline 0.9%)	NA	60	NA	28	NA	NA
	Control	18	IV: Methotrexate, 5-FU and LV (8 pt) and 5-FU and LV (6 pt)	NA	10	NA	5	NA	NA
Carmignani [115]	HIPEC	10	HIPEC: MMC (10–12.5 mg/m^2, 90 min)	NA	NA	NA	NA	NA	NA
	EPIC	7	EPIC: 5-FU (650 mg/m^2, day 1–5) (1 L peritoneal dialysis solution buffered with 50 mEq/L of sodium bicarbonate)	NA	NA	NA	NA	NA	NA
	HIPEC + EPIC	10	HIPEC: MMC (10–12.5 mg/m^2, 90 min), EPIC: 5-FU (650 mg/m^2, day 1–5)	NA	NA	NA	NA	NA	NA
Glehen [55]	EPIC	123	Multiple drug regimens used EPIC: (1 L peritoneal dialysis solution)	72	NA	39	19	NA	16
	HIPEC + EPIC	112							
	HIPEC	271							
Elias [116]	EPIC + IV chemo	16	EPIC: MMC (drug dose not reported) (day 1) and 5-FU (drug dose not reported) (days 2–5) (2 L peritoneal dialysis solution)	NA	NA	NA	NA	NA	NA
			IV: 5-FU and LV bimonthly for 6 months						
	IV chemo	19	IV: 5-FU and LV bimonthly for 6 months	NA	NA	NA	NA	NA	NA
Gomez [117]	HIPEC/EPIC	266	Multiple drug regimens used	88	NA	44	32	33	NA
Da Silva Gomes [118]	EPIC + SPIC	36	EPIC: MMC (10–12.5 mg/m^2, day 1), 5-FU (650 mg/m^2, day 2–5)	NA	NA	NA	NA	NA	NA
			SPIC: 5-FU (650 mg/m^2, day 1–5) + IV: MMC (10 mg/m^2 in women and 12.5 mg/m^2 in men, day 3) (once per month for 6 months) (1 L peritoneal dialysis solution)						
	HIPEC + EPIC	34	HIPEC: MMC (10–12.5 mg/m^2) (90 min)						
			EPIC: 5-FU (650 mg/m^2, day 1–5) (1 L peritoneal dialysis solution)						
Elias [119]	HIPEC	23	HIPEC: oxaliplatin (460 mg/m^2, 30 min) + IV: LV (20 mg/m^2) and 5-FU(400 mg/m^2)	NA	NA	NA	54	NA	NA
	EPIC	23	EPIC: MMC (10 mg/m^2, day 0) + 5-FU (650 mg/m^2, day 1–4) (1 L/m^2 peritoneal dialysis fluid)	NA	NA	NA	28	NA	NA

(continued)

Table 5.3 (continued)

Clinical studies		*N*	Chemotherapeutic regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 3 J (%)
Hadi [120]	HIPEC and/or EPIC	70	Multiple drug regimens used	NA	NA	NA	NA	NA	NA
Yan [121]	HIPEC and/or EPIC	30	HIPEC: MMC (10–12.5 mg/m^2) (90 min) EPIC: 5-FU (650 mg/m^2, day 1–5), (2 pt) floxuridine	72	64	NA	NA	NA	NA
Fuzun [122]	Non-heated IPEC and/or EPIC	29	Non-heated IPEC: 5-FU (1000 mg, 20 min) EPIC: 5- FU (750 mg/m^2, day 1–5) (carrier fluid unknown)	72	NA	13	NA	NA	7
Hansson [123]	SPIC	85	(CRC-PMP) SPIC: 5-FU (550 mg/m^2) IV: LV (60 mg/m^2), day 1–6, 4–6 week intervals 8 courses (ovarium-DMPM) SPIC: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2), day 1–6, 4–6 week intervals 8 courses	NA	NA	NA	NA	NA	NA
	HIPEC + EPIC	28	(CRC 8) HIPEC: oxaliplatin (460 mg/m^2) IV: 5-FU (500 mg/m^2) + LV (60 mg/m^2), EPIC: 5-FU (550 mg/m^2, day 1–5) + LV (60 mg/m^2) (PMP 17) HIPEC: MMC (12 mg/m^2) EPIC: 5-FU (550 mg/m^2, day 1–5) + LV (60 mg/m^2) (Ovarium 2) HIPEC oxaliplatin (460 mg/m^2) EPIC: paclitaxel (20 mg/m^2, day 1–5) (DMPM 1) HIPEC cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) EPIC: paclitaxel (20 mg/m^2, day 1–5)	NA	NA	NA	NA	NA	NA
	HIPEC + EPIC + SPIC	2	cfr higher	NA	NA	NA	NA	NA	NA
Saxena [124]	HIPEC + EPIC	34	HIPEC: MMC (10–12 mg/m^2, 90 min) EPIC: 5-FU (650–800 mg/m^2, day 1–5) (1 L peritoneal dialysis solution)	NA	NA	NA	NA	NA	NA
	HIPEC	12	HIPEC: MMC (10–12 mg/m^2, 90 min)	NA	NA	NA	NA	NA	NA
	EPIC	17	EPIC: 5-FU (650–800 mg/m^2, day 1–5) (1 L peritoneal dialysis solution)	NA	NA	NA	NA	NA	NA
Elias [125]	HIPEC	440	Multiple drug regimens were used	NA	NA	NA	NA	NA	NA
	EPIC	83	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (600 mg/m^2, day 2–5) (0.8–1 L/m^2 peritoneal dialysis solution)						

(continued)

Table 5.3 (continued)

Clinical studies		*N*	Chemotherapeutic regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 3 J (%)
Chua [111]	HIPEC	30	HIPEC: MMC (10–12.5 mg/m^2) or HIPEC: Oxaliplatin (460 mg/m^2) + IV 5-FU (400 mg/m^2) and LV (20 mg/m^2)	NA	NA	NA	NA	19	NA
	EPIC	23	EPIC: 5-FU(650–800 mg/m^2, day 1–5) (1 L peritoneal dialysis solution)	NA	NA	NA	NA	28	NA
	HIPEC + EPIC	45	cfr higher	NA	NA	NA	NA	38	NA
Lam [126]	HIPEC	56	HIPEC: oxaliplatin (400 mg, 60 min.) + IV 5-FU (800 mg)	91	NA	46	NA	NA	6
	HIPEC + EPIC	37	HIPEC: MMC (12–15 mg, 60 min.) EPIC: 5-FU (1000 mg, day 1–5) (1.5 L peritoneal dialysis solution)	86	NA	51	NA	NA	22

Table 5.4 Clinical studies: EPIC in gastric carcinoma

Author	Year	*N*	Drug regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 5 J (%)
Yu et al. [127]	1998	125	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (700 mg/m^2, day 4–5) (1 L peritoneal dialysis solution)	NA	NA	54	NA	NA	NA
		123	None	NA	NA	37	NA	NA	NA
Cheong et al. [84]	2006	154	EPIC: MMC (15 mg, day 0) + 5-FU (500 mg/m^2) and Cisplatin (40 mg/m^2)(day 1–4)(repeated every 4 w for 12 cycles) (500 mL 0.9% saline solution)	NA	NA	NA	NA	11.4	NA
Kwon et al. [128]	2014	65	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (700 mg/m^2, day 4–5) IV: 5-FU + cisplatin or epirubicin (1 L 0.9% saline solution)	NA	NA	NA	47.4	NA	53.1
		180	IV: 5-FU + cisplatin or epirubicin	NA	NA	NA	26.7	NA	29.7

renal or hepatic function, MMC is given one-half the calculated dose. Other centres implementing this schedule used a dose of MMC varying between 10 and 15 mg/m^2. Some adapt their dose depending on sex, 10 mg/m^2 in women and 12.5 mg/m^2 in men [118]. A higher incidence of postoperative neutropenia has been described in female patients after HIPEC with MMC. The underlying mechanism causing this sex difference is still unclear [134, 135].

Hereafter, on day 2 till day 5, 5-FU is administered intraperitoneally. Initially a dose of 20 mg/kg (max dose 2 g) was used, but to decrease toxicity, the dose was reduced to 15 mg/kg (max 1800 mg) [131, 132, 136]. Reliable cell kill has been achieved with much lower doses in

Table 5.5 Clinical studies reporting on survival after EPIC in DMPM

Author		*N*	Chemotherapy regimen	OS 1 J (%)	OS 2 J (%)	OS 3 J (%)	OS 5 J (%)	Median OS (months)	RFS 3 J (%)
Sugarbaker [129]	HIPEC	42	HIPEC: doxorubicin (15 mg/m^2) + cisplatin (50 mg/m^2) (90 min)	NS	NS	NS	44	NS	NS
	HIPEC + EPIC	58	IV: ifosfamide (1300 mg/m^2, 90 min during HIPEC) + sodium methanethiolate (Mesna) (256 mg/m^2) EPIC: paclitaxel (20 mg/m^2, day 1–5)	NS	NS	NS	52	NS	NS
	HIPEC + EPIC + SPIC	29	(8 pt) SPIC: Paclitaxel (20 mg/m^2, day 1–5, 1 week of every month) (21 pt) SPIC: pemetrexed (1000 mg/m^2) + IV: cisplatin (75 mg/m^2) (cycles every 3 weeks)	NS	NS	NS	75	NS	NS
Yan [130]	HIPEC	24	HIPEC: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) (90 min)	82	67	57	49	NS	NS
	HIPEC + EPIC	46	EPIC: paclitaxel (20 mg/m^2, day 1–5)						

in vitro cell lines [132]. In more recent studies, the calculation of the 5-FU dose is either based on body surface area (500 and 800 mg/m^2) or on body mass (15 mg/kg) [40, 67, 113, 115, 128, 137]. The large differences in concentrations used when the dose of 5-FU was calculated on body surface area were not explained by the authors. The most frequently used dosimetry was 650 mg/m^2.

Alterations in locoregional pharmacokinetics of intraperitoneal 5-FU over a 5-day schedule of drug instillation have been noted [87]. This is not taken into account in current EPIC schedules; the concentration used each day is kept constant. A dose reduction of 25% may be used in patients older than 65 years of age, patients with prior extensive chemotherapy or patients who have had abdominal or pelvic radiation therapy [113].

The instillation of fluids is repeated every 24 h. Unfortunately, the concentration of intraperitoneal infused 5-FU declines rapidly; only 1% remains after 3 h [138]. Repeating intraperitoneal infusions more frequently should result in maintained higher intraperitoneal drug concentrations.

The timing of MMC and 5-FU administration is variable. MMC is administered on the day of operation or on the first postoperative day. 5-FU is administered for 4 or 5 consecutive days starting on the first or second postoperative day, depending on the timing of MMC instillation. In one study, EPIC was initiated as soon as it was deemed likely that patients had no postoperative complications and passed gas and their temperature was 38 °C or less. A dose of intraperitoneal drugs was administered for 6 consecutive days. Infusion started between 4 and 14 days after surgery [107]. When major complications arose during EPIC, the treatment was halted prematurely. This schedule was used for colorectal, appendix and gastric cancer. Other intraperitoneal drugs might be added to 5-FU-based EPIC such as lederfolin (125 mg/m^2) for primary colon and appendicular tumours or cisplatin (25/40 mg/m^2) for

Table 5.6 Instruction for the use of 5-FU and taxanes during EPIC

Post-op days 1–5:
5-fluorouracil
1. 5-FU mg (650 mg/m^2 × m^2) (maximum dose 1400 mg), and 50 meq sodium bicarbonate in cc 1.5% dextrose peritoneal dialysis solution via IP catheter on . Last dose
2. Infuse as rapidly as possible via Tenckhoff catheter. Dwell for 23 h and drain for 1 h prior to next instillation
3. Use 1 L 1.5% dextrose peritoneal dialysis solution for body surface 1–2 m^2, 1.5 L for body surface >2 m^2
4. Continue to drain abdominal cavity after last dose until Tenckhoff catheter is removed
5. During initial 6 h after chemotherapy infusion, patient's bed should be kept flat. The patient should be on the right side during infusion. Turn at ½ h post infusion onto the left side and continue to change sides at ½ h intervals for 6 h
6. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy
7. Remove venous compression boots during first 6 h after chemotherapy administration to facilitate turning
Paclitaxel
1. Paclitaxel mg (20–40 mg/m^2 × m^2) (maximum dose 80 mg) in cc 1.5% dextrose peritoneal dialysis solution via IP catheter on . Last dose
2. Infuse as rapidly as possible via Tenckhoff catheter. Dwell for 23 h. Drain from Tenckhoff × 15 min before draining all catheters for 1 h prior to next instillation
3. Use 1 L 1 5% dextrose peritoneal dialysis solution for body surface 1–2 m^2, 1.5 L for body surface >2 m^2
4. Continue to drain abdominal cavity after last dose until Tenckhoff catheter is removed
5. During initial 6 h after chemotherapy infusion, patient's bed should be kept flat. The patient should be on the right side during infusion. Turn at ½ h post infusion onto the left side and continue to change sides at ½ h intervals for 6 h
6. Monitor with pulse oximeter during the first 6 h of intraperitoneal chemotherapy
7. Remove venous compression boots during first 6 h after chemotherapy administration to facilitate turning

Modified from: Sugerbaker PH. Technical handbook for the integration of cytoreductive surgery and perioperative intraperitoneal chemotherapy into the surgical management of gastrointestinal and gynaecologic malignancy, 4th edition, 2005

primary ovarian and gastric cancers [39, 84]. When this EPIC schedule is used as adjunct to CRS and HIPEC, MMC is administered during HIPEC and only 5-FU is administered as the EPIC treatment. The same concentrations of 5-FU are used as described above.

A second schedule is based on taxanes and is used for diffuse malignant peritoneal mesothelioma (DMPM) and ovarian cancer. Intraperitoneal paclitaxel, 20 mg/m^2/day, is administered for 5 days. The instillation is initiated on the first postoperative day [129, 130, 139]. In selected patients, especially those who have ascites, EPIC with paclitaxel (20–40 mg/m^2 for 5 days) followed by SPIC is recommended [139].

Again the instillation is repeated every 24 h. Luckily for paclitaxel, the intraperitoneal drug concentration remains constant up to 23 h after instillation [140].

Thirdly, other drugs might be used for EPIC such as cisplatin (25 mg/m^2) for primary ovarian tumours [39].

The duration of EPIC, currently 4–5 days, has no pharmacologic basis. But we do know instillation is best administered within 24 h of resection [141].

In addition to the chemotherapeutic drugs and their dosages used during EPIC, the type and volume of intraperitoneal infused carrier fluid is also variable. The intraperitoneal fluid volume is one of the principle factors influencing intraperitoneal drug distribution. The more fluid is infused, the better the intraperitoneal distribution [92]. The maximum volume is limited by discomfort to the patient due to abdominal distention and elevation in intra-abdominal pressure. The volume of intraperitoneal infused fluid diminishes over time due to absorption [138].

In initial studies by Sugarbaker, 2 L were infused intra-abdominally, but this caused too much abdominal discomfort [87, 131, 136]. They reduced the abdominal volume to 1 L. In some other studies, only 500 mL is used [93, 112]. To optimize the abdominally infused

volumes in relation to individual variations in intra-abdominal volume, some centres use a body surface area-based volume, 0.8–1 L/m^2 [31, 125, 142].

The most frequently used carrier fluid is 1.5% glucose peritoneal dialysis fluid, but Ringer lactate or saline 0.9% solutions are also used [40, 93, 112]. Several studies explored the effect of different carrier fluids on changes in intra-abdominal volume over time and on intra-abdominal drug concentrations. Larger intraperitoneal volumes are maintained with high molecular weight solutions: 4% icodextrin, 6% hetastarch and hypertonic 3% sodium chloride solutions [138, 140]. The use of different carrier fluids does not influence the decline in intraperitoneal 5-FU concentrations over time [138]. The use of a hetastarch drug carrier results in longer intraperitoneal retention of paclitaxel leading to higher concentrations for a longer time [140]. In two studies, peritoneal dialysis fluid was buffered with sodium bicarbonate (50 mEq/L) [115, 120]. We would advise a body surface area-based volume, 0.8–1 L/m^2, of 1.5% glucose peritoneal dialysis or hetastarch solution to be used.

Another way of improving the fluid distribution is abdominal massage and shifting the patients during EPIC. Especially Trendelenburg position is useful in improving distribution to the diaphragm [92]. Instruction for the use of 5-FU and taxanes during EPIC advise changing the patients position during intraperitoneal drug instillation (Table 5.6). It is unclear if such measures have been implemented in clinical studies.

5.7 Pharmacology and Rationale of Intraperitoneal 5-FU

Muggia pointed out that 5-fluorouracil is an essential component of chemotherapeutic regimens for treating gastrointestinal cancers. 5-FU is an inhibitor of the enzyme thymidylate synthetase that catalyses the methylation of thymine in the synthesis of thymidine, which is a precursor of DNA [143–145]. It enters the cell directly and is then metabolized to its active metabolite [144].

5-FU is not chemically compatible with other drugs in a mixed solution for infusion or instillation which limits its intravenous and intraperitoneal use along with other agents.

Although a small molecular weight molecule (130.08 Dalton), 5-FU has an AUC ratio > 400 which makes it a favourable drug for intraperitoneal administration [108, 136] (Table 5.2). Figure 5.2 demonstrates the dose intensification associated with intraperitoneal 5-FU administration. The plasma concentration is significantly lower than the intraperitoneal concentration due to inactivation of the drug in the systemic circula-

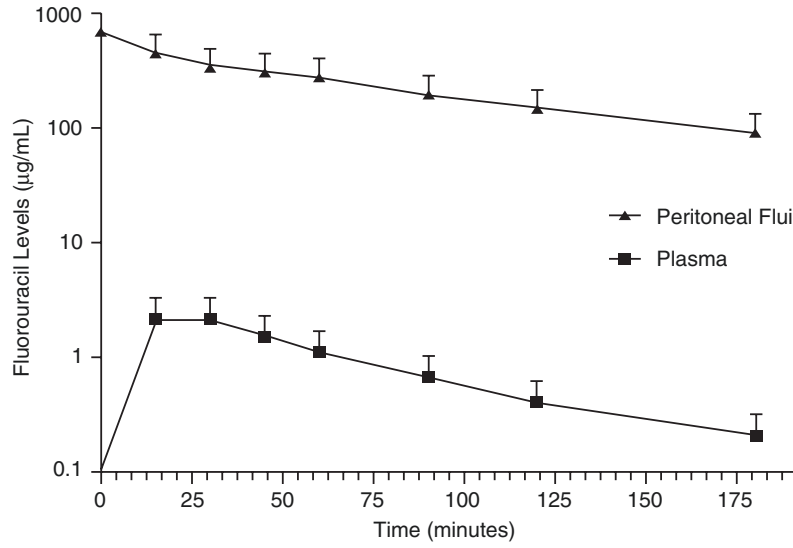

Fig. 5.2 5-FU concentrations in peritoneal fluid and plasma after EPIC administration [67]

tion by dihydropyrimidine dehydrogenase, an enzyme that is present in the liver in abundance and in the mucosa of the gastrointestinal tract and peripheral lymphocytes [146]. However, since the clinical activity of the drug is cell cycle dependent, this benefit is lost if repeated daily instillations are not performed. Clinical data has shown a high concentration of 5-FU after intraperitoneal instillation. Being a small molecule, it gets rapidly cleared from the peritoneal cavity, yet the rapid metabolism at various sites maintains a large area under the curve ratio of peritoneal fluid to plasma. Also, the early postoperative period allows a repetitive exposure of the drug to peritoneal surface tissues to allow increased activity of its cell cycle-specific activity [67].

5.8 Pharmacology and Rationale of Intraperitoneal Taxanes

Currently, the two clinically available taxanes are paclitaxel and docetaxel. The taxanes are antimitotic agents that reversibly stabilize the microtubule against depolymerisation, thereby disrupting normal microtubule dynamics. When cells re-enter cell cycle, they develop multiple or lobulated nuclei with abnormally arranged nuclear pores and numerous gaps in the lamina ultimately leading to cell death [69, 98, 147]. These agents also have the ability to induce apoptotic death in susceptible cells. They stimulate the phosphorylation of bcl-2, a protein that is part of the apoptosis mechanism in many cancer cells and inhibits apoptosis when overexpressed [148, 149]. Phosphorylation of bcl-2 decreases its anti-apoptotic effects and leads to programmed cell death. Additionally, paclitaxel and docetaxel have also shown, both in vitro and in vivo, to inhibit angiogenesis at low concentrations that do not affect cancer cell proliferation [149, 150].

These agents exert cytotoxic activity against a broad range of tumours. Because of their high molecular weight, 853.9 Dalton for paclitaxel and 861.9 Dalton for docetaxel, these molecules have a remarkable high AUC ratio of 1000 and 552, respectively (Table 5.2). This translates into a clear pharmacokinetic advantage for intraperitoneal administration (Fig. 5.3) [70, 140, 144].

5.9 Mortality and Morbidity of EPIC

A major concern in regard to the use of EPIC as adjuvant therapy after CRS is the added morbidity and mortality (Table 5.7).

Overall mortality varies from 0 to 18% [39, 40, 55, 113, 115, 116, 119, 120, 130, 152]. In one study, an overall mortality rate of 12% was noted, but this was due to the inexperience of the surgical team; during a later period, the mortality

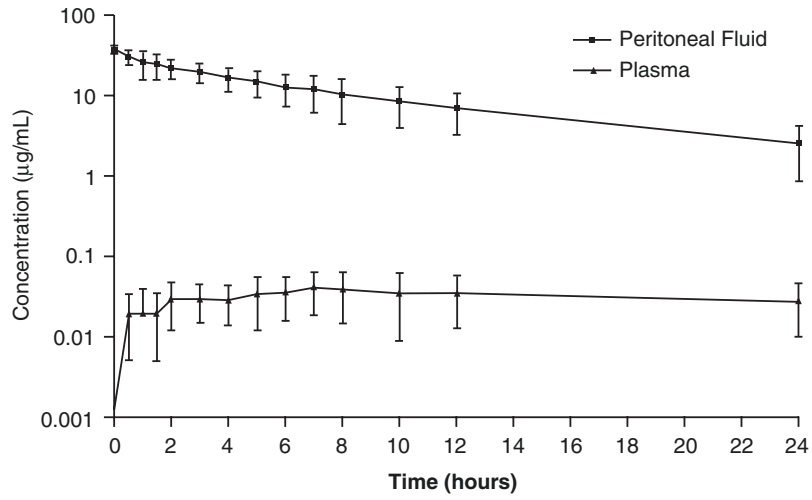

Fig. 5.3 Plasma and peritoneal fluid concentration versus time following a single EPIC administration of paclitaxel (20–40 mg/m^2) [151]

Table 5.7 Clinical studies: morbidity and mortality of EPIC

Clinical studies	Year	Tumour	*N*	HIPEC regimen	Morbidity (%)	Grade III (%)	Grade IV (%)	Digestive fistula (%)	Mortality (%)
Sugarbaker [113]	1995	CRC	51	SPIC: 12 cycles of intraperitoneal 5-FU combined with systemic MMC	NA	NA	NA	1.8	1.7
				EPIC + adj. IPC: 5-FU and MMC+ 5 cycles of 5-FU and MMC					
				EPIC: MMC and 5-FU					
Yu [152]	1998	Gastric cancer	125	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (700 mg/m^2, day 4–5)	28.8	NA	NA	NA	4.8
			123	None	20.3	NA	NA	NA	0.8
Elias [40]	2001	CRC	27	HIPEC: MMC (5, 8, or 10 mg/L) (21 pt) and MMC (20 mg/m^2) (6 pt) + cisplatin (200 mg/m^2)	NA	NA	NA	18	11
			37	EPIC: MMC (10 g/m^2, day 1) + 5-FU (500 mg/m^2, day 2–6)	NA	NA	NA	18	8
Cavalieri [39]	2000	CRC	40	Multiple drug regimens were used	35	NA	NA	11.4	12
Vaillant [107]	2000	CRC	133	EPIC: 5-FU (600 mg/m^2, day 4–6)	19.5	NA	NA	NA	1,5
			134	No adjuvant therapy	12	NA	NA	NA	0
Elias [116]	2004	CRC	16	EPIC: MMC (day 1) and 5-FU (days 2–5)	50	NA	NA	NA	18
			19	IV: 5-FU and LV bimonthly for 6 months	37	NA	NA	NA	0
Carmignani [115]	2004	CRC	10	HIPEC: MMC (10–12.5 mg/m^2, 90 min)	14.8	NA	NA	NA	0
			7	EPIC: 5-FU (650 mg/m^2, day 1–5)					
			10	HIPEC: MMC (10–12.5 mg/m^2, 90 min), EPIC: 5-FU (650 mg/m^2, day 1–5)					
Glehen	2004	CRC	123	Multiple drug regimens used (Table 5.8)	23	NA	NA	8.3	4
			112						
			271						
Elias	2006	CRC	23	HIPEC: oxaliplatin (460 mg/m^2, 30 min) + IV: LV (20 mg/m^2) and 5-FU (400 mg/m^2)	47.8	NA	NA	0	0
			23	EPIC: MMC (10 mg/m^2, day 0) + 5-FU (650 mg/m^2, day 1–4)	56.5	NA	NA	26.1	8.7
Hadi	2006	CRC	70	Multiple regimens	39.4	NA	NA	8	5.6
Yan	2006	CRC	30	HIPEC: MMC (10–12.5 mg/m^2, 90 min)	NA	43	10	30	0
				EPIC: 5-FU (650 mg/m^2, day 1–5), EPIC: floxuridine (2 pt)					
Fuzun	2006	CRC	29	Non-heated IPEC: 5-FU (1000 mg, 20 min)	41	NA	20	NA	0
				EPIC: 5- FU (750 mg/m^2, day 1–5)					

(continued)

Table 5.7 (continued)

Clinical studies	Year	Tumour	*N*	HIPEC regimen	Morbidity (%)	Grade III (%)	Grade IV (%)	Digestive fistula (%)	Mortality (%)
Cheong	2006	Gastric cancer	154	EPIC: MMC (15 mg, day 0) + 5-FU (500 mg/m^2) and cisplatin (40 mg/m^2) (day 1–4) (repeated every 4 w for 12 cycles)	22.7	NA	NA	NA	2.6
Yan	2006	DMPM	24	HIPEC: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) (90 min)	NA	29	13	NA	8.3
			46	EPIC: paclitaxel (20 mg/m^2, day 1–5)	NA	26	15	NA	0
Hansson	2008	CRC PMP ovarium DMPM	85	(CRC-PMP) SPIC: 5-FU (550 mg/m^2) IV: LV (60 mg/m^2) (day 1–6, 4–6 week intervals 8 courses) (ovarium-DMPM) SPIC: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) (day 1–6, 4–6 week intervals 8 courses)	41	NS	NS	8.1	4
			28	(CRC 8) HIPEC: oxaliplatin (460 mg/m^2) IV: 5-FU (500 mg/m^2) + LV (60 mg/m^2), EPIC: 5-FU (550 mg/m^2, day 1–5) + LV (60 mg/m^2) (PMP 17) HIPEC: MMC (12 mg/m^2) EPIC: 5-FU (550 mg/m^2, day 1–5) + LV (60 mg/m^2) (ovarium 2) HIPEC: oxaliplatin (460 mg/m^2) EPIC: paclitaxel (20 mg/m^2, day 1–5) (DMPM 1) HIPEC: cisplatin (50 mg/m^2) + doxorubicin (15 mg/m^2) + EPIC: paclitaxel (20 mg/m^2, day 1–5)					
			2	cfr higher					
Saxena	2010	CRC	34	HIPEC: MMC (10–12 mg/m^2, 90 min) EPIC: 5-FU (650–800 mg/m^2, day 1–5)	NA	18	12	NA	0
			12	HIPEC: MMC (10–12 mg/m^2, 90 min)	NA	17	33	NA	0
			17	EPIC: 5-FU (650–800 mg/m^2, day 1–5)	NA	6	18	NA	0
Elias	2010	CRC	440	Multiple drug regimens were used	NA	26.2		7.6	3.2
			83	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (600 mg/m^2, day 2–5)					
Chua	2013	CRC	30	HIPEC: MMC (10–12.5 mg/m^2) or HIPEC: oxaliplatin (460 mg/m^2) + IV 5-FU (400 mg/m^2) and LV (20 mg/m^2)	NA	44		14	NA
			23	EPIC: 5-FU(650–800 mg/m^2, day 1–5)					
			45	cfr higher	NA	44		13	NA
Kwon et al	2014	Gastric cancer	65	EPIC: MMC (10 mg/m^2, day 1) + 5-FU (700 mg/m^2, day 4–5)	10.8	1.5	3	NA	3.1
				IV: 5-FU + cisplatin or epirubicin					
			180	IV: 5-FU + cisplatin or epirubicin	8.9	5	2	NA	1.7
Lam	2015	CRC	56	HIPEC: oxaliplatin (400 mg, 60 min) + IV 5-FU (800 mg)	NA	19.6		NA	NA
			37	HIPEC: MMC (12–15 mg, 60 min) EPIC: 5-FU (1000 mg, day 1–5)	NA	43.2		NA	NA

dropped to 5% [39]. A second study reported a mortality of 18%, but mortality was associated with a high PCI and simultaneous resection of liver metastases [116]. In well-selected patients and in experienced hands, mortality varies between 0 and 9% [39, 40, 55, 113, 115, 119, 120, 130, 152]. Mortality is related to multiple intraoperative (diffuse PC with a PCI > 28, combined liver resections) and preoperative (obesity, clotting factor deficit) risk factors [40]. The cause of death varied widely: stroke, diffuse intravascular coagulation, abdominal sepsis either caused by perforation or not, respiratory failure, aplasia, acute renal insufficiency, pulmonary embolism and cardiac failure. The mortality after EPIC and HIPEC is not significantly different [53].

Treatment of PM with CRS and EPIC is associated with a high overall morbidity: 14.8–56.5% [39, 55, 115, 116, 119, 120, 152]. This morbidity after CRS and EPIC is not significantly different of that seen after CRS and HIPEC [40]. In the majority of patients, morbidity is caused by intra-abdominal complications: bowel perforation (28%) [113], anastomotic leaks (3–5%) [39, 113, 152], abdominal sepsis without anastomotic leak (8–21%) [40, 119, 120, 152], gastrointestinal fistula (8–30%) [39, 40, 55, 119–121] or bleeding (0–9%) [39, 119, 120, 152]. Some unusual abdominal complications are also reported: chyle leak (1.6%) [152], intestinal obstruction (2.4%) [152], wound infection (3.2–13%) [121, 152] and gallbladder perforation (4%) [115].

In several studies, EPIC is associated with a prolonged postoperative paralytic ileus [107, 152]. A median duration of postoperative paralytic ileus of 21 days is reported. Increased age and extent of CRS lead to a higher incidence of postoperative paralytic ileus [77].

Although the rate of anastomotic leaks after EPIC is similar to that of HIPEC, the rate of gastrointestinal fistula formation is higher [39, 40, 55, 119–121]. A possible hypothesis for the high rate of digestive fistulas is that a 'floating period' hampers the process whereby digestive sutures are rapidly sealed by physiologic postoperative adhesions [119]. Intestinal obstruction, prior abdominal/pelvic radiation therapy or prior intraperitoneal chemotherapy further increases the rate of postoperative fistula formation [113]. The presence of an ileostomy in this context was not a statistically significant prognostic factor with regard to the need for additional surgery [39].

In one study comparing gastric resection with or without EPIC, EPIC resulted in a significant higher incidence of abdominal sepsis/abscesses without anastomotic leak and of postoperative bleeding. Most of these cases could be treated conservatively so the difference in re-interventions was not significant [152].

The rate of extra-abdominal complications is approximately 54% [40]. The most frequently reported complications are urinary infection (13–22.6%) [119, 121], pulmonary infection (13%) [119], cardiac complications (13%) [121], neutropenia (3%) [121], seizure (3%) [121] and deep vein thrombosis (2.3%) [77].

A low-grade transient leukopenia is described in 2.4% of patients after gastric resection and EPIC [152]. After CRS and EPIC for PC from CRC, the incidence of clinical significant leukopenia or thrombocytopenia is also low [107, 153]. In one study, a death was caused by cerebral haemorrhage caused by thrombocytopenia, and in a second one, a patient died of aplasia [55, 153]. In a third study, three deaths occurred due to pancytopenia, two of which had earlier treatment with intravenous MMC. It is unclear if these patients were treated with EPIC, HIPEC or without IPC [120].

When the complications are compared by the Clavien-Dindo classification, 43% had a grade I–II complication [121, 154]. The incidence of grade III complications varies between 8 and 43% [39, 40, 55, 119, 130, 152]. The most frequent grade III adverse events in order of incidence are a low haemoglobin level, central line sepsis, urinary tract infection with elevated temperature and leucocytosis, dehydration requiring intravenous therapy and delirium. Other, more rare grade III adverse events included stroke, pleural effusion, thrombocytopenia and pulmonary embolism (requiring removal of intravenous catheter). Grade IV complications of 10–40% are reported [121]. Postoperative bleeding requiring urgent return to the operating room, respiratory failure requiring orotracheal intubation, pulmo-

nary embolism (requiring ICU admission), anastomotic leak, pancreatic leak, duodenal leak and bile leak are the reported grade IV adverse events.

Multiple factors increase morbidity: the extent of PM, and consequently the extent of CRS, the use of either EPIC or HIPEC, the number of units of blood needed, simultaneous liver metastases resection and the duration of surgery [55, 120]. The incidence of postoperative morbidity alters little with the accumulation of experience in contrast to mortality [39].

When EPIC is added to CRS and HIPEC, most studies show an increased morbidity and mortality [55, 121, 126], higher rates of pleural effusion, intra-abdominal collection and pneumothorax [121].

The use of EPIC generally seems to be well tolerated by patients. In contrast to morbidity, reflecting the complications caused by CRS and EPIC, tolerance reflects the postoperative problems solely caused by EPIC. The occurrence of chemical peritonitis, as described after SPIC with cisplatin and 5-FU, seems to be non-existent [107]. Abdominal distention and pain have been reported in 7–10% of patients when large volumes, >1 L, of fluid are infused [93, 107, 155]. Nausea and vomiting are present in 4–25% of the patients, but it is unclear if this is related to morbidity or tolerance [107, 156]. With experience, the risk of technical problems, such as leaks around the catheter or obstruction of the catheter, can be reduced. Leaks were observed in 7.5% of patients [107].

The reported median hospital stay after EPIC is 23–25 days [40, 130].

These data support continued application of this management plan in selected patients. Good performance status, absence of significant comorbidities, uncomplicated CRS, no heavy systemic pretreatment and CCR-0 are requirements for patient selection.

5.10 Clinical Studies on EPIC

5.10.1 Ovarian Cancer

Little data exist concerning treatment of PM from ovarian cancer with EPIC. In two series, by Gomez et al. and Hansson et al., patients with PM from ovarian cancer were included in EPIC treatment regimens [117, 123]. Unfortunately, the data for ovarian cancer were not analysed separately from other tumour origins. In a third retrospective case series, including 51 patients, the survival was assessed in patients treated with CRS plus HIPEC and EPIC. The study group consisted of cancers originating in the ovaria, fallopian tube, endometrium and uterus. The mean survival was 22.8 months. The authors concluded that CRS, HIPEC and EPIC are crucial options in patients with advanced gynaecological cancers [157]. Lastly, one case report on CRS and EPIC for ovarian carcinosarcoma has been published [158].

Although no strong clinical evidence on the treatment of ovarian PM with EPIC exists, data from three randomized controlled trials evaluating SPIC based on cisplatin might provide some insight on the use of postoperative IPC [81, 82, 159, 160]. This level-one evidence demonstrated a significant benefit of SPIC for patients with advanced ovarian cancer after CRS. They compared a combination of intravenous chemotherapy and SPIC, to intravenous chemotherapy alone. Reported OS in the SPIC groups was 41–52 months. The first treatment was administered during the early postoperative period, similar to EPIC schedules. Mainly due to catheter-related problems, the number of patients who completed all cycles of SPIC ranged from 42 to 71%. Sub-analysis of these data comparing the groups who received a single cycle during the early postoperative period to those who received multiple cycles could provide useful information.

5.10.2 Colorectal Carcinoma and High-Grade Appendical Carcinoma

Several publications reported on the use of EPIC in CRC and in high-grade appendical carcinoma (Table 5.5). The first two reports on EPIC were presented by Sugarbaker. The first, published in 1990, reported solely on the in vivo pharmacokinetics of MMC and 5-FU during EPIC. No survival data were reported [87]. The second trial, reporting the results of 51 patients with PC from CRC and 130 patients with PM from appendical

carcinoma treated with EPIC, was published in 1995 [113]. Patients were included over a period of 10 years. There was some maturation of treatments strategies during this decade from SPIC over SPIC and EPIC to EPIC alone. A 3-year survival of 36 and 73% was attained for colorectal and appendical carcinoma, respectively. This significant survival difference was attributed to the inclusion of low-grade appendical carcinomas. Due to these results, in subsequent trials, low-grade appendical carcinomas were excluded. Clearly, the bias in patient selection and the three different treatment strategies used during the inclusion period obscure the results.

A retrospective case series by Pestieau et al. reported on 104 patients with PM of CRC treated with CRS, HIPEC and EPIC [114]. The first group (n = 5) was treated for synchronous PM, and the second group (n = 99) presented with metachronous PM after primary resection in an outcentre hospital. The major difference between the groups was the timing of IPC in relation to primary resection. For the first group, a 5-year OS of 100% was reported. Median survival in the second group depended on CCR, 24 months in the CCR 0 group and 12 months in the CCR 1–2 groups.

In a study by Vaillant et al., 317 patients had treatment (either CRS and EPIC or CRS alone) randomly assigned to them [107]. Patients with resectable, T3N0M0 (stage II) or N + M0 (stage III), CRC were included. Of the intended 350 patients, only 317 patients were included. The trial was prematurely closed because the option of no adjuvant treatment after resection of stage III colon cancer was no longer considered ethical. 5-year OS and PFS rates were higher in the treatment group compared to CRS alone (74% vs. 69% and 68% vs. 62%, respectively). The difference did not reach statistical significance. Tumour recurrences were observed in 33 patients (24.8%) in the EPIC group and in 42 patients (31.3%) in the control group.

Cavalieri et al. evaluated the treatment of PM with CRS and either HIPEC or EPIC in 40 patients of whom 20 had ovarian cystadenocarcinoma, 14 mucinous CRC, 4 malignant mesothelioma and 2 appendicular adenocarcinoma [39]. HIPEC was the first choice of treatment, but when the intraoperative decline of the patient's general condition did not permit a longer operative time, EPIC was performed instead. At a median follow-up of 20 months, the 2-year OS of the series was 61.4%, with a median survival of 30 months. Only pooled results were presented, and no differentiation was made between tumour type and EPIC versus HIPEC.

Elias et al. performed a retrospective study of 64 patients who had PM arising from CRC, 19 (29.6%) of whom also had systemic metastases [40, 119]. Thirty-seven patients were treated with CRS and EPIC and 27 patients with CRS and HIPEC. OS was lower in the EPIC group than in the HIPEC group, but not significantly.

Matheme et al. compared 18 patients treated with CRS and EPIC to 18 patients from the Nordic chemotherapy trials with similar characteristics who were treated with intravenous chemotherapy without surgery [112]. All patients were diagnosed with isolated PM from CRC. The EPIC group also received SPIC with a median of 3 cycles. Median survival was 32 months in the EPIC group compared to 14 months in the intravenous chemotherapy group.

Carmignani et al. performed a prospective case series reporting on 27 patients treated with CRS and complete resection of distant metastases. Ten received HIPEC with EPIC and seven EPIC alone [115]. All patients had PM from CRC and systemic metastases (16 liver, 6 lung, 4 liver and lung and 1 supraclavicular lymph node). Median survival for the entire group was 15.2 months, but after CCR0, a median survival of 20.6 months was achieved. An additional survival benefit after CRS with either HIPEC or EPIC compared to CRS alone was not explored.

Glehen et al. retrospectively analysed data of 506 patients with isolated PM from CRC [55]. Data were collected from 28 French centres. Two hundred seventy-one patients were treated with CRS and HIPEC alone, 123 patients underwent CRS and EPIC alone, and 112 patients underwent CRS and both HIPEC and EPIC. The chemotherapeutic schemes for EPIC and HIPEC varied widely (Table 5.8). Likewise, the adjuvant intravenous chemotherapy regimens administered were diverse. OS rates were higher with the perioperative association of HIPEC with EPIC (21 months) compared to HIPEC (19.2 months) or EPIC (19.2 months) alone, but this difference

Table 5.8 Type of drugs and regimens used for HIPEC and EPIC

	HIPEC		EPIC	
Drug	No. patients	%	No. patients	%
MMC	274	71.4	2	0.9
MMC + cisplatin	48	12.5	–	–
Oxaliplatin	32	8.4	–	–
MMC + 5-FU	–	–	113	52.1
5-FU	–	–	95	43.8
Others	29	7.7	7	3.2
Total	383	100	235	100

was not significant. All groups showed increased survival compared to historical data.

Elias et al. attempted the first randomized controlled trial including CRS and EPIC in a treatment regimen for isolated PM of CRC in 2004 [116]. Although inclusion of 90 patients was intended, only 35 patients were included. The low accrual was caused by patient dissatisfaction with the randomisation and inclusion criteria. Referred patients specifically came to be treated with CRS in combination with EPIC. Despite a strong scientific rationale for this approved clinical research, patients considered the trial unethical and detrimental to their right to choose their treatment. All patients received neoadjuvant intravenous 5-FU- and leucovorin-based chemotherapy regimens for at least 3 months. Patients were randomized after complete CRS to either EPIC with adjuvant intravenous chemotherapy (5-FU based), 16 patients, or systemic chemotherapy alone, 19 patients. Seven patients from the first group were too debilitated after treatment with EPIC to receive adjuvant intravenous chemotherapy within 1 month after surgery. Despite the low accrual, a surprising 60% 2-year OS is reported in both trial arms.

Gomez et al. reported on the use of CRS and HIPEC, EPIC or both in nine Spanish institutions [117]. Two hundred sixty-six patients were included of which 51 had PM from CRC. Again, a multitude of chemotherapeutic regimens were used, and the data on different tumours were pooled together so no strong conclusion can be made.

In a retrospective analysis by Da Silva Gomes et al., data on 70 patients with isolated PM from CRC, who had a CCR-0 resection and were treated with IPC, were analysed [118]. Thirty-six patients were treated with CRS, EPIC and SPIC. Thirty-four patients were treated with HIPEC of which nine received additional EPIC. No conclusions could be made about EPIC due to the absence of separated data analyses.

Elias et al. compared treatment consisting of CRS combined with either EPIC or HIPEC [119]. Both groups consisted of 23 patients selected from earlier trials [40, 153]. Five-year OS was higher, albeit not significantly, in the HIPEC group compared to the EPIC group (54% and 28%, respectively). PM recurred significantly more frequent in the EPIC group (57%) than in the HIPEC group (26%).

Hadi et al. treated multiple cancer types with either HIPEC or EPIC [120]. The different treatment regimens reflected evolution in IPC schedules used at their hospital. Data were not selectively analysed for the different cancer types.

Yan et al. analysed 30 patients with isolated PM from CRC treated with CRS and IPC. It was unclear which patients were treated with EPIC and/or HIPEC [121]. The median survival was 29 months, with 1- and 2-year OS of 72% and 64%, respectively.

Between 1996 and 2005, Fuzun et al. collected data from 29 patients treated with CRS combined with IPC for isolated PM from CRC [122]. IPC consisted of non-heated intraperitoneal perioperative chemotherapy or EPIC. The 1-year, 3-year and 5-year OS was 72%, 13% and 7%, respectively.

Hansson et al. analysed 123 patients treated with CRS and IPC for PM [123]. The primary tumour types were 59 CRC (51 colon cancer and

8 rectal cancer), 52 pseudomyxoma peritonei (38 high-grade tumours and 14 low-grade tumours), 8 DMPM and 4 recurrent ovarian cancers after third or fourth line of systemic chemotherapy. An initial 85 patients were treated with SPIC, hereafter 28 patients were treated with HIPEC and EPIC, and 2 patients received HIPEC, EPIC and SPIC. Six patients were treated with CRS alone and two patients had unresectable disease. The median survival of the 59 CRC patients was 27 months at a mean follow-up of 36 months.

Saxena et al. evaluated risk factors for complications after treatment with CRS and IPC: in 64 patients [124], 34 (54%) were treated with both HIPEC and EPIC; in 12 patients (19%), only HIPEC was administered; and in 17 patients (27%), only EPIC was administered. No data on survival were reported.

In a retrospective case series, Elias et al. reported on 440 patients treated with CRS and IPC for PM originating from 4 types of primaries in 23 French centres [125]. The primary tumour originated from colon in 341 patients, rectum in 27 patients, appendical cancer without pseudomyxoma in 41 patients and small bowel in 31 patients. All included patients had CCR0 resections. Eighty-three patients (16%) had undergone EPIC. In multivariate analysis, EPIC and HIPEC showed no advantage over one another.

In a prospective case series, Chua et al. evaluated the use of CRS and IPC [111]. All patients were treated with an intention to administer both HIPEC and EPIC. However, in circumstances where high-risk surgical procedures were performed and there was a reasonable risk of complications, EPIC was withheld. In patients treated without the availability of HIPEC due to resource limitation, EPIC was delivered as the sole IPC regimen. There were 98 patients with PC of CRC origin; 45 patients received HIPEC and EPIC, 30 patients HIPEC and 23 patients EPIC. The median PFS was 33 months for the HIPEC and EPIC group, 19 months for HIPEC alone and 20 months in the EPIC alone group. This difference was significant when the HIPEC and EPIC group was compared to the HIPEC or EPIC groups. The 5-year OS was 41% in the HIPEC and EPIC group, 46% in the HIPEC alone group and 44% in the EPIC alone group.

Lastly, Lam et al. compared 93 patients with CRC or high-grade appendical PM treated with CRS and HIPEC + EPIC or CRS and HIPEC alone [126]. Survival did not differ between IPC regimens. The 3-year OS and PFS rates were 50 and 21% for HIPEC + EPIC and 46 and 6% for HIPEC alone.

There is currently one ongoing trial evaluating EPIC and HIPEC after CRS in patient with PM from appendical, rectal or colorectal origin. The details of this study are outlined further in this chapter (NCT01815359, ICARuS trial).

5.10.3 Gastric Cancer

The historical prognosis of gastric cancer is very poor [161, 162]. Major advances in the multimodal treatment strategy for gastric cancer, D2 resection, ECC (epirubicin, cisplatin and capecitabine), ECF (epirubicin, cisplatin and 5-FU), chemoradiation and trastuzumab, have changed the clinical management of gastric cancer over the last 15 years. Multiple phase III trials revealed a survival benefit after treatment with these improved perioperative intravenous chemotherapy schedules and adjuvant treatment strategies [163–166]. The reported 5-year OS is currently 36–71% [163, 165, 167–169]. Unfortunately, for advanced gastric cancer, stage IIIB, the 5-year PFS rates remain limited, 37.6% [169]. Studies of recurrence patterns after curative surgery for stage III and IV gastric cancer demonstrate that in about 50% of patients, the peritoneum is the first site of recurrence [128, 169]. Even at death, the tumour often remains confined to the abdominal cavity [9, 170, 171]. EPIC has been propagated to eradicate residual microscopic peritoneal disease after resection of stage III gastric cancer and improve PFS an OS. Furthermore, EPIC has been used as treatment for stage IV gastric cancer with isolated PM.

Three studies evaluated the use of EPIC after resection of gastric cancer (Table 5.6). Yu et al. compared curative gastric resection with or

without EPIC in a randomized controlled trial [137]. Patients with all grades, I–IV, of gastric cancer were included with exclusion of systemic metastases. Gastric resection with EPIC resulted in improved 5-year OS compared to surgery alone (54% and 38%, respectively). When analysed by stage, the difference in 5-year OS was not significantly different between stage I, II and IV diseases. In patients with stage III disease, there was a significant increase of 5-year OS (57% vs. 23%) in the EPIC group.

In a study by Cheong et al., a median survival of 11.4 months was reported [84]. Patients with stage IV gastric cancer without systemic metastases were treated with CRS, EPIC and SPIC every 4 weeks for 12 cycles. In patients where a CCR0 resection could be achieved, median survival was 25.5 months. Although the investigator initially planned 12 cycles of SPIC, only a median of 4 cycles were administered.

In a third study by Kwon et al., 245 patients with stage III, macroscopically serosa-invading, gastric cancer were included [128], 65 were treated with curative resection with EPIC and 180 with curative resection alone. The 5-year OS and PFS for the EPIC group were 47.4% and 53.1%, respectively, and those for the non-EPIC group were 26.7% and 29.7%, respectively. The rates of peritoneal recurrence for the EPIC group and the non-EPIC group were 18.5% and 32.2%, respectively.

The use of EPIC as an adjuvant treatment for stage III, macroscopically serosa-invading, gastric cancer has the possibility to prevent peritoneal recurrence, thus improving survival at an acceptable morbidity and mortality. One study concerning the adjuvant treatment of gastric cancer with EPIC is currently ongoing; the details are described later (EPIC-GC, NCT02205008) [163]. Depending on these oncoming results, multimodal treatment protocols will probably be further improved.

5.10.4 Diffuse Malignant Peritoneal Mesothelioma

The group of Sugarbaker has reported on their results of EPIC in DMPM in two reports; a third manuscript has currently been accepted including data from these two earlier reports [129, 139, 172]. These studies reveal a progressively more aggressive treatment of DMPM. Currently CRS is complemented with HIPEC, EPIC and SIPC. The results show that this aggressive treatment leads to a 5-year OS of 75%. Seeing the rarity of this disease, it will be impossible to perform a RCT on its treatment. Current data warrants the use of aggressive treatment using CRS and multiple forms of IPC for DMPM. Yan et al. report the results of a multi-institutional database collecting data for all patients who underwent CRS and HIPEC between 1989 and 2009 for DPMP [48]. Ninety-four patients were treated with EPIC as part of their regimen; unfortunately, no results are reported on this subgroup. OS data for the complete group are similar to those reported by Sugarbaker.

5.11 Discussion

The introduction of CRS and HIPEC has greatly improved the prognosis of patients with PM [13, 14, 19, 49, 78, 79]. In spite of these improvements, the majority of patients still die of PM [51]. The use of EPIC might be a tool to consolidate and further improve outcome.

CRS is a vital part of curative treatment for PM. CCR is the main prognostic indicator of survival in PM treatment [13]. The additional benefit of IPC is still subject to discussion [173, 174]. Some data suggests the added benefit of IPC is marginal. A similar 2-year survival of 60% was noted comparing CRS and CRS+ EPIC [55]. Three and five-year OS of 45.5 and 29.64% have been reported after CRS and systemic chemotherapy [175]. In direct opposition, a much larger amount of data supports the adjuvant use of IPC. One phase III study has clearly identified the benefit of CRS and HIPEC in PM of CRC [13, 14]. A large amount of retrospective data supports the use of CRS in combination with HIPEC. Moreover, EPIC diminishes local recurrence of stages III and IV gastric cancer. Ongoing randomized trials comparing CRS to CRS+ HIPEC will hopefully clarify the separate contribution of both therapies (NCT00769405;

GASTRIPEC, NCT02158988; PRODIGE 7, EudraCT Number: 2006-006175-20) [173, 174]. Despite these considerations, both CRS and IPC currently have an important role in the treatment of PC. EPIC is one of these IPC modalities that deserves further exploration.

EPIC is used as sole adjuvant treatment after CRS for isolated PM. This strategy leads to improved OS and PFS compared to palliative treatment. In spite of a more pronounced effect of EPIC in comparison to HIPEC in an experimental rat study, this benefit cannot be reproduced in human subjects [50, 176]. The large body of evidence currently supporting CRS and HIPEC has made it the primary choice in treating PM of CRC. In contrast, little data exists concerning EPIC and all of it of low quality. The use of EPIC or HIPEC as adjuvant treatment strategies to CRS is currently being explored in a phase II trial, the ICARuS (Intraperitoneal Chemotherapy After cytoReductive Surgery) trial (NCT01815359). Patients with isolated PM from appendical, rectal or colon cancer are treated with CRS and randomized to either treatment with HIPEC (MMC) or EPIC (5-FU and LV). The primary outcome measure is 3-year PFS. Surgical grade III–V complications/toxicities or chemotherapy-related grade IV or V toxicities are the secondary outcome measures. Inclusion commenced in March 2013 and 220 patients should be included by March 2018.

Some authors have suggested situations in which the use of EPIC might be acceptable. Firstly, the treatment of PM with CRS and IPC is best performed concomitantly with the primary resection [113, 114]. In case treatment with HIPEC is not available, rather than performing a second procedure or implementing a wait-and-see strategy, EPIC can be performed. They argue that EPIC is preferable to no treatment or to poorly performed HIPEC. In our opinion, if one is unable to perform a correct CRS and HIPEC, they should abort all further extensive surgery and refer the patient to an established PM treatment centre. Secondly, EPIC has been proposed as salvage treatment strategy in PM patients if after CRS, the intraoperative decline of the patients impedes the addition of HIPEC to the procedure. The exposure of a patient, in no condition to receive HIPEC, to a technique with substantial mortality and morbidity seems unwarranted.

The adjuvant use of EPIC to D2 resection in stage III gastric cancer leads to a promising reduction in local recurrence [128, 137]. Especially patients with nodal disease extending towards the lateral margins of excision are likely to benefit from EPIC. This treatment strategy is currently under investigation in the EPIC-GC trial (NCT02205008). Patients with gastric adenocarcinoma who are candidate for curative D2 resection of the stomach are randomized to either EPIC (MMC and 5-FU) and adjuvant systemic chemotherapy with S-1 or adjuvant systemic chemotherapy with S-1. The primary end point is 3-year PFS. Secondary outcome measures are surgical toxicity grade III–V and chemotherapy toxicity grade III–V. Inclusion commenced in October 2012, and 230 patients should be included by November 2018. Unfortunately, extrapolation of data retrieved from an oriental population to a Western population is flawed. A geographical difference in survival from gastric cancer has been noted [177]. Moreover, the use of S-1 is prohibited in some populations due to intolerance.

Lastly, EPIC has successfully been used in combination with CRS, HIPEC and SPIC for DMPM [129]. This suggests that the addition of EPIC to other treatment strategies has an additional benefit, alas at the cost of higher morbidity [55, 121, 126].

In our opinion, the question is no longer ‘Should we use EPIC or HIPEC?’ but ‘In which patients could EPIC add an additional benefit to CRS and HIPEC?’. Similar to the results in DMPM, the addition of EPIC to CRS and HIPEC has resulted in promising results in PM of CRC. The key, as always, will probably be patient selection. We would suggest the addition of EPIC to CRS and HIPEC in patients with little comorbidity, CCR0 and no prior extensive pretreatment. Tumour biology will probably play an increasingly important role; patients with stable disease or clear response to prior treatment could benefit most of this additional treatment.

The morbidity and mortality related to CRS and EPIC are similar to those reported after CRS and HIPEC. The combination of D2 gastric resection and EPIC for stage III disease is associated with a trend towards increased morbidity and mortality [152]. The majority of complications are related to surgery. Complications specifically related to EPIC are intra-abdominal abscesses in the absence of anastomotic leaks, gastrointestinal fistula formation and intra-abdominal bleeding. This might be caused by depletion of local clotting factors due to abdominal lavage and by depressed local immunity due to cytostatic drugs. The morbidity related to neutropenia or aplasia due to EPIC is low [152]. The morbidity after CRS and EPIC is caused by a multitude of complications many of which have a low incidence and are only reported in a minority of studies. The mortality is clearly related to experience. As such, patients in need of such treatment should be referred to an established PM treatment centre.

Unfortunately, most studies concerning EPIC are of low quality. A large amount of these studies were reviewed for meta-analysis by Cao et al. [50]. Eventually, only two studies were retained for analysis with a very limited number of patients: 34.

The optimal way of administering chemotherapeutic drugs during the early postoperative period is still unclear. Some factors have been examined: the intraperitoneal infused fluid volume, carrier fluid, patient position and drug pharmacokinetics. But as many factors remain to be clarified, the use of different, suboptimal, EPIC regimens in current studies leads to bias in interpretation of the data.

In conclusion, although EPIC has been used for a long time now, many questions remain concerning its optimal use. Further research should first concentrate on the duration of drug instillation, number of cycles needed to produce cell kill and effect of different tumour biology. When these issues have been clarified, an optimal EPIC regimen will become evident and can be explored in randomized control trials. CRS and HIPEC will probably stay the basis for treatment of PM, but EPIC might provide an additional benefit in well-selected patients.

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Imaging of Peritoneal Cancers

6

Stephanie Nougaret

6.1 Introduction

Primary malignancies of the peritoneum are rare with secondary neoplastic involvement being a more common presentation. Many primary malignancies of the peritoneum have typical CT/MRI features which lead to their diagnosis. Most of these lesions originate from the mesenchyme, and a majority of them are benign. In contrast, secondary involvement of the peritoneum is quite frequent and most of the masses are malignant at histopathology. Tumors that arise elsewhere in the abdomen can reach and spread through direct extension, lymphatic dissemination, via hematogenic course, or seeding through the peritoneum. Currently, the role of preoperative imaging in patient with peritoneal metastases (PM) is to identify patients with advanced disease in whom a complete cytoreduction (CC-0/1) may not be feasible because of either the location or the volume of disease. The extent of disease before CRS partly determines whether a complete cytoreduction can be performed or not. Furthermore, the documentation of the disease locations enables to provide a surgical road map.

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In this short chapter, we will review the imaging characteristics of primary and secondary peritoneal tumors with a dedicated emphasis on how the radiologist can guide the management.

6.2 Primary Peritoneal Cancers

All primary peritoneal cancers are very uncommon (Table 6.1).

With the exception of cystic mesotheliomas, primary peritoneal cancers have a very poor prognosis despite aggressive management.

Primary peritoneal lesion can be distinguished on imaging using their composition pattern characteristics (solid or cystic) [1–3].

Table 6.1 Classification of peritoneal neoplasm

Primary peritoneal malignant tumors	Secondary neoplasms
• Mesothelial origin Malignant mesothelioma Cystic mesothelioma Well-differentiated papillary mesothelioma • Epithelial origin Primary peritoneal carcinoma • Smooth muscle origin Leiomyomatosis peritonealis disseminate • Desmoplastic small round cell tumor	Carcinomatosis • Ovarian • Gastrointestinal • Breast • Endometrial • Lung • Melanoma • Cervix • Adrenal • Pseudomyxoma peritonei

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6.2.1 Solid Pattern Lesion

6.2.1.1 Malignant Mesothelioma

Malignant peritoneal mesothelioma (MPM) is a rare but aggressive tumor similar to the pleural MM that occurs mostly in middle-aged males. Like pleural MPM, there is a link to asbestos exposure, though the association is weaker, especially in women. Peritoneal mesotheliomas account for 10–20% of MPMs.

On imaging, MPMs present either as diffuse or focal disease with diffuse form presenting poorer prognosis.

MPM may either present with variable appearance ranging from a very "dry" appearance consisting of solid nodules (Fig.6.1) to a "wet" appearance with ascites, peritoneal thickening, organ encasement, and solid nodules (Fig. 6.2) [1–3]. The mesentery may present with multiple small nodules or diffuse fat stranding which encases the mesenteric vessels (Fig. 6.2). Bowel wall thickening may also be present from direct mesenteric extension or peritoneal implants. The greater omentum aspect ranges from subtle fat stranding to the classic omental cake appearance. Unlike pleura mesothelioma, calcifications and calcification plaques are uncommon [1].

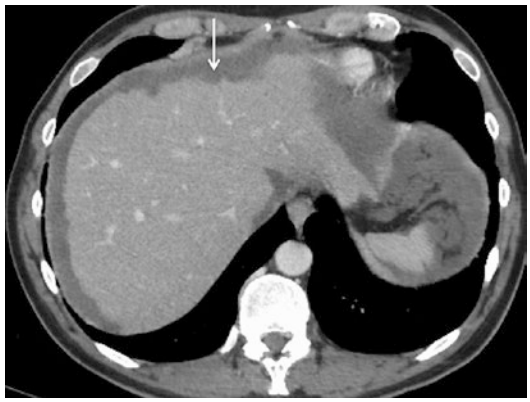

Fig. 6.1 Malignant peritoneal mesothelioma [1]. Non-contrast CT scan shows confluent large masses invading the large bowel (*arrow*) in keeping with a "dry" appearance of malignant mesothelioma

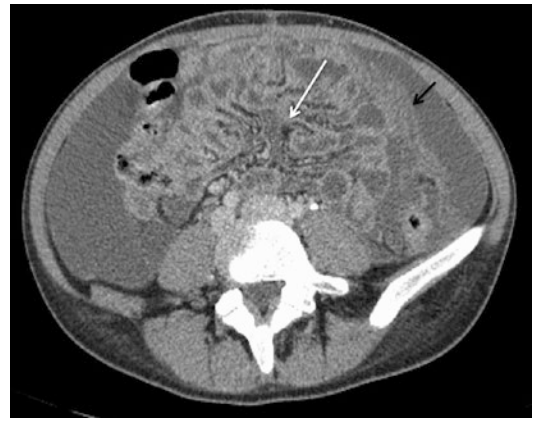

Fig. 6.2 Malignant peritoneal mesothelioma [1]. Contrast CT scan shows a diffuse omental caking (black arrow) and diffuse encasement of the mesentery (white arrow) associated with ascites giving a "wet" aspect of the abdominal cavity in a patient with malignant mesothelioma

6.2.1.2 Primary Peritoneal Serous Carcinoma

Primary peritoneal carcinoma (PPSC) is a serous papillary carcinoma affecting mostly postmenopausal women. Since peritoneal and ovarian epitheliums have the same embryologic origin, serous peritoneal carcinomatosis arising from these two sites is very similar. However, some differences can be found.

In PPSC, the abdominal peritoneum is more largely involved than the pelvic peritoneum. In ovarian serous cancer, complex ovarian masses are usually present in contrast to PPSC.

Extensive calcification of omental caking is present in many cases and is a useful CT finding for excluding mesothelioma.

The classic diagnostic criteria for PPC are (a) normal ovaries, (b) larger involvement of the abdomen compared to the pelvis, and (c) limited ovarian involvement without stromal invasion [2–5].

6.2.1.3 Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a highly aggressive malignancy. DSRCT affects mostly children and young adults.

The classic appearance of DSRCT on CT is a single or multiple, lobulated, solid, soft tissue mass which originate from the peritoneum. The masses may be calcified with central areas of necrosis. Given its highly aggressive potential, liver and lymph nodes metastases may be found [6, 7].

- *Leiomyomatosis peritonealis disseminata* is a rare benign disease that primarily affects women of reproductive age and is associated with uterine leiomyomas. This disease entity is characterized by the presence of multiple subperitoneal nodules composed of smooth muscle cells with a similar appearance of uterine leiomyomas [8, 9].

6.2.1.4 Sarcomas

Primary sarcomas of the peritoneum are rare as they usually arise from the retroperitoneum, with the liposarcoma subgroup the most frequent. In advanced cases, the tumor is very large and the peritoneal or retroperitoneal origin cannot be clearly assessed on cross-sectional imaging.

Apart from liposarcoma, the peritoneal sarcomas don't have any distinguishing features and generally manifest at CT as large, solitary masses [10, 11].

Liposarcomas present usually with two component: a fat attenuation part consistent with areas of well differentiation and associated soft tissue solid portion representing dedifferentiation content (Fig.6.3).

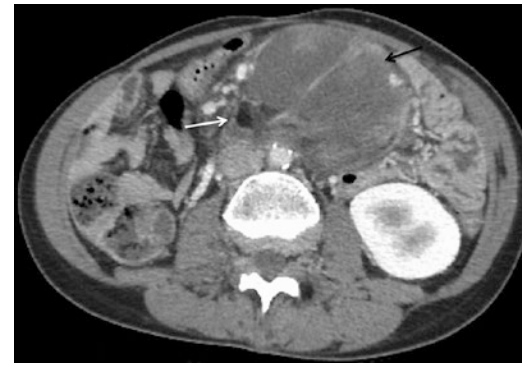

Fig. 6.3 Liposarcoma of the mesentery: large complex mass with two component, a very low attenuating part consistent with fat and representing the well-differentiated part and a solid enhancing component consistent with a undifferentiated part (black arrow)

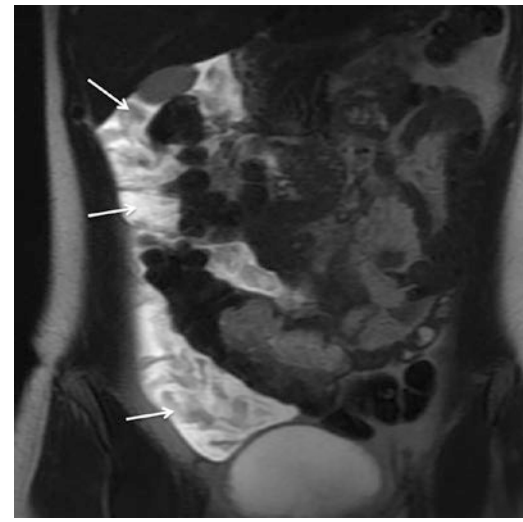

Fig.6.4 Cystic mesothelioma: shows a large, peritoneum-based multilocular cystic mass (white arrow). Note the thin cyst walls. No prominent soft tissue component is present

6.2.2 Cystic Pattern Lesion

6.2.2.1 Cystic Mesothelioma

Cystic mesothelioma (CM) is a benign tumor with a predilection for peritoneal surfaces of the pelvic viscera. It occurs mainly in young to middle-aged women. The tumor consists of multiple clusters of cysts lined with mesothelium separated by fibrous tissue. It's a nonaggressive tumor, but it may recur in 25–50% of the patients.

Classic imaging finding are multilocular thin-walled cystic masses. They occur mainly in the pelvis. On CT, the cysts are low attenuation and may demonstrate a thin wall enhancement after injection. MRI confirms the cystic composition of the mass, with high T2 signal intensity (Fig. 6.4) [12, 13].

The absence of significant mass effect, organ encasement, scalloping, calcification, soft tissue mass, or solid nodules helps distinguish cystic mesothelioma from malignant metastatic disease such as pseudomyxoma peritonei.

6.2.2.2 Lymphangiomas

Lymphangiomas may represent either congenital malformations of the lymphatic system or benign neoplasms and typically appear as large, thin-walled, multiloculated cysts at CT with T2 hyperintense signal on MRI (Fig. 6.5) [14].

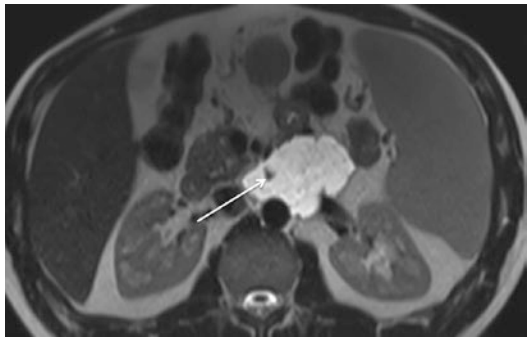

Fig. 6.5 T2-weighted MRI shows a multiloculated T2 hyperintense lesion with thin wall consistent with a lymphangioma (white arrow)

6.3 Secondary Peritoneal Cancers

Tumor can spread throughout the peritoneum via three mechanisms: direct, intraperitoneal spread, lymphatic invasion, and hematogenous dissemination. Here, we will focus on peritoneal seeding, which is highly frequent in ovarian or colorectal cancer [15, 16].

6.3.1 Pattern of Peritoneal Metastases (PM)

6.3.1.1 Detection of Peritoneal Metastases

Early PC can be missed on imaging. Early signs are:

- Apparition of ascites in a patient with a previous history of gastrointestinal of ovarian cancer, especially if loculated [17, 18]
- Abnormal enhancement of the peritoneum
- Subtle thickening, fine reticulonodular pattern, and nodularity along peritoneal surfaces (Fig. 6.6) [17, 18]

Detection of early sign of PM may be improved using oral contrast especially for small bowel

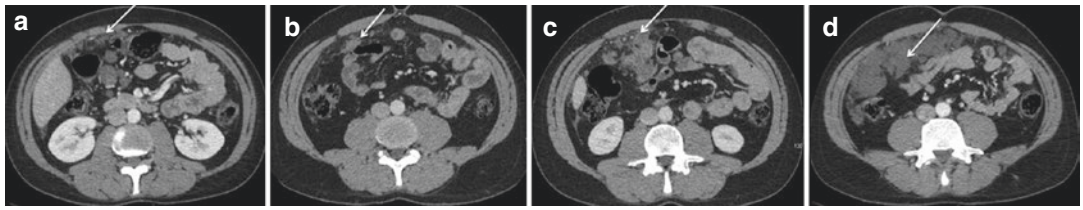

Fig. 6.6 Axial contrast-enhanced CT images show various morphologic patterns of peritoneal carcinomatosis ranging from very subtle disease to bulky infiltration in four patients with a history of colon cancer: a subtle fat stranding pattern (arrows in **a**), single nodule (arrow in **b**), multiple nodules (arrow in **c**), and omental caking (arrow in **d**)

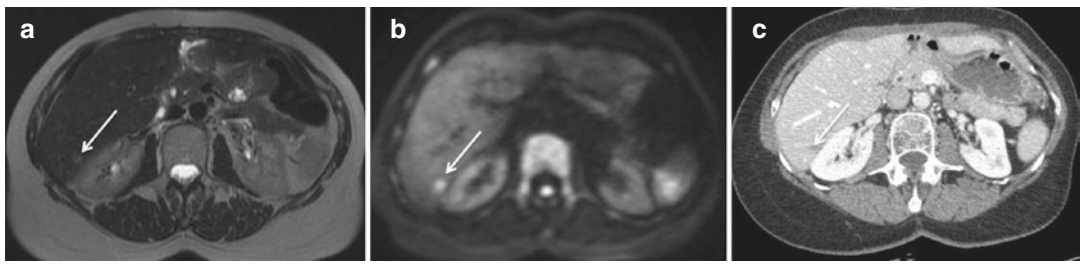

Fig. 6.7 Axial T2-weighted MR image (**a**) and contrast CT scan (**b**) show a vague T2 hyperintense (**a**) and CT hypodense (**c**) lesion within the liver surface which is easily depicted on diffusion-weighted imaging sequence (**c**), illustrating the added value of diffusion-weighted imaging in this case

serosal involvement. Moreover, recently, diffusion-weighted imaging (DWI) has been shown to detect larger number of implants compared to standard CT imaging (Fig. 6.7) [19–23]. DWI is a functional imaging tool that provides information about water mobility and tissue cellularity. Schematically, in highly cellular tissues such as tumor, water movements are restricted. Therefore, water molecules within such tissue retain their signal, which is shown on the DWI sequence as a hyperintense signal (Fig. 6.7). It has been shown that DWI increases the detection of peritoneal implants.

- In advanced cases, peritoneal deposits have a variable appearance from nodular to plaque-like appearance (Fig. 6.6). In advanced cases, nodules conglomerate and encase the abdominal organs.

6.3.1.2 What Are the Areas to Look at in a CT to Detect PM?

– Pelvis: The aspect of pelvic involvement is very variable and ranges from subtle thickening of the Douglas pouch to nodules and organ encasement (Fig. 6.8). Pelvic wall extension must be scrutinized, as it is a contraindication to optimal debulking. Invasion of the pelvic wall should be suspected if implants lie within 3 mm of the pelvic sidewall or when the iliac vessels are surrounded or distorted by tumor.
– Greater Omentum (Fig. 6.6).
– The greater omentum is commonly involved in patients with peritoneal metastases. Imaging signs range from subtle infiltrative stranding, nodules to confluent masses (called "omental caking") (Fig. 6.6).
– Mesentery
– The CT appearance of mesenteric CT and MR imaging may vary greatly from diffuse fat stranding called "misty mesentery" (Fig. 6.9) to clustered multiple small ovoid soft tissue nodules and to large masses (Fig. 6.10). Heavy mesenteric involvement causes rigidity and retraction, drawing the bowel loops together [24].
– Lymph nodes: Description of suprarenal lymph nodes especially at the level of celiac axis and porta hepatis must be reported. Indeed, this is frequently an indication for neoadjuvant chemotherapy. Lymph nodes may be seen along the mesentery root. Classic imaging characteristics suspicious for lymph nodes involvement are

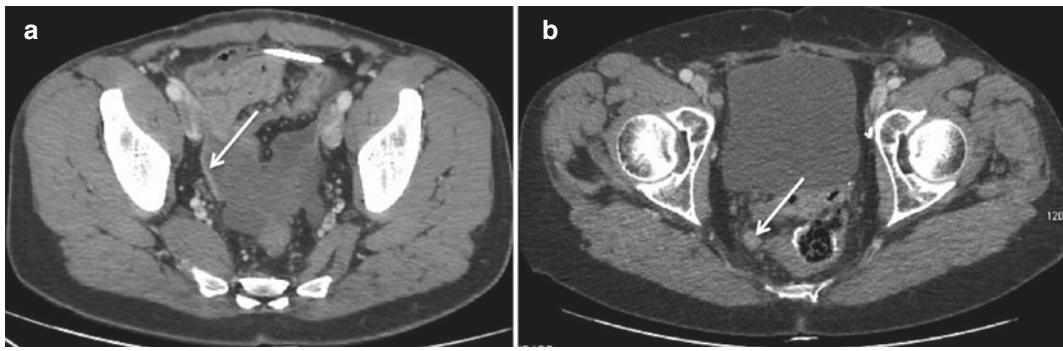

Fig. 6.8 Axial contrast CT showing thickening of the Douglas pouch (**a**) and soft tissue nodule on the mesorectal fascia (**b**)

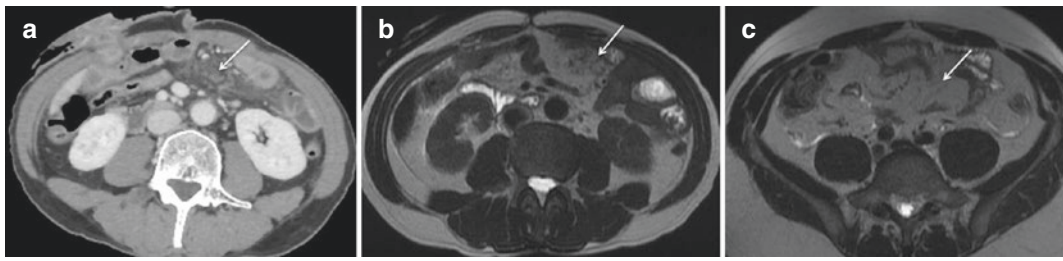

Fig. 6.9 Axial contrast CT shows diffuse infiltration with fat stranding of the mesentery (**a**) with corresponding image on T2-weighted image MRI (**b**). Note the difference of the absence of fat stranding in a normal mesentery in (**c**)

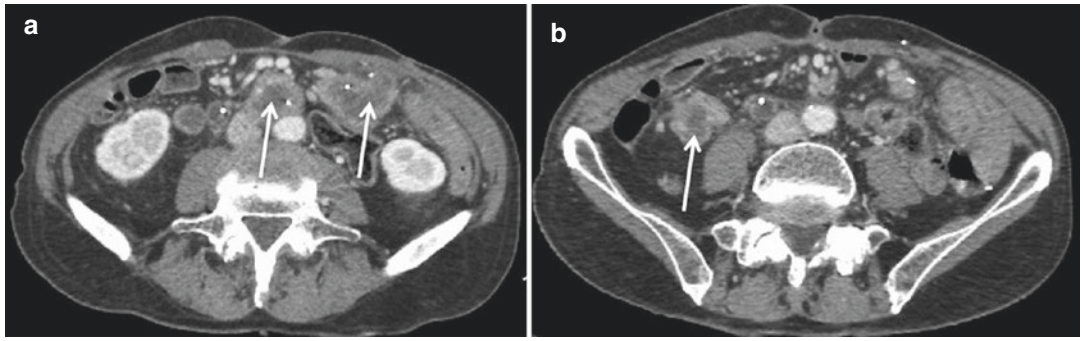

Fig. 6.10 Axial contrast CT demonstrating large nodules involving the mesentery (**a**) and a nodule within the small bowel serosa in a patient with colon cancer carcinomatosis (**b**)

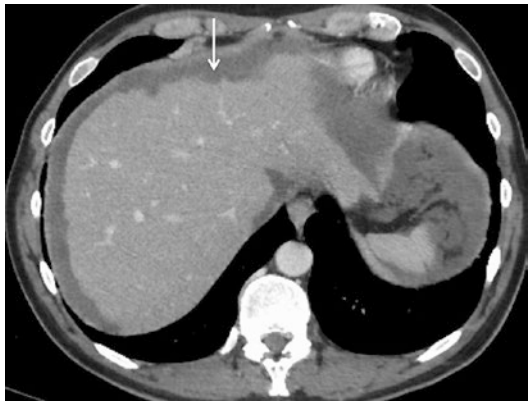

Fig. 6.11 Axial contrast-enhanced CT image shows massive carcinomatosis with diffuse liver capsule scalloping (white arrow). Note the diaphragm involvement with diaphragm nodular thickening (black arrow)

nodes size in short axis up to 10 mm, rounded necrotic nodes. Peritoneal lymphatics drain into the cardiophrenic lymph nodes, and their enlargement is indicative of peritoneal disease. These mediastinal lymph nodes are considered to be enlarged when the short axis exceeds 5 mm.

– Surface:

Liver Care must be taken to differentiate simple subcapsular deposit and perihepatic metastasis with liver parenchyma invasion (Fig. 6.11). Subcapsular deposits typically cause scalloping of underlying parenchyma with sometimes not well-defined border and shape. Reformatted images can be helpful to raise the final diagnosis.

Spleen Subcapsular deposits of the spleen results in scalloping of underlying parenchymal tissue and can invade the parenchyma.

Subphrenic Space Involvement Disease in these spaces is best detected with contrast-enhanced MRI and on reformatted coronal and sagittal imaging (Fig. 6.11).

Bowel Detection of serosal bowel implants is difficult. Focal nodules involving both serosal and adjacent mesentery are the classical appearance of bowel involvement (Fig. 6.10). CT usually underestimates small bowel involvement. MRI has been reported to be superior to CT scan in the assessment of the intestinal tract and mesenteric involvement.

Pleura Pleural effusion alone is not sufficient to assess stage IV disease. Cytology evaluation must be performed.

- Ligaments:

Lesser Omentum, Gastrohepatic, and Hepatoduodenal Ligament

Careful evaluation of these locations must be performed in order to exclude involvement.

Gastrosplenic, Splenorenal, and Splenopancreatic Ligaments and Lesser Sac

The gastrosplenic ligament connects the greater curvature of the stomach to the spleen. Carcinomatosis nodules are frequently involving this area (Fig. 6.12).

→Particular Form

Pseudomyxoma peritonei is caused by a ruptured adenocarcinoma of the appendix [25, 26]. CT and MRI have been shown to predict resectability [26].

The rupture of the appendix cause a mucinous seeding thought the peritoneum with specific imaging features:

- Diffuse scalloping of the capsular margins of the intraperitoneal organs such as liver and spleen. The scalloping sign is the most important diagnostic feature helping in the discrimination of pseudomyxoma peritonei from simple ascites. Indeed, the mucinous ascites has usually a very low attenuation.
- In more advanced cases, diffuse encasement of organs may be seen.
- On MRI, because of mucinous content, pseudomyxoma peritonei implants appear to be T2 hyperintense. Again, scalloping and organ encasement help differentiate it from ascites (Fig. 6.13).

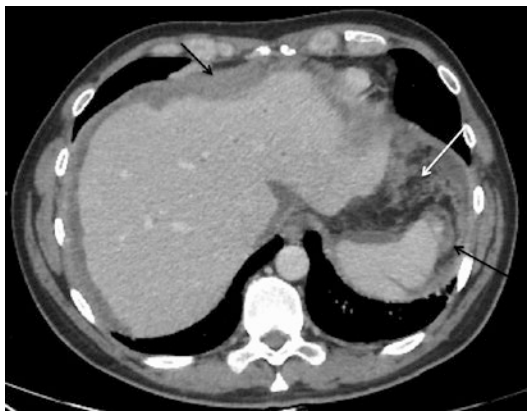

Fig. 6.12 Axial contrast-enhanced CT images show multiple nodules in the gastrosplenic ligament (white arrow). Note the associated capsular scalloping of the liver and spleen (black arrow)

6.4 The Radiologist's Role Is to Provide Information to the Surgeon That Affects Some Crucial Decisions [17]

6.4.1 The Distribution of Disease: Evaluation of Critical Sites

One of the important prognostic factors in patients undergoing in cytoreductive surgery and HIPEC is the completeness of cytoreduction. Though there are difference scores and definitions, the commonly used score is the completeness of cytoreduction score by Paul Sugarbaker and CRS is performed with the goal of leaving behind no residual disease (CC-0) or residual disease measuring <2.5 mm (CC-1) [27–29]. The radiologist's report should not comment on resectability but describe the disease distribution accurately to alert the surgeon about the presence of disease in some crucial

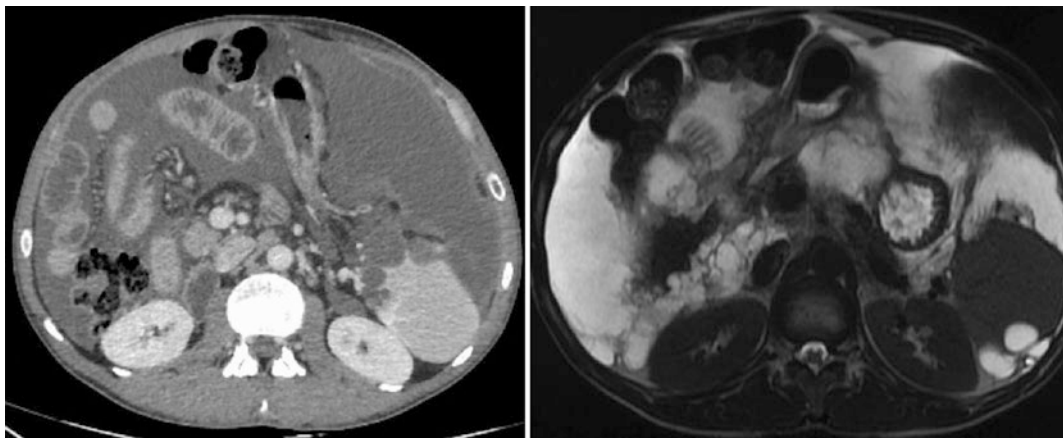

Fig. 6.13 Axial contrast CT showing diffuse organ encasement and spleen scalloping related to pseudomyxoma peritonei or with corresponding image on axial T2-weighted image. Note the T2 hyperintense signal similar to ascites

Table 6.2 Criteria of potentially nonresectable disease to look for on CT and MRI

– Extensive involvement of small bowel or root of the mesentery
– Lymph nodes above celiac axis
– Pleural effusion (needs to be histology proven)
– Pelvic sidewall invasion, bladder trigone involvement
– Parenchymal liver metastases, subcapsular liver implants close to the right hepatic vein
– Implants of >1 cm: diaphragm, lesser sac, porta hepatis, intersegmental fissure, gall bladder fossa, gastrosplenic, gastrohepatic ligament

areas that precludes a complete cytoreduction [30]. Depending on the available surgical expertise and the extent of disease, neoadjuvant chemotherapy may be indicated prior to the surgical debulking. In some cases, it may be the association of multiple sites of difficult resections which guide the treatment plan. Criteria of potentially unresectable disease are summarized in Table 6.2.

6.4.2 Involvement of Various Organ Systems

The radiologist must provide information about involvement of organ systems that may be managed by different teams of surgeons. The commonly involved areas are the urinary system—kidney, ureters, and bladder—that may require involvement of the urosurgical team, parenchymal or hepatic surface deposits that require a hepatobiliary surgeon, and the presence of intrathoracic disease that requires involvement of a thoracic surgeon.

6.4.3 The Disease Sites That Are Not Visible to the Surgeon During Exploration?

Parenchymal liver and splenic deposits intraluminal gastrointestinal tract deposits (stomach, bowel, colon), and pleural metastases as these sites of disease may not be detected at the intraoperative inspection. Though intraoperative ultrasound may detect large liver metastases, it may miss the smaller ones. The presence of disease at any of these sites should be looked for and reported.

6.5 The Role of Imaging in the Evaluation of Disease Extent

Ultrasound The role of US for the staging of peritoneal metastases is limited. Ultrasound is mostly used for peritoneal biopsies.

CT Oral and intravenous contrast continues to be the imaging modality of choice for the evaluation of patients undergoing cytoreductive surgery [31, 32]. However, the major limitation is its inability to detect small lesions. Indeed, the reported sensitivity of CT for the detection of peritoneal deposits less than 1 cm is only 25–50%. The other drawback of a CT scan is its inability to pick up bowel surface deposits. Performing a positive contrast study may improve the visualization of serosal and mesenteric deposits. However, calcified metastases may be obscured by the positive contrast [33–37].

MRI The use of MRI has increased in the recent years, and though initial reports showed an accuracy similar to that of CT scan, the use of fat suppression, diffusion-weighted imaging and postcontrast imaging has greatly increased its sensitivity and specificity [30, 38–40].

DWI is specifically useful for detecting PM including bowel surface deposits, mesenteric deposits, peritoneal deposits in the pelvis, hepatic capsular deposits, and lesser sac deposits [37, 41–44]. The rate of detection of PM <1 cm is better with DWI [45–47]. Fujii et al. reported a sensitivity and specificity of 90% and 95.5%, respectively, for the detection of peritoneal carcinomatosis [41]. However, cardiac motion and susceptibility artifacts from air can significantly degrade image quality at air-tissue interfaces, such as the lung bases or bowel, and therefore obscure small peritoneal implants [44].

6.6 PET-CT

The added value of PET-CT in the initial disease evaluation is still under debate [48]. Some studies suggest that PET-CT may be a more accurate than CT alone for evaluating the extent of peritoneal metastases [49, 50]. PET-CT is particularly useful for the diagnosis of metastatic lymph nodes. Nam et al. showed that PET-CT is better than surgico-pathological staging by detecting supraclavicular metastatic nodes [49]. Detection of such nodes precludes aggressive cytoreductive surgery.

Pitfalls in assessing the extent of disease on PET-CT are generally due to inability to detect tumor implants in areas where FDG physiologically accumulates (bowel loops, urinary tract) and difficulty in visualizing small implants due to a low spatial resolution (5–6 mm) [51, 52].

Moreover, PET-CT is the modality of choice for detecting tumor local or distant recurrence [53] provided the distance from surgery is sufficient. Indeed, its specificity may be reduced immediately after surgery because intense radiotracer uptake can be seen both in the inflammatory tissue and tumor [54].

Conclusion

Accurate imaging evaluation of is the key to the management of patients with primary and secondary peritoneal tumor. CT remains the most commonly used modality though some centers use a combination of CT and MRI or prefer MRI alone. A combination of morphological and functional MR imaging sequences may lead to better tumor detection, evaluation of disease extent, and assessment of treatment response.

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7 Diagnostic Laparoscopy for the Evaluation of Peritoneal Metastases

Almog Ben-Yaacov, Joseph Dux, and Aviram Nissan

7.1 Background

Peritoneal surface malignancies (PSM) represent a group of neoplastic disorders spread to the peritoneum. PSM can be primary, growing from the peritoneum (mesothelioma and primary peritoneal carcinoma), or secondary, resulting from the metastatic spread of colon cancer, appendiceal cancer, rectal cancer, ovarian cancer, and gastric cancer as well as peritoneal dissemination of various rare tumors.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated encouraging results in improving survival outcome of PSM from various primary tumor types.

Patient selection for CRS and HIPEC is important. Based mainly on cross-sectional imaging modalities such as computed tomography (CT) scan, positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI), surgeons try to evaluate the volume and distribution of peritoneal disease. Modern cross-sectional imaging modalities are not sensitive enough for the evaluation of peritoneal disease and therefore, in many cases, underestimate the true extent of the disease.

Diagnostic laparoscopy is an effective and accurate tool for the selection of candidates for CRS and HIPEC. It can be used as an adjunct to cross-sectional imaging to improve patient selection for CRS and HIPEC.

This chapter provides a comprehensive review of the role of diagnostic laparoscopy in peritoneal surface malignancies.

7.2 The Advent of Video Laparoscopy

Video laparoscopy was introduced during the 1980s–1990s of the twentieth century. The development of fiber-optic scopes and high-resolution video cameras has minimized perioperative surgical stress leading to a shorter hospital stay and a faster postoperative recovery time. A lot of simple and complex major abdominal surgeries are performed by laparoscopy. The ability to visualize all the peritoneal surfaces and regions of the abdominal cavity allows its use as a diagnostic tool for conditions which cannot be diagnosed by clinical evaluation alone. It allows sampling of fluid and tissue for a pathological diagnosis at the same time.

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Laparoscopic ultrasound can also be performed during diagnostic video laparoscopy (DVL) to better evaluate intra-abdominal organs that are not amendable for inspection [1].

The advantages of diagnostic video laparoscopy are:

1. Direct visualization of the visceral and peritoneal surfaces, thus aiding in establishing a diagnosis.
2. Reduction of the surgical trauma associated with exploratory laparotomy.
3. Minimal morbidity and postoperative pain.
4. Can be performed as an outpatient procedure.
5. The findings can be recorded and transmitted or presented for discussion with physicians not present in the operating theater.

The disadvantages of DVL are:

1. It is an invasive procedure that, although rare, may cause severe injuries to abdominal organs.
2. The entire abdominal cavity and pelvis are not always accessible especially in patients with previous abdominal surgery creating adhesions [1].

DVL is being used routinely as a staging procedure before definitive surgery for certain cancers like gastric cancer, esophageal cancer, and hepatobiliary and pancreatic cancers by some surgeons [2–5].

7.3 Diagnostic Laparoscopy for Peritoneal Metastases (PM)

Cytoreductive surgery (CRS) and HIPEC have led to a significant prolongation in survival of certain patients with peritoneal metastases [6–10]. However, given the high morbidity that results from this procedure, only those patients who are likely to benefit should be selected for it. Early recurrence occurs in patients with advanced disease arising from certain tumors, and they suffer morbidity without any benefit in survival [11, 12]. Only those patients in whom a complete cytoreduction is possible should be taken up for the procedure. This decision should be taken in multidisciplinary meetings [13].

The two most important prognostic indicators are the peritoneal cancer index (PCI) by Sugarbaker and the completeness of cytoreduction as determined by the completeness of cytoreduction score (CC score). The PCI is a quantitative assessment of cancer distribution throughout the abdomen and the pelvis [14]. It combines the size of the largest nodule, also known as the lesion score with the distribution of the disease diving the abdominal cavity into 13 regions (0–12). The PCI is the summation of the scores of each region and ranges from 0 to 39 [14]. A CC-0 score indicates that no visible peritoneal seeding exists following the cytoreduction; a CC-1 score residual disease <2.5 mm in size. Both CC-0 and CC-1 are considered to be "complete cytoreduction." A CC-2 score indicates tumor nodules between 2.5 mm and 2.5 cm; and a CC-3 score indicates tumor nodules >2.5 cm or a confluence of unresectable tumor nodules. CC-2 and CC-3 cytoreductions are considered incomplete [15].

In patients with colorectal PM when the predicted PCI is >17–20, CRS and HIPEC should not be offered since it offers no benefit over systemic chemotherapy alone; similarly for gastric cancer, this cutoff is a predicted PCI of 13 [6, 7]. Though there is no defined cutoff for ovarian cancer, in general patients with a lower PCI have a better outcome [8]. Contrary to the above, in more indolent tumors like low-grade pseudomyxoma peritonei and peritoneal mesothelioma, CRS and HIPEC are performed irrespective of the PCI provided a complete cytoreduction can be obtained. Exceptions to the prognostic value of PCI include noninvasive diseases like low-grade pseudomyxoma peritonei and peritoneal mesothelioma [9, 10]. In these conditions however, an incomplete cytoreduction offers little benefit to most patients and its imperative to exclude such patients from extensive surgery. Patients undergoing CRS + HIPEC who achieve a complete cytoreduction (CC-0 or CCR-1) have significantly longer survival compared to those who do not [16–18].

Thus in selecting patients for CRS and HIPEC, two important factors to be considered are:

- The predicted PCI
- The probability of a complete cytoreduction

7.4 Determining the Disease Extent and Resectability

Imaging modalities form the cornerstone of preoperative evaluation of patients undergoing CRS and HIPEC. A contrast-enhanced CT scan of the thorax abdomen and pelvis is the most commonly used modality. It rules out major distant metastases and may predict the extent of disease [19, 20]. The sensitivity of a CT scan in detecting PM varies from 60 to 93% and is largely dependent on the lesion size and location [21]. The sensitivity of a CT scan ranges from 59 to 94% for lesions >5 cm, 9 to 28% for lesions <5 cm, and only 11 to 28% for lesions <1 cm [21–23]. It accurately predicts the PCI only in 33% of the patients as shown in a multi-institutional study [23]. There was a significant underestimation of the intraoperative (true) PCI by the CT scan (mean CT-PCI, 8.7 ± 5.5; intraoperative PCI 12.9 ± 7.4; $P = 0.003$). However, in this study which included patients with colorectal PM alone, the underestimation was clinically relevant only in 12% of the cases. Koh et al. compared the CT-PCI with the surgical PCI and found an accuracy of 60%, 33% underestimation, and 7% overestimation of the PCI on the preoperative CT scan in a small cohort of 19 patients, demonstrating a statistically significant difference in radiological PCI versus intraoperative PCI in nearly all abdominopelvic regions [23].

The difference was more commonly seen in certain regions—the right upper quadrant, bilateral lower quadrants, distal jejunum, and distal ileum. Similarly, in the previous study of 32 patients, the discrepancy between the CT and surgical findings was most significant in the small bowel region where a negative CT scan finding but a true exploratory laparotomy finding of peritoneal lesions occurred in 23–35% of cases in the different segments of the small bowel. CT has the limitation of being unable to determine the small bowel and mesenteric involvement accurately. The sensitivity for these regions ranged between 8 and 17% in one series and 18 and 55% in another [21, 23].

MRI has been used by various investigators for evaluation of disease extent. It requires up to 6 h of fasting and bowel preparation and has to be performed per protocol to yield accurate results. Contrast MRI has a sensitivity of 87% and a negative predictive value of 73% in detecting PM per segment of the abdominal cavity [24].

MRI results are dependent on the expertise of the interpreter, and in experienced hands, it may be more accurate especially for detecting bowel surface lesions and lesions <1 cm in size [25, 26].

An [^{18}F]FDG positron emission tomography (PET)-CT scan has been reported to have a sensitivity of 58–100% in detecting PM [27, 28]. It has the limitation of being unable to detect very small tumors and mucinous tumors and overlap with other non-cancerous conditions. In patients with low-grade PMP, the positive predictive value of a PET-CT to assess completeness of cytoreduction was found to be 27% [29].

Thus current imaging modalities seem to be lacking in accuracy in predicting the extent of the disease as well as the possibility of a complete cytoreduction. However, imaging criteria for inoperability have been defined, and these help to exclude certain patients initially.

Multiple extra-abdominal metastasis or bulky (>2 cm) suprarenal retroperitoneal lymph nodes are considered absolute contraindications.

Other contraindications are extensive bowel resection that is likely to compromise the future quality of life, e.g., two or more sites of segmental small bowel obstruction, patients requiring a total gastrectomy with a total colectomy; involvement of the pancreatic head, bladder trigone, and porta hepatis; and massive or diffuse involvement of pleural space [30]. Metastases at other sites except up to three easily resectable liver metastases in colorectal PM and resectable liver metastases synchronous with PM from ovarian cancer are not contraindication for CRS and HIPEC.

Thus, it is not just the extent of disease but also the site of disease that may preclude a complete CRS. Reported rates of unresectability range from 20 to 40% [31, 32]. The morbidity of incomplete surgery ranges from 2 to 23% and the mortality from 20 to 36% [31].

An unnecessary laparotomy is a waste of resources for both the hospital and the patient and delays other treatment that could be more effective. It also has a negative psychological impact on the patients and caregivers [32].

Before submitting a peritoneal carcinomatosis to peritonectomy with HIPEC, it is necessary to assess the prognosis and feasibility. It is thus fundamental to preemptively know the following with accuracy: origin of the tumor, PCI, degree of involvement of the small bowel and its mesentery, and number and extension of the organ resection to perform.

7.5 Role of Diagnostic Video Laparoscopy

The role of DVL in the evaluation of peritoneal metastases has evolved and increased in the last decade large due to better and more stringent definition of the indication of CRS and HIPEC. In a multi-institutional study of more than 1200 patients treated by CRS and HIPEC, DVL was used in 8% of the patients [33]. Only 10% of the experts at a consensus meeting in 2006 considered it to be an essential tool; however the number would be larger if such a consensus is carried out now [28]. It was considered to have limited feasibility due to the presence of adhesions arising from previous surgeries and large peritoneal deposits and port site recurrence was a concern [28, 34]. With the increasing popularity and acceptance and awareness about CRS and HIPEC, more patients are referred for surgery up front. Moreover, in certain conditions like colorectal and gastric PM, extensive disease though technically resectable is a contraindication for CRS and HIPEC, thus making an accurate assessment imperative.

Early studies have shown that a DVL can reduce the number of unnecessary laparotomies in intra-abdominal malignancies [35]. A prospective comparison of laparoscopy and CT scan showed that in a series of patients, CT scan identified peritoneal disease in only 47.8%, whereas subsequent laparoscopy detected peritoneal spread in 100% of the patients [36].

7.6 Evidence for DVL

The studies reporting the utility and outcomes of DVL are heterogeneous in terms of disease sites included and the indications (Table 7.1).

In a study from Japan, DVL with HIPEC was performed in all patients with PMP of appendiceal origin. Subsequently, another diagnostic procedure with CRS was performed. The study did not evaluate the role of laparoscopy in predicting resectability since HIPEC was performed in all patients irrespective of PCI or resectability [45]. Most of the other studies include patients from multiple primary sites, whereas some have specifically evaluated its role in a single disease condition (mesothelioma, PMP, ovarian cancer) [39, 40, 45]. The exclusion criteria employed by some investigators were the presence of massive mucinous ascites, large omental cake, or a recent laparotomy with a thorough evaluation of PM [35]. The goal of performing a DVL is to exclude patients who are unlikely to have complete CRS and thus avoid an unnecessary laparotomy. In colorectal PM, some patients with extensive disease can be offered neoadjuvant chemotherapy with the possible benefit of downstaging and subsequent CRS and HIPEC. Not just systemic chemotherapy but also intraperitoneal chemotherapy is administered through, and implantable port has been used to treat patients with gastric and colorectal PM [46, 47].

The ability of laparoscopy to exclude patients with unnecessary surgery is indicative of its negative predictive value. This was reported only in two studies; in both, the negative predictive value was 100% [39, 40]. Similarly, the percentage of patients deemed resectable who actually have a complete CRS is the positive predictive value of the procedure. The reported positive predictive value ranged from 62.9 to 98%. Seven to forty

Table 7.1 Utility and outcomes of diagnostic video laparoscopy for peritoneal metastases

Year [Ref.]	Primary site (s)	No. of patients	Average duration (min)	Failure to access (%)	Positive predictive value	Negative predictive value	% of patients excluded from CRS	Understaging (%)	Complications (%)	Port site metastases
2005 [37]	Ovary, CRC, appendix, rare tumors	11	38		87.5%		27	12.5	1.06	
2006 [38]	Ovary, CRC, stomach, PMP, rare tumors	97	30	1.03	98%			2.06	2.06	–
2006 [39]	Ovary	65	–	–	87%	100%	13	8.2	–	–
2009 [34]	Ovary, CRC, appendix, rare tumors	197	30		97%		7	2.04	2.04	
2009 [40]	Mesothelioma	33	40	–	96.6	100%	9%	–	–	–
2012 [41]	Ovary, CRC, stomach, PMP, rare tumors	351	30	0.28				1.42	1.75	–
2013 [42]	CRC, appendix, malignant mesothelioma	45		4.5%	62.9		40%			
2014 [43]	Appendiceal, colorectal, gastric, ovary, rare tumors	73	–	13.7	85.4	–	27.7%	–	–	–
2015 [44]	CRC, appendix, gastric, ovary, rare tumors	217	–	7.3	91.9		31.3		0.4	

percent of the patients were not taken up for CRS and HIPEC based on the DVL findings. The reasons for exclusion were extensive disease, predominantly on the small bowel which precluded a complete cytoreduction or a high PCI than acceptable for the disease site [37, 40, 42, 43]. Iversen et al. reported an overstaging in 4.4% of the patients, while other investigators reported understaging in 1.4–12.5% [37, 42]. One of the limitations of laparoscopy is the evaluation of retroperitoneal structures like the ureters and the pancreas [40, 43]. Other difficult areas in DVL are the hepatic pedicle and infiltration of the diaphragmatic muscle. An accurate assessment of these areas is more reliable on imaging studies than DVL. Most of the studies report the known benefits of laparoscopy like short hospital stay, less postoperative pain, and better cosmesis. The rate of complication was uniformly low ranging 0–<1%.

Fagotti et al. evaluated the role of laparoscopy in addition of a clinical and radiological evaluation in 65 patients undergoing laparotomy for advanced ovarian cancer. Optimal debulking was achieved in 34 of the 39 patients (87%) whose disease was judged completely resectable on the basis of laparoscopy findings, giving DVL an accuracy of 90% for predicting a complete cytoreduction. The negative predictive value of clinical-radiological evaluation was 73%, whereas the NPV of laparoscopy was 100% (i.e., in no cases did the disease determined to be unresectable of DVL become resectable on exploratory laparotomy). The positive predictive values (PPV) of clinical-radiological evaluation and laparoscopy were both 87% [39]. Subsequently, the same investigators came up with a predictive index value (PIV) based on objective parameters determined at pre-cytoreduction laparoscopy, the "Fagotti score" [48]. The score is a sum of the individual score of seven sites of disease (Table 7.1). Patients with a score of ≥8 had a 100% chance of having a suboptimal/incomplete CRS. The laparoscopic parameters chosen for the score were for describing the disease extent rather than for predicting a complete cytoreduction [48]. The score has been prospectively validated—at a PIV of ≥8, the probability of optimal cytoreduction (residual tumor ≤1 cm) at laparotomy is 0 [49, 50]. A learning curve has been defined for this procedure [51]. Its reproducibility has been demonstrated at nonacademic peripheral centers as well [52]. Of note is the fact that in these reports on ovarian cancer, "optimal debulking" that is residual disease <1 cm is used to determine the completeness of surgery instead of the CC score (Fig. 7.1).

7.7 Technical Aspects in DVL for Peritoneal Metastases

The ability to perform DVL efficiently and safely is depended on careful planning of the procedure. Trocar placement is crucial in order to obtain access to all parts of the abdomen and pelvis and to avoid injuring the underlying structures. Many of the patients who are candidates for DVL already had previous surgical procedures. Placing trocars in the midline allows the sites to be resected easily during a subsequent CRS and HIPEC; it is important to place trocars in the midline as far as possible [43, 53, 54].

The placement of the first trocar is based upon the location of the previous surgical scars, on the preoperative imaging, and on clinical and physical findings. Our preferred method for pneumoperitoneum is either by optic trocar insertion and direct insufflation, or for patients with surgical scars we recommend the Hassan technique. A 0-degree or 30-degree scope can be used.

After the creation of a pneumoperitoneum, we insert two to three more trocars. Placing the 5 mm trocars in the midline is not always feasible for obtaining high-quality staging of the entire peritoneal cavity. The other common sites for trocar placement are the right and left iliac fossae [43, 44]. Most surgeons prefer the left subcostal region for the first site of entry as it avoids injuring the bowel. However, a large omental cake may preclude the use of this site [34, 38]. In case of dense midline adhesions, two separate accesses may be made on either side of the midline [34]. After CRS and HIPEC, these trocar sites can be excised and used for placement of the inflow and outflow drains during the HIPEC (Fig. 7.2).

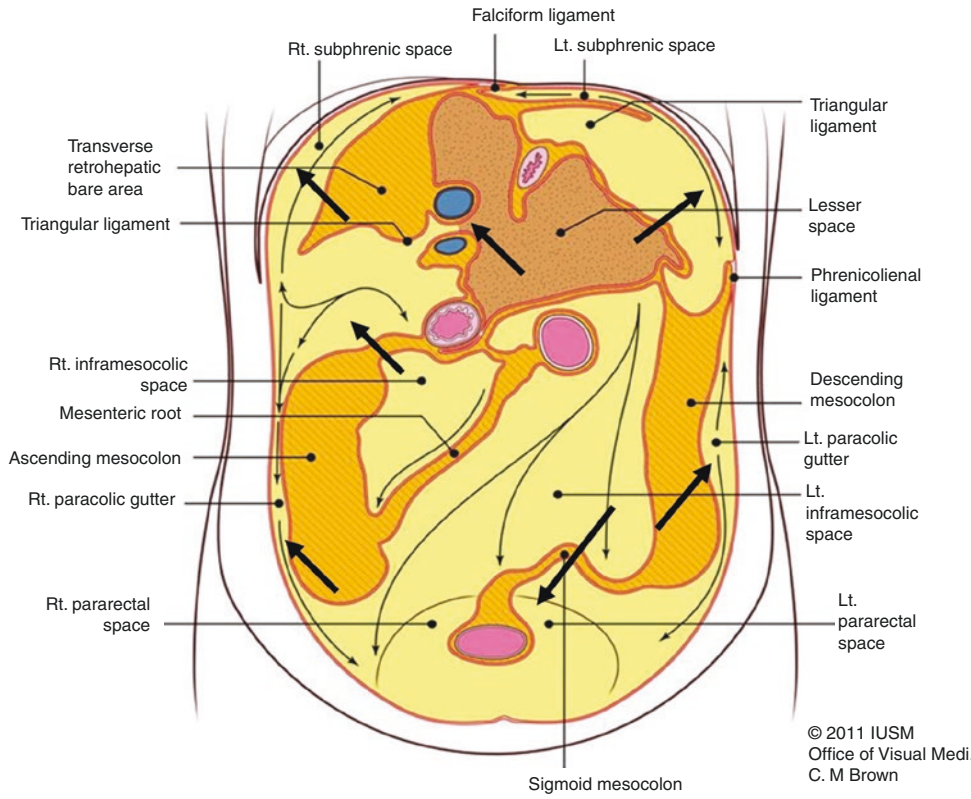

Fig. 7.1 Areas in the peritoneal cavity that requires visualization during diagnostic video laparoscopy for the evaluation of peritoneal surface malignancies

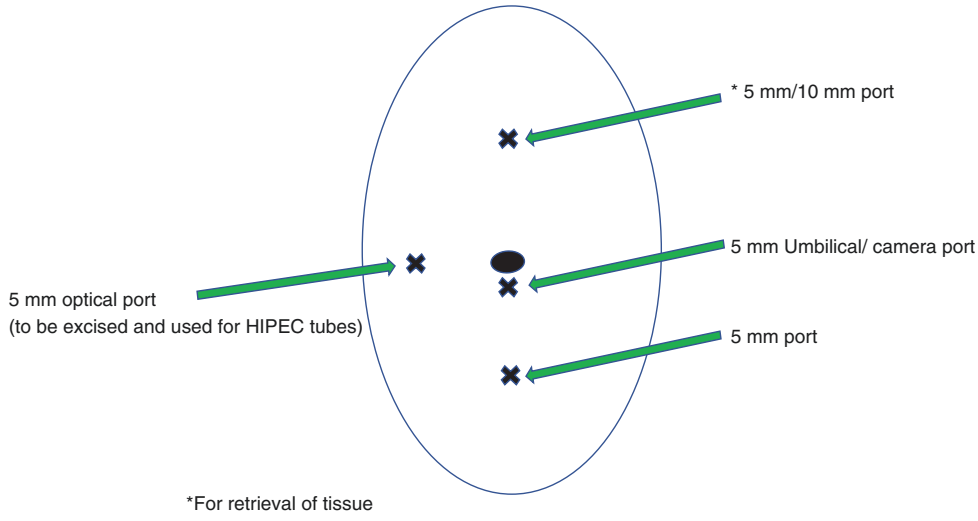

Fig. 7.2 Suggested trocar placement during diagnostic video laparoscopy in patients with known peritoneal surface malignancies. It is important to place as many trocars in the midline in order to facilitate a future cytoreductive surgery. In case where tissue samples should be obtained, a 10 mm trocar should be placed in order to safely retrieve the tissue harvested. In many cases, at least one trocar should be placed off midline in order to achieve better exposure and tissue manipulation. In such cases, the trocar site is resected at the cytoreduction and used for placing one of the HIPEC tubes

Lysis of adhesions poses the risk of bowel injury, but some amount of adhesiolysis is required to allow systemic visualization of the entire abdominal cavity to evaluate the extent and distribution of disease. The ascitic fluid is removed to enable better visualization and a cytological examination performed. Confirmatory biopsies are performed if indicated. In patients who have received neoadjuvant therapy, biopsies are needed for the evaluation of the pathological response. Diaphragmatic biopsies can cause tumor infiltration into the diaphragmatic muscle or perforation into the pleural cavity and should be avoided. Important point to note is the visualization of areas exposed to gravity, namely, Morison pouch, peri-splenic, peri-hepatic, behind segment 1 of the liver close to the IVC, the portal bridge (pont hepatique), omental bursa, the mesentery of the small bowel, and the pelvis (Fig. 7.3). In order to make a complete assessment of all regions of the peritoneal cavity, the table is tilted to four positions—steep left and right Trendelenburg and steep left and right reverse Trendelenburg [37, 41, 42]. The PCI should be scored for each region and the total PCI calculated.

It is feasible that a laparoscopic ultrasound could be used to assess the diaphragmatic and pancreatic involvements and liver metastases [32]. Such an evaluation may be limited by the presence of adhesion.

Complications such as injuring a hollow viscous or a major blood vessel are rare. Insufflation-related complications include air emboli, pneumomediastinum, or pneumothorax.

Though port site recurrence is a concern in patients undergoing DVL or curative surgical resection of non-metastatic gastrointestinal and gynecological tumor, the reported incidence is low. Conlon et al. reported on 1650 DVL procedures performed in 1548 patients with primary tumors arising from the upper gastrointestinal tract. Four thousand two hundred and ninety-nine trocars were placed in these patients, and port site recurrence was reported in 13 patients (0.8%) [55]).

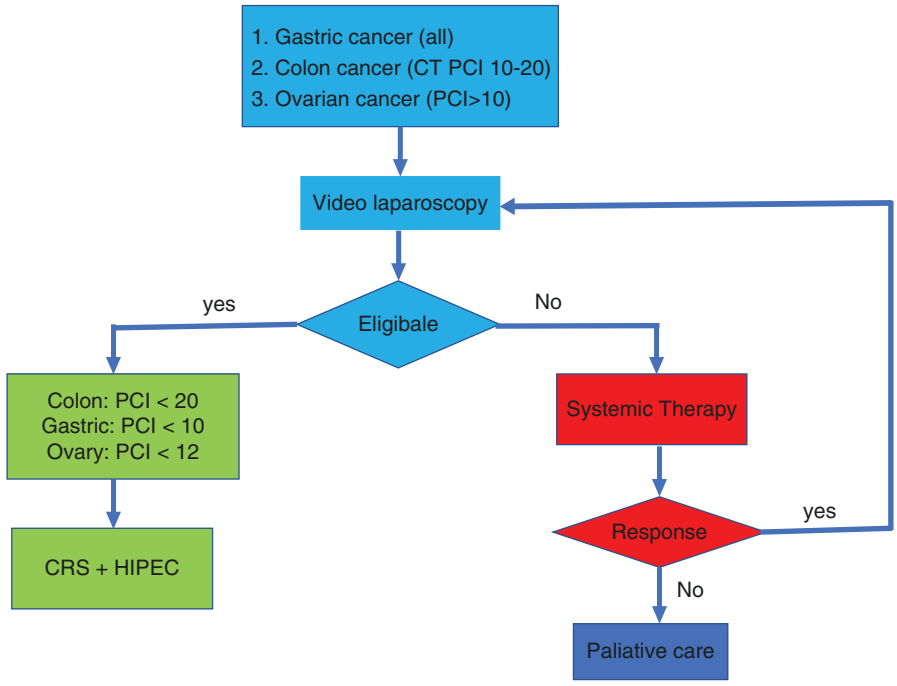

Fig. 7.3 Flowchart of patients with known PSM. Patients are being evaluated by diagnostic video laparoscopy and, if not suitable for CRS + HIPEC, referred for systemic therapy. If a patient responds to systemic therapy, a second DVL may be indicated

Abu-Rustum et al. reported on port site metastases documented in 20 of 1964 patients (1.18%) who underwent a laparoscopic procedure for a malignant intra-abdominal condition [56]. However, port site recurrence in patients with PM is common, and hence all port sites should be excised during potentially curative surgery.

7.8 Single-Port Laparoscopy

In this procedure, the SPL device is inserted into the umbilicus or lateral to it after a direct incision of 3 cm was made into the abdominal wall [57]. This technique may be safer in patients with extensive adhesions. The outer seal cap allows a 360° rotation that is useful for inspection of the entire abdominal cavity using the change in the position of the surgeon and the assistant. The technique described by Leblanc et al. involves inclining the table vertically for up to 30° with the head low for inspection of the pelvis and head down for inspection of the upper abdomen and tilting laterally to visualize the flanks.

7.8.1 Advantages and Limitations of DVL

The potential advantages of DVL as a staging modality for PM are:

- Evaluation of the mesentery (superficial lesions and retractions)
- Evaluation of lesions on the anti-mesenteric margin
- Evaluation of the omental bursa, pelvic cavity, diaphragm, and abdominal wall
- Prediction of the PCI by evaluating all 13 regions
- The possibility of peritoneal washing and biopsies for the typing of the primitive tumor
- The prediction of the probability of a complete cytoreduction during CRS
- Reevaluation of response to neoadjuvant therapies
- As a part of a second-look strategy for early detection of PM in patients at high risk [34]

Some of the limitations are:

- Evaluation of the depth of infiltration of lesions on the diaphragmatic surfaces
- Evaluation of pancreatic involvement
- Evaluation of the ureters and pelvic side wall
- Necessity of a skilled laparoscopic surgeon

Some of the disadvantages can be offset by using a laparoscopic ultrasound during the procedure. This allows:

- A good evaluation of the thickness of lesions of the diaphragm
- The qualitative and quantitative evaluation of pancreatic involvement and that of retroperitoneum
- Evaluation of hepatic metastases and their resectability

7.9 Assessment of Pleural Involvement

Pleural involvement can occur in patients with peritoneal metastases and is commonest in ovarian cancer and patients of PMP with extensive disease. Fifteen percent of the patients with ovarian cancer present with a pleural effusion that shows a positive cytology for malignant cells [58]. A diagnostic thoracoscopy can help in sampling of the pleural fluid when other tests are inconclusive and in determining the presence and extent of pleural deposits. In one study, 4 (36%) of 11 patients with ovarian cancer and a negative cytological examination of pleural fluid had macroscopic pleural malignancy on thoracoscopy [59]. Though invasive, such a procedure may change the treatment decision and may be necessary when the suspicion is high, especially when selecting patients for CRS as extensive involvement would preclude a complete cytoreduction. The role of thoracoscopy in other patients is less defined, and its use should be individualized.

7.10 Detection of Occult Peritoneal Metastases

Aminolevulinic acid (ALA)-mediated photodynamic diagnosis (ALA-PDD) has been used for detecting occult peritoneal metastases. ALA is a prodrug of heme biosynthesis that has an affinity for cancer cells. After oral administration, it accumulates in the cancer cells and gets converted to protoporphyrin IX (PpIX). When tissue is illuminated with light of a specific wavelength (blue light 440 nm), the tumor tissue emits fluorescence of a specific color (red) leading to its easy identification [60]. This process also leads to the generation of cytotoxic-free radicals. ALA-PDD have been used in detecting and treating a variety of precancerous and cancerous lesions like dysplasias arising in Barret's esophagus, ulcerative colitis, stomach; precancerous and cancerous lesions arising from the skin cancers [60–62].

This strategy can be used to detect occult tumors which are missed by white light. Areas of inflammation could produce false-positive results [63]. In a study by Kishi et al., staging laparoscopy (SL) using ALA-PDD was performed in 13 advanced gastric cancer patients with serosa-invading tumors, and the detection sensitivity of ALA-PDD was compared to the observations using WL. The tumor detection rate using ALA-F was significantly higher than the detection rate using WL (72% vs. 39%, respectively; $P < 0.0001$) [64]. Peritoneal metastases were detected in five patients using SL with ALA-PDD, and liver metastases were detected in one patient. These metastases were confirmed using histological examination. Three metastatic lesions that were invisible under WL were detected under ALA-F.

The same authors reported outcomes of the same strategy in 38 patients in 2016. Twelve of the 38 patients (32%) were diagnosed with peritoneal metastases by conventional laparoscopy. However, laparoscopy with ALA-PDD detected peritoneal metastases in 4 (11%) of the 26 remaining patients. Three of these four patients had negative cytological results from the evaluation of the peritoneal fluid [65].

7.11 Therapeutic Uses of Video Laparoscopy in Peritoneal Surface Malignancies

7.11.1 Pressurized Intraperitoneal Aerosol Chemotherapy

In this therapy, a carbon-dioxide pneumoperitoneum is created and infused with an aerosolized chemotherapeutic agent to create a "therapeutic capnoperitoneum" [66]. Preclinical data has shown better distribution and higher tissue concentrations of chemotherapy agents in PIPAC compared with conventional intraperitoneal chemotherapy [67, 68]. The dose used is 1/10; the dose of systemic chemotherapy and the systemic absorption is also low. This procedure is performed laparoscopically, and multiple applications are performed at six-weekly intervals [69]. The morbidity is low and hospital stay is short. Currently, this therapy is used for treating patients who have developed resistance after one or more lines of chemotherapy as well as those with chemotherapy-resistant ascites [70]. Its role as a neoadjuvant therapy before CRS and HIPEC is being evaluated. No negative impact on quality of life has been reported. Reported histological response rates for therapy-resistant carcinomatosis of ovarian, colorectal, and gastric origin are 62–88%, 71–86%, and 70–100%, respectively [70].

7.11.2 Laparoscopic HIPEC

Lotti et al. have described the technique of laparoscopic HIPEC which combines the theoretical advantages of the open and closed techniques. In their technique, stirring of the abdominal contents is performed from time to time during a closed HIPEC procedure [71]. Laparoscopic CRS is being performed with good results for treatment of patients with limited peritoneal disease and is usually followed by HIPEC which is performed by the closed technique [72]. Though manual stirring through a hand-assisted laparoscopic device has been reported in laparoscopic HIPEC in a pig model, it is unclear if HIPEC reaches the wide portion of the anterior abdominal wall [73].

In the technique describe by Lotti et al., at the end of CRS, four Jackson-Pratt drains are inserted in the abdominal cavity and are the outflow channels [71]. The entire length of the wound, between the xiphoid and the pubis, is divided in four parts, and the skin is closed with four continuous locking sutures, and three 12 mm balloon trocars are placed at the junction between sutures. The upper trocar is connected to the HIPEC inflow tube, the middle trocar to the heated CO_2 insufflator, and the lower trocar to the smoke evacuator device. After 5 min of stirring, CO_2 insufflation is stopped, the patient is placed in Trendelenburg position, and pneumoperitoneum is evacuated under vision through the lowest trocar. Perfusion continues in a closed-technique fashion for 10 min, so as to perfuse the anterior abdominal wall with the perfusate. During this phase of perfusion, the abdomen is shaken manually and the inclination of the operating bed is frequently changed, to further promote the distribution of the perfusate into the abdomen.

After 10 min, pneumoperitoneum is again established, and the cycle restarts. During a 90-min HIPEC, alternating cycles of laparoscopic stirring (5 min) and closed perfusion (10 min) are performed.

The alternation between pneumoperitoneum-laparoscopic stirring and voiding of the pneumoperitoneum-closed perfusion allows the anterior abdominal surface to be in contact with the perfusion fluid for an adequate lapse of time. An experimental study carried out in pigs showed that the absorption of oxaliplatin was more in the closed HIPEC procedure as compared to the open procedure [73]. Although the resulting increase in IAP could have a positive effect on penetration of cytotoxic drugs in tissues, this effect is still under study [73, 74]. The authors concluded that further evaluation of this technique is needed, to demonstrate a clinical benefit, and the effect of pneumoperitoneum on the absorption of chemotherapeutic drugs needs to be determined as well.

7.11.3 Laparoscopic CRS and HIPEC

For selected patients with limited disease extent (PCI < 10) and low PMP, laparoscopic CRS and HIPEC have been used with the goal of reducing the morbidity and hospital stay [75–77]. The reported conversion rates were low and improved with experience. Patient selection is important. The drawbacks of this approach are difficulty in properly assessing certain areas like the small bowel mesentery, technical difficulty in obese patients and those with extensive prior surgery, the potential for dissemination of malignant cells (debatable), and prolonged operative times [77]. With growing experience, the utility of such procedures could increase specifically in patients with more extensive disease.

This may be applied only in highly selected patients with low grade as well as low volume disease.

Conclusions

Diagnostic video laparoscopy is an accurate and feasible tool for better evaluating patients with PM for CRS and HIPEC. It is used as an adjunct to CT, PET, or MRI.

It is safe, efficient, and prevents some patients the need to go through unnecessary laparotomy, and it allows the surgeon to better evaluate the extent of the disease and response to neoadjuvant treatment and to plan CRS + HIPEC more accurately.

DVL can identify patients with extensive disease who may be better treated with neoadjuvant therapy for the possibility of downstaging of disease. Multiple procedures can be performed in such patients where both morphologic and pathological response to therapy can be assessed. The role of laparoscopy in the management of PM has been further enhanced by introduction of new treatments like pressurized intraperitoneal aerosol chemotherapy (PIPAC) where it is used for both diagnosis and treatment delivery. Moreover, in selected patients, CRS and/or HIPEC is being performed laparoscopically.

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8 Combined Resection Liver Metastases and Peritoneal Metastases

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8.1 Introduction

The liver and the peritoneum are common sites for cancer spread especially from gastrointestinal tract primary tumors. In isolated cancer spread to both the liver and the peritoneum, surgical treatment that comprises of resection of the metastatic disease has led to a significant improvement in the survival over systemic chemotherapy alone which was the standard of care. The mode of spread to the liver and the biological behavior of the tumor vary depending on the primary site of origin. In gastrointestinal primary tumors, the spread is through the portal circulation or via direct intra-abdominal lymphatic channels, whereas the hematogenous route is employed by tumors' other primary sites. The rationale for liver resection in these cases is that the tumor is confined to the abdominal cavity and remains there for prolonged periods. Hence, adequate treatment of the primary tumor combined with liver resection may provide a chance for cure. While this is true for colorectal and neuroendocrine liver metastases (LM), the approach to LM from other primary sites comparatively more selective, considering a more aggressive disease biology [1].

Peritoneal metastases (PM) are less common as compared to LM, and they have a poorer prognosis as compared to LM as shown in patients with colorectal cancer. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have drastically improved the survival and quality of life of selected patients with peritoneal metastases (PM) arising from various primary sites [2, 3]. Though initially considered a contraindication to radical surgery for PM, several studies have shown that long-term survival is possible in patients with combined resection of LM and PM with an acceptable morbidity and mortality. The two common primary sites in which such combined resections with or without HIPEC are performed are colorectal cancer and ovarian cancer. This chapter describes the pathophysiology and surgical management of LM and PM occurring synchronously.

8.2 Colorectal Cancer

At the time of diagnosis of a primary colon cancer, LM are found in approximately 20% of patients as compared to PM found in 10% of patients. These

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colorectal liver metastases (CRLM) are preferably treated by surgical resection [3–5], achieving a 5-year survival rate of 35–45% [4, 6, 7].

Five-year survival rates are routinely reported to be 40%, and 10-year survivals as high as 25% have been documented [4–7]. Similarly, a median OS of 63 months can be obtained in patients with PM treated with CRS and HIPEC [2].

8.2.1 Difference Between Peritoneal Metastases and Other Sites of Metastases

In colorectal cancer, though liver metastases are more common compared to PM, they are less aggressive. Sugarbaker and collaborators studied the growth of peritoneal and liver metastases and pointed out several differences in the biology of CPM and colorectal liver metastases (Table 8.1) [8]. Liver metastases arise as a result of portal dissemination and have a lower metastatic potential as compared to PM which spread more rapidly. Single cells or small clusters of cancer cells then lodge within the venous sinusoids of the liver and derive their blood supply from the hepatic artery. Until the time that they grow very large and develop central necrosis, the disease remains confined to the liver. Once necrosis sets in, the capillaries within the tumor are disrupted leading to tumor spread to the systemic circulation, especially the lungs.

Table 8.1 Comparison and contrast of liver metastases with peritoneal metastases from colorectal cancer (Adapted from [8] with permission)

	Liver metastases	Peritoneal metastases
Mechanism of dissemination	Portal vein	Peritoneal space
Mode of progression	Expansion of a parenchymal mass	Exfoliation
Metastatic efficiency	Low	High
Incidence with primary resection	20%	10%
Incidence with diagnosis of recurrence	50%	60%
Response to modern systemic chemotherapy	60%	30%
Benefit from re-operative surgery requires R-0 resection	Yes	Yes
Preventive strategies in existence	No	Yes

The liver metastases have a doubling time of 3 months, and only when the metastases become quite large—10 cm—do satellite liver metastases form as a result of cancer emboli within liver lymphatics [9]. The liver metastases progress by expansion of the tumor mass in the liver, and as the intratumoral pressure increases, cells are forced into the systemic circulation and the pulmonary circulation being in immediate continuity; lung metastases are the commonest site of progression in patients with LM. The time to progression is long and may take months to years; however if the LM are completely resected or respond to systemic chemotherapy, progression may not occur at all [9].

However, PM have an alternative and more aggressive mechanism of abdominal and pelvic progression. The cells exfoliate from the primary tumor to produce PM, and this represents a more aggressive phenotype [10]. Even small tumor nodules can shed cancerous cells that form new implants. This exfoliation process causes a far more rapid disease progression, and all quadrants of the abdominal cavity are involved by the disease process within a few months.

The metastatic potential of liver metastases is extremely low. The portal venous blood may be contaminated by millions of cancer cells, and yet only a few implants grow within the liver parenchyma. In contrast to this, PM have a very high metastatic potential [10–12]. The implantation can be as high as 1:1. It has been shown that the trauma produced by an operative intervention may greatly increase the efficiency of cancer cell implantation within the peritoneal space [13].

At the time of diagnosis of a primary colon cancer, LM are found in approximately 20% of patients as compared to PM found in 10% of patients. However, the incidence of PM is much higher in patients with recurrent disease; the

estimated incidence of LM is 50%. This can be attributed in part to the implantation of malignant cells during surgical handling of the primary at and around the surgical site producing recurrence in future.

The response to systemic chemotherapy is also different, while approximately 60% of LM will respond only about 30% of patients with peritoneal metastases will respond to modern systemic chemotherapy with 15% or less showing a complete response [14].

8.2.2 Outcomes with Systemic Chemotherapy in Patients with Colorectal Cancer with Metastases at Different Organ Sites

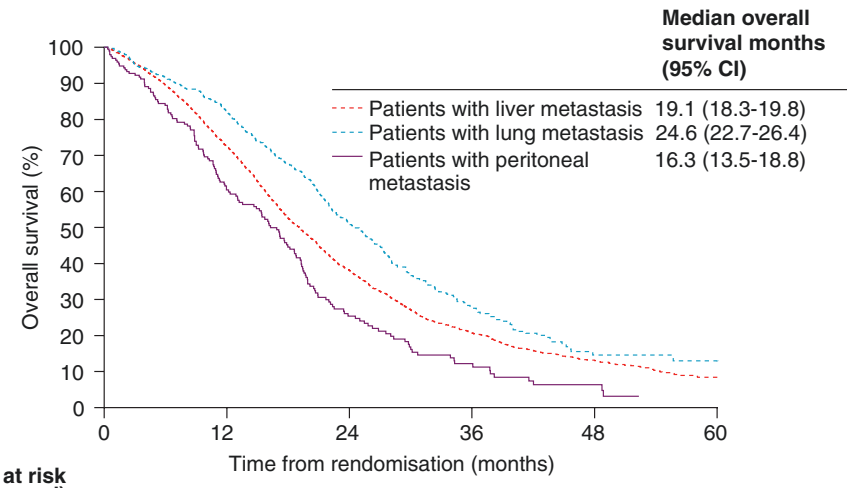
Systemic chemotherapy was considered to be the standard treatment for metastatic colorectal cancer. Over the years with improvisation and introduction of new chemotherapy regimens and the use of targeted therapies, there has been an improvement in the overall survival of these patients with a median overall survival reaching 30 months in some studies. Most of these studies had patients with metastases at one or more primary sites. Jan Franko and other investigators carried out an analysis of patients from various chemotherapy trials with peritoneal metastases and showed that peritoneal metastatic colorectal cancer is associated with substantially shorter overall survival by 30–40% as compared with non-peritoneal disease sites,[1] although some retrospective studies have not identified worsened prognosis [15–19].

Franko et al. analyzed individual patient data for previously untreated patients enrolled in 14 phase 3 randomized trials done between 1997 and 2008. The trials that exclusively enrolled patients with PM or those in which a formal evaluation of the peritoneal disease was made prior to enrollment were included in the analysis [20]. Of the 10,553 patients analyzed, 9178 (87%) had metastases at sites other than the peritoneum (4385 with one site of metastasis, 4793 with two or more sites of metastasis), 194 (2%) patients had isolated PM, and 1181 (11%) had PM with metastases at other sites; the patients' characteristics and treatment protocols were matched in these three groups. Patients with PM were more likely to be women ($p = 0.0003$), have colonic primary tumors ($p < 0.0001$), and have a performance status >1 ($p < 0.0001$). There was a higher proportion of patients with *BRAF* mutations in the PM alone group (8 [18%] of 44 patients with available data) and PM with other sites of metastases (34 [12%] of 289), compared with patients with non-peritoneal metastatic colorectal cancer (194 [9%] of 2230; $p = 0.028$ comparing the three groups). OS (adjusted HR 0.75, 95% CI 0.63–0.91; $p = 0.003$) was better in patients with isolated non-peritoneal sites than in those with isolated PM. Patients with two or more sites of metastases (excluding the peritoneum) (adjusted HR 1.04 for overall survival, 95% CI 0.86–1.25, $p = 0.69$), PM and metastases at one other site (adjusted HR 1.10, 95% CI 0.89–1.37, $p = 0.37$) and those with isolated PM, all experienced a similar overall survival. The worst survival was seen in patients with PM and two or more other sites of metastases (adjusted HR 1.40; CI 1.14–1.71; $p = 0.0011$).

This analysis concluded that patients with colorectal PM have a significantly shorter overall survival than those with other isolated sites of metastases (Fig. 8.1). In patients with several sites of metastasis, poor survival is a function of both increased number of metastatic sites and peritoneal involvement (Fig. 8.2). The pattern of metastasis and in particular, peritoneal involvement, results in prognostic heterogeneity of metastatic colorectal cancer [20].

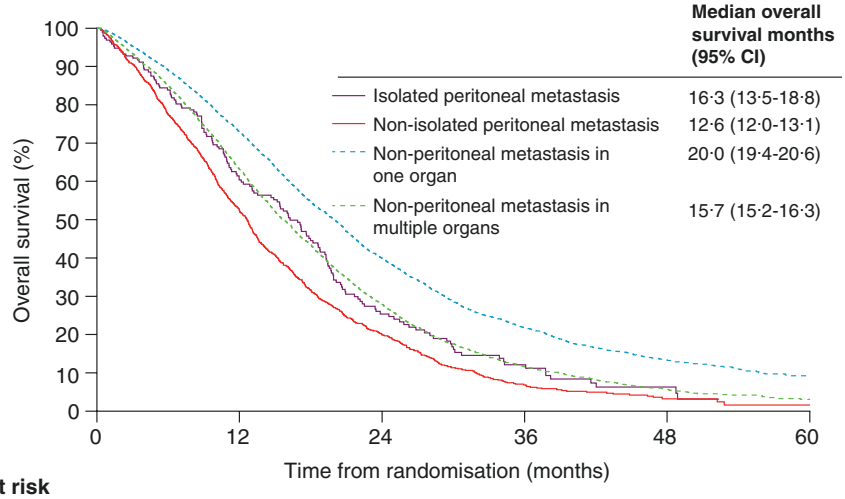
8.2.3 Combined Resection of Colorectal Peritoneal Metastases and Liver Metastases

The presence of simultaneous liver and peritoneal metastases has been considered a contraindication for aggressive treatment of either [5, 21, 22]. In 1999, Elias et al. reported the results of 12 patients who underwent synchronous resec-



Number at risk (number censored)						
Patients with liver metastasis	3179 (2)	2187 (127)	901 (355)	328 (221)	93 (144)	26 (43)
Patients with lung metastasis	623 (0)	483 (30)	238 (81)	73 (76)	15 (33)	5 (9)
Patients with peritoneal metastasis	193 (0)	110 (8)	38 (14)	13 (7)	4 (3)	0 (2)

Fig. 8.1 Overall survival in patients with colorectal cancer and a single site of metastases (From [20] with permission)



Number at risk (number censored)						
Patients with isolated paritoneal metastasis	193 (0)	110 (8)	38 (14)	13 (7)	4 (3)	0 (2)
Patients with non-isolated paritoneal metastasis	1181 (4)	583 (43)	175 (75)	35 (43)	9 (11)	2 (5)
Patients with non-paritoneal metastasis in one organ	4385 (3)	3031 (183)	1302 (499)	462 (338)	122 (208)	35 (61)
Patients with non-paritoneal metastasis in multiple organ	4790 (3)	2873 (176)	977 (468)	243 (253)	56 (98)	12 (27)

Fig. 8.2 Overall survival in patients with colorectal cancer with isolated peritoneal metastases, non-isolated peritoneal metastases, non-peritoneal metastases in one organ, and non-peritoneal metastases in multiple organs (From [20] with permission)

tion of liver and peritoneal metastases from multiple primary sites but majority with colorectal LM. The PM were an incidental finding in all these patients, and though not reported in terms of PCI, some of the patients had extensive disease with the number of peritoneal nodules ranging from 20 to 150 [23]. The authors reported no mortality but a higher incidence of bile leakages (33%). Seven patients were recurrence free at a median follow-up of 14.4 months. Major hepatectomies (involving resection of more than two Couinaud's segments) were performed in some of the patients as well [24]. Subsequently, several other investigators have reported a survival benefit of performing a synchronous resection of LM and PM with an acceptable morbidity and mortality (Table 8.2).

In another publication by Elias et al. in which there were additional 14 patients with PM and LM both diagnosed preoperatively, HIPEC was in 8/24 patients and EPIC in the remaining following a complete cytoreduction of both LM and PM [24]. They selected young patients with a good performance status, who had low-volume peritoneal disease that was asymptomatic, were responsive to 3 months of preoperative chemotherapy, and had liver metastases that were easily resectable (not invading the hepatic veins or vena cava and porta hepatis). There was one perioperative death and morbidity was seen in 58% of the patients. Three-year overall and disease-free survival rates were, respectively, 41.5% (confidence interval (CI), 23–63) and 23.6% (CI, 11–45). Seven patients were disease-free with a mean follow-up of 27.8 months after their last surgery, three having a repeated hepatectomy. Three patients developed a peritoneal recurrence and 13 had recurrence in the liver. The only significant prognostic factor for survival was a number of LMs of less than 3 ($p < 0.01$) [24].

In another study of 27 patients from the Washington cancer center, in addition to PM, 16 patients had liver metastases, 6 patients had lung metastases, 4 had liver and lung metastases, and 1 had supraclavicular lymph node metastases. Median OS for the entire group was 15.2 months [25]. The median overall survival (OS) was 20.6 months in patients who had a complete cytoreduction at all sites and 9 months ($p = 0.047$) in patients with an incomplete cytoreduction. Postoperative morbidity and mortality were 14.8 and 0%, respectively. In 14 patients with a PCI < 13, the median OS was 17.7 months, which was significantly longer than that of 9 months for the 13 patients with a PCI greater than 13 ($p < 0:0471$).

Kianmanesh et al. reported outcomes in 16 patients with LM and PM undergoing a synchronous or staged resection (resection of LM was performed prior to 2 months after CRS and HIPEC) [26]. Three patients had prior to CRS and HIPEC, ten had concomitant minor liver resection, and three had differed liver resections (two right hepatectomies) 2 months after CRS and HIPEC. The mortality rate was 2.3% (one patient). The median OS was 38.4 months (CI, 32.8–43.9). Actuarial 2- and 4-year survival rates were 72% and 44%, respectively. The survival rates were not significantly different between patients who had CRS and HIPEC for PM alone (including the primary resection) versus those who had synchronous resection of LM (median survival, 35.3 versus 36.0 months, $P = 0.73$). Of note was the fact that patients were stratified according to Gilly's score and patients with ascites and malignant bowel obstruction were also taken up for potentially curative surgery [26].

Chua et al. compared 16 patients undergoing resection of LM and PM both with HIPEC to those undergoing CRS and HIPEC alone. Patients with both PM and LM had a lower PCI ($p = 0.03$), were less likely to undergo HIPEC ($p < 0.001$), received less intraperitoneal chemotherapy (HIPEC or EPIC or both) ($p = 0.007$), had a shorter mean operative time ($p = 0.001$), and required less blood transfusion ($p = 0.02$). There was no difference in survival between patients who had PM alone or PM with LM and underwent aggressive treatment ($p = 0.77$) [28].

Similarly, Varban et al. found no difference in survival between 128 patients undergoing CRS and HIPEC for colorectal PM to those undergoing CRS and HIPEC with liver resection for both PM and LM. The median number and size of the liver lesions were 1 (range, 1–7 lesions) and 3.0 cm (range, 0.4–12 cm), respectively [29]. The median

Table 8.2 Outcomes in patients undergoing synchronous resection of colorectal LM and PM with or without HIPEC

Ref no Year	No of patients	Comparative group	Other sites of metastases	Mean number of LM	Median PCI	IPC	Morbidity	Mortality	Overall survival (OS)	*P* value (OS LM + PM vs PM)
[23] 1999	12	No	No			EPIC	33%		NR	
[24] 2004	24	No	No	4.4		HIPEC/ EPIC	58%		41.5% (3-year OS) 23.6% (5-year OS)	
[25] 2004	27	No	Lung	–	≤13- *N* = 14 >13- *N* = 13	HIPEC	14.8		Median OS 15.2 months	
[26] 2007	16	Yes	–	–	–	HIPEC	39%	2.3%	Median OS 38.4 months 72% (2-year OS) 44% (4-year OS)	0.73
[27] 2008	13	Yes	No	–	–	–			Median OS 18 months 19% (3-year OS) 0% (5-year OS)	
[28] 2009	16	Yes	No	2.1 (1–7)	8	HIPEC	31% (grade 3-4)	0	Median OS 36 months 65% (2-year OS)	0.77
[29] 2009	14	Yes	No	1		HIPEC	57.1%		Median OS 23.0 months 43.3 (2-year OS) 14.4 (4-year OS)	
[30] 2010	8	Yes	No	–	–	HIPEC/ EPIC	33%	0%	–	
[31] 2011	42	Yes	12/42 patients not operated		2	–	30%	0%	Median OS 42 months 18% (5-year OS)	0.02 (compared with patients not resected)
[32] 2013	37	Yes	No	2 (1–16)	11	HIPEC/ EPIC	51%	8%	Median OS 32 months 40% (3-year OS) 26% (5-year OS)	0.04
[33] 2015	36	Yes	No		7	HIPEC/ EPIC	34.6%	1.3%	Median OS 24.4 months 33% (3-year) 18% (5-year)	0.03 for OS 0.02 for DFS

Ref no Year	No of patients	Comparative group	Other sites of metastases	Mean number of LM	Median PCI	IPC	Morbidity	Mortality	Overall survival (OS)	*P* value (OS LM + PM vs PM)
[34] 2016	9	Yes	No	–	18.5	HIPEC	14%	3%	Median OS 50.9 months 76%(2-year OS)	0.235
[35] 2016	25	Yes	No			HIPEC	32% (grade 3–4)	4%	70.2% (2-year OS) 13.4% (2-year DFS)	0.04
[36] 2017	22	Yes	No	2(1–6)		HIPEC			Median OS 36 months 40% (5-year OS)	$p > 0.05$

EPIC early postoperative intraperitoneal chemotherapy

OS for patients with LM was 23.0 months. Two-year and four-year survival rates in patients with and without LM were 43.3% and 14.4% and 36.8% and 17.4%, respectively, which were not statistically different (log-rank $P = 0.39$). Most patients had a single small metastasis that required a minor hepatic resection. The group with PM alone included those with ascites, and the LM and PM group included patients with bowel obstruction. The patients were not stratified according to PCI, and three patients had the diagnosis of LM made during surgery for PM [29].

Glockzin et al. reported outcomes in 63 patients undergoing CRS and HIPEC with hepatobiliary procedures, out of which 8 had liver resection for parenchymal metastases. One patient developed major morbidity. The survival for this subgroup was not reported separately [30].

In a single institution study, out of the 1340 operated patients for CLM from 1985 to 2010, 42 (3%) had unexpected PM. Only patients ($n = 30$; 71%) who had PM limited to two abdominal regions [median peritoneal cancer index (PCI), 2 (1–6)] underwent resection of PM [31]. Twelve patients did not undergo surgical resection due to the extent of peritoneal disease. The OS of the 30 patients who underwent synchronous resection of LM and PM was 18% at 5 years (median, 42 months). Thirty-three percent of the patients had peritoneal recurrence though the PCI was low. No factor was found to have an impact on survival. Patients with T4 primary tumors and bilobar liver metastases were independent predictors of unexpected finding of PM during surgery.

Maggiori et al. compared 37 patients with synchronous resection of LM and PM with 61 patients with PM alone [32]. Patients undergoing CRS and HIPEC with liver resection fared worse in terms of OS compared to those undergoing CRS and HIPEC alone (40% vs 66%, $p = 0.04$). Moreover, patients with PCI < 12 and no liver metastases had a median OS of 76 months compared to PCI < 12 and 1–2 liver metastases (40 months) and PCI >12 or >3 liver metastases (27 months). Patients with a PCI of 12 or more [odds ratio (OR), 4.6], those with nodal involvement of histopathology (OR, 3.3), those who did not receive adjuvant chemotherapy (OR, 3.0), and those who had LM (OR, 2.0) had an inferior OS, and these factors were independent predictor of a poorer OS. Among patients who developed a recurrence during follow-up, patients in the PM and LM group had significantly more hepatic recurrences than patients in the PM alone group (61% vs 12%, respectively, $P < 0.001$). The number of peritoneal recurrences (55% vs 42%, $P = 0.279$) and recurrences at other sites (48% vs 52%, $P = 0.736$) did not differ between the two groups. The authors recommended that in patients with a PCI of less than 12 and 1 or 2 easily resectable LM, complete surgical resection followed by HIPEC could be offered if they meet the selection criteria (good performance status, no extra-abdominal disease, complete resection of PM is possible, R-0 resection of the liver disease is possible, and absence of disease progression after 2–3 months of systemic chemotherapy). Aggressive surgical treatment must be very carefully evaluated for patients with PM with a PCI of 12 or more, associated with LM [32].

In another study of 36 patients undergoing resection of LM and PM, the median OS was 24.4 months. Eighteen had a PCI > 7 and >3 LM, and the median survival in this group was 21.8 months compared to 18 patients with PCI ≤ 7 and LM ≤ 3 with median survival of 38.4 months. The median disease-free survival for the whole group was 8.5 months [33].

In a retrospective series by Lorimier et al. of 22 patients with PM and LM treated from 1999 to 2001, the survival after CRS, HIPEC, and resection was similar to that in 36 patients undergoing surgery for LM alone [36]. All the patients who had a CC-0 resection underwent HIPEC with mitomycin C or oxaliplatin. Radiofrequency ablation was used in addition to hepatic resection in some patients. No significant difference was found between the two groups. The median OS were 36 months (range, 20–113) for the PM and LM group and 25 months (14–82) for the PM group ($p > 0.05$) with 5-year OS rates of 38% and 40%, respectively ($p > 0.05$). The median DFS were 9 months (9–20) and 11.8 months (6.5–23), respectively ($p = 0.04$). The occurrence of grade III–IV morbidity and a cytoreduction score CCR > 0 ($p > 0.05$) were independent predictors

of a poorer OS. Resection of LM and a CCR > 0 were independent predictors of poorer OS. The impact of the number of liver metastases on DFS or OS was not reported in this study.

Berger et al. reported outcomes in 103 patients undergoing CRS and HIPEC with resection of LM. These patients included those with appendiceal primary tumors and with capsular involvement of the liver as well. There were 28 patients with colorectal liver metastases of whom 18 patients had parenchymal liver metastases. Nine patients had concurrent CRS and HIPEC and resection of LM, while nine others had resection of LM performed before or after the HIPEC procedure. The median OS of these 18 patients was 50.9 months which was similar to 59.6 months in patients with PM alone.($p = 0.64$). Survival was longer than 2 years in ten of these patients, with the longest follow-up period being 71 months. These long-term survivors had a median PCI of 10 (for all 103 patients) [37]. The selection criteria used were no progression on at least 3 months of systemic chemotherapy, a good performance status, and a predicted PCI of <21. Complications related to liver resection were seen only in two patients, and both were managed by interventional radiology procedures. Patients in the LM and HIPEC group showed significantly more grade III complications ($p = 0.009$) [37].

In a meta-analysis of 16 studies reporting survival after resection of colorectal LM in a total of 378 patients with PM, accounting for 17% of all patients undergoing resection of colorectal LM and extrahepatic disease, patients with PM constituted 3% of all patients with liver metastases undergoing surgical resection [38]. This review summarized OS after resection of LM and PM as a proportional meta-analysis which is a more representative measure of true outcome compared with using median OS figures alone.

The proportional meta-analysis of survival data for these patients showed a 3- and 5-year OS of 37% (95% CI = 31–43%, significant heterogeneity (I^2) = 0%) and 17% (95% CI = 9–25%, I^2 = 65%), while the brief quantitative analysis showed a relative risk of mortality by 5 years for this group of 1.59 (95% CI = 1.16–2.17) compared to those patients who had LM alone and had a surgical resection. The median OS of patients with LM and PM was 25 months compared to 29 and 42 months with lymph node and lung metastases, respectively, in addition to LM [38].

Unfortunately, it was not possible with the available data to present overall 5-year DFS figures which would give the best indication of possible cure after resection.

In another meta-analysis comprising of 1142 patients undergoing resection of colorectal PM and LM, the median disease-free survival was 12 (range, 4–22) months, median overall survival was 30 (range, 14–44) months, and median 5-year survival rate was 19% (range, 0–42%). Median 5-year survival of patients with R0 hepatectomy with resection of extrahepatic was 25% (range, 19–36%). Based on the site of extrahepatic disease, median survival of patients with lung metastases was 41 (range, 32–46) months, porto-caval lymph node metastases was 25 (range, 19–48) months, and PM was 25 (range, 18–32) months. The most important factor influencing survival was complete resection of disease at both metastatic sites [39].

A third meta-analysis also showed similar findings. Patients with extrahepatic disease to the lungs had a median OS of 45 (range, 39–98) months versus lymph nodes (portal and para-aortic) 26 (range, 21–48) months versus peritoneum 29 (range, 18–32) months. The median OS also varied by the amount of liver disease—42.2 months (<2 lesions) versus 39.6 months (two lesions) versus 28 months (≥3 lesions) [40].

Interestingly, in everyone of the three meta-analyses, several studies included patients receiving intraperitoneal chemotherapy (IPC), while others did not. The number of patients who received some form of intraperitoneal chemotherapy is too small to derive any meaningful conclusion regarding the benefit of its addition to surgical resection. If the resection was performed at a center specializing in peritoneal surface malignancies, IPC was used provided complete tumor removal was achieved. Not all studies reported the PCI as well. In studies reporting outcomes of LM considering PM as a site of extrahepatic disease, PCI was not reported. In some studies, a formal exploration of the

whole peritoneal cavity was not performed either and only disease which was visible and resectable through an upper abdominal incision was resected.

In another meta-analysis that included only six studies all of which used either HIPEC or EPIC, authors concluded that patients with LM and PM from colorectal cancer show a trend toward a lower overall survival after curative resection and HIPEC, when compared to patients with isolated peritoneal metastases after CRS and HIPEC (pooled HR1.24, CI 0.96–1.60). However, patients with metastatic colorectal cancer show a tendency toward increased median OS after CRS and HIPEC combined with resection of liver metastases when compared to treatment with modern systemic chemotherapy [41].

Elias and collaborators in a study of 287 patients with LM, 119 patients with PM, and 37 patients with both found no difference in survival in the 3 groups of patients treated with liver resection, CRS and HIPEC, or both [42]. Based on this study, they developed a graphic nomogram that is simple to calculate and easy to use and can determine the prognosis of patients according to the number of LM, the PCI, or both. This nomogram is based on the number of liver metastases, the PCI, and the planned procedure (CRS and HIPEC, liver resection, or CRS and HIPEC with liver resection) and predicts the probability of survival at 1, 3, and 5 years. However it is based on retrospective data from a single institution and needs to be validated prospectively.

8.2.4 Some of the Questions that Arise When Dealing with Colorectal Peritoneal and Liver Are Listed Below

8.2.4.1 Should a Combined Resection Be Performed?

PM can be an incidental finding in a patient undergoing liver resection for LM, or both could be diagnosed on imaging before surgery. Rarely, parenchymal LM are detected during surgery for PM. The median overall survival reported in the various studies reporting outcomes of combined resection ranges from 18 to 50.9 months [23–37]. These studies are retrospective in nature and have small numbers, and the patients represent a highly selected group. Nevertheless, this could be considered significantly better than the median OS of 16.3 months and 15.0 months in patients with isolated PM and those with multiple sites of metastases, respectively [20]. Even in patients who received targeted therapy in addition to systemic chemotherapy, the median OS in these two groups was 17.1 and 16.8 months, respectively [20]. In all the studies, a comparison has been made between patients with both LM and PM and those with either LM or PM alone undergoing surgical resection of all the metastases where the benefit of surgery is already defined. The survival results are similar to patients with PM alone treated with surgery and inferior to those with liver metastases as shown above. There is no comparison with systemic chemotherapy as the sole treatment. Hence, the question still arises—can systemic therapy produce similar results in this highly selected group of patients? Conducting a trial comparing surgical resection and systemic chemotherapy would be ideal but almost impossible for these patients as randomization may be considered unethical and conducting a trial for a complex surgical procedure is difficult. Based on the current available evidence, combined resection of PM and LM can be recommended in selected patients.

8.2.4.2 Selection Criteria

Such resections should be performed in patients with

a. good performance status
b. no extra-abdominal disease
c. less than 3 liver metastases
d. PCI < 12
e. patients who have no progression on systemic chemotherapy
f. complete resection of tumor at both sites is possible [32].

These criteria may not be considered all inclusive. It must be also kept in mind that the recommendation to perform surgery for patients with a PCI of <12 and with 1–3 LM comes from a retrospective study of 37 patients that were treated over a 15-year period, and though the surgical quality did not differ, the intraperitoneal chemotherapy type and regimens as well as the systemic chemotherapy used were very heterogenous [32]. In another study, a PCI >7 and >3 LM resulted in a poorer survival. However, both these factors were taken together, and the impact of each factor individually was not evaluated [33]. There are patients with a low PCI (<12) and 1–2 LM that are easily resectable. In these patients surgery is warranted. Similarly there are patients with a PCI >12 and >3 LM in whom surgery is probably not beneficial and should not be performed. There are two other subgroups—patients with a high PCI and limited easily resectable LM and patients with more extensive but resectable LM and a low PCI. Multiple studies have shown that the number and distribution of LM have no impact as long as they can be resected with negative margins [43]. In the study by Maggiori, the survival was 27 months when the PCI was >12 or the number of liver metastases was >3 [32]. This is still higher than the survival obtained by systemic chemotherapy alone. The negative impact of a high PCI is greater than that of the number of liver metastases and cannot be offset by the use of systemic chemotherapy. Hence, it is not advisable to perform surgery in patients with a high PCI. In the other scenario, when the peritoneal disease is limited, and the number of LM is >3, the treatment should be individualized. The median OS of 27 months is still superior to the survival obtained by systemic chemotherapy alone, and aggressive surgical treatment can still be considered in these patients though new selection criteria need to be defined. Moreover, radiofrequency ablation was used in 19% of the patients in addition to resection of LM. The role of surgery in such patients needs further evaluation. Such cases may often be the ones in which PM are an incidental finding in patients undergoing resection of LM.

8.2.4.3 Extent of Resection: Should a Major Hepatectomy Be Performed (Resection of >2 Couinaud's Segments)

Multiple studies have shown that the number and distribution of liver metastases have no impact as long as they can be resected with negative margins [43]. Liver metastases can grow very large, and even patients with one or two metastases may require a hepatectomy. Multiple studies have shown an acceptable morbidity and mortality of such procedures even when they are combined with CRS [31, 35–37]. There may be an increased risk in patients who receive some form of intraperitoneal chemotherapy as demonstrated in the study by Maggiori [32]. However, these complications are related more to the cytoreductive surgery than the liver resection, and this has been demonstrated in other studies as well. Such cases need to be individualized and decisions taken by a multidisciplinary team.

8.2.4.4 Prognostic Factors

The prognostic factors that have a survival benefit are resection of the liver metastases with negative margins, a CC-0 resection for the peritoneal metastases (it is important to note here that for high-grade malignancies like colorectal cancer, a CC-0 resection where there is no visible residual disease is ideal and not CC-1 where there is residual disease measuring up to 2.5 mm), PCI < 12, no lymph node metastases, and use of systemic chemotherapy.

8.2.4.5 Role of Systemic Chemotherapy

In most of the studies, patients have received systemic chemotherapy though its role has not been evaluated separately [23, 24, 32, 33, 36]. Elias et al. used systemic chemotherapy in all patients, and surgery was not performed in patients who had disease progression on chemotherapy [23, 24, 32]. The use of chemotherapy was a predictor of better OS. Extrapolating from the treatment of PM where systemic therapy is used more often than not, it would be prudent to use it in such patients.

Table 8.3 Management of colorectal LM and PM occurring synchronously

No. of LM	PCI	Prerequisites	Treatment strategy
1–2	<12	Good PS, no other site of metastatic disease, no progression on SC, resection of LM with negative margins, CC-0 for PM	Combined resection of LM and PM + IPC + SC
≥3	>12		SC
1–2	>12		SC
≥3 resectable	<12	Good PS, no other site of metastatic disease, no progression on SC, resection of LM with negative margins, CC-0 for PM	Individualized treatment Combined resection of LM and PM + IPC + SC can be considered in some patients

IPC intraperitoneal chemotherapy, *PS* performance status, *SC* systemic chemotherapy

8.2.4.6 Intraperitoneal Chemotherapy

The use of intraperitoneal chemotherapy is variable. EPIC and HIPEC have both been performed with several drug regimens, which makes it impossible to draw conclusions of the benefit [31, 32]. Many studies have not used intraperitoneal chemotherapy at all. What is known, however, is that IPC adds to the morbidity and this should be kept in mind while performing HIPEC or EPIC in these patients. The benefit of HIPEC in addition to CRS alone in patients with isolated PM will be defined by the PRODIGE 7 trial (NCT00769405).

Based on the above evidence, the following recommendations that can be made for patients with synchronous colorectal LM and PM are listed in Table 8.3.

8.2.4.7 Survival

Few studies reported an inferior survival for patients undergoing resection of LM and PM as compared to PM alone where as other studies reported no difference in the survival. Resection of LM itself was a predictor of a poorer OS itself though there was no significant difference in OS in the two groups. Some long-term survivors were seen, but the 5-year disease-free survival was not reported by any of the studies.

8.3 Ovarian Cancer

Ovarian cancer has a propensity for intraperitoneal dissemination. Though dissemination occurs through other routes—lymphatic and hematogenous—it is less common. It has been demonstrated that the hematogenous route is partly responsible for the high incidence of ovarian cancer metastases to the omentum [44, 45]. Other sites of spread like the retroperitoneum, distant organs, and submesothelial tissue indicate deployment pathways other than the intraperitoneal route for cancer spread in ovarian cancer [46–50].

In metastasis of ovarian cancer cells via the hematogenous route, intravasation, which is the invasion of cancer cells through the basal membrane into blood or lymphatic vessels, is the first step. The cancer cells then transit in the blood or lymph and undergo extravasation, which is the exit of cells from the blood or lymph vessels [45, 51].

This liver is a common site for hematogenous spread. Up to 15% of the patients with epithelial ovarian cancer (EOC) will be diagnosed with FIGO stage IV disease, for example, the presence of parenchymal liver metastases [52]. LM account for 18% and were the second most common cause of stage IV disease in a GOG study [53]. LM are seen in up to 50% of patients dying of EOC [54].

Liver involvement can occur synchronously with peritoneal involvement. Intraparenchymal metastases must be distinguished from surface deposits that are infiltrative and require non-anatomical liver resections. Intraparenchymal metastases are surrounded by a rim of normal liver tissue on all sides. When the involvement of the liver and peritoneum is both limited, a synchronous resection of the PM and LM can be carried out.

8.3.1 Outcomes of Combined Resection of Peritoneal and Liver in Ovarian Cancer

In patients with ovarian cancer, synchronous resection of intraparenchymal liver metastases has been performed with CRS, especially in patients with solitary liver metastases. In patients with both advanced and recurrent ovarian cancer, resection of one or more liver metastases has been performed with CRS with good long-term survival [55]. However, none of these studies used any form of IPC. The goal of such resection should be to resect the LM with a negative margin and obtain a complete cytoreduction for the PM. Several retrospective studies have reported that such resections can be performed with an acceptable morbidity and mortality. In 1999, Bristow et al. first reported a survival benefit of resecting LM in patients with EOC who had undergone an optimal cytoreduction [56]. Loizzi et al. reported outcomes of liver resection in 29 patients with primary or recurrent ovarian cancer with LM. The median OS after liver resection was 19 months for patients with primary and 24 and 10 months, respectively, for patients undergoing secondary and tertiary cytoreduction [57]. On univariate analysis, the histology, performance status at the time of primary tumor diagnosis, number of hepatic lesions, the presence of extrahepatic disease, and treatment with platinum-based chemotherapy were the factors influencing survival. Lim et al. reported outcomes in 16 patients undergoing resection of LM from epithelial ovarian cancer. However, they performed liver resection only in patients with superficial liver metastases which were probably peritoneal metastases infiltrating the liver rather than true LM caused by hematogenous spread [48]. In a series of 70 patients with advanced and recurrent ovarian cancer reported by Neumann et al., only 58.6% could undergo complete tumor removal, and the median survival in these patients was 42 months [58].

Meredith et al. reported outcomes in 26 patients undergoing resection of LM and PM in patients with recurrent ovarian cancer at the time of secondary cytoreductive surgery [59]. Patients had more extensive liver resections comprising of resection of more than two Couinaud's segments as well. Median OS was significantly higher for patients who underwent an optimal cytoreduction (27.3 vs 8.6 months) and those who were disease-free for 12 months or more before the second surgery (27.3 vs 5.7 months). Neither the number nor the distribution of LM had an impact on OS. Similar outcomes were reported by Pekmezci in eight recurrent ovarian cancer patients with a median disease-free survival of 39 months [60]. This series included a mix of patients with LM alone and those with LM and PM. In another series of 24 patients undergoing resection of LM and PM in the setting or recurrent disease, the median OS was 62 months. Twenty-one percent of the patients had complications related to the hepatectomy, the commonest being a bile leak [61]. The outcomes of resection of LM and PM from ovarian cancer are listed in Table 8.4 [62].

The common prognostic factors reported in these studies were optimal CRS (<1 cm residual disease), negative resection margins, a disease-free interval of >12 months, fewer number of liver metastases, and fewer sites of disease. Major hepatic resections have also been performed with acceptable morbidity and a benefit in survival [57, 64].

None of these studies used IPC. Moreover, the patients included a combination of those undergoing resection of LM alone and those undergoing resection of LM and PM both especially in the setting of recurrent disease [48, 58]. These studies also do not quantify the extent of PM in terms of the PCI which is an important prognostic factor both in advanced and recurrent ovarian cancer.

The ideal way to demonstrate the benefit of resection of LM would be to conduct a randomized controlled trial. But as Gasparri et al. have pointed out, such a trial is unlikely to be conducted due to ethical considerations, the years needed to accrue a significant number of patients, and the complexity of the surgery involved.

Table 8.4 Surgical and oncologic outcomes in patients undergoing CRS with resection of liver metastases (adapted from [62])

Ref. No. Year	No of patients	Optimal CRS	Type of liver resection	Negative resection margins	OS (months)	Prognostic factors
[56] 1999	37	16%	–	NA	Overall: 18.1 Optimally cytoreduced pts: 38.4 Suboptimally cytoreduced pts: 10.3	Residual disease GOG PS Number of salvage chemotherapy regimen
[48] 2009	16	100%		100%		55% 5-year OS for stage IIIC pts 51% 5-year OS for stage IV pts
[59] 2003	26	80.8%	Segmentectomy 69.2% Trisegmentectomy 3% Left hepatectomy 3.8% Right hepatectomy 15.4%	NA	26.3 Optimal CRS 27.3 Suboptimal CRS-8.6 $P = 0.031$	Residual disease: <1 vs. >1 cm DFI: <12 vs. >12 months Distribution of disease: abdomen > pelvis or pelvis ≥ abdomen
[61] 2003	24	66.7	Wedge resection 12.5 Segmentectomy 70.9 Trisegmentectomy 8.3% Lobectomy 8.3%	54.1%	62 (95%CI-41–83)	No significant prognostic factors found
[57] 2005	29	NA	NA	NA	Hepatic disease alone 25 (9–44) Multi-organ recurrence 8 $P = 0.033$	Number of hepatic lesions; Presence of other sites of disease; Treatment with platinum-based chemotherapy
[63] 2008	10	100%	Bisegmentectomy 10% Trisegmentectomy 40% Lobectomy 50%	50%	33 (95% CI 19–56)	Size of largest tumor ≥5 cm Negative resection margin ($p = 0.024$)

8.4 Other Primary Sites with Both Liver and Peritoneal Metastases

The reports of combined resection of LM and PM from other primary sites are scarce. Glockzin et al. reported perioperative outcomes of hepatobiliary procedures combined with CRS and HIPEC for PM and LM from various primary sites [30]. The hepatobiliary procedures included resection of the Glisson's capsule and bile duct apart from liver resections. Primary tumor was of appendiceal origin in 29 patients, of ovarian origin in 12 patients, and of colorectal origin in 11 patients. Less frequent entities causing peritoneal carcinomatosis were mesothelioma (8%), gastric cancer (3%), primary peritoneal cancer (3%), or other (one patient each with leiomyosarcoma of the uterus and renal-cell carcinoma). The authors concluded that hepatobiliary procedures were need in one-third of the patients in addition to peritonectomies and visceral resections commonly used to obtain a complete CRS and the liver specific complications were low in such procedures [30].

Berger et al. reported outcomes of 103 CRS/HIPEC procedures (38%) performed in 101 patients with the PM arising from colorectal cancer (27%), appendix (33%; high-grade tumors), low-grade appendiceal mucinous neoplasm

(13%), ovarian cancer (6%), gastric cancer (5%), mesothelioma (5%), and other malignancies (11%) including hepatocellular carcinoma ($n = 3$), cholangiocarcinoma ($n = 2$), pancreatic cancer ($n = 2$), gallbladder cancer ($n = 1$), melanoma ($n = 1$), Mullerian tumor ($n = 1$), and teratoma ($n = 1$) [37]. These included patients with capsule involvement ($n = 84$, 82%) and parenchymal metastases in 14 cases (14%), mainly from colorectal origin ($n = 9$). Thus, most of these patients had PM alone rather than hematogenous spread to the liver. There were a few cases in which the liver was involved by direct local invasion of an intra-abdominal tumor ($n = 2$) or by a primary tumor of the liver (cholangiocarcinoma, $n = 2$; hepatocellular carcinoma, $n = 1$). Most liver resections (55.3%) were superficial resections (capsular resections), whereas 46 procedures (44.7%) consisted of parenchymal resection. The survival outcomes were reported in patients with colorectal cancer and high-grade appendiceal tumors [37]. In patients with high-grade appendiceal tumors, the corresponding OS difference in patients with resection of LM and PM was similar to a group of patients with PM alone ($P = 0.54$). The authors concluded that liver resection-related morbidity is low and overall morbidity/mortality rates are comparable to other extensive CRS/HIPEC procedures. These results hold little value since hepatic capsular resections were included and would not be classified as a hepatobiliary resection by most surgeons.

The role of combined resection of LM and PM in primary other than colorectal cancer and ovarian cancer is undefined.

8.5 Technical Aspects

A thorough preoperative assessment is essential to determine the exact extent of the LM (volume and distribution) and determine the future liver remnant which should be 20–25%. A diagnostic laparoscopy could be used to assess the extent of the peritoneal disease. There is no guideline for the ideal liver remnant when HIPEC is planned as hepatotoxicity is known after HIPEC especially with the use of certain drugs like oxaliplatin. Patients may have transient liver dysfunction though a severe morbidity has not been reported.

The principles of cytoreductive surgery are followed, and the goal of such surgeries is to achieve a complete cytoreduction. An incision from the xiphoid to the pubis is employed to allow a thorough exploration and the performance of CRS. Techniques for safe resection like the selective use of portal triad clamping, an emphasis on maintaining low intravascular volumes during parenchymal transection, and meticulous hemostasis and biliostasis should be employed [62].

Peritonectomy procedures create large raw surface with massive loss of serum demanding transfusion of colloid solutions or fresh frozen plasma.

The liver-first approach allows the liver resection to be performed with minimal blood loss followed by the cytoreduction. However, in many cases the liver disease is associated with significant right upper quadrant PM mandating RUQ peritonectomy and lesser sac peritonectomy procedures before the liver can be approached. In case a complete CRS is not possible, the resection of the liver disease would not be of any value and lead to morbidity. It is easier to predict resectability of LM on preoperative imaging as compared to predicting resectability of PM. Hence, it is prudent to approach the peritoneal disease first and then perform the liver resection once a complete cytoreduction has been obtained. Intraoperative ultrasound should be used if available.

When the FLR is in adequate, a staged resection can be performed. Strategies like portal vein embolization can be used to increase the size of the FLR. Such procedures have been performed indicating the feasibility though the numbers are too small to draw any conclusions.

8.6 Ablative Techniques

Ablative techniques have been for the local treatment of liver metastases. They are used in cases where surgical resection is not possible due to the patient's age and comorbidities or the tumor size and location. The commonly used methods are

radiofrequency ablation (RFA), cryoablation, and microwave ablation (MWA). Recurrence rates from RFA have been shown to be approximately three times lower than that of cryotherapy but approximately three times higher compared to resection when used as a first-line treatment in patients with resectable disease [9, 10, 64]. RFA is safe and effective both percutaneously and surgically, but its limitations include increased impedance as temperatures reach 100 °C, a small zone of active heating and decreased effectiveness with charring [11, 12]. It cannot be used for tumors located in close proximity to blood vessels are large biliary channels [65].

Microwave ablation (MWA), alternatively, does not rely on conduction of electricity and is not limited by charring. It also remains effective in temperatures above 100 °C, provides a potentially larger ablation zone, and can be performed more quickly [11, 12]. However, it is less widely available and is more expensive, and the experience with MWA for treatment of LM is limited.

The existing literature on outcomes following intraoperative MWA of colorectal cancer liver metastases is sparse [66, 67].

These strategies have a higher rate of local recurrence as compared to surgical resection. In carefully selected patient, with colorectal LM <3 cm in size, the local control rates and OS are approaching those obtained with surgical resection in recent reports [68–71]. The role of such therapies in the management of LM in addition to or as an alternative to surgical resection in patients who have PM as well remains unknown. For colorectal liver metastases, several investigators have used RFA and cryoablation in addition to/as a replacement for surgery. The role of such procedures is currently undefined. Wherever possible, a surgical resection should be performed [31].

Conclusions

Combined resection of LM and PM with or without intraperitoneal chemotherapy can be performed in selected patients with an acceptable morbidity and mortality and benefit in overall survival. For patients with colorectal cancer, such procedures can be performed in patients with a PCI < 12 and 1–2 easily resectable liver metastases. Negative margins at resection of LM and a CC-0 for the PM should be obtained in all patients. They are not recommended for a PCI of >12. For patients with a low PCI (<12) and ≥3 LM, the prognostic factors and selection criteria need to be better defined to extend the benefit of surgical treatment to some of these patients. The role of intraperitoneal chemotherapy in this situation needs further evaluation. Similarly, in advanced and recurrent ovarian cancer, such combined resections can result in a survival benefit in selected patients. Patients with optimal residual disease, negative resection margins for the LM, a disease-free interval of >12 months (for recurrent ovarian cancer), fewer LM, and fewer sites of PM derive the maximum benefit.

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9 Management of Complications of CRS and HIPEC

Aditi Bhatt and Akash M. Mehta

9.1 Introduction

The potential clinical benefits of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have for long been overshadowed by its relatively high morbidity and mortality compared to other surgical procedures. It takes 3–12 months on an average for the quality of life to return to normal [1]. As the experience with the procedure has increased, the 'patient selection' criteria have become more disease specific and objective, clinical pathways have been developed for optimal perioperative management of patients, the experience of surgical teams has improved and formal teaching programs have been instituted which have all led to a reduction in both the morbidity and mortality. Nevertheless, as for any surgical procedure, the morbidity cannot be reduced beyond a point; the morbidity is not always reflective of a surgeon's skill as there are other factors contributing to it as well. More experienced institutes are able to 'rescue' patients who experience morbidity. In a complex procedure such as CRS and HIPEC, multidisciplinary management is required; hence, it is not just the experience of the surgical team but that of the institute as well that is important for optimizing the short-term outcomes.

9.2 Incidence of Morbidity and Mortality Following CRS and HIPEC

In several large series of CRS and HIPEC performed for peritoneal metastases (PM) arising from various primary sites, the rates of grade 3–4 morbidity range from 12 to 66% and mortality from 0 to 4.3% (Table 9.1). Two largest single-institution studies of 1200 and 1125 patients reported grade 3–4 morbidity and 30-day mortality rates of 9.6% and 20% and 1.5% and 2.2%, respectively. These patients were treated over a period of 20 and 25 years [25, 26]. The most common complications are enteric complications comprising of anastomotic leaks and bowel perforations, haematological complications and infectious complications.

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Table 9.1 Incidence of morbidity and mortality following CRS and HIPEC

Ref no year	No. of patients	Primary site	Mortality (%)	Overall morbidity (%)	Grade 3–4 morbidity (%)	Most common complications
[2] 1996	60	Various	5		35	
[3] 1999	200	Various	1.5		27	Peripancreatitis, enteric complications
[4] 2003	216	Various	3.2	30.5	23.6	Enteric complications
[5] 2003	49	Mesothelioma	0	38		Hepatic complications
[6] 2004	102	CRS	7.8	65	35	Enteric complications
[7] 2006	209	Various	0.9		12	Enteric complications
[8] 2006	103	PMP	11	54	54	Infectious complications
[9] 2006	110	PMP	0	38		Hepatic complications
[10] 2006	356	PMP	2.0	74.2	40.2	Haematological complications
[11] 2007	70	Mesothelioma	3.0	41	14	Bleeding
[12] 2007	106	Various	4	–	66	Enteric complications
[13] 2007	501	Various	4.3	43.1		
[14] 2008	124	Various	1.6	56.6	29.8	Enteric complications
[15] 2009	523	Colorectal	3.3		31%	Enteric complications
[16] 2009	405	Mesothelioma	2		31	Enteric complications
[17] 2010	1290	Various	4.1		33.6	Enteric complications
[18] 2012	284	Various	3.5	49	17	Infectious complications
[19] 2012	2298	PMP	2		22	
[20] 2013	566	Epithelial ovarian	0.8		31.3	
[21] 2013	960	Colorectal PMP	3		34	Haematological complications
[22] 2014	1000	Various	3.8		34	
[23] 2016	1000	PMP	0.8		15.2	Infectious complications
[24] 2016	247	Various	1.2		16.6	Infectious complications

Enteric complications include anastomotic leaks, perforations and fistulas

9.3 Risk Factors

The various factors that have shown a significant impact on the morbidity and mortality following CRS and HIPEC are sex, age, primary colonic anastomosis, number of peritonectomy procedures, number of visceral resections, number of anastomosis, incomplete cytoreduction, disruption of the umbilical fissure, dose of chemotherapeutic agent, intra-abdominal HIPEC temperature and histopathologic grade [3, 4, 7, 27–29].

9.3.1 Patient Factors

Age >60 years has been associated with a higher morbidity and mortality [30]. Serum albumin level of <3 g/dL has been associated with a higher 30-day morbidity [31]. A poor performance status results in a higher morbidity and mortality [30–32]. Obesity was associated with a higher rate of 30–90-day morbidity in one series and increased incidence of venous thrombosis in another. The 30-day morbidity was not higher in obese patients compared to nonobese patients [33, 34].

9.3.2 Surgical and Disease-Related Factors

The PCI is one of the most consistent independent predictors of morbidity and/or mortality from CRS and HIPEC [4, 21, 30, 32]. A higher

PCI results in more extensive surgery which may be responsible for the higher morbidity. Several studies have shown that two or more bowel anastomoses have a significant impact on morbidity of patients undergoing CRS and HIPEC [30, 32, 35]. An increasing number of peritonectomies also increase the morbidity. Only the number of anastomoses has an impact on morbidity not the number of organs resected [35].

Diaphragmatic stripping and/or resection leads to diaphragmatic dysfunction and pulmonary complications. Diaphragm resection increased the 90-day mortality but not the major morbidity in one study, whereas another study showed an increase in the morbidity but not the mortality [36, 37]. Patients with diaphragm involvement had longer operative times, increased perioperative transfusions, longer intensive care unit and hospital stay and a lower probability of complete cytoreduction in one study [37].

Studies have shown that though performing a distal pancreatectomy to obtain a complete cytoreduction followed by HIPEC is safe, the major morbidity and mortality are higher than normal even when the procedure is performed at experienced centres. In a review of 118 CRS and HIPEC procedures at 7 institutions that included distal pancreatectomy, the major morbidity at 30 and 90 days was 44% and 7.6%, respectively, which was higher than normal, and the pancreatic fistula rate of 33% was also significantly higher than that in patients who do not undergo a pancreatic resection [38].

Hepatic resections do not result in an increased morbidity but may result in an increase in the mortality [39, 40].

9.3.3 Preoperative Systemic Chemotherapy

Preoperative systemic therapy has not been associated with an increased morbidity and mortality following CRS and HIPEC [41, 42]. The use of bevacizumab in colorectal cancer has increased the overall complication rate in one series, whereas it had no impact in another series [43, 44].

9.3.4 Importance of the Learning Curve

CRS and HIPEC are associated with a prolonged learning curve that peaks at 120–140 procedures [45, 46]. Over the years, reduction of postoperative mortality has been reported from tertiary centres worldwide. In the series of 1000 patients, comparing the first 300 patients to the last 300, the grade 3/4 morbidity rates reduced from 13.7 to 6.7% and 30-day mortality from 3.0 to 0.7% [25].

In the other series of 1125 patients, 320 patients were treated in the first 5 years and 560 in the next 5 years. Postoperative morbidity (52% vs. 50%, $p = 0.672$) was not different, but mortality significantly decreased (5% vs. 2%; $p = 0.030$). The morbidity was evaluated at 90 days in this series to get a better idea of the overall morbidity [26].

In another single-institution study of 1000 procedures, the experience was divided into 5 time periods, and the morbidity progressively decreased as the experience increased ($p < 0.01$). The mortality rate ranged from 2.6 to 7.0% over the five quintiles without significant differences [23]. In a French multicentric study, Glehen et al. reported a reduced morbidity and mortality when the procedure was performed at institutes that had at least 7 years of experience in performing the procedure [18]. This probably reflects improvements in technical aspects of the surgery as well as in patient selection and optimization of perioperative and postoperative care pathways.

9.3.5 Predictive Tools and Scores

Various tools and strategies have been developed to identify patients at a higher risk of major postoperative complications after CRS and HIPEC. In a series of 426 patients, Baratti et al. found 3 factors predictive of a 100% morbidity rate – PCI > 30, more than 5 visceral resections and a poor performance status. The major morbidity was 65.7% when at least two of the factors were present [32].

In a single-institution study of 247 patients, undergoing CRS and HIPEC for PM from various primary sites, the factors predictive of major complications in the multivariate analysis were a Charlson Comorbidity Index (CCI) score higher than 0 [odds ratio (OR), 2.505; $p = 0.035$], presence of preoperative symptoms (OR 1.951; $p = 0.064$) and prior resection status [no resection or prior CRS-HIPEC (OR 2.087) vs. prior resection without CRS-HIPEC (OR 3.209); $p = 0.046$]. These variables were used to create a tool predictive of postoperative complications. The authors recommended the use of this tool for counselling patients preoperatively, though it needed further validation [24].

Malfroy et al. developed a predictive morbidity score based on the outcomes in 122 patients treated over an 18-month period [47]. Five parameters recorded on the first postoperative day and considered to be statistically, clinically and practically relevant are:

- Peritoneal cancer index over 14: which has in several reports emerged as a strong indicator of short-term and long-term survival.
- Diaphragmatic peritonectomy: which leads to diaphragmatic dysfunction and pulmonary complications.
- Drain output of >1500 in the first 24 h: which leads to hypovolemia, electrolyte imbalance, haemodynamic instability and arrhythmias.
- Need of vasopressors: when vasopressor is needed to maintain the circulatory function, it is indicative of the patients' greater postoperative frailty.
- Fluid requirement of >70 mL/kg on day 1.

Patient with complications had 4–5 of these risk factors present, whereas those without complications had <4 risk factors, and this difference was statistically significant on multivariate analysis. This score had a specificity of 92.9% and negative predictive value of 83.9%. The authors recommended that patients with a score of >3 would benefit with a longer stay in the ICU. They recommended further testing and validation of the score in a larger cohort [47].

9.4 30-Day Versus 90-Day Morbidity

Conventionally morbidity and mortality are calculated as adverse event occurring up to the 30th postoperative day. However, complications can occur late in a complex procedure like CRS and HIPEC, and mortality after 30 days is not uncommon. Mise et al. performed a receiver operating characteristic analysis in 4000 patients undergoing hepatopancreatobiliary procedures which showed that surgery-related deaths occurred up to 99 days after the procedure and deaths related to the disease occurred beyond day 118. And hence, the 90-day mortality provides a better evaluation of the surgical mortality [48]. Recent studies also suggested that 90-day surveillance should be mandatory after major surgical procedures in order to better define postoperative complications [49, 50].

Hence, for CRS and HIPEC also, the 90-day morbidity and mortality provide a better evaluation of the surgical outcome. This was demonstrated by Malfroy et al. in their study—the morbidity at 30 days was 20% and 50% at 90 days. Many surgeons now report the 90-day morbidity and mortality outcomes [47].

9.5 Scoring Systems for Surgical Morbidity

The reported rates of major morbidity range between 25 and 60% for CRS and HIPEC, and this has been the bane of this procedure which offers the only possibility of long-term survival to selected patients with PM [51, 52]. Inconsistent reporting and lack of uniform classification of complications are a major confounding factor that needs to be considered when interpreting these results. A peculiarity of CRS and HIPEC is the overlap of surgical (due to the CRS component) and medical (due to the intraperitoneal chemotherapy) complications; the effects of these can be additive. For instance, postoperative anaemia could be due to bleeding and/or marrow suppression due to chemotherapy; deterioration in the renal function could be due to third space loss and hypotension and/or due to the use of high dose of cisplatin [7].

At a consensus meeting in Milan, morbidity was defined as any adverse event related to surgical manipulation during the procedure. Toxicity was defined as any adverse event that can be clearly related to the chemotherapy component. Mortality was an adverse event resulting in death [53]. However, this distinction between medical and surgical complications is not made while reporting complications of CRS and HIPEC.

Grading systems for complications of surgical procedures have been developed to quantify their severity; compare outcomes between different procedures, surgeons and institutions; and determine their impact on the short- and long-term outcomes related to the procedure. For a valuable quality assessment, relevant data on outcomes must be obtained in a standardized and reproducible manner to allow these assessments to be made [54, 55].

Terms, such as minor, moderate, major or severe complications, have been inconsistently used among authors and centres and over time periods [56]. A number of attempts were made in the 1990s to classify surgical complications; the most popular of them is the one proposed by Clavien and Dindo [56–60] (Table 9.2).

9.5.1 The Clavien-Dindo Classification

Clavien et al. first classified complications based on the therapy used to treat them and differentiated three types of negative outcome after surgery, (a) complication, (b) failure to cure and (c) sequela [56].

Complications and sequelae both add new problems to the existing condition; the difference between the two is that sequelae are consequences inherent to the procedure, whereas complications are unexpected events. Failures are events in which the purpose of the procedure is not fulfilled. The complications were further graded according to their severity. The initial classification proposed in 1992 divided complications into 4 grades described in Table 9.1.

In this classification, the grade was based on the therapeutic intervention required to treat the complication. This approach allowed identification of most complications and prevented downgrading of major negative outcomes. This is particularly important in retrospective analyses. The authors proposed a revised version in 2004—the Clavien-Dindo classification (Table 9.3) [61]. The number of grades was increased, and more weightage was given to life-threatening complications requiring intensive care management. The length of hospital stay for gauging complications was removed. The patient perspective was introduced by adding ‘disability at the time of discharge’ in the classification. Complications that required management in the intensive care unit were graded higher. CNS complications that have a higher risk of mortality and usually require ICU management were graded higher. The length of hospital stay which is often not recorded or varies according to institutional practices was no longer a criterion for grading of complications.

The classification was tested in a cohort of 6336 patients undergoing elective general surgery and significantly correlated with complexity of surgery ($P < 0.0001$) and the length of the hospital stay ($P < 0.0001$). In an international survey that

Table 9.2 Grading of complications according to their severity as proposed by Clavien et al. in 1992

Grade	Description
Grade 1	Complications are alterations from the ideal postoperative course, non-life-threatening and with no lasting disability. Complications of this grade necessitate only bedside procedures and do not significantly extend hospital stay
Grade 2	Complications are potentially life-threatening but without residual disability. Within grade 2 complications, a subdivision is made according to the requirement for invasive procedures
Grade 3	Complications are those with residual disability, including organ resection or persistence of life-threatening conditions
Grade 4	Complications are deaths as a result of complications

Table 9.3 The Clavien-Dindo classification for grading surgical complications (From reference [61] with permission)

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, electrolytes and physiotherapy. This grade also includes wound infections that are opened at the bedside
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parenteral nutrition are also included
Grade 3	Requiring surgical, endoscopic or radiological intervention
Grade 3a	Intervention not under general anaesthesia
Grade 3b	Intervention under general anaesthesia
Grade 4	Life threatening complication (including CNS complications)[a] requiring intensive care management
Grade 4a	Single organ dysfunction (including dialysis)
Grade 4b	Multi-organ dysfunction
Grade 5	Death of a patient
Suffix d	If the patient suffers from a complication at the time of the discharge, the suffix 'd' (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

CNS, central nervous system; *IC*, immediate care; *ICU*, intensive care unit
[a]Intracerebral haemorrhage, ischaemic stroke, subarachnoid bleed excluding transient ischaemic attacks

tested the reproducibility, majority of the users found in simple, logical, useful, easily reproducible and comprehensive irrespective of the level of training of the user and the country of origin [62]. Five years later, the authors noted a dramatic increase in the use of the classification in many fields of surgery and a high degree of concurrence among patients, nurses and physicians in grading of complications in difficult scenarios [62].

Considering its simplicity and reproducibility, a number of outcome studies have used this classification system, which focuses on the most severe complication. The various degrees of severity not only correlate between surgeons, nurses and patients but also compare well with the overall cost of the procedure, length of hospital stay and other pertinent factors [63, 64].

The limitation of this classification is that it scores only the complication that is most severe or has the highest grade. A patient with multiple complications of a lower grade may be perceived as being 'worse' than one with a single complication of a higher grade.

Elias et al. proposed a modification of this classification to better suit patients undergoing CRS and HIPEC (Table 9.3) [65].

9.5.2 The Comprehensive Complication Index (CCI)

The Clavien-Dindo classification is based on an ordinal scale and considers the grade of the most severe complication; it may not be reflective of the overall burden of complications when multiple complications develop in the same patient. Clavien et al. considered summing up the grades of all the complications, but this would mean giving more weightage to the less severe complications. Consequently, they used the 'operation risk index' which is widely used in economics and synthesizes the perspectives of different stakeholders [65].

The patients and physicians' evaluation is considered separately. The median reference values from the physicians (MRV_{phys}) and patients (MRV_{pat}) for each grade of complication were then multiplied ($MRV_{phys} \times MRV_{pat}$) and compared: for example, a grade 1 complication such as wound infection drained at the bedside (e.g. $MRV_{phys} = 15$ and $MRV_{pat} = 20$; i.e. $15 \times 20 = 300$) had a much lower weight than a grade 3b complication such as a reoperation due to a complication ($MRV_{phys} = 65$ and $MRV_{pat} = 70$; i.e. $65 \times 70 = 4550$). In a next step, these figures were

summed [($MRV_{phys} \times MRV_{pat}$)] to incorporate all postoperative complications of different severities occurring in an individual patient, giving a 'raw' CCI that reflects the totality of the postoperative morbidity experience. To ease the clinical applicability of the CCI, different transformations (logarithmic, square and third roots) were tested to find a distribution of CCI scores close to a normal distribution and to set the lower CCI limit at '0' and the upper at '100'. The CCI can be readily computed on the basis of tabulated complications according to the Clavien-Dindo classification (available at www.assessurgery.com) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

The CCI summarizes all postoperative complications and is more sensitive than existing morbidity endpoints. The CCI could be used as an endpoint for randomized controlled trials and may reduce the sample size [66]. Whereas the Clavien-Dindo classification has been used widely for grading the complications following CRS and HIPEC, the CCI has not been used so far.

9.5.3 The Common Terminology Criteria for Adverse Events (CTCAE)

Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings.

The National Cancer Institute issued the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 on May 29, 2009, and this version was last updated on June 14, 2010 [68].

The classification for complications of surgical procedures is described in Table 9.4. This classification includes 310 specific types of complications and 5 severity grades; the grades are different for each complication [6]. This differentiates it from the Clavien-Dindo classification in which a common grading system is applied to each complication.

To standardize reporting of complications after CRS/HIPEC, the Common Terminology Criteria for Adverse Events (CTCAE) grading system was proposed in a consensus conference in Milan in 2006 (Table 9.5) [53].

The rationale to use the CTCAE classification for complication grading after CRS/HIPEC was the better comparability with adverse events of systemic chemotherapy.

9.5.4 Comparison of Clavien-Dindo and CTCAE classifications

A comparison and assessment of the two systems were made by Lehman et al. Complications after 147 consecutive CRS and HIPEC procedures were recorded and graded independently by a panel of experts using both classification systems [67]. Complications occurred in 37% (54/147) of patients, 6.8% (10/147) were reoperated, and 3 (2%) patients died. The most frequent complications were intestinal fistula or abscess, pulmonary

Table 9.4 Modification of the Clavien-Dindo classification proposed by Elias [from reference 65 with permission]

Grade 0	No complications
Grade 1	Complications requiring either no intervention or minor intervention such as oral antibiotics, bowel rest or basic monitoring
Grade 2	Complications requiring moderate interventions such as intravenous medication (e.g. antibiotics or antiarrhythmics), total parenteral nutrition, prolonged tube feeding or chest tube insertion
Grade 3	Complications requiring hospital readmission, surgical intervention or radiologic intervention
Grade 4	Complications producing chronic disability, organ resection or enteric diversion
Grade 5	Complications that result in death

Table 9.5 Classification of surgical and medical complications according to the CTCAE classification

Adverse event	Grade				
	1	2	3	4	5
Surgical and medical procedures	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non- invasive intervention indicated; limited age- appropriate instrumental ADL	Severe or medially significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Table 9.6 A comparison of various classifications for grading complications

	CTCAE ver 4.0	Clavien-Dindo	JCOG PC criteria
Complications specified	Yes	No	Yes
Grading definitions	Defined for each complication	Single common definition for all complications	Defined for each complication (following the general definition of the Clavien-Dindo classification)

complications and ileus. Grading of complications with the CTCAE classification resulted in a significantly higher major morbidity rate compared to the Clavien-Dindo classification (25 vs. 8%, $p = 0.001$). A group of residents, experienced surgeons and medical oncologists evaluated a set of 12 real complications, either with the Clavien-Dindo or CTCAE classification. Evaluating a set of complications, residents, surgeons and oncologists correctly assessed significantly more complications with the Clavien-Dindo compared to the CTCEA classification ($p < 0.001$). In addition, all participants evaluated the Clavien-Dindo classification as more simple. Residents ($p < 0.001$) and surgeons ($p < 0.01$) required less time with the Clavien-Dindo classification; there was no difference for oncologist [67].

The Clavien-Dindo classification was easier to use but would miss reporting important complications like the haematological toxicity or nephrotoxicity if they were not severe enough to require treatment. The CTCAE classification is more cumbersome to use; however, all complications are recorded.

The authors proposed that the Clavien-Dindo classification should be used because of its simplicity; the CTCAE should be reserved for the assessment of critical parameters like nephrotoxicity or haematotoxicity.

The other drawback of the Clavien-Dindo classification compared to the CTCAE classification is that specific complications are not named. Hence, different investigators used different terms for each complication. For example, the terms ‘paralytic ileus’, ‘small bowel obstruction’ and ‘colonic obstruction’ may have been used for the same clinical condition [68]. The Japan Clinical Oncology Group (JCOG) proposed another classification to overcome these limitations called the JCOG postoperative complications criteria – JCOG PC criteria. In this system, the common complications are specified and listed [68]. There are 72 surgical complications experienced commonly in surgical trials, focusing on 17 gastrointestinal complications, 13 infectious complications, 6 thoracic complications and several other complications in this list. The grading criteria are defined simply and optimized for surgical complications. This is useful for making comparisons between different studies. These criteria can be used to supplement the Clavien-Dindo classification. A comparison between the Clavien-Dindo, CTCAE and JCOG PC classifications is provided in Table 9.6. Once

again, these criteria have not been used or validated for patients undergoing CRS and HIPEC.

Sugarbaker et al. classified 48 common complications according to the CTCAE criteria, and that classification is used as a reference in this chapter [10, 69].

9.6 Failure to Rescue

Siber et al. in 1992 first showed that the factors that led to the occurrence of complications and those that led to the mortality were different [70]. Among 5972 patients undergoing two common general surgical procedures, they studied the deaths occurring in patients overall, the percentage of patients who developed complications and the deaths occurring in patients who developed complications. Deaths resulting from postsurgical complications were termed as 'failure to rescue'. Whereas complications were more due to patient-related factors, 'failure to rescue' was dependent on the hospital characteristics and not on other factors. In another study, Gahferi et al. showed that though the rates of complications were similar in two hospitals, the mortality rates among these patients varied greatly and the rate of 'rescue' from complications was dependent on the hospital's ability to recognize the complication early on in its course and administer the treatment necessary to recover from it [71].

An analysis of the morbidity is important as it has an impact on the short-term and long-term outcomes and cost.

However, morbidity may not be the ideal tool to judge the quality of the surgery.

Passot et al. listed several reasons for this:

- The reporting of morbidity is not standardized, and hence it is difficult to gauge the severity of complications [72]. Depending on which classification is used and the postoperative period analysed, the morbidity rate could widely change.
- Long-term experience has shown that the morbidity does not decrease over time; it's the salvage of patients who develop complications that increases. This was shown in a study of 666 patients undergoing CRS and HIPEC, treated by the same authors from 2009 to 2014. From 2012 onwards, a standardized perioperative clinical pathway was introduced, which focused on patient selection, nutrition, renal protection, pain management, prevention and early detection of complications. Major complications occurred in 341 patients (51%), of which 15 patients died. Though the complication rate before and after the introduction of the pathway remained the same (54.75% vs. 48.9%, respectively; $P = 0.138$), the failure-to-rescue rate significantly decreased after introducing the clinical pathway (9.02% vs. 1.02%; $P < 0.001$). On multivariate analysis, only renal complications were associated with the failure to rescue [73].
- Since the survival after potentially curative surgery has been improving due to the availability of newer and more effective systemic therapies, a delay in starting adjuvant therapy because of complications should be avoided. Hence, the return to intended oncologic therapy (RIOT) could be a better tool to evaluate the quality of surgery. This is important in patients undergoing CRS and HIPEC especially in patients with ovarian cancer where systemic therapy should not be delayed because of surgical complications [74].

9.7 The Normal Postoperative Course of a Patient Undergoing Cytoreductive Surgery and HIPEC

As compared to other surgical procedures, certain physiological changes take place which may be considered pathological following other surgical procedures. These clinical and biological changes were first described by Elias et al. as 'natural history' of an uncomplicated CRS followed by intraperitoneal chemotherapy [75]. In this study of 31 patients, the postoperative course of all patients was considered uneventful, and they were discharged within 15 days of the surgery.

These changes include:

- Temperature of 38°C for up to 10 days following surgery, in absence of surgery which is due to a systemic inflammatory response syndrome, with no documented infection. The rise in temperature may persist for up to a month after the procedure.
- Pain, evaluated on a visual analogue scale from 1 to 10, is around 4 for the first 4 days, and then the scores decline.
- High drain output decreasing progressively from 450 to 50 mL from the first to the seventh postoperative day.
- High nasogastric tube drainage of up to 1000 mL over 24 h declining from the sixth postoperative day onwards. The tube should be kept in situ till the output is minimal and the bowel function has returned.
- Increased frequency of bowel movements noted in 63% of the patients, up to 6/day between days 6 and 14 with no positive stool cultures.
- Sixty-three percent of the patients had transitory diarrhoea from days 4 to 6. The median number of stools was 6/day between day 4 and day 14, without positive stool cultures.
- Transient severe hypophosphatemia on days 2 and 3 attributed to hyperthermia-induced renal tubulopathy. The condition was self-resolving and did not respond to a daily administration of phosphorus (4 g/24 h). The insulin requirement was increased during this period.
- The haemoglobin remained stable at 10 g/dL in uncomplicated cases.
- The leucocyte count decreased progressively from 12,000/mm^3 to 5000/mm^3 till the 12th postoperative day.
- Platelet counts decreased from 200,000/mm^3 at day 1 to 120,000/mm^3–150,000/mm^3 at days 3 and 4 before progressively increasing until day 15, even though 50% of the patients underwent a splenectomy. Haematopoietic growth factors were not used.
- There was a transient moderate elevation of the liver enzymes (two to three times of the upper normal limit) on days 1–4 possibly due to electroevaporation of the hepatic surface deposits.
- Transient hyperbilirubinemia due to cholestasis is seen [75].

9.8 Specific Complications and Their Management

9.8.1 Gastrointestinal Complications

Gastrointestinal complications occur relatively frequently, though accurate data on their incidence is lacking, with estimates ranging between 3 and 34% [76].

An overview of common gastrointestinal complications and grade-specific treatment options is provided in Table 9.1 and the reported incidence in various reports in Table 9.7 [72].

9.8.2 Enteric Leaks and Fistulas

Enteric leaks, either from anastomoses or iatrogenic injuries to the bowel surface, are a major source of morbidity. Enteric content may cause peritonitis and sepsis or may form localized collections and abscesses; these may form a fistula by communicating with the exterior. A fistula occurs when there is an abnormal communication between two epithelialized surfaces, permitting the loss of electrolytes and fluids, and can lead to a wide variety of pathophysiological complications including wound infection, sepsis, malnutrition and electrolyte imbalance [80] (Table 9.8).

9.8.3 Pathogenesis and Risk Factors

There are several risk factors for enteric leaks in patients undergoing CRS and HIPEC apart from the usual risk factors for these complications. The extensive nature of the surgery and prolonged duration increase the risk of bowel complications

Table 9.7 Common gastrointestinal complications after CRS and HIPEC [69]

Organ system	Grade 1 asymptomatic and self-limiting	Grade 2 symptomatic requiring medical management	Grade 3 invasive intervention required	Grade 4 ICU care or return to the operating room
Anastomotic failure	Subclinical, afebrile, radiological diagnosis	Antibiotics, febrile	Percutaneous drainage	Reoperation
Fistula	Subclinical, afebrile, radiological diagnosis	Antibiotics, febrile	Percutaneous drainage	Reoperation
Pancreatic fistula	Elevated enzymes in drains	TPN and somatostatin	Percutaneous drainage	Reoperation
Pancreatitis	Elevated enzymes	<3 Ranson's score	4–6 Ranson's score	Reoperation
Bile leak	Bile only in the drain	Bile in the drain, febrile	Percutaneous drainage	Reoperation
Chyle leak	Transient	Prolonged 1 week	Ceases prior to discharge	Persists past hospital discharge
Prolonged ileus	N/G tube for <2 weeks	N/G > 2 weeks	N/G > 3 weeks	Persists past hospital discharge
Small bowel obstruction	Abdominal pain	Abdominal pain, N/G reinsertion	Repeat radiologic studies	Reoperation
Hartmann pouch leak	Afebrile	Antibiotics, febrile	Percutaneous draining	Reoperation
Enterostomy tube	Skin irritation at entrance site	Tube displaced to the floor	Interventional radiology procedure	Abscess formation, surgical drainage
Oral pain/ ulceration	Soreness/erythema	Erythema, ulcers, can eat solids	Ulcers, requires liquid diet only	Alimentation not possible
Nausea/ vomiting	Transient vomiting	Vomiting, antiemetics	Vomiting, IV therapy	Vomiting, surgical intervention
Diarrhoea	Transient <2 days	Tolerable, >2 days	Intolerable, IV therapy	Dehydration Prolonged IV therapy
Ascites	Mild	Fluid restriction	Symptomatic, percutaneous tap	Compromising vital functions, ICU care

Table 9.8 Incidence of various gastrointestinal complications in large series of patients treated at high-volume centres

Ref year	No of patients	Primary tumour site	Major complications	GI Grade 3–4 morbidity
[4] 2003	207	Colon, PMP, ovarian	Digestive fistula (14), prolonged ileus (11), intraperitoneal abscess (5)	15% 30 events
[7] 2006	205	PM, PMP, ovarian	Anastomotic leak (17), bowel perforations (6), biliary fistula (1), pancreatic fistula (2), ileus/gastric stasis (4)	15%; 30 events
[77] 2009	123	Colorectal, PM, PMP, ovarian	Anastomotic leak (7), digestive perforation (11), pancreatitis (1), bile leak (1), ileus (3)	19%; 23 events
[78] 2011	456, (including debulking surgery)	PMP (appendix)	Anastomotic leak (7), pancreatic complications (5), intestinal fistula (8)	4.55; 20 events
[79] 2011	147	Colon, PMP (appendix)	Anastomotic failure (2), fistula (4), pancreatitis (1), bile leak (1), chyle leak (1), prolonged ileus (0), small bowel obstruction (1), vomiting (5), diarrhoea (0), ascites (0)	8%; 15 events

[81]. Patients with a high PCI, those that have resection of multiple segments of bowel and therefore multiple anastomoses, are at an increased risk for developing bowel leak [4, 82]. Other risk factors are a higher number of peritonectomy procedures, prior systemic chemotherapy, use of VAC and increased intraoperative blood loss [2, 3]. The average number of anastomoses performed varies in different series; hence, as proposed by Younan et al., the bowel complication (BC) to anastomosis (A) ratio which ranges from 7.2 to 17.4% would give a better idea of the rate of complications in addition to the bowel leak rates [82].

Multiple prior debulkings or previous CRS procedures lead to the formation of dense adhesions. The risk of these complications in reiterative procedures is higher [81, 82].

HIPEC was found to have a negative impact on the strength of the colonic anastomosis in experimental studies [83, 84]. However, others have shown that not all drugs have a negative impact – mitomycin-C had a negative impact, whereas 5-FU and paclitaxel at a normal temperature did not [85, 86]. Hyperthermia alone may not have a negative impact [87].

The high incidence of enteric leaks is due in part to impaired healing of tissues after HIPEC and in part to the lack of the greater omentum to seal off small leaks which would have probably remained subclinical in other settings.

There is a possibility of spontaneous bowel perforation in patients undergoing HIPEC which happens at a distance from the anastomotic site. The possible causes of this are partial-thickness damage to the intestinal wall during adhesiolysis or tumour removal, increased risk of injury if the bowel is in contact with the tip of the inflow catheter, negative suction at the tip of the outflow catheter leading to bowel injury or shrinkage of tumour nodules on the bowel wall in response to the chemotherapeutic drugs used in HIPEC [76].

9.8.4 Technical Aspects and Preventive Measures

9.8.4.1 Closed Versus Open Method

Some surgeons anticipate a greater risk of complications with the closed method and have adopted the open method in preference [2, 3]. Elias demonstrated uneven distribution of methylene blue in the closed method and suggested that uneven distribution and circulation of perfusate that occurred during the closed method increased the risk of enteric complications [88, 89]. However, the incidence of anastomotic leaks and bowel perforations has not been higher in series where HIPEC is performed by the closed methods and this presumption is no longer valid [4, 76]. To prevent hyperthermia damage to small bowel surfaces, Glehen et al. recommend the placement of inflow drains under the cupolas of the diaphragms and not in direct contact with the intestinal wall.

9.8.4.2 Timing of the Anastomosis

Bowel anastomoses can be performed either after or before HIPEC. When the anastomoses are performed after HIPEC, the edges of the bowel that are a site of tumour implantation get perfused, and thus treated proponents of the first alternative argue that delaying the anastomosis permits a better distribution of heat and drugs inside the peritoneal cavity. Additionally, the potential adverse effects of heat and chemotherapy on the bowel anastomosis can be avoided. Once again, a higher incidence of anastomotic leak or bowel perforations has not been observed when the anastomoses are performed before HIPEC [90, 91].

9.8.4.3 Bowel Handling During Surgery

Though it is difficult to completely avoid serosal injuries during extensive adhesiolysis (a common component of many cytoreductive cases), meticulous examination of the entire small and large bowel, and careful repair of any injuries, before abdominal closure is essential. Similarly, in patients undergoing a rectum-preserving pelvic peritonectomy, the rectum must be closely inspected for any serosal tears (typically on the anterior wall); use of a Heald anal stent may be considered in these patients to ensure adequate rectal decompression during the early postoperative period.

9.8.4.4 Technique of Anastomosis

No specific recommendations regarding anastomotic technique in the context of CRS and HIPEC have been made; bowel anastomoses are

constructed according to local protocols, although most peritoneal malignancy surgeons prefer, where possible, handsewn end-to-end anastomosis with interrupted sutures. If administration of EPIC is planned, a double-layered anastomosis is often considered. A recent ESCP Collaborating Group audit on anastomotic technique after right hemicolectomy and ileocaecal resection demonstrated a higher odds of leak after stapled versus handsewn anastomosis (adjusted OR 1.43; 95% CI: 1.04–1.95; P = 0.03) [92]; however, this snapshot audit excluded cytoreductive procedures for peritoneal malignancy.

9.8.4.5 Diverting Stoma

Little consensus exists as to the feasibility and safety of colorectal anastomoses after anterior resection during CRS and HIPEC. Though establishment of an end colostomy is potentially safer than a high-risk anastomosis, available evidence suggests that only a minority of patients will ever undergo a reversal; in a study of 336 patients who underwent a Hartmann's procedure as part of CRS and HIPEC, only 21 patients underwent an attempt at reversal, which was successful in only 16 patients (4.7%). Moreover, more than half of the patients in whom a reversal was attempted developed grade 3 complications [93]. Longstanding policy in many peritoneal malignancy centres has been to establish circular stapled side-to-end colorectal anastomoses with a defunctioning loop ileostomy, which can be subsequently reversed. One recent study has demonstrated that the formation of a defunctioning stoma is associated with lower rates of anastomosis-related morbidity; however, reversal of the stoma required a laparotomy in 18% of cases and had an associated morbidity of 50% [94]. Routine defunctioning is not a universally accepted approach, and an increasing number of peritoneal malignancy centres are reporting low complication rates using a technique of oversewing a stapled colorectal anastomosis with plicating interrupted sutures, without formation of a diverting stoma [79, 95]; in one report of 29 patients undergoing this technique of colorectal reconstruction during CRS and HIPEC, no clinically manifesting anastomotic leaks were observed [95].

In an interim analysis of the PRODIGE 7 study, the rate of enteric leaks was higher in the HIPEC group as compared to the non-HIPEC group. Though this difference did not reach statistical significance, leaks occurred even in the presence of a defunctioning stoma. The presence of a stoma did not prevent leaks but reduced the incidence of peritonitis. Hence, the authors recommend that a protective stoma should be performed in case of more than two areas of bowel wall repair, of more than two bowel anastomoses or of rectal resection (unpublished data; personal communication by Francois Quenet).

9.8.4.6 Management of Enteric Leaks

Enteric leaks present relatively late in the postoperative period, compared to other gastrointestinal surgical procedures. In a study of 203 patients undergoing CRS and HIPEC (with enteric leaks occurring in 23 patients), enteric complications manifested at a median duration of 10 days after surgery (range 3–28 days) [82]. The relatively late occurrence of enteric complications may be attributed to the delayed recovery of bowel function which may delay the manifestation of a leak or to late tissue failure that can occur in these patients. Even with intestinal contents leaking in the peritoneal cavity, overt clinical signs may not been seen due to removal of the peritoneum itself.

If an enteric leak is suspected, a high index of suspicion should be maintained resulting in a low threshold for early cross-sectional imaging (Fig. 9.1).

Various strategies exist to deal with enteric leaks, varying from early repeat laparotomy (during the first 10 days) to nonoperative management utilizing a combination of percutaneous radiological procedures, antibiotic treatment and parenteral nutrition. Some centres have adopted a low threshold for repeat laparotomy to deal with enteric leaks which become apparent in the early postoperative period, while others successfully utilize more conservative management strategies. Clearly, the choice of strategy depends not just on the timing in the postoperative course and the patient's physiological condition, but also on institutional policy and various practical issues, e.g. the availability of emergency interventional radiology services, nutritional teams to support parenteral nutrition, etc.

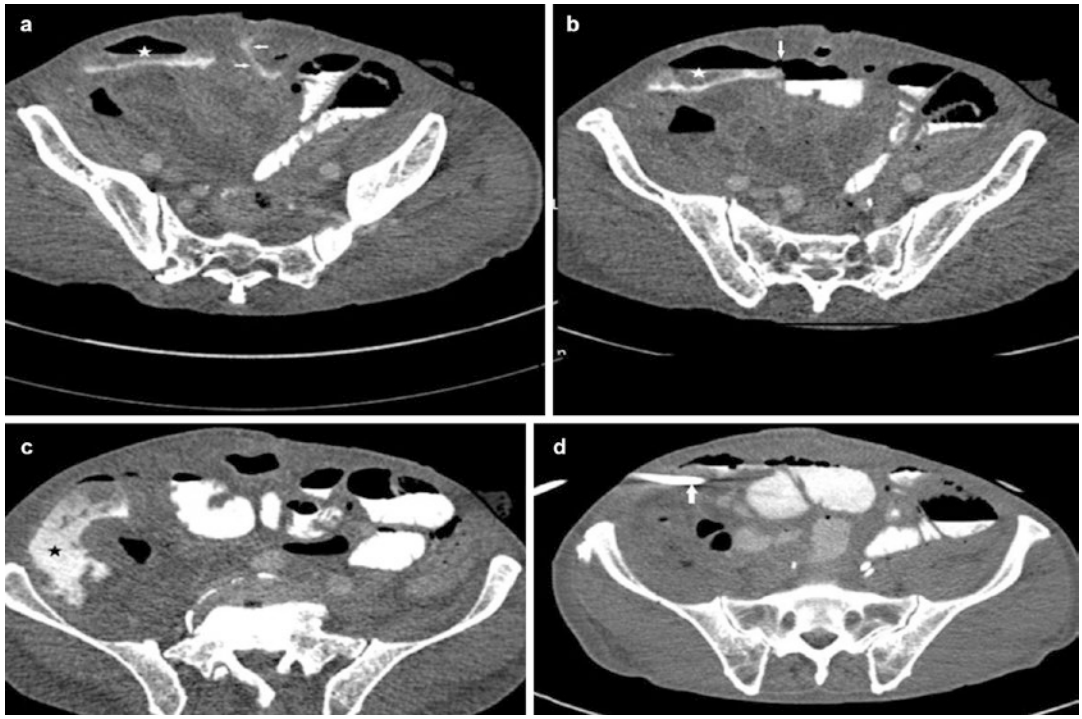

Fig. 9.1 CT images of enterocutaneous fistula (arrows in **a**), bowel perforation (arrow in **b**) and intra-abdominal collection (*) during surveillance due to severe small bowel adhesions and small bowel obstruction. Percutaneous drain (arrow in **d**) was placed under CT guidance

In the aforementioned study of 23/203 patients with enteric leak after CRS and HIPEC, 5 patients were managed conservatively, while a surgical intervention was performed in 18. All the patients with rectal anastomotic leaks had a defunctioning stoma fashioned [82].

Enterocutaneous Fistulas

Enterocutaneous fistulas have been estimated to occur in 4–34% of patients after CRS and HIPEC. A recent overview of 918 patients undergoing CRS and HIPEC reported an enteric fistula rate of 5.8% (53 patients) [81]. In these 53 patients, a 5.7% mortality rate was observed; major morbidity rates were significantly higher than among the remaining 865 patients. Risk factors contributing to the occurrence of enteric fistulas include extensive adhesiolysis, significant residual disease after incomplete cytoreduction, application of abdominal VAC systems, recent systemic chemotherapy or radiotherapy, malnutrition, smoking and the administration of intraperitoneal chemotherapy [81].

Classification of fistulas is based on anatomical location (proximal versus distal small bowel versus colonic) and output (low, <200 mL/24 h; intermediate, 200–500 mL/24 h; high, >500 mL/24 h). In the aforementioned report on 53 patients with an enteric fistula, approximately half of fistulas were low output, a third were high output and the remainder intermediate [81]. In general, low-output fistulas are likely of colonic origin, while high-output fistulas more often originate in the small bowel. This classification loosely correlates with the probability of spontaneous fistula closure: higher rates of spontaneous closure occur in low-output, colonic fistulas, while high-output small bowel fistulas are unlikely to close spontaneously. In this regard, the aspect of the fistula is important: a fistula with visibly everted mucosa will have a lower likelihood of closing spontaneously (Fig. 9.2).

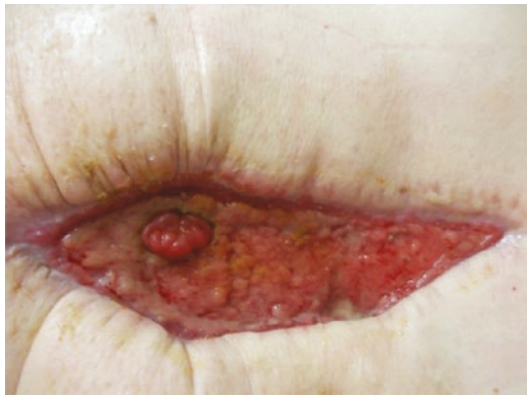

Fig. 9.2 Small bowel fistula with mucosal eversion

Regardless of classification, enterocutaneous fistulas cause significant morbidity due to sepsis, wound management problems, loss of nutritional status and electrolyte disturbances. The successful management of enterocutaneous fistulas should therefore address these issues. The initial management is dictated by the clinical condition of the patient: emergency invasive procedures are indicated in septic patients and may consist of either surgical drainage of collections with closure or defunctioning of the fistula or, alternatively, percutaneous radiological drainage of associated collections (Fig. 9.1). In non-septic patients, initial management is guided by the timing relative to surgery. Within the early postoperative period (commonly limited to the first 10 days), surgical intervention may be considered; fistulas becoming apparent after that timeframe are commonly managed conservatively. The three goals of conservative fistula management are the maintenance and improvement of nutritional status and electrolyte homeostasis, optimization of wound management and control of fistula output. Nutritional optimization commonly necessitates total parenteral nutrition, which also contributes to decreasing fistula output. Intravenous administration of proton pump inhibitors helps to decrease gastric secretions, while the role of somatostatin analogues (e.g. octreotide) is more controversial.

The likelihood of fistula closure after conservative management strategies depends on many factors, including the output and aspect of the fistula, any intestinal obstruction distal to the fistula and the overall condition of the patient. It is estimated that spontaneous closure rates of approximately 50% may be achieved with conservative management strategies incorporating radiological drainage of sepsis, replacement of electrolytes and nutritional support, with a median time to closure of 29 days (range 9–74 days) [81]. A third of patients will require surgical intervention, either as primary treatment or following failure of conservative management [81]. This commonly entails major surgical procedures incorporating extensive adhesiolysis, segmental bowel resection and abdominal wall reconstruction.

9.8.4.7 Gastroparesis, Ileus and Obstruction

It is estimated that virtually all patients will develop a degree of postoperative gastroparesis, due to the combination of radical greater (and lesser) omentectomy and HIPEC. The radicality of the greater omentectomy does not seem to affect the occurrence of postoperative gastroparesis: a randomized clinical trial investigating omentectomy with versus without preservation of the right gastro-epiploic artery showed no differences in time to full oral diet, occlusion of nasogastric tubes or total admission time [96].

Gastric drainage, either with a nasogastric tube or a draining gastrostomy, is a component of most, if not all, peritoneal malignancy protocols. In patients in whom the stomach underwent major surgical manipulation (either gastrectomy or major resection of tumour off the gastric wall), mechanical obstruction may occur, either due to an anastomotic stricture (occurring in 2.5% of patients undergoing a partial gastrectomy in a recently published large series [97]) or localized ischaemia. Treatment depends on local anatomy and may vary from endoscopic balloon dilatation and stenting to surgical (laparoscopic or open) gastro-jejunostomy.

Extensive intestinal manipulation contributes to the relatively high incidence of ileus after CRS; however, HIPEC in itself is surmised to be an important determinant of postoperative ileus. An experimental study showed an irreversible decline in responses to nerve stimulation when

exposed to high temperatures and not in responses to direct muscle stimulation. Thus, hyperthermia leads to true neurological paralysis of the bowel wall [98].

In the past, ileus was a vaguely defined phenomenon; however, the term 'postoperative ileus' has recently been defined as the interval from surgery to the passage of flatus/stool and tolerance of an oral diet [99].

Maintaining and optimizing nutritional status during the period of ileus are essential and will commonly include early administration of parenteral nutrition.

True bowel obstructions are rare in the immediate postoperative phase and are mostly due to internal or abdominal wall herniation, although special attention should be paid to the patency of stomas, if present. In the longer term, adhesive bowel obstruction may be a significant cause of morbidity. The rate of true (i.e. not recurrence-related) adhesive bowel obstruction following CRS and HIPEC is estimated at 0.5–2% [79].

Despite the absence of conclusive evidence, it is reasonable to assume that the extent of parietal peritonectomy is an important determinant of adhesion formation. Postsurgical adhesions begin to form in as little as 3 h after surgery [100]. Currently, it is believed that injury or irritation of the peritoneum results in an outpouring of serofibrinous fluid rich in mediators of inflammation. Coagulation of the exudate results in the fibrinous adhesions of injured peritoneal surfaces that may persist and form permanent fibrous adhesions [101]. Though it is hypothesized that the use of intraperitoneal chemotherapy can lead to an increase in adhesions, many chemotherapeutic agents have a suppressive effect on tissue healing, an important factor in adhesion formation. However, different chemotherapeutic drugs have different properties.

In general, it is recommended to make an important distinction between adhesive small bowel obstruction after CRS and HIPEC and in patients after more 'general' abdominal procedures. The clinical adage of maximum 24–48 h of conservative management of a small bowel obstruction prior to considering surgical intervention is not routinely recommended for this patient population. Most specialized peritoneal malignancy centres will recommend maximum conservative management with nasogastric decompression, bowel rest and, frequently, total parenteral nutrition. Moreover, recurring bowel obstructions in a patient with a history of peritoneal malignancy should raise the suspicion of peritoneal recurrence; therefore, close coordination with and even transfer to a peritoneal malignancy centre are often recommended.

Peritonitis Without a Bowel Perforation/Fistula

This is an uncommon complication that was first reported by Honore et al. [102]. Postoperative peritonitis is a severe and life-threatening complication that can arise from any abdominal surgery and has a mortality rate of 36–44%. [110–112]. In 15% of the cases, the cause of the peritonitis (i.e. underlying perforation) cannot be found (Fig. 9.3) [103].

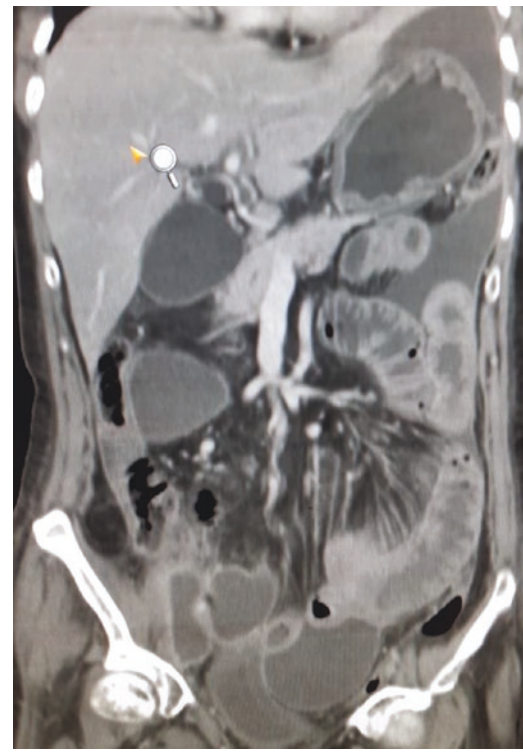

Fig. 9.3 Plain CT scan of patients with peritonitis without bowel perforation. Bowel loops are thickened and dilated

Among the 607 patients who had undergone CRS and HIPEC, at a tertiary care centre, 123 (20%) developed an intra-abdominal complication, and 81 of these required a surgical intervention, and 52 (9%) of these have acute postoperative peritonitis. There was no underlying enteric complication in seven (1%) of these patients [104]. Thus, in all the patients of postoperative peritonitis, no underlying cause was identified in 13%.

All these patients had extensive surgery with a median PCI of 27 and the duration of surgery was >10 h.

The surgical management was not different from that used in other cases of peritonitis – eliminating the source of infection (which was not found in these cases), reducing bacterial contamination (with extensive peritoneal lavage) and preventing persistent or recurrent intra-abdominal infection (with adequate postoperative peritoneal drainage) [104]. All patients received empirical antibiotic therapy with broad-spectrum antibiotics and culture-specific antibiotics till all the cultures were negative. These patients had a high rate of medical complications, and 3/7 required further surgical intervention.

The author provided some plausible explanations for this phenomenon. Despite the absence of any clinical or experimental data, they attributed it to bacterial translocation which could be due to the loosening of intercellular tight junctions due to bowel oedema [105]. A temporary decline in the immunity following the prolonged surgery could be another factor responsible for bacterial translocation. The exaggerated inflammatory response following surgery could lead to a reduction in the cell-mediated immunity which is directly proportional to the extent of the surgery [101, 106–108].

Postoperative Adhesions

Adhesions cause one-third of large and small bowel obstruction and more than two-thirds of small bowel obstructions. Postsurgical adhesions begin to form in as little as 3 h after surgery [109]. Currently, it is believed that injury or irritation of the peritoneum results in an outpouring of serofibrinous fluid rich in mediators of inflammation. Coagulation of the exudate results in the fibrinous adhesions of injured peritoneal surfaces that may persist and form permanent fibrous adhesion.

Sugarbaker reported a 2% incidence of adhesions in 196 patients undergoing CRS and EPIC that required surgical intervention for bowel obstruction in the absence of tumour recurrence or infective complications [110]. Specifically, CRS due to its extensive nature poses an increased risk of adhesion formation due to extensive damage to the peritoneum. Though it is hypothesized that the use of intraperitoneal chemotherapy can lead to an increase in adhesions, these agents have a suppressive effect on tissue healing, an important factor in adhesion formation. However, different chemotherapeutic drugs have different properties. 5-fluorouracil is known to impair wound healing and decrease adhesion formation [111]. Mitomycin-C irritates the mesothelial cells leading to an increase in the formation of adhesions [112]. Similarly, cisplatin and carboplatin are associated with an increased risk of formation of adhesions [113].

Sugarbaker recommends performing a thorough peritoneal lavage following CRS to remove blood clots and tissue debris that promote adhesion formation. The choice of irrigating solution may be very important [114, 115]. Mesothelial damage with swelling of the underlying tissue can occur with hypotonic and many non-buffered irrigating solutions. Dextrose solutions which are widely used for peritoneal dialysis are known intraperitoneal irritants and promote the formation of adhesions.

In another study of 307 patients receiving intraperitoneal chemotherapy for ovarian cancer, 4% of the patients developed bowel obstruction due to adhesions that required a surgical intervention. A large proportion received intraperitoneal mitoxantrone [116]. Patients receiving multiple cycles of IP cisplatin are prone to develop a fibrous cocoon with bowel obstruction (Fig. 9.4).

The incidence of adhesions not related to tumour following HIPEC leading to bowel obstruction is low. Sugarbaker reported adhesive obstruction in 1/147 patients undergoing HIPEC [79].

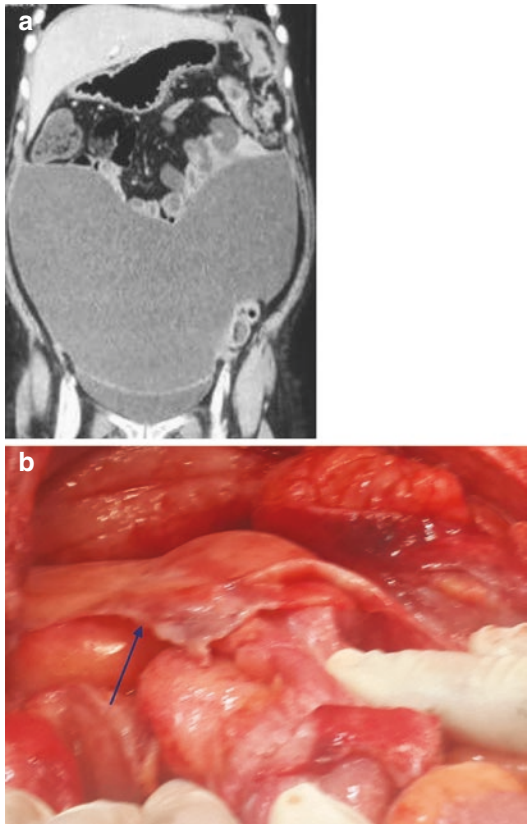

Fig. 9.4 (**a**) CT image of a fibrous cocoon in a patient who received intraperitoneal cisplatin through a port. (**b**) Intraoperative photograph of the same patients showing the thickened membrane covering the bowel (blue arrow)

9.8.4.8 Stoma-Related Complications

Besides structural problems with stomas (including prolapse, stricture and retraction), the main stoma-related complication after CRS and HIPEC is that of high output (defined in most centres as consistent output >1 L/24 h), with associated risks of acute kidney injury and electrolyte imbalances. The extent of (small) bowel resections obviously impacts the risk of high-output stomas, although this occurs frequently even in patients who have had no small bowel or gastric resections. Usually, high-output stomas can be managed with a combination of loperamide and/or codeine, adequate fluid and electrolyte replacement and oral fluid restriction, using isotonic drinks (e.g. St Mark's solution). Only in rare cases will patients require long-term intravenous fluid replacement or early stoma reversal. A high index of suspicion for intra-abdominal collections should exist in patients with persistently high stoma output, and a low threshold should be maintained for cross-sectional imaging. Close liaison with a dietician and stoma specialist is essential.

9.8.5 Intra-abdominal, Non-digestive Complications

9.8.5.1 Post-splenectomy Complications

Splenectomy is frequently performed during CRS, especially for PMP. In the largest single-centre experience in Basingstoke, no instances of overwhelming post-splenectomy sepsis have been reported, probably due to the development and implementation of post-splenectomy prophylaxis protocols and early administration of antibiotics in patients who develop infective complications [25].

Contrary to this, in a prospective case-controlled study of 39 patients undergoing splenectomy, Dagbert et al. reported a higher incidence of grade 3–4 complications in the splenectomy group compared to the control group (59 vs. 35.9%, $p = 0.041$) as well as more pulmonary complications (41 vs. 7.7%, $p = 0.0006$). Multivariate analysis identified splenectomy as the only predictor of overall major complications (odds ratio = 2.57, 95% confidence interval = 1.03–6.40). Mortality was similar in both groups. During the study period, 32% of the patients required a splenectomy, and the authors recommended preservation of the spleen when possible [117].

In another series of 195 patients of which 52% underwent a splenectomy, the haematotoxicity of HIPEC and the requirement of postoperative granulocyte colony-stimulating factor were reduced in patients undergoing a splenectomy. The nadir of white cell and platelet count was higher in patients undergoing splenectomy [118].

9.8.5.2 Pancreatic Complications

The pancreas is manipulated while performing a total omentectomy and during a splenectomy.

Sometimes resection of the distal pancreas is required due to heavy tumour infiltration at the splenic hilum or on the pancreatic capsule. The procedures pose a risk of pancreatic complications in patients undergoing CRS and HIPEC. Indeed, pancreatic complications are one of the most common causes of postoperative morbidity together with gastrointestinal fistula and respiratory adverse events.

Patients can have a rise in the serum amylase alone, pancreatitis or postoperative pancreatic fistula.

Pathogenesis and Risk Factors

Splenectomy is a known risk factor for pancreatic trauma and poses a risk of pancreatic complications even in patients undergoing CRS and HIPEC [119, 120]. It has been proposed that renal impairment leads to pancreatitis, but the hyperamylasemia seen in these patients is due to a decline in the excretion, and hyperamylasemia should be considered an indicator of pancreatic injury [121]. Tansung and Sugarbaker postulated that peripancreatitis is due to iatrogenic tears in the pancreatic capsule inflicted by surgical manipulation. Capsular tears result in a leakage of pancreatic enzymes into the abdominal cavity immediately adjacent to the pancreas, leading to damage of surrounding structures accompanied by local regional sepsis. If a distal pancreatectomy has been performed, the risk of POPF is higher though it is similar to that observed in patients undergoing pancreatic resection for primary pancreatic tumours [122].

The other risk factor for postoperative pancreatitis is the use of a high dose of cisplatin >240 mg/m^2 as demonstrated by Kusamura et al. High doses of cisplatin are known to interfere with the tissue healing and pose an increased risk of pancreatic complications. These authors recommended a dose reduction for cisplatin in patients undergoing extensive upper abdominal surgery, especially those with other risk factors for major morbidity. The other reported risk factors for POPF are requirement of >6 units of blood transfusion, PCI > 20 and a prolonged operating time [7].

Diagnosis

After CRS and HIPEC, there is third space fluid loss due to the large raw areas that are created and also due to the thermal, mechanical and chemical injury during surgical manipulation. Any leak from the pancreas would thus get diluted making diagnosis difficult.

The resection of parietal peritoneum could modify the immunological and neurological responses to trauma/surgical stress, thus making the clinical presentation mild. The signs of peritoneal irritation are diminished. There is early formation of adhesions leading to localization of the secretions which again does not manifest overtly. Post CRS and HIPEC, there is a more protracted systemic inflammatory response syndrome which would overlap the manifestations of pancreatic complications.

Postoperative pancreatitis is defined as the presence of criteria 1 and 3 (listed below) with or without the presence of the criteria 2:

1. Severe abdominal pain associated with a serum amylase level superior to three times the upper limit of the normal range (ULN)
2. Evidence of pancreatic parenchymal damage as reported in an exploratory laparotomy performed for any postoperative complication
3. Absence of other concomitant enteric complications (such as gastrointestinal fistula or perforation) [123]

POPF represents failure of healing/sealing of a pancreatic-enteric anastomosis, or it may represent a parenchymal leak not directly related to an anastomosis such as one originating from the raw pancreatic surface and is defined according to the criteria established by the international study group on pancreatic fistula (ISGPF) [124]. The amylase level in the drain fluid or any other intra-abdominal fluid after the third postoperative day has to be three times the upper limit of the normal serum value with or without associated clinical findings like abdominal pain, distension, bowel dysfunction, delayed gastric emptying, fever (38 °C) and increase in the leucocyte count and C-reactive protein (Table 9.9). There are three grades of POPF based on the severity [124].

Table 9.9 Grading of postoperative pancreatic fistulas [124]

Grade	A	B	C
Clinical condition	Well	Often well	Ill appearing/bad
Specific treatment[a]	No	Yes/no	Yes
UC/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death due to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

[a]Partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal

The grade of severity may only be decided after complete follow-up, including discharge from the hospital or death, when the ultimate effect of the POPF on outcome can be determined.

Incidence and Management

The reported incidence of pancreatic complications ranges from <1 to 6% [2]. In a series of 270 consecutive procedures, POPF was observed in 13 (4.8%) cases. Three cases were classified as major (grade C). The median duration of the POPF was 12 days (range: 3–64 days). Most patients were managed conservatively with only one patient requiring a surgical exploration. There was no resultant morality following POPF, but the hospital stay was significantly longer in these patients compared to those who did not have a fistula. Two patients developed postoperative pancreatitis. 12.3% of the patients had hyperamylasemia which was attributed to pancreatic manipulation during the surgery [121].

In a series of 225 cases of CRS and IPC, the Tansung and Sugarbaker reported POPF in 225 patients which was termed as 'peripancreatitis' [125].

Downey et al. reported POPF in 26% of the 54 patients who had a distal pancreatectomy as part of CRS and HIPEC. This rate was similar to POPF in patients undergoing distal pancreatectomy for pancreatic adenocarcinoma. It also included patients who did not have a formal pancreatectomy, but pancreatic tissue was detected in the splenectomy specimen. However, most of the patients in the HIPEC group had grade B or C fistulas, whereas those in the non-HIPEC group had grade A fistulas.

In another series of 29 patients undergoing CRS for advanced ovarian cancer, 29% of the patients developed a POPF [126].

In another series of 217 patients, 17 patients (6.3%) developed postoperative POPF. None of these patients died during their in-hospital stay. Multivariate analysis identified three independent risk factors for POPF: transfusion of >or = 6 units of blood (P = 0.029), operation duration of >or = 9 h (P = 0.035) and splenectomy (P = 0.020). Conservative management of POPF was instituted in all 17 patients and was successful in 16 (94%) with the time to closure averaging 26 days. Though the procedure-related mortality was not significantly increased, the hospital stay was significantly prolonged ($P < 0.001$) [127].

In a multi-institutional study of patients treated at 7 centres across the world, outcomes in 118 patients who had a distal pancreatectomy were reported. The indications for distal pancreatectomy were infiltration of the pancreas by tumour (n = 24; 20%) or without splenic involvement (n = 76; 64%), invasion of the pancreatic capsule (n = 10; 9%) or iatrogenic damage to the pancreas during CRS (n = 8; 7%). The 90-day postoperative mortality was 7.6%, and the rate of severe morbidity (Clavien-Dindo ≥III) was 44%. POPF was observed in 39 cases (33%), of which 48.7% had a grade B and 28.2% had grade C fistulas. The independent risk factors for POPF were a PCI > 20 (risk ratio: 3.01; P = 0.022) and an operative time more than 550 min (risk ratio:

2.74; $P = 0.038$). The occurrence of POPF was not associated with a higher risk of 90-day mortality (5.1% vs. 8.8%, not significant) [52].

The management is similar to POPF arising in other situations. Most of the patients can be managed conservatively. Percutaneous drainage or stent placement may be required. In cases of suspected infection or sepsis, a surgical intervention may be required.

Several techniques have been employed to prevent the development of POPF after distal pancreatectomy including handsewn suture closure, transection and closure using a stapling device, pancreatic transection using various energy devices, reinforcement of the stump with a seromuscular patch or pancreaticoenteric anastomosis, sealing with fibrin sealants, pancreatic stent placement and administration of octreotide. The superiority of any one technique has not been proven yet [128].

Thus, though the incidence of POPF is not high in patients undergoing CRS and HIPEC with pancreatic resection, these tend to be of a higher grade, associated with major morbidity, and lead to significant prolongation in the hospital stay. Patients for such procedures should be carefully selected; young, fit patients with low-grade disease in which the risk of developing early metastases is low are preferred candidates for this procedure. Such procedures should also be performed in expert centres to obtain optimal results [52].

9.8.5.3 Urological Complications

Involvement of the urinary tract by peritoneal disease often requires urological resections and reconstruction. This varies from simple resection of a cuff of the dome of bladder to total cystectomies and/or ureteric resections with reconstructions. Urological procedures as a part of CRS are performed in 7–14% of cases [129–131]. The most common urological complication is the occurrence of a urinary fistula. This is especially the case after resection and subsequent reconstruction of the ureter. In the case of resection of the pelvic ureter, a recent report suggests that the reconstructive technique may be associated with the risk of urinary fistula: simple end-to-end reconstruction was associated with a 28.5% of urinary fistula, while this risk was 0% after ureteroneocystostomy (ureteric reimplantation into the bladder, enforced by a psoas hitch) [31].

Overall, urological interventions during CRS and HIPEC increase the risk of major postoperative complications (estimated at 30–45%), although long-term survival does not seem to be affected [129–131].

9.8.6 Cardiopulmonary Complications

9.8.6.1 Respiratory Complications

Respiratory mechanics will be altered following an extended midline abdominal incision. This will be exacerbated by chest drain insertion and diaphragmatic stripping. Additionally, the potential for a long operative time in the lithotomy position with the necessity for the reverse Trendelenburg position for periods of surgery can result in basal atelectasis and impaired mucociliary clearance [132]. This is especially important in those with a high body mass index, particularly where there is excessive abdominal distribution of body fat. Many patients undergoing CRS and HIPEC will have pre-existing respiratory conditions such as chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma or respiratory muscle weakness secondary to malnutrition. Low preoperative arterial oxygen saturation, recent respiratory infection, anaemia and age are positively associated with an increased risk of postoperative respiratory complications [132]. Where there are particularly high intraoperative fluid shifts with large volume blood or blood product transfusion, the risk of acute respiratory distress syndrome, transfusion-related lung injury or pulmonary fluid overload should be considered. The effects of prolonged general anaesthesia with systemic and epidural opioids will reduce minute volume and may result in further inadequacies of ventilation and hypercapnia in the first postoperative hours.

Patients with a number of these risk factors are likely to benefit from delayed extubation in a critical care unit. This allows time for chest radiograph

to confirm chest drain position and the status of lung fields, careful titration and optimization of analgesia, lung recruitment manoeuvres to improve atelectasis and optimal head-up positioning of patients. Approximately half of all patients in our centre will be transferred to critical care with invasive ventilation in place. Extubation is usually within 12 h. Prophylactic extubation onto non-invasive ventilation or high flow nasal oxygen has not been consistently shown to reduce respiratory complications following abdominal surgery [133, 134]. It does, however, improve arterial oxygenation, reintubation rates and intensive care unit length of stay in those found to be hypoxaemic after extubation [134].

Adequate analgesia, combined with a physiotherapy program, is associated with a reduced intensive care unit length of stay [135]. Careful preoperative patient counselling and preparation for physiotherapy have been shown to reduce postoperative respiratory complications, and this combined with ongoing postoperative physiotherapy is important in reducing respiratory complications and improving recovery [136].

Respiratory complications, beyond simple basal atelectasis (a common radiographic finding after most abdominal surgery), are a common occurrence after CRS and HIPEC. Several factors predispose patients undergoing this procedure to developing respiratory complications:

- Patients may have compromised preoperative pulmonary function due to malnutrition and presence of significant volumes of (mucinous) ascites.
- Extensive upper abdominal surgery, including diaphragmatic peritonectomy, leads to occult communication between the peritoneal and pleural cavities and passage of fluid to the pleural cavity during HIPEC [47].
- The systemic inflammatory response to surgical trauma leads to intrapleural fluid accumulation.
- Prolonged anaesthesia time and restriction in respiratory movement postoperatively, which may in part be due to inadequate analgesia, increase the risk of basal atelectasis and pulmonary complications.
- Partial- or full-thickness diaphragmatic resection weakens its contractility at least temporarily further compromising pulmonary function [47].
- Perioperative fluid shifts leading to third space losses and hypoalbuminemia.
- Significant intraoperative crystalloid and colloid infusions.

The most common respiratory complications and their grade-specific treatments are listed in Table 9.10.

Table 9.10 Common respiratory complications and grade-specific treatment following CRS and HIPEC (from [69])

Organ system	Grade 1 asymptomatic and self-limiting	Grade 2 symptomatic requiring medical management	Grade 3 invasive intervention required	Grade 4 ICU care or return to the operating room
Respiratory distress	Mild symptoms	Oxygen therapy or medications required	Endotracheal intubation	Tracheostomy required
Pleural effusion	Asymptomatic	Fluid restriction/ diuretic required	Thoracentesis required	Compromised, chest tube insertion
Pneumonia	Minimal symptoms	Antibiotics and respiratory therapy	Bronchoscopy	Intubation required
Acute respiratory distress	Mild symptoms	Moderate respiratory support	Prolonged respiratory support	Tracheostomy, ICU
Chest tube removal/ displacement	Radiological diagnosis	Heimlich valve	Chest tube insertion	Tension pneumothorax
Pneumothorax	<10%	>10%	Heimlich valve	Chest tube reinserted

Basilar Atelectasis

It is the most common finding on the chest film after abdominal surgery, but it is a nonspecific finding. Many predisposing factors, such as previous bronchitis, chronic obstructive lung disease and prolonged anaesthesia time, may affect the incidence of atelectasis. Other factors affecting the incidence of complications are such as type and duration of anaesthesia, patient position, inhaled fraction of oxygen, lack of positive end-expiratory pressure and presence of paralysis caused by muscle relaxants [137, 138]. Whereas some authors have found that one of the factors affecting extubation failure is the generous use of fluids, others have not had a similar experience [139, 140]. Patients with segmental or lobar atelectasis take longer to get extubated. Fluid restriction, adequate pain management, early mobilization and physiotherapy help to limit the atelectasis and lead to early recovery.

Pleural Effusion

Pleural effusion is a relatively common event described in many reports, and though there are several predisposing factors, stripping of the subphrenic peritoneum is the most common predisposing factor. The reported incidence of pleural effusion varies between different studies and ranges from 3 to 30% [3, 14, 141]. Some surgeons routinely insert a chest tube in patients undergoing subphrenic peritonectomy. Others perform it only for patients who have rent in the diaphragm or in cases of full-thickness diaphragm resection [141]. In a study of 147 patients, Sugarbaker et al. did not find an increased risk of pulmonary complications in patients undergoing subphrenic peritonectomy [142].

In a study of 42 patients from the Wake Forest University, pleural effusions developed in 64% of the patients [143]. Most effusions (74%) occurred 1–3 days after CRS and HIPEC and lasted <4 days. Mitomycin-C-induced pulmonary toxicity was considered to be one of the factors responsible for pleural effusions [144–146]. Most of them resolve when the fluid infusion is restricted and the positive fluid balance is reduced [147, 148].

Pneumonia

The incidence of pneumonia ranged from 3 to 10% in various reports [4, 13, 142, 149]. It may or may not be associated with a pleural effusion. Most of these are mild and resolve with a short course of antibiotics. One completely iatrogenic cause of postoperative chest infection is malpositioning and manipulation of chest tubes; if a chest tube needs to be reinserted or manipulated, this should occur under the same sterile conditions as the primary insertion.

Adult Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS)—or postoperative lung oedema—is characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to hypoxemia that is refractory to usual oxygen therapy. Clinically, ARDS is characterized by severe hypoxemia, bilateral radiographic pulmonary infiltrates and no clinical evidence of cardiogenic pulmonary oedema. The severity of ARDS is classified based on three PaO_2/FiO_2 cut-off values on PEEP $\geq$ 5 cm H_2O at ARDS onset: severe ($\leq$100 mmHg), moderate (>100–$\leq$200) and mild (>200–$\leq$300) [150]. There are known risk factors that could be avoided, in order to reduce the risk of developing ARDS like reducing the number of transfusions, limiting the positive fluid balance, avoiding nonprotective mechanical ventilation and preventing gastric aspiration. Surgical trauma itself can lead to ARDS. Patients with ventilator-associated pneumonias are also at an increased risk of ARDS. One of the most crucial factors is positive fluid balance, and timely restriction of fluid intake can reduce the requirement of postoperative mechanical ventilation and ARDS [151]. ARDS, a potentially life-threatening complication, has been reported after CRS and HIPEC, more commonly in patients undergoing extensive surgery. In most cases fibrosis does not set in early, and it is usually reversed by fluid restriction and mechanical ventilation.

Sugarbaker et al. reported ARDS in two patients who had extensive cytoreduction and hyperthermic perfusion of both the pleural and peritoneal spaces

with mitomycin-C [152]. Reoperation in both patients failed to show a septic source within the abdomen for progressive adult respiratory distress syndrome, and they could not identify any other underlying cause for the ARDS. The authors concluded that aggressive surgery for the treatment of peritoneal metastases can be sufficiently traumatic to be considered a cause of adult respiratory distress syndrome [152]. There are few other case reports of ARDS following CRS and HIPEC [153].

9.8.6.2 Mitomycin-C-Induced Pulmonary Toxicity

Though mitomycin-C (MMC) has the pharmacokinetic advantage of high intraperitoneal concentration with limited systemic absorption and toxicity, some systemic exposure does occur. A rare complication of this systemic penetration of MMC is interstitial pneumonitis. The risk is higher following repeated intraperitoneal administration, prior systemic chemotherapy and use of a high dose of the drug or in certain individuals more prone to toxicity.

MMC-induced pulmonary toxicity manifests as an interstitial pneumonitis which can lead to pulmonary fibrosis and severe, terminal respiratory insufficiency. While treatment can prevent crippling fibrosis, there are some patients who, despite optimal therapy, will progress onto fibrosis [154]. This toxicity is seen both after intravenous and intraperitoneal administration and can occur early or late. Following the first report in 1978, several others have reported this complication following MMC-based HIPEC [144, 155, 156]. The first prospective study on the relationship between intravenous MMC and pulmonary toxicity concluded that this toxicity is a dose-dependent side effect of MMC that should be considered only when patients receive over a 20 mg/m^2 cumulative dose [157]. This model was supported by later pharmacological evidence that there is a direct relationship between body surface area and MMC plasma clearance, as well as between plasma exposure and haematological toxicity [158]. However, the pathophysiological mechanisms of pulmonary toxicity following intraperitoneal MMC are unknown since it occurs after standard recommended doses as well.

Treatment of MMC-induced pulmonary toxicity comprises of fluid restriction and ventilatory support if required. Steroids have been used for the treatment though the benefit is unknown [154].

9.8.6.3 Venous Thromboembolic Events

Venous thromboembolic events (VTEs) are thought to be common: a recent multicentre report of 192 patients undergoing CRS and HIPEC found VTE in 26 patients (13.5%) [159]. Interestingly, the majority of VTEs were found to occur in the splenic/portal/mesenteric venous systems (11/192 patients; 5.7%); pulmonary emboli (PE) occurred in 10 patients (5.2%) and deep venous thrombosis (DVT) in 5 (2.6%). Moreover, the majority of VTEs (80%) occurred after discharge. A separate single-centre study reported a PE rate after CRS and HIPEC of 4.4%, though the majority of patients with CT-proven PE did not develop significant cardiorespiratory dysfunction or require escalation of care [160]. In some peritoneal malignancy centres, routine duplex scanning of the calf veins is a standard part of the postoperative protocol after CRS and HIPEC. In an audit of 200 consecutive CRS and HIPEC patients in the Peritoneal Malignancy Institute, Basingstoke, 188 patients underwent a routine duplex calf scan, and an asymptomatic DVT was found in 10 patients (5.3%) (unpublished data). However, it is unclear whether treatment of these asymptomatic DVTs will actually reduce the risk of clinically significant PEs.

In patients in whom a pulmonary embolus is suspected, CT-pulmonary angiography (CT-PA) is essential and, in most centres, the diagnostic modality of choice. In patients who have had previous thromboembolic events, PMI, Basingstoke, has a long-standing policy of preoperative insertion of an inferior vena cava (IVC) filter, which can be removed within 90 days, though this is not mandatory.

9.8.6.4 Circulatory Complications

Cardiac events occurring after CRS and HIPEC include ischaemic events and dysrhythmias. Though major intraoperative haemodynamic

fluctuations can contribute to cardiac ischaemia, current standards in goal-directed fluid therapy and cardiac output monitoring are expected to mitigate these fluctuations [161–164].

A large proportion of patients will require circulatory support in the first hours postoperatively. This is due to large intraoperative and ongoing fluid shifts, blood loss, vasodilatation from epidural analgesia and altered Starling forces resulting from protein losses, systemic inflammation and cytokine release. Metabolic rate increases significantly, and interventions to meet this increased demand are vital to avoid myocardial ischaemia and end-organ damage [148]. Ongoing fluid shifts from abdominal and thoracic drains will require close monitoring and replacement and complicate fluid balance in the immediate postoperative period [165]. Postoperative bleeding is unusual where close intraoperative management of coagulopathy is adhered to, but vigilance for this is vital in the first hours. Systemic inflammation resulting from hyperthermia, cytotoxic agents and a large visceral resection will result in the release of inflammatory biomarkers. This initiates a humoral cascade resulting in a hyperdynamic circulation, increased capillary permeability and increased metabolic demands.

Cardiovascular support with vasopressor agents and carefully titrated intravenous fluid therapy is the mainstay of early postoperative cardiovascular support. Adequate oxygen delivery should be optimized with early treatment of postoperative anaemia. Additionally, intraoperative protein losses combined with preoperative malnutrition may result in severely low serum albumin levels [166]. Administration of human albumin solutions or synthetic colloids may be required to increase intravascular oncotic pressures and maintain circulatory volume.

9.8.7 Haematological Complications

Haematological complications are largely due to systemic absorption of chemotherapeutic agents. The grading of haematological complications according to their severity is provided in Table 9.11.

9.8.7.1 Neutropenia

The estimated incidence of neutropenia after CRS and HIPEC ranges from 2 to 10%. Though rare, neutropenia can cause significant morbidity: in one study, 66% major morbidity rates were observed in neutropenic patients [3].

The main cause of neutropenia is considered to be chemotherapy-related. MMC is associated with neutropenia in 4–39% of patients [167, 168]. Intraperitoneal cisplatin (with/without doxorubicin) is also associated with high rates of postoperative systemic toxicity [2]. In one study comparing oxaliplatin- to MMC-based HIPEC, higher rates of neutropenia were demonstrated in the cohort receiving oxaliplatin, although this study implemented a longer duration of intraperitoneal oxaliplatin administration (2 h) than is usual in most centres (30 min). Concomitantly, a separate large multicentre study did not find any differences in rates of haematological toxicity following oxaliplatin- or MMC-based HIPEC [169].

When the absolute neutrophil count falls below 500/cc, use of granulocyte colony-stimulating factors is recommended; some sur-

Table 9.11 Haematological complications following CRS and HIPEC (from [69])

Organ system	Grade 1 asymptomatic and self- limiting	Grade 2 symptomatic requiring medical management	Grade 3 invasive intervention required	Grade 4 ICU care or return to the operating room
Neutropenia (cells/mm^3)	3000–2000	2000–1000	1000–0	Sepsis
Platelets 1000/mm^3	99–50	50–10	10–0	Bleeding
Anaemia/bleeding	No replacement	≤4 units	>4 units	Reoperation

geons use a higher cut-off for it. Antibiotic prophylaxis is also advisable in this situation.

9.8.7.2 Bleeding Complications

Haemorrhagic complications after CRS and HIPEC can occur due to several factors:

- Extensive surgery leading to creation of large raw surfaces that could bleed in the early postoperative period
- Coagulopathy
- Drug-induced haemorrhage (following oxaliplatin-based HIPEC)

In a study of 200 patients undergoing CRS and HIPEC, postoperative bleeding requiring >4 units of blood transfusion occurred in 4.5% of patients and was associated with increased intraoperative blood loss [4]. In other studies, the estimated incidence of postoperative bleeding is 1.8–8% [6, 149].

Coagulopathy, manifesting as prolongation of prothrombin time (PT), activated partial thromboplastin time (APTT) and/or thrombocytopenia, is a recognized complication of cytoreductive surgery, even in the absence of HIPEC. It is probably dilutional in origin due to fluid resuscitation and fluid shifts. Some centres have implemented intraoperative protocols consisting of routine administration of tranexamic acid and cryoprecipitate during CRS and HIPEC [170]; in addition, a randomized controlled trial comparing intraoperative administration of Octafibrin (a plasma-derived fibrinogen concentrate) to administration of cryoprecipitate in patients undergoing CRS and HIPEC for low-grade appendix tumours is currently underway at the Peritoneal Malignancy Institute, Basingstoke.

Oxaliplatin-based HIPEC has been associated with a higher incidence of postoperative haemorrhagic complications as compared to other agents (especially MMC). In a study of 47 patients undergoing oxaliplatin-based HIPEC, 38% developed postoperative bleeding complications [171]. In a separate, multicentre study of 771 patients treated with oxaliplatin-based HIPEC, 14.3% of patients developed haemorrhagic complications, on average 8.9 days after surgery. When compared to similar patients treated with other intraperitoneal agents, oxaliplatin was a significant and independent risk factor for haemorrhagic complications (15.7% versus 2.6% for other agents) [172]. Some centres have attempted to mitigate the haemorrhagic risks associated with oxaliplatin-based HIPEC by decreasing the intraperitoneal dose from 460 mg/m^2 to 260–400 mg/m^2 [173].

Most postoperative bleeding can be dealt with by addressing coagulopathy using transfusion of blood, fresh frozen plasma or cryoprecipitate. If bleeding persists and leads to haemodynamic instability, angiographic embolization or surgical exploration may be required.

9.8.8 Acute Kidney Injury

Acute kidney injury is mostly transient and caused by pooling of fluid in compartments outside the effective circulation but may be exacerbated by nephrotoxic medication (analgesia, antibiotics, etc.) and ureteric injury/obstruction. In patients undergoing CRS and HIPEC for peritoneal mesothelioma or ovarian cancer, intraperitoneal cisplatin may contribute to postoperative renal dysfunction; this effect may be mitigated by considering dose reductions in patients with preoperative renal impairment, or by concomitant intravenous administration of sodium thiosulfate, starting with a loading dose after 30 min of HIPEC and continued as an infusion for 12 h.

In the phase I–II CHIPASTIN trial, the dose of cisplatin exceeding 70 mg/m^2 was associated with severe nephrotoxicity, and thereafter 70 mg/m^2 at 42 °C for 1 h was considered the most appropriate by the French group [174]. However, another phase I study concluded that a 100 mg/m^2 dose of cisplatin for HIPEC in recurrent platinum-sensitive ovarian cancer has an acceptable safety profile [175].

9.8.9 Wound Complications

Wound complications vary from superficial erythema to dehiscence and wound abscesses and

occur in approximately 30% of patients (unpublished data). Treatment is highly individualized and ranges from observation to laying open of the wound and application of negative pressure systems. Though prevention of all wound complications is difficult, risk factors have been identified, particularly BMI >30. This may help in identifying patients who might benefit from proactive wound management protocols including negative pressure therapy onto the abdominal incision (unpublished data).

9.8.10 Other Complications

Some of the other common and uncommon complications and their grades are listed in Table 9.12.

Central line sepsis is reported in 6–9.2% [10]. Sugarbaker reported a high incidence of sepsis and subclavian vein thrombosis when the subclavian vein was used for central venous access. Accordingly, he recommended that intraoperative central venous monitoring be performed through an intra-jugular line to minimize venous thrombosis and this line should be removed on the seventh day and be replaced by a peripheral central line if required [11]. Urinary tract infection constituted 7–9.2% of all complications in one study. The use of a Foley catheter for up to 10 days in women undergoing extensive pelvic peritonectomy was one factor responsible for it, and more frequent emptying of the catheter tubing could in part prevent it by minimizing the stasis [10, 11].

Table 9.12 Other complications and their grades [69]

Organ system	Grade 1 asymptomatic and self- limiting	Grade 2 symptomatic requiring medical management	Grade 3 invasive intervention required	Grade 4 ICU care or return to the operating room
Neurological complications				
Mental status	Transient lethargy	Somnolence <50% of waking hours	Somnolence >50% of the waking hours	Coma, ICU care
Orientation/ intellect	Mild confusion	Mild disorientation but able to care for self	Disorientation, unable to care for self	Grossly disoriented, combative, psychotic
Stroke	Transient ischaemic attack	RIND	Stroke unit care	ICU care
Neuropathy/ nerve paralysis	Transient symptoms	Persistent symptoms	Functional deficit resolved before discharge	Functional deficit after discharge
Wound complications				
Intra-abdominal	Minimal symptoms	Prolonged antibiotics	Percutaneous drainage	Reoperation
Wound	Cellulitis and swelling	Antibiotics	Open wound	Reoperation
Infectious complications				
Line sepsis	Entrance site only	Positive cultures, elective line removal	Bacteremia, urgent line removal	Septic shock, ICU care
Line thrombosis	Swelling, minor	Swelling, moderate, elective line removal	Anticoagulation, line removal	Clot lysis
Pneumothorax	Radiology (+) only	Oxygen therapy, in-hospital observation	Chest tube insertion	Tension pneumothorax
TPN intolerance	Mild	Moderate	Severe	Discontinuation
Skin/abdominal wall				
Allergic	Urticaria	Bronchospasm	Bronchospasm requiring medication	Anaphylaxis with ICU care
Wound dehiscence	Skin sutures	Fascia defect <6 cm	Fascia defect >6 cm	Reoperation

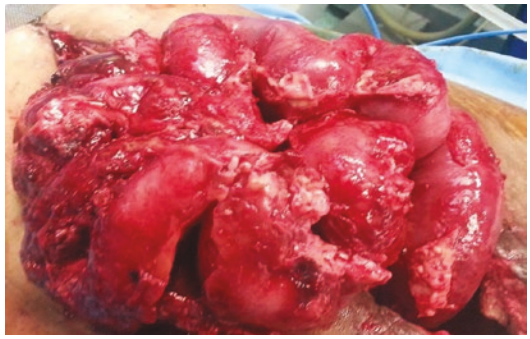

Fig. 9.5 Dysfunctional rigid bowel in a patient who received intraperitoneal cisplatin and Adriamycin

9.8.11 Rare Complications

There are case reports of rare complications occurring after CRS and HIPEC. Neurological complications like tonic-clonic seizures, cerebrovascular stroke and encephalopathy have been reported [176, 177]. Lampl et al. reported two cases of diaphragmatic hernia in patients who had undergone stripping and/or resection. Such herniation can occur early or late in the postoperative period [178]. A colobronchial fistula has also been reported. This complication can be life-threatening and requires surgical management [179].

Some patients may develop a reaction to intraperitoneal Adriamycin. Figure 9.5 is the picture of the bowel of a patient who received 15 mg/m^2 of Adriamycin with 50 mg/m^2 of cisplatin. She presented 3 weeks postoperatively with a leak from the ileotransverse anastomosis. The bowel was rigid and pipelike. The proximal stoma failed to function, and she died 3 months postoperatively of intestinal failure. Paul Sugarbaker was of the opinion that she had had a reaction to Adriamycin (personal communication).

9.9 Long-Term Implications of Complications

The impact of postoperative complications on long-term outcomes after CRS and HIPEC is variable. In patients treated for appendiceal tumours, minor or major postoperative adverse events have not been demonstrated to significantly influence survival in multivariate analysis, when compared to histological subtype, lymph node metastasis and completeness of cytoreduction [177]. In contrast, in patients undergoing CRS and HIPEC for CPM, the occurrence of major postoperative complications has been shown to adversely affect long-term survival: in one study, patients with grade ≥3 complications had a significantly decreased overall survival compared to patients with no or mild complications (22.1 versus 31.0 months, respectively) [178]. Similarly, another study of 113 patients undergoing CRS and HIPEC for colorectal or appendiceal peritoneal metastases showed that the occurrence of major postoperative complications was independently associated with decreased oncological outcome [179]. In addition, a recent study of 1270 patients undergoing CRS and HIPEC for a variety of peritoneal malignancies demonstrated that the occurrence of gastrointestinal leaks was associated with a significantly decreased overall survival, even after complete CRS and HIPEC [180].

Irrespective of complications, most studies indicate that quality of life immediately after CRS and HIPEC is lower compared to preoperative levels but starts improving from approximately 3 months postoperatively to ultimately reach or even exceed preoperative quality of life at 6–12 months [1].

The morbidity results in additional financial burden to patients where the procedure is not or only partly covered by insurance [181].

9.10 Clinical Care Pathways

At some of the expert centres, perioperative clinical care pathways have been established in an attempt to control the morbidity and mortality of the procedure. The pathway used at Hospital Lyon Sud is described here. This pathway focuses on six aspects of management which are the following [182].

Preoperative Patient Selection

Imaging is performed within 72 h of the planned procedure.

Patients are in a clinical trial where feasible.

Nutrition

Preoperative evaluation of BMI, albumin and prealbumin is done for all patients.

Use of immunonutrition.

Early use of parenteral or enteral nutrition when expected duration of fasting is >48 h.

Pain Management

Use of epidural analgesia if there is no contra-indication.

Preoperative information about analgesia.

Renal Protection

Evaluation of renal function.

Discontinuation of nephrotoxic drugs before the procedure.

Preoperative hydration is used for all patients.

Prevention of Complications

Discontinuation of medications that increase the risk of bleeding.

Mobilization on the first postoperative day.

Chest physiotherapy daily.

Use of pneumatic compression device and low molecular weight heparin to prevent DVT.

Early nutrition.

Preoperative bowel preparation.

Use of granulocyte colony-stimulating factor when the neutrophil count is <500/cc.

Early Detection of Complications

Postoperative management is done in a step-down unit with continuous cardiorespiratory monitoring, physical examination twice a day, daily blood work and chest X-ray.

Conclusions

The morbidity of CRS and HIPEC can be controlled by proper patient selection, preoperative optimization, surgical experience and perioperative multidisciplinary management. However, complications which depend on many other factors other than the quality of the surgery will continue to occur, and early diagnosis and management are important to 'rescue' patients with complications. A high index of suspicion for complications specific to this unique patient population should be maintained. The 90-day and not just the 30-day morbidity and mortality should be reported. A systematic grading of complications is essential to evaluate a surgeon/centre's own performance, compare treatment outcomes and assess the clinical benefit and cost-effectiveness of the procedure.

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Part II

Disease Specific Applications of Cytoreductive Surgery and HIPEC

10 Cytoreductive Surgery and Intraperitoneal Chemotherapy for Advanced Epithelial Ovarian Cancer

Kayomarz Sethna, Shabber Zaveri, and Aditi Bhatt

10.1 Introduction

Epithelial ovarian cancer is diagnosed in an advanced stage in 75% of the patients, and majority of them develop recurrent disease despite optimal frontline therapy. Cytoreductive surgery (CRS) aimed at removing all macroscopic disease is the standard of care. Intraperitoneal chemotherapy in addition to systemic chemotherapy has shown a survival benefit which has prompted the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in these patients. Patients who can undergo complete tumor removal are preferably treated with CRS first followed by chemotherapy. Neoadjuvant chemotherapy is reserved for those who cannot undergo complete tumor removal. The most important prognostic factor so far has been the completeness of tumor removal. Tumor recurrence is common despite maximal surgical efforts, and the commonest site for recurrence is the peritoneum. HIPEC appears to be a promising approach in these patients and is currently being evaluated in clinical trials.

10.2 Pathology

According to the WHO classification, ovarian cancers are classified as surface epithelial, sex cord, and germ cell tumors. Epithelial tumors are the commonest. The commonest variety of epithelial tumors is the serous variety, the less common ones being mucinous, clear cell, endometrioid, and transitional cell tumors (Brenner's) [1]. Serous histology is the most common, representing 70% of epithelial ovarian cancer (EOC) [2].

10.3 Pathogenesis

The long-accepted theory is that all epithelial ovarian cancers share a common origin. The epithelium is subjected to repeated trauma of ovulation and exposed to inflammatory cytokines. Repetitive insults alter the DNA of epithelial cells and promote malignant change [3].

This theory however has remained unsupported as no premalignant lesion has been identified in the ovary and the progression of the low-grade tumor to a high-grade tumor is rarely seen [4]. This statement is borne out by the histopathology findings in patients who have undergone prophy-

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lactic oophorectomy due to a genetic predisposition to ovarian cancer. Isolated foci of cancer have been frequently found in the fallopian tube rather than in the ovary; this phenomenon was first reported by Peik et al. in patients with BRCA mutation and a strong family history of ovarian cancer [5]. Subsequently, similar findings were reported by other investigators in sporadic tumors as well [6, 7]. So it is likely that the primary tumor starts in the fallopian tube and goes on to involve the ovary [8, 9]. Tumors arising from the fallopian tube are generally high-grade tumors and are detected in an advanced stage [10].

The similarities between ovarian serous carcinomas, fallopian tube carcinomas, and primary peritoneal serous carcinoma and their resemblance to tumors of Mullerian origin have led to the suggestion that each of these cancer types develops from a common cell lineage, the embryonic Mullerian system [11].

Their hypothesis that ovarian cancer does not arise from ovarian tissue is supported by clinical findings, indirect evidence, and logic, and concrete evidence to support the cell of origin is lacking.

- The three most common subtypes of these tumors, referred to as serous, endometrioid, and mucinous, are morphologically identical to carcinomas of the fallopian tube, endometrioid, and endocervix, respectively.
- A cystic component comprising epithelial cells of non-ovarian origin is often seen in serous epithelial tumors, and both benign and mucinous epithelial tumors form cystic lesions.
- Benign ovarian epithelial-like tumors are at least as frequent outside the ovary (para-tubal and para-ovarian cystadenomas) as they are within this organ.
- Primary peritoneal carcinomas that are histologically and clinically identical to ovarian carcinomas may be seen outside the ovary and may develop in individuals in whom the ovaries were removed several years previously and for reasons other than cancer [12–15].
- Women with familial ovarian carcinoma predisposition due to germline mutations in either BRCA1 or BRCA2 continue to be at an increased risk of developing serous extra-ovarian carcinomas (usually referred to as primary peritoneal carcinomas) after undergoing prophylactic salpingo-oophorectomies [16–18].
- Serous, endometrioid, and mucinous ovarian carcinomas express the same set of HOX genes as epithelial cells from normal fallopian tube, endometrium, and endocervix, respectively [19]. HOX genes are specific for different body parts.

The various tissues to which ovarian epithelial tumors resemble, including the lining of fallopian tubes, endometrium, and endocervix, and these structures share a common embryological origin, unrelated to that of the ovary, which is the paramesonephric or Mullerian duct.

There are two hypotheses for the origin of epithelial ovarian cancer and that of PPSC.

The coelomic theory (no longer accepted) proposed that coelomic epithelium that is present on the surface of the ovaries first undergoes Mullerian metaplasia and then malignant change.

The Mullerian theory (widely accepted) proposes that Mullerian epithelium is present on the ovarian surface or within its substance and around it as well and these Mullerian cells undergo malignant degeneration.

A large multi-institutional prospective study (Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial) showed no benefit of annual screening with CA 125 and transvaginal ultrasound since despite screening over 70% of the women presented with stage 3 and 4 disease [20].

10.4 Tumor Spread in Ovarian Cancer

Metastases from ovarian cancer are predominantly peritoneal surface dissemination. Lymphatic and hematogenous routes are the other pathways for dissemination. Initial spread may be to the uterus, adnexa, rectum, and pelvic peritoneum by way of intraperitoneal seeding. Direct extension and involvement of these structures are also possible [21].

Cells exfoliate from the ovarian tumor and are carried in the peritoneal fluid upward via the paracolic gutter toward the right diaphragmatic stomata. The cells get deposited on the peritoneal surface of the diaphragm, and some may pass on to the mediastinal lymphatics. The left diaphragm is less commonly affected due to the anatomical barrier of the phrenicocolic ligament. The left paracolic gutter though can be seeded by the malignant ovarian cells. The greater omentum has a large phagocytic capacity for cancer cells so that this organ is almost always infiltrated by the tumor. Heavy seeding of the omentum can result in an "omental cake" [22].

Lymphatic spread is common to the pelvic and para-aortic nodes [23, 24]. Hematogenous spread to organs occurs in about 5% of cases, but these metastases are rarely seen at presentation. Ascites can be present in low-volume peritoneal disease as well as in high-volume disease [24]. Ascites in ovarian cancer results from blockade of the subperitoneal lymphatics with tumor cells that reduced the fluid absorption and increased secretion of vascular endothelial growth factor (VEGF) by the cancer cells leading to increased permeability of the vessels and formation of ascites [25, 26]. Peritoneal involvement in ovarian cancer is stage III as opposed to most other cancers where it is classified as stage IV.

Approximately 75% of patients with EOC are diagnosed with stage 3 and 4 disease that include patients with pleural involvement.

Fifteen percent of the patients have involvement of the pleural space at the time of diagnosis—either a pleural effusion alone or pleural metastases as well. Malignant pleural effusions can arise from direct pleural involvement by tumor, hematogenous metastases to the pleura, or spread through pleuroperitoneal lymphatic channels [27].

Thus ovarian cancer presents in an advanced stage in most cases, and the peritoneal cavity is commonly involved. This provides the rationale for using locoregional therapies like cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of advanced ovarian cancer.

10.5 Presentation

Epithelial ovarian cancers are relatively asymptomatic in the early stages. Patients may present with nonspecific symptoms as the disease progresses. These symptoms include an increasing abdominal girth associated with dull constant pain, feeling of fullness after meals, urgency and frequency of micturition, bloating, reflux, and early satiety [28].

10.6 Investigations

In advanced ovarian cancer, the investigations are ordered to confirm the diagnosis and select the appropriate therapy. Routine blood workup is done for all patients. In addition the performance status and comorbidities are evaluated. A poor general health may preclude an aggressive therapeutic strategy. However, if the deterioration in general condition is recent, instituting definitive therapy could lead to an improvement in the health status. The other important factor is the disease extent. All patients need to undergo evaluation for the feasibility of a complete cytoreductive surgery (CRS). Such decisions are best taken by a multidisciplinary team of experts.

10.6.1 Tumor Markers

10.6.1.1 CA 125

This is a high molecular weight glycoprotein. Almost all serous tumors and also a majority of endometrioid and clear cell variants secrete it [29]. CA125 is not specific for ovarian cancer and may be raised in a number of benign conditions such as uterine cancer, non-Hodgkin's lymphoma, lung cancer, and even liver cirrhosis [30–32].

The CA-125 levels do not correlate accurately with the extent of the disease. Some studies have shown that CA-125 > 500 is a predictor of incomplete cytoreduction or suboptimal debulking, while others have not found it to be accurate [33–36]. Chi et al. reported that 50% of the patients who have a CA-125 of >500 require upper

abdominal procedures to achieve complete cytoreduction [37]. A > 75–80% decline in CA-125 after CRS has been associated with a prolongation in the disease-free survival [38, 39]. Some investigators have suggested that a decline in CA-125 is the better predictor of residual disease than the surgeon's assessment of it [40].

10.6.1.2 HE4

Human epididymis 4 protein is secreted by the respiratory and reproductive tracts [41]. More than 50% of ovarian cancer patients who do not show elevated CA125 levels have elevated HE4 levels [42]. Based on this fact, a Risk of Ovarian Malignancy score was developed which could predict an ovarian malignancy with a high sensitivity and specificity [43]. HE4 levels have also been elevated in a fraction of cases where CA 125 cannot be detected, leading to its evaluation for monitoring response to therapy, for detecting recurrences, and for early detection [44]. High concentration of plasma HE4 is an independent preoperative marker of poor prognosis in patients with advanced ovarian cancer [45].

10.6.2 Imaging

10.6.2.1 Computerized Tomography

A CT scan of the abdomen and pelvis is the most commonly used imaging tool. It helps characterize the mass and evaluate the extent of the disease as well. There are other conditions which can mimic advanced ovarian cancer like tuberculosis, and these need to be ruled out. The extent of disease is important for predicting a complete cytoreduction/optimal cytoreduction and has a prognostic value as well. The local extent of the primary tumor is assessed. Involvement of the pelvic side walls, iliac vessels, rectosigmoid, and bladder needs to be evaluated to predict the feasibility of a complete resection [46]. Peritoneal metastases present as nodular soft tissue lesions or as more subtle findings including linear or plaque-like thickening of the parietal or visceral peritoneum [47]. Implants from serous tumors have foci of calcifications [48]. The majority of peritoneal lesions show moderate enhancement after contrast medium. Rarely, mixed solid and cystic or purely cystic lesions are found [39]. Diffuse small bowel serosal involvement with <150 cm of the bowel free, involvement of the hepatoduodenal ligament, retraction of the mesenteric root, and bladder neck involvement on CT are signs of inoperability on CT scan [49].

CT along with clinical parameters has been validated as a tool for predicting the probability of a complete cytoreduction by several investigators [50, 51]. In multicenter trial evaluating the ability of CT scan and CA125 to predict suboptimal debulking, Chi et al. came up with a predictive score based on nine parameters. Age ≥ 60 years, CA-125 ≥ 500 U/mL, retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm, and diffuse small bowel adhesions/thickening were each assigned a predictive value score of 1. Perisplenic lesions >1 cm, small bowel mesentery lesions >1 cm, and root of the SMA lesions >1 cm were each assigned a score of 2. ASA 3–4 was assigned a score of 3, and lesser sac lesions >1 cm were assigned a score of 4. No cutoff was recommended for selecting patients for surgery, but a high score implied a lower probability of optimal debulking [50].

Probably the most useful, reliable, and reproducible prognostic tool to assess the extent of PM is the peritoneal cancer index (PCI) developed by Sugarbaker [52]. The abdomen and the pelvis are divided by lines into nine regions (regions 0–8) and the small bowel into four regions. The lesion size (LS) of the largest implant is scored – LS-0 means no implants are seen in that particular area, LS-1 refers to implants that measure up to 0.5 cm in greatest diameter, LS-2 refers to nodules measuring 0.5–5 cm, and LS-3 refers to implants 5 cm or greater in diameter. Confluent tumor deposits or tissue adhesions are categorized as LS-3. The PCI is the sum of the LS score in each region and ranges from 0 to 39. The PCI quantifies the extent of peritoneal metastases (PM) within each region of the abdomen and pelvis and sums the LS score for each region as a total varying from 1 to 39 for the peritoneal cav-

ity. The PCI can be correlated with the likelihood of complete CRS and survival in advanced ovarian cancer certain [53]. The BIG-RENAPE and RENAPE working groups have developed the PeRitOneal MalIgnancy Stage Evaluation (PROMISE) internet application (www.e-promise.org) to facilitate tabulation and automatically calculate the peritoneal cancer index (PCI). This application offers computer assistance to produce simple, quick, but precise and standardized pre-, intra-, and postoperative reports of the extent of peritoneal metastases. The radiological, pathological, and surgical scores can be generated. Not only the peritoneal metastases but other aspects like peritoneal thickening, involvement of adipose tissue, and fluid density are taken into consideration in this application. It can be used by less experienced centers as well and can help in research and multicentric studies related to peritoneal metastases [54].

The sensitivity of helical CT for peritoneal tumors less than 1 cm was found to be only 25–50% compared with 85–95% for larger tumor deposits [55]. In a multi-institutional study, Esquivel et al. found that the preoperative CT PCI score underestimated the extent of carcinomatosis in 33% of patients [56].

10.6.2.2 MRI

MRI has a sensitivity of more than 80% and a specificity of 84% in the characterization of ovarian lesions. MRI is highly specific for benign lesions such as dermoid and endometrial cysts. A lesion is considered benign if any one or more of the following criteria are present: size less than 4 cm, wall is less than 3 mm in thickness, and the presence of features typical of dermoid cysts or endometrioma. Additional features that suggest malignancy include the presence of ascites or peritoneal deposits or organ metastases [57–59]. Some investigators have reported a greater accuracy of MRI in predicting the PCI as compared to CT [60]. It has shown to be better for detecting small-volume disease and small bowel and mesenteric involvement as well compared to CT [61]. MRI requires a stringent protocol – bowel preparation, 6 h of fasting, and prolonged scan time. The detection of advanced-stage ovarian carcinoma requires T2-weighted imaging with fat suppression, T1-weighted imaging with fat suppression before and after the administration of an intravenous contrast material, and diffusion-weighted imaging of the entire abdomen and pelvis in the axial and coronal planes, as well as the standard pelvic imaging sequences. The optimal thickness of axial sections is 5 mm or less, and post contrast imaging should be performed no longer than 5 minutes after contrast injection. If performed later, contrast that has diffused into the ascitic fluid can obscure the peritoneal lesions [62].

In a prospective comparative study, whole-body MRI showed a greater accuracy compared to CT and PET-CT for detecting bowel surface and mesenteric lesions and a similar rate of detection of extra-abdominal metastases [63]. Contrary to this, another comparative study found no significant differences between MRI, CT, and PET/CT for staging though PET-CT was more accurate for supradiaphragmatic disease [64].

10.6.2.3 PET

Staging of newly diagnosed ovarian cancer is more accurate with PET or PET-CT than with conventional CT scan [65]. Sensitivities of 78–97% and specificities of 55–90% have been reported with the use of PET alone for the detection of peritoneal carcinomatosis [66]. Some of the common findings on PET-CT in patients with ovarian cancer are avid uptake in well-defined nodules as well as diffuse uptake by the peritoneal and serosal surfaces. It has the added advantage of detecting nodal metastases in patients with normal-sized pelvic and para-aortic nodes [67].

Some of the imaging findings predictive of incomplete tumor removal are listed in Table 10.1.

10.6.3 Diagnostic Laparoscopy

Laparoscopy allows direct visualization of the peritoneal surfaces, the small bowel and its mesentery, and small tumor nodules missed on imaging can be detected on laparoscopy. The disadvantages are its inability to evaluate retro-

Table 10.1 Signs of non-resectability on imaging [62]

Potentially non-resectable disease
Extensive involvement of the small bowel or mesenteric root
Involved lymph node superior to the celiac axis
Pleural infiltration
Pelvic sidewall invasion
Bladder trigone involvement
Hepatic parenchymal metastases or implants near the right hepatic vein
Implants larger than 2 cm in diameter in the diaphragm, lesser sac, porta hepatis, intersegmental fissure, gallbladder fossa, or gastrosplenic or gastrohepatic ligament

Table 10.2 Fagotti laparoscopic score [70]

The Fagotti score
Omental cake
Peritoneal carcinomatosis
Diaphragmatic carcinomatosis
Mesenteric retraction
Bowel infiltration
Stomach infiltration
Liver metastases
Each parameter is attributed a score of 0 if not involved and 2 if involved. Cytoreduction is incomplete in 100% of the patients if the score is ≥8

peritoneal structures like the ureters and pancreas, the omental bursa near the celiac axis, hepatic and splenic parenchymal metastases, and the depth of involvement of the hepatic pedicle and the diaphragm [68]. Fagotti et al. evaluated the role of laparoscopy in addition of a clinical and radiological evaluation in 65 patients undergoing laparotomy for advanced ovarian cancer. Optimal debulking was achieved in 34 of the 39 patients (87%) whose disease was judged completely resectable on the basis of laparoscopy findings leading to an accuracy of 90% for predicting a complete cytoreduction. The negative predictive value (NPV) of clinical-radiological evaluation was 73%, whereas the NPV of laparoscopy was 100% (i.e., when laparoscopy predicted an incomplete CRS, all patients were unresectable at laparotomy). The positive predictive values (PPV) of clinical-radiological evaluation and laparoscopy were both 87% [69]. Subsequently, the same investigators came up with a predictive index value (PIV) based on objective parameters determined at pre-cytoreduction laparoscopy, the "Fagotti score" [70]. The score is a sum of the individual score of seven sites of disease (Table 10.2). Patients with a score of ≥8 had a 100% chance of having a suboptimal/incomplete CRS. The parameters were chosen to describe the extent of intra-abdominal disease rather than predicting a complete cytoreduction [70]. The score has been prospectively validated—at a PIV of ≥8, the probability of optimal cytoreduction (residual tumor ≤1 cm) at laparotomy is 0 [71, 72]. The learning curve has been defined for this procedure [73]. Its reproducibility has been demonstrated at nonacademic peripheral centers as well [74]. Thus, a combination of clinical parameters, imaging findings, and diagnostic laparoscopy is required for selecting patients for CRS.

10.6.4 Assessment of Pleural Involvement

Fifteen percent of the patients with ovarian cancer present with a pleural effusion. The third most common cause of a malignant effusion is ovarian cancer. That cytological tests are more frequently positive in patients with ovarian cancer than in other tumor types [75]. A positive cytology is needed to categorize the effusion as malignant. In the absence of a positive cytology, when there is a strong suspicion of pleural involvement, a diagnostic thoracoscopy can be performed to look for pleural deposits. In one study, 4 (36%) of 11 patients with OC and a negative cytological examination of pleural fluid had macroscopic pleural malignancy on thoracoscopy [76]. Though invasive, such a procedure may change the treatment decision and may be necessary when the suspicion is high.

In addition, immunohistochemistry may be used when the diagnosis is in doubt [77].

10.7 Staging of Ovarian Cancer

Advanced ovarian cancer constitutes stages III and IV. In 2014, the classification was revised. According to the new classification, the presence of retroperitoneal lymph node involvement without intraperitoneal dissemination beyond the pelvis constitutes stage IIIA1; microscopic peritoneal metastasis beyond the pelvis irrespective of retroperitoneal lymph node metastasis, IIIA2; and macroscopic extra pelvic tumor spread up to 2 cm stage IIIB and >2 cm stage IIIC, both irrespective of the presence of retroperitoneal lymph node metastasis, respectively [78]. With respect to the extent of peritoneal disease, both stages IIIB and IIIC remain heterogeneous group as patients with few nodules outside the pelvis would be grouped along with patients with diffuse carcinomatosis. A better method of stratification of these patients would be according to the peritoneal cancer index (PCI) developed by Paul Sugarbaker. Among the stage IV patients, patients with malignant pleural effusion or pleural are categorized as IVA. FIGO IVB includes patients with intra- and extra-abdominal parenchymal metastases and extra-abdominal lymph node metastasis. Moreover, patients with inguinal lymph node metastasis and transmural bowel infiltration with mucosal involvement are now considered as FIGO stage IVB. However, despite these changes, some controversial issues, especially with respect to FIGO stage IV, remain still unsolved. Some of the patients classified as stage IV may have a better prognosis than others; for example, those with solitary liver or parenchymal metastases, transmural bowel infiltration, or umbilical deposits are known to do better than patients with multiple extra-abdominal metastases (lung, mediastinal, and cervical nodes) [79].

10.8 Treatment of Advanced Ovarian Cancer

The treatment of advanced ovarian cancer is a combination of cytoreductive surgery (CRS) and chemotherapy. CRS performed before the institution of chemotherapy, also referred to as primary CRS, essentially comprises removal of all macroscopic disease and is the current standard of care for surgery for advanced ovarian cancer. The term "debulking surgery" (primary debulking surgery – PDS) is equally popular but usually refers to procedures in which the goal is to leave a residue of <1 cm (optimal debulking). The completeness of surgery is defined according to the maximum diameter of the residual disease nodules. Complete cytoreduction is generally used for cases where there is no visible residual disease according to the completeness of cytoreduction score (Table 10.3) by Sugarbaker et al. [52]. The other commonly used term is "optimal cytoreduction" which is defined by the Gynecologic Oncology Group (GOG) as residual disease measuring <1 cm in maximal diameter [80].

Table 10.3 Scoring systems for completeness of cytoreductive surgery

Scores for completeness of cytoreductive surgery			
Completeness of cytoreduction (CC) score [52]		GOG criteria for "optimal debulking" [80]	
CC-0	No visible residual disease	RD0	No visible residual disease (zero residual disease
CC-1	Residual disease 0–2.5 mm		
CC-2	Residual disease 2.5 mm–2.5 cm	RD 1	Residual disease <1 cm (*optimal debulking*)
CC-3	Residual disease >2.5 cm	RD 2	Residual disease >1 cm (suboptimal debulking)

10.8.1 Evidence for Cytoreductive Surgery As First-Line Therapy for Advanced Ovarian Cancer

Meigs et al. first observed that a "definitive operation" before chemotherapy led to improved survival compared with "partial removal" or "biopsy only" [81].

Subsequently, Griffiths et al. in 1975, in a series of 102 patients, reported that the survival time was improved in proportion with a reduction in the residual disease size below 1.6 cm. Above this limit, the size of the residual disease had no impact on survival [82]. Another study by Hoskins et al., of a subgroup of 294 patients from a GOG study, showed that in patients with residual disease >2 cm, size of the residual lesions had no impact on the survival. Patients with residual disease <2 cm experienced a prolonged survival [80]. The same authors retrospectively reviewed 394 patients from a GOG study all of whom had residual disease <1 cm and concluded that apart from the size of residual disease, the other factors influencing survival are extent of disease, age, tumor grade, and the number of residual lesions [83]. Bristow et al. performed a meta-analysis of studies reporting outcomes of cytoreductive surgery and systemic chemotherapy for patients with advanced ovarian cancer. In 6885 patients included in 53 studies, the patients who had no residual tumor had a survival of 46.9 months compared to 30 months in patients who had any size of residual disease ($p < 0.001$). Similarly, when patients with residual tumor size of 1–10 mm were compared with those having residual disease >10 mm, there was a difference in median survival in favor of the first group of 4.9 months for stage IIIC and 2.3 months for stage IV [84]. Despite this compelling evidence, the Gynecologic Oncology Group (GOG) defines optimal debulking as residual implants less than 1 cm [85, 86]. The assessment of residual tumor is done intraoperatively and is subjective and often inaccurate due to induration of tissues and failure to explore the entire abdominal cavity thoroughly as pointed out by Chi et al. [86]. There is a clear benefit of complete removal of all macroscopic disease, and this should be the goal of CRS. The completeness of cytoreduction score by Sugarbaker is a standardized way of recording the extent of residual disease [52]. Extensive upper abdominal surgery comprising procedures like diaphragm resection and splenectomy may be required to achieve a complete CRS, and the same must be performed, in conjunction with specialist surgical teams if required [87, 88]. Though spread to these regions is considered indicative of an aggressive tumor biology, complete cytoreduction in this area has shown to have a survival benefit as well [83, 89, 90].

The presence of a moderate to large pleural effusion (occupying greater than a third of the hemithorax) has been associated with an inferior survival [91, 92]. For patients with pleural effusion showing malignant cells or pleural implants, a combined approach of abdominal and thoracic CRS can be employed provided the patient can tolerate the procedure and complete tumor removal is possible [93]. A video-assisted thoracoscopic surgical (VATS) approach is recommended for the thoracic part of the procedure. Chi et al. have proposed an algorithm for management of these patients in which they recommend surgery for the thoracic and abdominal disease both if a complete cytoreduction is possible [94].

However, most of these patients would end up getting neoadjuvant chemotherapy due to extensive disease not amenable to a complete CRS [76, 94]. In others, the performance status could preclude an aggressive surgical effort before chemotherapy.

10.8.2 The Role of Neoadjuvant Chemotherapy (NACT)

In patients where complete cytoreduction or optimal residual disease could not be obtained, the concept of interval CRS/interval debulking surgery (IDS), in which another attempt is made at complete tumor removal following a few cycles of systemic chemotherapy, was introduced. Three large randomized controlled trials were performed to evaluate the benefit of this approach of which two showed no survival benefit [95–97]. The percentage of patients who could be optimally cytoreduced in these trials was small.

Subsequently, the term neoadjuvant chemotherapy (NACT) has been used for chemotherapy which is administered prior to any attempt at cytoreduction [98]. NACT has some theoretical advantages which include an increased rate of complete cytoreduction; the possibility of less extensive surgery leading to a reduced blood loss,

morbidity, and hospital stay; an improved quality of life; and the potential to test disease biology based on response to therapy [98]. Furthermore, it has been suggested that NACT followed by interval CRS does not worsen the prognosis for patients with advanced ovarian cancer [99]. In a meta-analysis of 21 studies comprising 835 patients, Bristow et al. reported an inferior survival for the NACT approach. Increasing percent maximal cytoreduction was positively associated with median cohort survival. An increase in the number of chemotherapy cycles prior to surgery was associated with an inferior survival; each additional cycle of NACT led to a 4.1-month reduction in median survival. The authors concluded that early surgical intervention was associated with a survival benefit [100].

This approach was further evaluated in two randomized controlled trials. In an EORTC trial randomizing 670 patients to PDS or 3 cycles of NACT followed by IDS, 180 patients who received NACT have a survival and quality of life similar to the 165 patients undergoing PDS [101]. Postoperative morbidity and mortality (within 28 days of surgery) tended to be higher after PDS.

In the CHORUS trial, there were 120 patients each in the PDS and NACT arms [102]. Survival was non-inferior in the NACT arm. Grade 3/4 postoperative adverse events and deaths (28 days after surgery) were more common in the PDS group (24 vs.14% and 6 vs. 1%, respectively). More NACT-IDS patients reported nonsignificant improvement in QOL at 6 and 12 months. This study also found that NACT-IDS significantly increased the incidence of optimal cytoreduction (RD,1 cm):73 vs. 41%. This increase in optimal cytoreduction did not translate into a significant improvement of progression-free survival (PFS) or median overall survival (OS) [102].

The results of these two trials have led many in the scientific community to conclude that NACT may be a better approach. However, the caveats in these trials were pointed out both by the authors themselves and critics as well [103, 104]. The median operative times in both trials were short (120–180 min) which has led to questioning the quality of the surgery. In the EORTC trial, it was shorter in the PDS arm which raised questions about the quality of the surgery in these trials [104]. Similarly, the rates of optimal CRS/debulking <1 cm were uniformly low (40% in the PDS arm in both trails). There were no upper abdominal procedures performed in both the studies [104]. This might suggest suboptimal efforts at PDS, supported by the fact that only 40% of patients were left with tumor <1 cm after PDS in both trials.

Moreover, the survival rates in the NACT arm matched those reported in other NACT studies, and the survival rates in the PDS arm were significantly lower than those reported in literature which emphasized the fact that the surgical interventions in these trials were not of similar standards as performed in other studies carried out in the same time period on similar patients [105–108].

Chi et al. performed a retrospective analysis of patients who had undergone PDS or NACT followed by IDS at their institution and met with the criteria of the EORTC trial [109]. Of 316 patients, 90% had PDS and 10% NACT followed by IDS. Only 29% had residual disease >1 cm as compared to 58.5% in the EORTC trial, the median PFS for PDS-treated patients was 17 months (95% CI, 14.9–18.5), and the median OS was 50 months (95% CI, 43.5–55.6) which is significantly higher than that reported in the EORTC trial (median OS-30 months). The median DFS by residual disease status was as follows: no gross residual, 24 months; residual ≤1 cm, 17 months; and residual >1 cm, 13 months. The median OS by residual disease status was as follows: no gross residual, 78 months; residual ≤1 cm, 50 months; and residual >1 cm, 36 months. In the EORTC trial, even patients who had optimal debulking after NACT had an inferior survival. This underlines two important points – the most significant factor affecting survival is complete tumor removal and NACT has a detrimental impact of overall survival (explained below).

From all the above evidence, it can be concluded that PDS or CRS performed upfront should be the standard of care for advanced ovarian cancer. The goal of such surgery should be to

attain complete removal of all macroscopic disease. The collaboration of other surgical teams should be sought when required especially for upper abdominal surgical procedures.

NACT should be reserved for patients who have a poor performance status that precludes an aggressive surgical effort or where a complete cytoreduction is not deemed possible by surgeons/surgical teams experienced in performing such procedures.

10.8.3 Is the NACT/Interval CRS Approach Non-inferior to Primary CRS?

Patients who are given NACT have a higher tumor burden and a higher chance of developing resistant disease. Goldie and Coldman in 1979 proposed a mathematical model that suggested that the likelihood of mutations resulting in drug resistance is dependent upon the tumor burden when chemotherapy is initiated [110]. Rauh-Hain et al. looked at the relapsed patients who were retreated with platinum-based chemotherapy and showed that 88.8% in the NACT-IDS group were considered platinum-resistant (recurrence within 6 months) compared with 55.3% in the PDS group ($p < 0.001$). In the study population consisting of 425 patients, 95 (22.3%) underwent NACT-IDS and 330 (77.6%) underwent PDS. After the initial platinum-based chemotherapy, 42 (44.2%) women in the NACT-IDS group were considered to have platinum-resistant disease compared with 103 (31.2%) in the PDS group ($p = 0.01$). Though the use of NACT was not an independent predictor of platinum resistance, in women who had a recurrence and were retreated with platinum-based chemotherapy, 32 (88.8%) in the NACT-IDS group had a recurrence within 6 months and were considered platinum-resistant compared with 62 (55.3%) in the PDS ($p < 0.001$). This showed that women who develop recurrence after NACT-IDS have an increased risk of developing platinum-resistant disease [111]. In another study of 384 patients, the IDS group, compared to the PDS group, showed a higher recurrence rate within 6 months (11.3 vs. 3.1%: $p = 0.01$) and a trend to higher recurrence rate between 6 and 12 months (30.6 vs. 19.9%) [112]. Thus, following NACT-IDS, the incidence of platinum resistance is higher.

In patients receiving NACT, the surgeon's evaluation of disease sites is impaired by scarring and fibrosis. Areas of microscopic disease have a benign appearance, and the presence of adhesions further impairs the evaluation. Hynninen et al. evaluated the accuracy of perioperative visual assessment of tumor dissemination at the start of PDS/diagnostic laparotomy or IDS and showed a worse sensitivity and accuracy at the time of IDS ($p < 0.001$). In this study, systematic visual evaluation of tumor spread was performed at the start of primary surgery/diagnostic laparotomy ($n = 39$) or interval surgery ($n = 16$). The peritoneal cavity was divided into 22 anatomical regions, and a comparison of the visual assessment was made with the histopathology findings in that region. The visual evaluation correlated well with the pathology findings in patients undergoing PDS and was significantly worse in those undergoing IDS ($p < 0.001$) [113].

In the meta-analysis published by Chi et al., looking at outcomes in patients undergoing NACT, the median survival of patients receiving NACT ranged from 10 to 42 months, with a weighted average median survival time of 24.5 months. This survival was similar to patients who underwent suboptimal primary surgery (residual disease >1 cm) and subsequent systemic chemotherapy in a large GOG trial, Gynecologic Oncology Group protocol #111, in which the median survival time was 24 months [100]. Overall, women in the NACT group had an 18% increased hazard of death from all causes compared with PDS (HR, 1.18; 95% CI, 1.11–1.26) [100].

In another review of 24 publications with 14,182 patients, the weighted average of median overall and progression-free survival was 43 and 17 months, respectively, after PDS, for the whole group. After IDS, median and progression-free survival were 33 and 14 months. The rate of complete cytoreduction after PDS was inferior to the obtained in patients with IDS (27 vs. 59%). However, the median survival in patients with

complete cytoreduction with primary cytoreduction was 23 months longer than in the group with interval debulking (69 vs. 45 months) [114].

In this large national study comprising 22,962 women, examining primary treatment for otherwise healthy women 70 years or younger with advanced stage EOC, primary CRS was associated with improved survival of approximately 5 months compared with NACT [115].

The above evidence suggests that patients receiving NACT have a poorer prognosis compared to those undergoing primary CRS/PDS and NACT followed by IDS/interval CRS cannot be considered equivalent to primary CRS/PDS. This treatment strategy should be reserved for patients who cannot withstand radical surgery or in whom a complete cytoreduction is not feasible. When NACT is given, patients should be taken up for interval CRS "as soon as possible," i.e., as soon as the disease becomes resectable which is usually after three cycles of chemotherapy.

10.8.4 Pathological Response to NACT and Its Significance

In patients with PM, the survival benefit of tumor response to chemotherapy has been demonstrated in patients with colorectal and appendiceal adenocarcinomas [116, 117].

There are published guidelines for grading of tumor regression following chemotherapy for advanced colorectal, pancreatic, and breast cancers, but not for epithelial ovarian cancers [118, 119].

In ovarian cancer PM, the prognostic impact of response to chemotherapy has not been studied. The morphologic alterations after neoadjuvant chemotherapy have been uniformly seen in all tumors regardless of types and sites.

Samrao et al. evaluated the impact of morphological alterations following chemotherapy like necrosis, fibrosis, inflammation, and residual tumor in 67 patients with advanced epithelial ovarian cancer undergoing NACT followed by IDS. Fibrosis was scored as mild (1+), moderate (2+), and severe (3+); necrosis was scored as absent (0), 1–50% (1+), and present >50 (2+); residual tumor was scored as <5% (1+), 5–50% (2+), and >50% (3+); and inflammation was scored as mild (1+) and extensive (2+) [120].

Fibrosis was associated with longer recurrence-free survival ($p = 0.0257$) with a median of 20 months for tumors with fibrosis (3+) versus 12 months for tumors with fibrosis (1+, 2+) and longer OS ($p = 0.0249$) with a median of 51 months for tumors with fibrosis (3+) versus 32 months for tumors with fibrosis (1+, 2+). Our results revealed that patients with tumors exhibiting fibrosis (1+, 2+), as well as necrosis (0, 1+), had significant shorter RFS and OS ($p = 0.059$ and $p = 0.0234$, respectively).

Unexpectedly, the size of residual tumor did not have an impact on survival. The authors stated that this might be due to the fact that it was evaluated at the primary site, that is, the ovaries where assessment is difficult due to the large size of tumors. Notably, in the study, it is not mentioned if there were any patients who experienced a complete pathological response to therapy (Table 10.4).

In another study of 124 patients who underwent NACT at a Japanese center, 8.9% of the patients had no residual tumor both at the primary tumor site and metastatic sites. The tumor response is classified into four grades: grade 0 was defined as a lack of clinical response to NACT; grade 1 as a mild response, with marked degenerative changes (necrosis, fibrosis, and tumor-induced inflammation), such that fewer than two-thirds of cancer cells were inviable; grade 2 as a marked response, with degenerative change in more than two-thirds of cancer cells; and grade 3 as no evidence of malignant disease in the primary tumor site or disseminated disease at surgical excision. Among other factors, a histological response grade of 0–1 was a poor predictor of OS [121].

Bohm et al. developed a three-tier chemotherapy response score (CRS) system and applied to an independent validation cohort of 71 patients. The CRS system was reproducible and showed prognostic significance for high-grade serous carcinoma. The authors concluded that the use of such a system in clinical practice could have an impact on patient care and research [122].

Thus, the response to NACT is a prognostic factor that should be evaluated further and utilized for planning further treatment in these patients.

Table 10.4 Chemotherapy response score (CRS) proposed by Bohm et al. [122]

Criteria for chemotherapy response score	
CRS 1	No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration
CRS 2	Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable
CRS 3	Complete or near-complete response with no residual tumor or minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules, up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases, no or very little residual tumor in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is microscopic residual tumor present
Regression-associated fibroinflammatory changes consist of fibrosis associated with macrophages, including foam cells, mixed inflammatory cells, and psammoma bodies, as distinguished from tumor-related inflammation or desmoplasia	

10.8.5 Surgical Strategies for Obtaining Complete Cytoreduction

Surgery for advanced ovarian cancer comprises a total abdominal hysterectomy with removal of both the tubes and ovaries, total omentectomy, pelvic and para-aortic lymphadenectomy, and removal of the affected areas of the peritoneum. Pelvic peritoneal deposits are common, and the primary ovarian tumor is often adherent to the peritoneum or to the rectosigmoid. An attempt to dissect the tumor off these structures should not be made. En bloc resection of the tumor with the uterus, ovaries and tubes, pelvic peritoneum, and rectosigmoid is indicated. Dissection proceeds in a centripetal fashion and involves the following [123]:

1. Stripping of the peritoneum off the anterior abdominal wall and pelvic side walls
2. Stripping of the peritoneum on the posterior bladder wall from dome to its reflection over the upper vagina
3. Dissecting the ureters free off their peritoneal attachment
4. Ligating the ovarian vessels as high as possible, preferably at the origin
5. Cutting across the retroperitoneum just caudal to the caecum on the right and the sigmoid or descending colon on the left
6. Ligation of the inferior mesenteric pedicle
7. Dissection of the posterior rectal plane if rectal excision is necessary
8. Ligation of the uterine vessels in the retroperitoneum
9. The vagina is transacted below the level of the peritoneal reflection
10. Exerting cephalad traction on the uterine side of the posterior vaginal wall, the pouch of Douglas is dissected off the anterior rectal wall to obtain a long rectal stump as possible
11. The rectum and its mesorectum are divided at the appropriate level

This approach allows CC0 resection in almost all cases deemed operable on radiological assessment.

A covering ileostomy may not be needed if the anastomosis is below the peritoneal reflection.

Figure 10.1 shows an ovarian tumor in situ with peritoneal deposits before and after complete tumor removal.

Apart from this, other peritonectomy procedures and visceral resections will be required which have been described elsewhere [124]. Importantly, surgical procedures involving the upper abdomen like subphrenic and subhepatic peritonectomies, diaphragm resection, splenectomy, cholecystectomy, distal pancreatectomy, hepatic resections, and resection of tumor at the

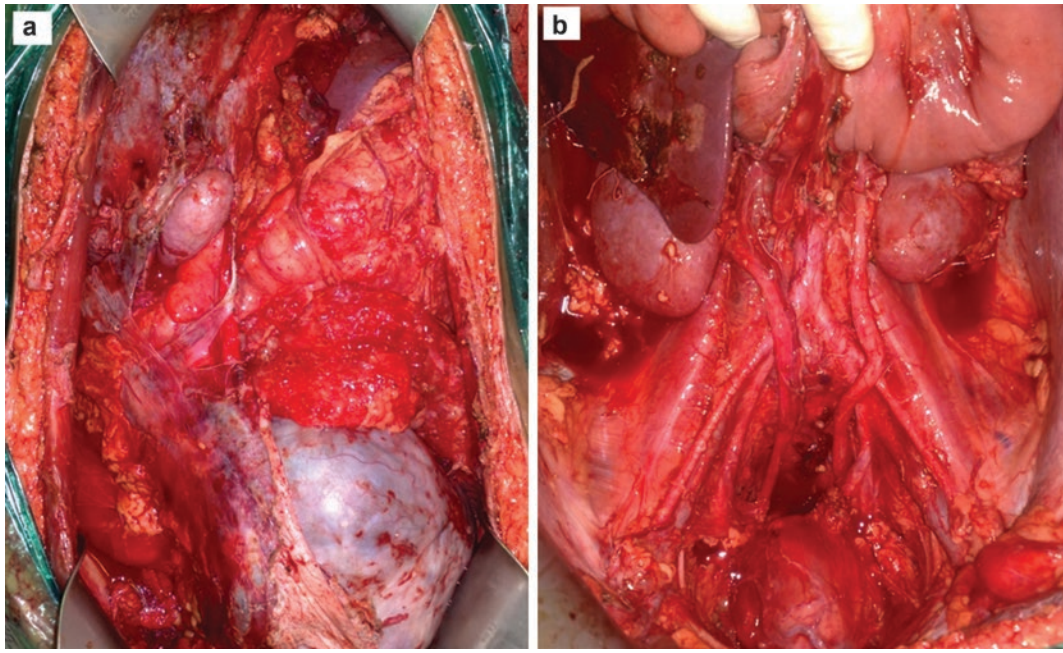


Fig. 10.1 (**a**) Ovarian tumor with peritoneal deposits; (**b**) pelvic peritonectomy completed

porta hepatis may be required to attain a complete cytoreduction. Whereas surgical oncologists dealing with peritoneal surface malignancies may be adept at these procedures, gynecologic oncologist may need the help of surgical oncologists or gastrointestinal/hepatobiliary surgeons.

10.8.6 Pelvic and Para-aortic Lymphadenectomy

The incidence of retroperitoneal lymph node involvement in advanced ovarian cancer ranges 50–80% [125]. Systematic retroperitoneal lymphadenectomy in patients with advanced ovarian cancer has a survival benefit in patients who have had a complete/optimal cytoreduction [126, 127]. Most of the evidence comes from retrospective or observational studies and one randomized controlled trial that was not statistically powered to determine the benefit on survival [128–130]. Systematic lymphadenectomy was defined as removal of at least 30 nodes (20 pelvic nodes and 10 para-aortic nodes) [131]. For patients with bulky nodes, if complete tumor removal is obtained, the survival is similar to patients with microscopic metastases/node-negative disease [132]. Some authors have suggested that debulking of enlarged nodes alone is enough though it has been proved that systematic lymphadenectomy has a survival benefit. This is reiterated by the fact that the patients with a higher number of lymph nodes sampled have a better survival and a high ratio of positive to total number of lymph nodes removed has a negative impact on survival [133, 134]. Lymphadenectomy is performed till the level of the renal veins.

Recently, the results of a large randomized trial were presented at the annual meeting of the American Society of Clinical Oncology. From December 2008 to January 2012, 650 women with newly diagnosed FIGO stage IIB–IV advanced ovarian cancer who had undergone macroscopic complete resection and had clinically and radiographic negative lymph nodes underwent random assignment to pelvic and para-aortic lymphadenectomy or no lymphadenectomy [135]. The patient characteristics and rates of receiving adjuvant chemotherapy were similar in both groups. Of the 323 women who

underwent lymphadenectomy, a median of 57 lymph nodes were removed (35 pelvic, 22 paraaortic). Of note, 56% of patients had micrometastases in the removed lymph nodes. Median OS was 65.5 months in the lymphadenectomy arm compared with 69.2 months in the no-lymphadenectomy arm (HR 1.057, 95% CI [0.833, 1.341]; $p = 0.65$). Moreover, both arms demonstrated a median progression-free survival of 25.5 months (HR 1.106, 95% CI [0.915, 1.338]). Lymphadenectomy, compared with no lymphadenectomy, required an additional hour of surgery (mean time: 340 vs. 280 min; $p < 0.001$), resulted in greater blood loss (median volume: 650 vs. 500 mL; $p < 0.001$), and more frequently necessitated transfusion (63.7 vs. 56.0%; $p = 0.005$). Systematic lymphadenectomy was associated with significantly higher rates of relaparotomy for complications (12.4 vs. 6.5%; $p = 0.01$), infections (25.8 vs. 18.6%; $p = 0.03$), and mortality within 60 days of surgery (3.1 vs. 0.9%; $p = 0.049$) as compared to patients who did not undergo lymphadenectomy. Though the authors recommend that lymphadenectomy can be omitted in patients with clinically and radiologically negative nodes, 56% of the patients had microscopic disease in lymph nodes. Stages II-IV represent a broad selection of patients. Other prognostic factors need to be looked into simultaneously before applying this strategy uniformly to all patients—patients with widespread peritoneal disease and those undergoing neoadjuvant chemotherapy are two such examples [135].

10.8.7 Surgery in Patients Who Have Received NACT

Surgery in this group of patients should be performed even more meticulously. A complete exploration of the peritoneal cavity should be performed employing an incision extending from the xiphoid to the pubis. All the adhesions should be lysed completely and all areas of the peritoneal cavity inspected thoroughly for the presence of residual peritoneal disease.

Some important concerns in this situation are:

- *Is it required to resect areas of complete tumor response*— should a biopsy be performed for staging, a formal peritonectomy, or nothing? It is not uncommon to find normal-looking peritoneum with few areas of scarring after NACT where imaging or exploration had shown disease previously.
- *What is optimal debulking in this situation?*

The reported rate of complete tumor response at metastatic sites is 8–10% [136]. Areas of scarring are known to harbor residual disease [136]. When disease recurs, it recurs at the same sites where disease was present before chemotherapy [137].

The residual tumor after neoadjuvant chemotherapy may contain cancer stem cells which are chemoresistant [138–140]. For such reasons, scar tissue after neoadjuvant chemotherapy could be an indiscernible source of disease recurrence. Therefore, in these patients who have a poorer prognosis and higher rates of disease recurrence and platinum resistance, a formal peritonectomy at previous disease sites is the more logical approach though the evidence to support this approach is limited [121]. The extent of the surgery should be balanced against the expected morbidity of such a procedure.

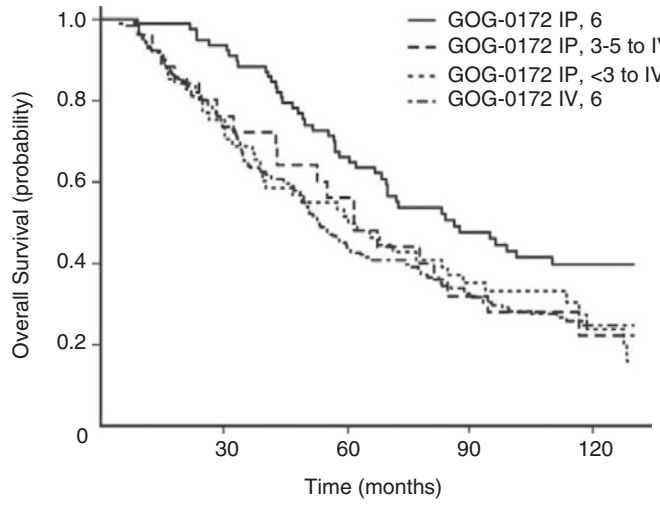
In patients who have a high disease burden that cannot be completely resected upfront, residual disease represents areas of chemoresistant cells and should be completely resected. Leaving behind residual disease after NACT leads to tumor recurrence. There is a survival benefit of complete removal of macroscopic disease at the time of primary CRS. The same principle should be applied to patients undergoing interval CRS, and optimal surgery in these patients should be no visible residual disease.

10.8.8 Rational for Intraperitoneal Chemotherapy for Ovarian Cancer

Ovarian cancer remains a locoregional peritoneal disease for prolonged time periods. This makes locoregional treatment an attractive therapeutic option. Intraperitoneal chemotherapy has

some known pharmacokinetic advantages—like high intraperitoneal drug concentration leading to better exposure of poorly vascularized tumor tissue to the drug. There is limited systemic absorption due to the plasma-peritoneal barrier which limits the toxicity [141]. A port implanted subcutaneously over the lower chest wall is connected to an intraperitoneal catheter and used to deliver multiple cycles of chemotherapy in the postoperative period. This is known as sequential intraperitoneal chemotherapy (SIPC). Of three large randomized controlled trials comparing SIPC and systemic chemotherapy with systemic chemotherapy alone as adjuvant therapy, though the first trial showed a survival benefit favoring the SIPC arm, it was carried out in the pre-taxane era, the second study showed a marginal benefit with increased toxicity and the third study showed a significant survival benefit in the SIPCE arm [142, 143]. This third trial, GOG 172, randomized 415 patients with residual disease ≤1 cm to receive IV paclitaxel and cisplatin or IV paclitaxel followed by IP cisplatin (day 1) and paclitaxel (day 8). The median OS was 65.6 months in the SIPC arm compared to 49.7 months in the IP arm ($p = 0.03$). This was despite only 42% of patients completing six cycles of IP chemotherapy. Grade ¾ toxicity was significantly greater and quality of life scores significantly worse in the IP arm [144]. In a meta-analysis of seven randomized trials evaluating the role of SIPC, the survival benefit of IP chemotherapy compared with IV chemotherapy alone (Relative risk, 0.88; 95% confidence interval, 0.81–0.95) was confirmed. Adverse events and catheter-related problems were more common in the SIPC arm and led to discontinuation of therapy. The authors concluded that where the institutional facilities are available, cisplatin-based intraperitoneal chemotherapy should be offered to patient who had complete CRS [145]. One of the main problems with this treatment has been a high incidence of port-related complications, poor tolerance leading to crossover to IV therapy, and failure to complete the intended course of treatment. In the GOG 172 trial, only 42% of the patients completed all six cycles of intraperitoneal chemotherapy. Wright et al. carried out a prospective cohort study of 823 women with stage III ovarian cancer diagnosed at six National Comprehensive Cancer Network institutions who had optimal CRS. Although the use of IP/IV chemotherapy increased significantly at these centers between 2003 and 2012, fewer than 50% of eligible patients received it. In the propensity score-matched sample, IP/IV chemotherapy as compared to IV chemotherapy was associated with significantly improved OS (3-year overall survival, 81 vs. 71%; hazard ratio, 0.68; 95% CI, 0.47–0.99) but also more frequent alterations in chemotherapy delivery route (adjusted rate discontinuation or change, 20.4 vs 10.0%; adjusted odds ratio, 2.83; 95% CI, 1.47–5.47) [146].

The other disadvantage of SIPC chemotherapy is its inability to penetrate deeply into tissues and thus is not useful for patients with macroscopic residual disease. However, an exploratory analysis of two GOG studies 114 and 172 carried out by Chan et al. reported a benefit survival benefit of IP chemotherapy in patients with gross residual disease <1 cm (AHR, 0.75; 95% CI, 0.62–0.92; $p = 0.006$) [147]. The explanation provided by the authors is as follows: when multiple regimens of both IV and IP chemotherapies are administered over time, it is possible that the first few cycles of treatment depend on the delivery of platinum via capillary flow to reduce the size of larger residual tumors. Subsequent IP treatments delivered regionally are more effective in small residual tumors. The study also provided a long-term follow-up (>10 years) of both trials and demonstrated a long-term survival advantage of SIPC over IV therapy. The use of SIPC was associated with a 23% reduction in the risk of death after matching variables like age, performance status, tumor grade and histology, and size of residual disease. Patients who completed all six cycles of IP chemotherapy experienced a longer OS compared to those who had completed fewer cycles (Fig. 10.2). Though fitter and younger patients were more likely to complete all the stipulated cycles, the survival benefit persisted after adjusting demographic and clinical factors like age and performance status on multivariate analysis [147].



No. at risk					
GOG-0172 IP, 6	78	73	50	31	19
GOG-0172 IP, 3-5 to IV	26	19	14	8	4
GOG-0172 IP, <3 to IV	61	46	30	18	7
GOG-0172 IV, 6	182	133	79	47	25

Fig. 10.2 Long-term overall survival based on number of cycles of intraperitoneal (IP) therapy ($p = 0.03$). Analysis restricted to patients in Gynecologic Oncology Group (GOG)-0172 who completed all six cycles of chemotherapy (both IP and intravenous [IV] arms). (From Ref [126] with permission)

Eligible patients had stage II-IV epithelial ovarian, peritoneal, or fallopian tube carcinoma. They were treated with bevacizumab 15 mg/kg IV on cycles 2–22 and randomized to receive six cycles of (1) arm IV carboplatin AUC 6/IV weekly paclitaxel 80 mg/m^2 (IV arm), (2) arm IP carboplatin AUC 6/IV weekly paclitaxel 80 mg/m^2/ (IP carbo arm), or (3) arm IV paclitaxel 135 mg/m^2 day 1/IP cisplatin 75 mg/m^2 day 2/IP paclitaxel 60 mg/m^2 day 8 (IP cis arm). Among 1560 trial participants, crossover to the IV-only therapy occurred in 16% randomized to IP carbo arm and 28% randomized to IP cis arm. Fifteen deaths possibly due to toxicity were relatively evenly distributed among treatment arms. The progression-free survival was not improved with IP chemotherapy. IV and IP carbo arms using weekly dose-dense paclitaxel were better tolerated than the IP cis arm. Neurotoxicity is a major problem on all arms. The reduced dose IP cisplatin regimen does not appear to be as effective as previously reported high-dose cisplatin regimens. Survival data is not yet mature.

Intraperitoneal chemotherapy acts only on minimal residual disease since the depth of tissue penetration is 2–3 mm after intraperitoneal administration.

10.8.9 Rationale for Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The cornerstone of ovarian cancer therapy is radical surgery. However, chemotherapy plays an equally important role, and the long-term prognosis depends to a large extent on the chemosensitivity of the tumor cells. Moreover, the survival benefit produced by normothermic intraperitoneal chemotherapy has prompted the use of HIPEC for these patients. HIPEC has the added advantage of using heat which has a direct cytotoxic effect and potentiates the action of certain chemotherapeutic agents (mitomycin C, cisplatin, oxaliplatin) and increases the tumor penetration of these drugs.

Hyperthermia can modify the cellular resistance to cisplatin as demonstrated by Hettinga et al. [148]. Relatively high doses of heat – 43° for 60 min—can interfere with cisplatin resistance by several mechanisms like drug penetration, adduct formation, and repair [149]. These are further elaborated in Table 10.5. Hyperthermia can increase the cytotoxicity of cisplatin in both platinum-sensitive and platinum-resistant cell lines [150].

Van Der Vaart et al. showed that cisplatin in combination with hyperthermia in vitro leads to a higher cisplatin ± DNA adduct formation which was a good predictor of the cytotoxic effect. The level of cisplatin-DNA adduct formation which is needed for a cytotoxic effect was observed in tumor nodules up to a depth of 5 mm. Hence, the effect of HIPEC is useful for patients who are cytoreduced to minimal residual disease (CC-0/1) [151].

When intraperitoneal chemotherapy is administered immediately after CRS, it leads to a reduction in tumor cell entrapment. The rationale to use HIPEC comes from the favorable results obtained in patients with PM arising from gastrointestinal primary tumors. CRS and HIPEC are the standards of care for pseudomyxoma peritonei arising from appendiceal primary tumors, malignant peritoneal mesothelioma, and colorectal PM with limited peritoneal spread [152–155]. In a small percentage of patients with gastric PM, it has shown a significant benefit in OS [156, 157].

Table 10.5 Cellular effect of hyperthermia related to cytotoxicity of cisplatin [150]

Effect of hyperthermia	Resistance mechanism that could be affected
Increase in membrane fluidity	Cisplatin accumulation
Membrane protein denaturation	Cisplatin accumulation
Cytoplasmic protein denaturation	Detoxification
Altered DNA conformation	DNA accessibility
Inhibition of DNA repair	Repair of Cisplatin-DNA adducts
Disturbance of normal cellular functions	Altered signal transduction and others
Gene expression, signaling	Response of cells to cisplatin-DNA damage

10.8.9.1 HIPEC Methodology and Drugs

HIPEC can be performed by the open (coliseum) or closed technique maintaining an intra-abdominal temperature of 41–43° C. It is performed only in those patients in whom complete cytoreduction is attained (CC-0 or CC-1) since it does not act of tumor nodules greater than 2–3 mm in size [158]. Any drug that is used for HIPEC should be retained in the peritoneal cavity with a limited systemic absorption leading to a high area under curve (AUC) ratio for IP versus IV administration [141].

One of the most commonly used drugs in this setting is cisplatin since it has a high AUC ratio and is a super drug for hyperthermia undergoing cytotoxic enhancement even at 42–44° C. Moreover, heat is also known to reverse platinum resistance [149].

The ideal dose of cisplatin has been evaluated in the CHIPASTIN trial. This phase I-II escalating dose trial established that 70 mg/m^2 of cisplatin for 1 h at 42 °C was the most appropriate protocol [159]. However other investigators have used a higher dose – 100 mg/m^2 dose of cisplatin for HIPEC in advanced ovarian cancer with no significant nephrotoxicity [160].

Oxaliplatin that is commonly used for HIPEC in colorectal and appendiceal tumors has been used in advanced ovarian cancer as well [161–163]. Oxaliplatin has only moderate cross-resistance with cisplatin or carboplatin [164].

Carboplatin has a favorable toxicity profile compared to cisplatin and has replaced it in many of the intravenous regimens [165]. When nephrotoxicity is a concern, it can be administered in full dose for HIPEC as opposed to cisplatin which requires a dose reduction [166]. When a high dose of carboplatin is used for HIPEC, the drug concentration achieved in the tumor tissue is similar or superior to that achieved by an equitoxic dose of cisplatin [167]. Carboplatin under-

Table 10.6 Various drug regimens for HIPEC in advanced ovarian cancer

Regimen	IP drugs	IV drugs	Carrier solution	Duration
Sugarbaker regimen [177]	Cisplatin (50 mg/m^2) Adriamycin (15 mg/m^2)	Ifosfamide 1300 mg/m^2 Mesna 260 mg/m^2	Peritoneal dialysis solution	90 min
National Cancer Institute Milan regimen [178]	Doxorubicin 15.25 mg/L cisplatin 43 mg/L			90 min

goes hyperthermic enhancement of cytotoxicity and has been shown to have a more homogenous distribution of platinum as compared to cisplatin [167, 168]. Phase 1 trials for HIPEC as first-line and second-line therapy found that carboplatin doses up to 800–1000 mg/m^2 were tolerable and did not preclude additional systemic therapy [169–171]. The duration of treatment is 90 min.

Paclitaxel (175 mg/m^2) alone or in combination with cisplatin (100 mg/m^2) at 41–43° C for 90 min has been used by some investigators for HIPEC in patients with advanced ovarian cancer [172, 173]. The morbidity was acceptable, and the drugs achieved high concentrations in the peritoneal tissue with low systemic absorption. The tissue penetration of paclitaxel was only 0.5 mm, compared to 2–3 mm for cisplatin [172, 174, 175]. The numbers in these studies are small, and further evaluation of toxicity and efficacy of such a regimen is needed. Unlike cisplatin, hyperthermia does not augment the cytotoxicity of paclitaxel [176].

Some of the common regimens for HIPEC are listed in Table 10.6.

10.8.9.2 Outcomes of CRS and HIPEC in Advanced Ovarian Cancer

HIPEC has been used in addition to CRS at the time of primary or interval CRS. The reported outcomes of CRS and HIPEC for advanced ovarian cancer are described in Table 10.7.

The initial evidence for HIPEC in addition to CRS was mainly from small retrospective single-institution series. The drug regimens and methodology were heterogeneous. The patients included those with primary and recurrent disease, both of which made the results difficult to interpret.

The HYPER-O registry, a multi-institutional retrospective registry, reported outcomes in 26, 19, and 12 patients with primary, interval, and second-look surgery, respectively [188]. The median DFS was 24.8, 16.8, and 29.6 months, respectively, and 19.6, 9.7, and 24.2 months, respectively, in the three subgroups. This was still inferior to the survival obtained in the intraperitoneal arm of the GOG-172 trial [144]. Though there were problems related to this study that there was no specified protocol for HIPEC delivery, the data are retrospective coming from different centers with varying selection criteria and did not include information on patients who did not undergo HIPEC. However, it showed that there was a potential for benefit with HIPEC.

A multicenter phase II trial from Italy to study upfront CRS + HIPEC for advanced EOC achieved a median PFS of 30.0 months and 5-year OS and PFS rates of 60.7 and 15.2%, respectively [189]. Gonzalez et al. studied the different time points of CRS + HIPEC to treat advanced EOC, and the median OS was 77.8 months for patients treated upfront, 62.8 months at first recurrence, and 35.7 months at second or subsequent recurrence [187].

Bakrin et al. reported outcomes with CRS and HIPEC in 92 patients from 13 French institutions treated with CRS and HIPEC from 1991 to 2010. A total of 60.1% of the patients received HIPEC as consolidation therapy, 26.1% with interval CRS, and 13% with primary CRS. For advanced EOC, median overall survival was

Table 10.7 Outcomes of CRS and HIPEC for advanced ovarian cancer (Adapted from reference [179] with permission) [179]

Ref no. Year	Study type	No. of patients	Indication	HIPEC open/ closed	Drug/s	Median DFS months	Median OS months	5-year OS
[180] 2004	SI prospective	8	Primary	Open	Cisplatin + mitomycin		33 ± 6	15%
[181] 2005	SI prospective	10	Primary, interval, second look	Open	Cisplatin + mitomycin; etoposide	41.2	70.2	
[182] 2005	Case control	29 + 19	Second look	Open	Cisplatin		64.4	
[183] 2006	SI prospective	19	Primary		Paclitaxel			63%
[184] 2009	SI prospective	31	Primary		Doxorubicin	26.2	34.1	
[185] 2010	MI, retrospective	31	Second look	Open	Oxaliplatin			67% (3 year)
[186] 2010	SI prospective	45	Primary	Closed	Cisplatin + mitomycin			55%
[187] 2010	Prospective MI registry	57	Primary, interval, second look	Open/ closed	Platinum/mitomycin, combination		30.0	
[188] 2011	Prospective MI, Phase II	26	Primary	Closed	Cisplatin + mitomycin	30		60.7%
[189]	SI retrospective	51	Primary	Closed	Carboplatin or mitomycin		28.5	28 ± 7%
[190] 2013	MI retrospective	92	Primary	Open/ closed	Cisplatin, oxaliplatin, mitomycin, doxorubicin, cisplatin + mitomycin, cisplatin + doxorubicin	11.8	35.4	17%
[172] 2015	MI prospective phase II	30	Primary	Open/ closed	Cisplatin + paclitaxel	13	22	
[191] 2016	MI retrospective	16	Primary, interval	Open/ closed			72.0	
[192] 2017	MI retrospective	173	Primary, interval, second look	Open/ closed	Cisplatin Oxaliplatin cisplatin + mitomycin cisplatin + doxorubicin	14.5–72.5	24.5–76.9	

35.4 months. The survival rates at 1, 3, and 5 years were 83, 47, and 17%, respectively. Median recurrence-free survival was 11.8 months. The results are significantly inferior to that reported with CRS alone or CRS and IP chemotherapy.

The authors pointed out that most of the patients in this series had advanced unresectable cancer including stage 4 ovarian cancer, thus forming a poor prognostic group of patients, and a direct comparison with other series would not be appropriate [190].

In another open-label prospective, multicentric phase II study, patients with primary, advanced (FIGO stage IIIC to IV), or recurrent EOC were treated with CRS + HIPEC with cisplatin (100 mg/m^2) and paclitaxel (175 mg/m^2). Thirty patients underwent HIPEC as part of frontline therapy (one patient at the time of primary CRS; 29 with interval CRS). By univariate and multivariate analysis of HIPEC as an upfront treatment, with or without neoadjuvant chemotherapy (NACT), it was associated with more severe postoperative complications compared to HIPEC used to treat recurring disease ($p = 0.002$ and $p = 0.004$, respectively. The median DFS and OS were 13 and 22 months in these patients, respectively. Due to the small numbers and short median follow-up, accurate assessment of the survival was not possible; this study showed the feasibility and safety of a combination of cisplatin and paclitaxel for performing HIPEC [172].

A retrospective cohort study from multiple Chinese centers included 46 consecutive patients of which 16 patients had advanced EOC (FIGO stage III C/IV). The median OS was 74.0 months (95% CI 8.5–139.5). The median OS for patients with PCI < 20 versus PCI > 20 was 76.6 months (95% CI 56.5–96.7) versus 38.5 months (95% CI 24.2–52.8) ($p = 0.01$, log-rank test). The median OS for patients with CC 0–1 versus CC 2–3 was 79.5 months (95% CI, 64.8–94.2) versus 24.3 months (95% CI 13.9–34.7) ($p = 0.00$, log-rank test). A univariate analysis identified three covariates indicative of improved survival, including CC 0–1, PCI ≤ 20, and ascites ≤1000 mL. Multivariate Cox regression analysis identified CC scores as the only independent predictors for better survival. Compared with CC 2–3, CC 0–1 was about seven times (hazard ratio = 7.2, 95% CI 1.9–27.0, $p < 0.01$) more likely to improve survival. Notably, this study, though having a small number of patients, showed a prolonged OS and three patients with advanced ovarian cancer experience and OS of >60 months with two patients disease free for >70 months [191].

An Italian multicentric retrospective study reported outcomes in patients treated with CRS and HIPEC over 16 years from 1998 to 2014 at 11 Italian centers experienced in treating peritoneal surface malignancies and ovarian cancer [192]. Fifty-three patients had primary CRS and HIPEC, 111 had interval CRS and HIPEC for a partial response to NACT, 17 for a pathological complete response (pCR) following NACT, and 45 patients who experience no response to NACT. The various drug regiments used included cisplatin alone, oxaliplatin alone, cisplatin in combinations with doxorubicin or mitomycin C, or paclitaxel. The median PCI for the four subgroups was 5–16.1, being the highest in nonresponders to NACT. Similarly, the rate of complete cytoreduction (CC-0) was the lowest in nonresponders to NACT. The median OS and DFS in the four subgroups were 57.2 and 37 months (primary CRS), 47.6 and 19.5 months in partial responders to NACT, 76.9 and 72.5 months in complete responders, and 24.5 and 14.5 months, respectively, in nonresponders to NACT. In this study, patients receiving NACT who had complete response to NACT experienced a superior DFS and OS compared to the other subgroups. This finding has not been reported before. Though the authors stated that this finding should lead the consideration of NACT for patients who have resectable disease upfront, the percentage of complete responders was 9.82%, and the survival in the other patients receiving NACT was inferior to those undergoing primary CRS and HIPEC [192].

10.8.9.3 Information Derived from Retrospective Data and Phase II Studies

Ovarian cancer may be considered a model disease for PM. The results of these retrospective and phase II studies have shown a median OS of 22–79 months and a median DFS of 12–72 months. In comparison studies reporting the outcomes for frontline therapy for ovarian cancer that did not include HIPEC have reported a median disease-free survival ranging from 12 to 33.2 months, median overall survival ranging from 26 to 58.2 months, and 5-year overall survival ranging from 19.5 to 49% [89, 90, 101, 143, 144, 193–198]. Some of the results are significantly inferior to the studies that did not use HIPEC, whereas others have shown a marginal improvement in survival.

There are several limitations of this data that should be kept in mind while interpreting these results:

- The number of patients is small; only multicentric study included >100 patients. Most clinical trials for ovarian cancer include a few hundred patients in each arm to be statistically powered to evaluate the impact of the treatment under evaluation on the predetermined end points.
- The study population included patients undergoing CRS and HIPEC at different time points in the history of ovarian cancer – primary CRS, interval, and second look often combined with patients undergoing treatment for recurrence. The time period spans several years, and the treatment protocols even within the small groups are heterogeneous.
- The selection criteria are not clearly defined, and most series comprise patients with extensive disease that were referred to specialized units after having undergone unsuccessful prior surgical attempts. This represents a poor prognostic subgroup.
- The definition of optimal debulking/complete CRS is variable.
- The extent of disease as determined by the PCI was not reported in many of these, and the prognostic factors were not defined.

Thus, the benefit of HIPEC in addition to CRS remains uncertain.

10.8.9.4 Clinical Trials for CRS and HIPEC for Advanced Ovarian Cancer

The results of the first randomized controlled trial for CRS and HIPEC in ovarian cancer were recently presented at the annual meeting of the American Society of Clinical Oncology. The OVHIPEC trial (Clinical Trials.gov identifier NCT00426257), a phase III randomized trial conducted by the Netherlands Cancer Institute, randomly assigned patients who showed at least stable disease after three cycles of carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) to receive interval cytoreductive surgery with or without HIPEC using cisplatin (100 mg/m^2). Randomization was performed perioperatively, and eligible patients had no residual mass greater than 2.5 mm. Three additional cycles of carboplatin and paclitaxel were given postoperatively. The primary end point was recurrence-free survival. Overall survival, toxicity, and quality of life were key secondary end points. A total of 245 patients were randomly assigned to one of the two treatment strategies. In an intention-to-treat analysis, interval CRS with HIPEC was associated with longer recurrence-free survival than interval cytoreductive surgery alone (15 vs. 11 months, respectively; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.49–0.86; p = 0.003). At the time of analysis, 49% of patients were alive, with a significant improvement in overall survival favoring HIPEC (48 vs. 34 months; HR, 0.64; 95% CI, 0.45–0.91, p = 0.01). The number of patients with grade 3–4 adverse events was similar in both treatment arms (28 vs. 24%, p = 0.61). Whereas the complete analysis is awaited, this trial has shown the benefit of HIPEC in addition to CRS in two poor prognostic subgroups. Patients were either deemed unresectable upfront and thus given NACT or had an unsuccessful attempt at complete tumor removal followed by chemotherapy and secondary CRS and HIPEC [199].

A similar multicenter phase III randomized trial in the interval setting has just started in Italy (CHORINE: Cytoreduction and HIPEC in the treatment of OvaRIaN cancEr). This study compares CRS + HIPEC (cisplatin + paclitaxel) vs. CRS alone in stage IIIC unresectable ovarian cancer with partial or complete response after three systemic cycles of carboplatin and paclitaxel, followed by three further cycles of carboplatin and paclitaxel (Clinical trials. Govt identifier NCT02124421). The primary outcome is 2-year disease-free survival. Ongoing clinical trials evaluating the role of HIPEC in advanced ovarian cancer are listed in Table 10.8.

A phase II randomized study: Cytoreductive surgery (CRS) with/without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC) followed by adjuvant chemotherapy as initial treatment of ovarian, fallopian tube, and primary peritoneal cancer is being conducted by the Mercy Medical Center in the United States (Clinical trials. Govt identifier NCT01628380). The primary end point is to compare the morbidity in the two arms. The secondary end points include assessment of the quality of life, the DFS at 2 years, and the overall survival at 1.3 and 5 years. The results of this trail are expected in 2020.

Another randomized trial is being conducted at the City of Hope Medical Center in the United States and compares CRS and HIPEC with or without normothermic intraperitoneal chemotherapy (Clinical trials. Govt identifier NCT01970722). The primary end point is safety and feasibility, and the secondary end points are evaluation of the quality of life and progression-free survival. Another phase II trial being conducted in the Bay Area in California evaluates the safety and feasibility of HIPEC for PM from various primary sites including ovary, fallopian tube, and primary peritoneal cancer (Clinical trials. Govt identifier NCT02349958).

Another phase III randomized trial is currently underway in Spain in which women with epithelial primary ovarian cancer (stage FIGO II, III, and IV) or tumor recurrence will undergo CRS and then be randomized to one of the two arms (Clinical trials. Govt identifier NCT02681432):

- HIPEC arm: CRS and HIPEC with paclitaxel (175 mg/m^2) for 60 min at a temperature of 42–43° followed by postoperative systemic IV chemotherapy with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2) for six cycles
- No HIPEC arm: CRS followed by postoperative systemic IV chemotherapy with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2) for six cycles

The primary end point is OS to be evaluated at 36 months, and the secondary end points are recurrence-free survival and morbidity at 60 days.

A phase II trial (NCT02567253) is underway at the Ghent University in Belgium, looking at the pharmacokinetic aspects of normothermic and hyperthermic intraperitoneal chemotherapy administered immediately after CRS.

10.9 The Need for New Predictive and Prognostic Markers/Tools

Primary CRS and adjuvant chemotherapy using a platinum agent and taxane are the standards of care for advanced epithelial ovarian cancer. The complete clinical response rate with this combined treatment is 50%, and a pathological complete response rate is obtained in 25–30% of the patients [200–202]. In a recent report of 322 patients from a single institution who underwent PDS and chemotherapy, a CC-0 resection was obtained in 35.7% and CC-0/1 in 55.9%. All 322 patients were complete responders to frontline therapy. However, at a median follow-up of 75.9 months after the initial diagnosis, 81 patients (25.2%) were disease free, 56 patients (17.4%) were alive with recurrent disease; 179 (55.5%) were dead due to progressive disease, and 6 patients (1.9%) died of intercurrent disease with no evidence of tumor. In another study of 303 patients, recurrence developed in 76.9% patients with residual disease ≥1 cm, 64.3% with residual disease <1 cm, and 40.9% of the patients with no residual disease [203].

Table 10.8 Currently ongoing clinical trials evaluating the role of HIPEC in advanced ovarian cancer

ClinicalTrials.gov ID	Phase	Primary institution/group	Malignancy	Treatment arms
NCT02349958	Nonrandomized	Bay Area Gynecology Oncology, USA	Ovarian, fallopian tube, uterine, mesothelioma, GI, cervical, primary peritoneal	All patients will undergo CRS and HIPEC
NCT02124421	Randomized, phase II	Mercy Medical Center, USA	Ovarian, fallopian tube, primary peritoneal	CRS + HIPEC + adjuvant chemotherapy vs. CRS + adjuvant chemotherapy
NCT01970722	Randomized, phase II	City of Hope Medical Center, UC	Ovarian, uterine, fallopian tube, primary peritoneal	All patients will undergo CRS and HIPEC, ± adjuvant IP chemotherapy and IV chemotherapy
NCT02567253	2	Ghent University Hospital, Belgium	Ovarian	CRS and HIPEC, varying temperature and dosage
NCT01628380	Randomized, phase III	A.O. Ospedale Papa Giovanni XXIII, Italy	Ovarian	CRS vs. CRS and HIPEC
NCT02681432	Randomized, phase III	Hospital General de la Ciudad Real, Spain	Ovarian	CRS vs. CRS and HIPEC

Thus, even after optimal frontline therapy, the recurrence rates in advanced ovarian cancer are high. Disease can recur in both treated and non-treated areas of peritoneum [204, 205]. A complete CRS does not affect the timing or pattern of recurrence though it reduces the absolute number of recurrences [203].

The only factors which have an impact on survival are the tumor stage and completeness of CRS. The disease extent as determined by the PCI is one of the most important prognostic factors in patients with PM from various primary sites undergoing radical surgery. Though, in general, extensive disease in the supracolic compartment is associated with a poorer survival, no criteria for patient selection are defined based on the extent or distribution of disease. Patients undergoing primary CRS despite undergoing removal of all macroscopic disease represent a heterogeneous patient population. Di Giorgio et al. in their retrospective study of 511 patients of whom 173 patients had advanced ovarian cancer reported a pathological complete response in 9.82% of the patients undergoing NACT. These patients experience a median DFS of 72.5 months and median OS of 76.9 months. Extrapolating this to patients with resectable disease upfront, there could be subgroups that could benefit from NACT.

This indicates a need for identifying criteria other than resectability alone for selecting patients for surgery. Though molecular subtyping is used to select the best chemotherapy regimen for patients in solid tumors, from a purely surgical perspective, it may have relevance too. Though not incorporated in clinical practice yet, molecular subtypes of high-grade ovarian cancer have been identified, and upregulation of certain pathways like the TGF-β pathway has shown to be predictive of an incomplete cytoreduction [206, 207].

Fotopoulou et al. pointed out that novel strategies relying on predictive and prognostic biomarkers and radiological classifications based on patterns of tumor dissemination and biology of advanced epithelial ovarian cancer in the future should be used to develop algorithms for patient selection for CRS based on the operative morbidity versus benefit of primary CRS [208].

As mentioned above, a uniform grading system for the pathological response to NACT needs to be developed. More effective treatment strategies are needed for patients who have a poor response to chemotherapy and cannot be cytoreduced completely thereafter.

Conclusion

Primary CRS followed by systemic chemotherapy has a survival benefit over other treatment strategies in patients with advanced ovarian cancer. The results of ongoing clinical trials will further define the role of HIPEC in this setting. Adjuvant normothermic intraperitoneal chemotherapy, in combination with systemic chemotherapy, has shown a survival benefit despite the various problems with administration. NACT followed by interval CRS is an option for patients who are not fit for primary CRS or have disease not amenable to complete CRS. HIPEC in addition to CRS has shown a survival benefit over CRS alone in these patients in a randomized phase III trial. The goal of CRS in the primary and interval setting should be complete removal of macroscopic disease especially in the setting of interval CRS where any amount of residual disease portends a poor prognosis. Despite aggressive therapy, majority of the patients develop recurrent disease. Prognostic and predictive factors need to be developed for patients with advanced epithelial ovarian cancer that will be helpful in selecting patients for surgery and serve as a basis for developing new therapies. More effective therapies are needed for patients who are poor responders to chemotherapy and/or have extensive disease.

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Surgical Management of Recurrent Epithelial Ovarian Cancer

11

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11.1 Introduction

A large proportion of the patients with advanced ovarian cancer develop disease recurrence within few years [1, 2]. Most of the patients who recur die within 5 years since recurrent disease is usually incurable [3]. Second-line therapy includes either chemotherapy or surgery or both chemotherapy and surgery but the outcomes remain poor.

Although most of the initial recurrences are frequently platinum sensitive, patients eventually develop resistance to platinum-based chemotherapy [3]. Resistance to chemotherapy, which is either intrinsic (primary) or acquired (secondary), is a major problem in the treatment of ovarian cancer and the main contributing factor in cancer-associated mortality. An aggressive locoregional therapy comprising of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to systemic chemotherapy has produced promising results. The optimal use of this combined modality treatment in addition to systemic therapy has the potential to provide a significant prolongation of the disease-free survival (DFS) and overall survival (OS) both in these patients.

11.2 Appropriate Terminology for Recurrent Disease

The time to recurrence after completion of first-line chemotherapy, i.e. the platinum-free interval (PFI), has been used to classify recurrent ovarian cancer into two broad groups—platinum sensitive or platinum resistant.

This division is arbitrary and was done for the purpose of study design and interpretation by the Gynecologic Oncology Group (GOG) [4]. The platinum-sensitive group comprises of patients who recur 6 months or more after cessation of platinum-based chemotherapy. The clinically resistant group consists of those patients who actually progress while receiving platinum-based therapy, whose best response to platinum-based therapy is stable disease, and who recur within 6 months of cessation of platinum-based treatment [5]. Within this group are patients who have progressed on chemotherapy or had a less than partial response (stable disease) and could be termed as ‘platinum refractory’. This is seen in 20% of the cases, and these patients have the lowest probability of responding to second-line ther-

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apy. Among the other platinum-resistant patients are those that have a complete clinical response after surgery and chemotherapy and recur within 6 months of cessation of therapy. This would include patients who had optimal and suboptimal cytoreductive surgery (CRS) both [5]. Subsequent recurrences are classified according to the PFI from the last treatment.

The PFI has been widely used as a clinical surrogate for predicting the response to chemotherapy and determining the prognosis [6]. However, there are several caveats in using this division. There is a variability in the use and timing of investigations used to diagnose a recurrence. This influences the time at which the relapse is diagnosed and hence the categorization of the patients as platinum sensitive or platinum resistant. Moreover, in the platinum-sensitive group, the 'platinum-free interval' affects the response to further systemic therapy, with patients who are platinum-free for more than 12 months having better outcomes than those with a shorter PFI [6].

At the fourth Ovarian Cancer Consensus Conference (fourth OCCC) in Vancouver in 2010, there was an agreement that future clinical trials should evaluate outcomes based on four subsets of patients [7]. This division is also based on the PFI and is as shown in Table 11.1.

With the increasing use of non-platinum and biological agents like poly-ADP-ribose polymerase (PARP) inhibitors and angiogenesis inhibitors that may have an impact on disease biology and response to subsequent therapy, the PFI may not be the only prognostic factor affecting outcomes. At Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup, the PFI was replaced by a broader term, i.e. treatment-free interval (TFI), which was further divided into the TFI from last platinum dose (TFIp), the TFI from last non-platinum therapy (TFInp) as well as last biological agent (TFIb) [8]. These classifications are being used to stratify patients for clinical trials that evaluate various systemic therapies.

Table 11.1 Classification of recurrence according to the platinum-free interval

Platinum-free interval	Subgroup
<1 month	Platinum refractory
1–6 months	Platinum resistant
6–12 months	Partially platinum sensitive
>12 months	Fully platinum sensitive

An additional prognostic factor that has been overlooked in these classifications is the completeness of the first surgery. Some patients who did not have an attempt at complete CRS by a surgical/gynecologic oncologist may or may not have a complete response after chemotherapy. They may be inappropriately classified as platinum resistant/platinum refractory. Classe et al. suggested that to distinguish patients with a true early relapse refractory to platinum, other criteria such as the completeness of primary surgery performed in an expert centre need to be added to the disease-free interval [9].

11.3 Pattern of Recurrence

The commonest site of recurrence in epithelial ovarian cancer is the peritoneum. Seventy five percent of recurrences occur in the peritoneum, and in almost 50% of these cases, the peritoneum is the only site of recurrence [10]. Nodal recurrence is the second most common and is usually associated with peritoneal disease. Distant metastases are a rare site of disease recurrence [10].

Disease can recur in both treated and non-treated areas of the peritoneum. Pelvic recurrences are more common than upper abdominal recurrences [11, 12].

A retrospective study of 104 patients showed that in comparison to patients receiving systemic chemotherapy alone, patients who received intraperitoneal chemotherapy were more likely to recur in the upper abdomen or in extra-abdominal nodes [13]. Most of the recurrences from ovarian cancer are diffuse. In a study of 270 patients, reported by Ferrandina et al., 'diffuse peritoneal carcinomatosis' was seen in 62.1% of cases, while recurrences presented as a single lesion or multiple nodules occurred in 9.9 and 26.7% of cases, respectively [14]. Peritoneal carcinomatosis was defined as 20 or more peritoneal nodules by Chi et al. [15]. Isolated recurrence has been

reported in patients with platinum-resistant disease as well [16]. It has been shown that the pattern of recurrence is dependent neither on the initial stage nor the completeness of CRS. A complete CRS does not affect the timing or pattern of recurrence though it reduces the absolute number of recurrences [17]. However, most of these studies consider <1 cm residual disease as a cut-off for complete cytoreduction though current evidence has shown that outcomes are better in patients with no residual disease as compared to any size of visible residual tumour [18].

11.4 Treatment of Recurrence

The treatment of recurrence essentially depends on the prior course of disease. It is important to review the prior treatment that has been administered—the surgical details and its completeness, the chemotherapy regimen, the time interval to recurrence—if complete remission was achieved or not.

The cornerstone of second-line therapy has been chemotherapy, and surgery is conventionally reserved for isolated localized recurrences. However, despite subjective and objective responses to second-line therapy and a prolonged disease-free and overall survival that is obtained in certain patients who have platinum-sensitive disease, the outcome of these patients is poor and cure is almost impossible [5]. The intent of treatment needs to be defined before starting any kind of therapy.

The tendency of recurrent disease to remain confined to the peritoneal cavity for prolonged periods forms a strong rationale for an aggressive locoregional approach comprising of CRS with or without hyperthermic intraperitoneal chemotherapy (HIPEC).

11.4.1 Evidence for Cytoreductive Surgery for Recurrent Ovarian Cancer

CRS can be performed as a second look following previous suboptimal surgery (secondary CRS) or for disease recurrence after complete response to first-line therapy (salvage CRS). The term 'secondary CRS' is broadly used for both situations. The completeness of surgery is defined according to the maximum diameter of the residual disease nodules. Complete cytoreduction is generally used for cases where there is no visible residual disease according to the completeness of cytoreduction score (Table 11.2) by Sugarbaker et al. [19]. The other commonly used term is 'optimal cytoreduction' which as defined by the Gynecologic Oncologic Group (GOG) as residual disease measuring <1 cm in maximal diameter [20].

Most of the evidence to support the use of CRS for recurrent ovarian cancer comes from retrospective studies [21–24]. These studies had a complete cytoreduction rate ranging from 50 to 87%. The median overall survival (OS) in patients undergoing complete cytoreduction ranged from 29 to 60 months. The criteria for complete CRS varied from no visible macroscopic residual disease to residual disease measuring <2 cm. Most of these studies have a short follow-up (1–4 years) and do not stratify patients according to PCI.

In a population-based study from the Netherlands, 408 patients who underwent secondary CRS at 38 centres experienced a median survival of 51 months [25]. Complete cytoreduction was achieved in 295 (72.3%) patients, with an OS of 57 months compared with 28 months in

Table 11.2 Scoring systems for completeness of cytoreductive surgery

Scores for completeness of cytoreductive surgery			
Completeness of cytoreduction (CC) score [19]		GOG criteria for 'optimal debulking' [20]	
CC-0	No visible residual disease	RD0	No visible residual disease (zero residual disease
CC-1	Residual disease 0–2.5 mm		
CC-2	Residual disease 2.5–2.5 cm	RD 1	Residual disease <1 cm (*optimal debulking*)
CC-3	Residual disease >2.5 cm	RD 2	Residual disease >1 cm (suboptimal debulking)

patients with incomplete cytoreduction (p = 0.001). Non-serous histology, a long progression-free interval (hazard ratio [HR], 0.29; 95% CI, 0.07–1.18), a good performance status (HR, 0.68; 95% CI, 0.49–0.94), secondary CRS without preoperative chemotherapy (HR, 0.72; 95% CI, 0.51–1.01) and complete CRS (HR, 0.46; 95% CI, 0.33–0.64) were prognostic factors for survival [25].

In a retrospective review of secondary CRS, Munkarah et al. found that patients with no gross residual disease after CRS had a survival of 44–60 months as compared to 35 months in those receiving chemotherapy alone [26]. Optimal cytoreduction was achievable in 38–87% of the study populations reviewed with acceptable perioperative complications and mortality. However, the impact of secondary CRS on survival could not be analysed due to (1) the inter-investigator differences in defining optimal cytoreduction, (2) the heterogeneity of the patients included (3) and the lack of information on postoperative therapy. Though most of these studies have drawbacks like small numbers, retrospective nature and lack of proper stratification based on prognostic variables, the survival reported is higher than that shown by modern multi-agent chemotherapy alone, especially in patients who had complete tumour removal (44–60 months) [26].

Bristow et al. published a meta-analysis of 40 studies, including 2019 patients, 13 studies were published between 1983 and 2000 and 27 (67.5%) were published between 2001 and 2007 [27]. Twelve of the 40 reports utilized prospective non-randomized data collection methodology; there were 27 retrospective analyses and one retrospective case-control study. The mean weighted median disease-free interval (DFS) prior to CRS for recurrent ovarian cancer was 20.2 months reflecting a tendency to select patients with platinum-sensitive disease for surgery. The parameter significantly associated with survival was the size of the residual disease. Each 10% increase in the proportion of patients left with optimal residual disease was associated with a 2.69-month increase in median survival time (95% CI 0.90 months to 4.49 months, p = 0.004). Similarly, each 10% increase in the proportion of patients undergoing complete surgical resection was associated with an increase in median cohort survival time of 2.84 months (95% CI 1.29 months to 4.38 months, p = 0.0008). The various limitations of this study pointed out by the authors were selection bias in selecting studies for the meta-analysis as well as patient selection in each study, the data collection interval was 25 years leading to heterogeneity in the chemotherapy regimens and other prognostic factors like tumour size, the number of lesions and performance status were not analysed [27].

In a Cochrane Database review of nine studies comprising of 1194 patients, there was a prolongation in overall survival in women who had a complete cytoreduction (no visible residual disease) and optimal cytoreduction (<1 cm residual disease) compared to those who had suboptimal cytoreduction (>1 cm residual disease) [28]. This meta-analysis included only those studies that has >50 women and had compared outcomes between optimal and suboptimal cytoreduction. There were no randomized controlled trials in this study. The authors concluded that though suggestive, this could not be taken as conclusive evidence, and the survival benefit could be due to a more favourable disease biology rather than the surgical effort alone. According to them, a randomized controlled trial was needed to further define the role of secondary CRS [29].

Bickell et al. used the Surveillance, Epidemiology and End Results Medicare database to assess the benefit of CRS in women who developed recurrence after first-line therapy for ovarian cancer [29]. Women who developed recurrence within 6 months of completion of first-line therapy were excluded from the analysis. Of the 1635 (80%) women who experienced recurrence, 265 (16%) were treated with secondary CRS and chemotherapy, 1171 (72%) with chemotherapy alone and 199 (12%) received hospice care. Propensity score adjusted log-logistic analyses showed that women undergoing surgery with chemotherapy had significantly greater survival compared with those receiving chemotherapy alone (hazard ratio [HR] = 1.33; 95% confidence interval [CI], 1.20–1.47). The estimated median survival of women treated with

chemotherapy was 4.1 years from time of diagnosis; those treated with secondary surgery and chemotherapy survived a median of 5.4 years; 67% of those receiving hospice survived an average of 2.2 years. The 403 women who received no secondary treatments were classified as nonrecurrent and had a median survival of 9.3 years. The authors concluded that secondary CRS with chemotherapy to treat recurrent ovarian cancer increases survival by 1.3 years compared with chemotherapy alone and pending ongoing randomized trial results may be considered a standard of care [29].

There is a clear benefit of secondary CRS in selected patients with recurrent ovarian cancer who have a complete cytoreduction. They experience a significantly greater DFS and OS compared to patients undergoing chemotherapy alone. However, the chemotherapy group also comprises of patients with poor prognostic factors like platinum-resistant disease, extensive disease not amenable to complete cytoreduction and those with a poor performance status. Currently, three clinical trials are underway which will define the role of secondary CRS further.

The DESKTOP III is a phase 3 randomized controlled trial evaluating the role of cytoreductive surgery for first recurrence that has completed accrual. The results are expected in 2019. Patients with a positive AGO score (described below) are randomized to chemotherapy alone or CRS and chemotherapy (ClinicalTrials.gov identifier: NCT01166737).

Another randomized controlled multicentric trial is currently underway in the Netherlands (Netherlands Trial Register number: NTR3337; the Dutch SOCceR trial) that randomizes women with platinum-sensitive recurrence to undergo secondary CRS followed by platinum-based chemotherapy or platinum-based chemotherapy alone. Inclusion criteria are FIGO stage IC-IV (FIGO system 1988), first-line treatment consisted of complete or optimal (≤ 1 cm) cytoreductive surgery and (neoadjuvant) platinum-taxol-based chemotherapy, ascites <500 mL (pocket <8 cm on ultrasound examination), complete resection seems possible (estimated by a gynaecologic oncologist), good performance status (ECOG 0–1) and administration of platinum-based chemotherapy is possible [30].

The GOG 213 is a phase 3 randomized controlled trial that will determine the impact of secondary CRS in addition to chemotherapy in recurrent platinum-sensitive ovarian, fallopian tube and primary peritoneal cancer patients (NCT00565851).

The results of these trials will be available only after a few years. Meanwhile, CRS continues to be incorporated into second-line therapy as there is strong evidence showing a survival benefit.

The issues that need to be dealt with while incorporating CRS into second-line therapy are:

- Criteria for selecting patients
- Role of CRS in patients with platinum-resistant/platinum-refractory disease
- Sequencing systemic chemotherapy with CRS, before or after

11.4.1.1 Selection of Patients

Selection of patients is important for attaining optimal results. Most studies report a favourable outcome in patients who recur more than 12 months after completion of first-line therapy and those who have complete/optimal cytoreduction [21–24, 31].

Other factors like a solitary site or limited number of sites of recurrence, complete response to first-line therapy and small maximum tumour diameter have also been associated with better survival outcomes [21–24, 31]. Only patients with minimal (<500 cc) or no ascites are subjected to surgery [32]. Women with symptomatic ascites, carcinomatosis, early relapse (i.e. less than 6 months) and poor general health are not likely to benefit from secondary CRS [33–35].

The AGO-DESKTOP study retrospectively analysed 267 patients who had undergone CRS for recurrent ovarian cancer and concluded that only those patients who had a complete CRS experienced a prolonged survival. A combination of performance status, early FIGO stage at the first surgery or no residual tumour after first surgery and absence of ascites could predict complete resection in 79% of patients. However, in patients with a negative score, a complete cytoreduction was achieved

in 58%. The authors proposed a two-step model—patients with a negative score should undergo a laparoscopic evaluation and those without carcinomatosis be taken up for secondary CRS. With this strategy, a complete cytoreduction was possible in 63% of the patients with a negative score [36]. The DESKTOP II study prospectively analysed the predictive value of three of these criteria also known as the AGO score (complete resection at first surgery, good performance status and absence of ascites) and found that when all three are met with, a complete cytoreduction can be achieved in 76% of the patients with a morbidity of 11% [37]. This score is the first prospectively validated instrument to positively predict surgical outcome in recurrent ovarian cancer. It can aid in the selection of patients who might benefit from secondary cytoreductive surgery. However, in a retrospective study of 192 patients, a large proportion of patients with a negative AGO score also had complete removal of macroscopic disease at the time of secondary CRS, and the authors concluded that a refinement in the score was needed to exclude women who were unlikely to benefit from surgery [38].

Once again, these criteria exclude a subgroup of patients who never had surgery by a gynecologic oncologist/surgical oncologist leading to residual/recurrent disease and could benefit from secondary CRS.

It is prudent to undertake only those patients for surgery in whom there is probability of achieving a complete CRS. The survival in patients undergoing incomplete cytoreduction is similar to those receiving chemotherapy alone. This makes it important for such treatment to be carried out at expert centres by surgeons experienced in performing such procedures.

Despite the large body of evidence in favour of secondary CRS, the selection criteria need to be more clearly defined.

11.4.1.2 Platinum-Resistant Disease

The platinum-resistant group includes patients who are platinum refractory (progression on chemotherapy or stable disease after first-line therapy) and those who are platinum resistant (recurrence within 6 months of complete response to first-line therapy).

For patients with platinum-refractory disease who have had an attempt at complete cytoreduction at an expert centre, the treatment is chemotherapy. However, if the primary cytoreduction was not performed by an expert surgical/gynaecologic oncologist, a secondary CRS can be attempted.

Most studies use recurrence within 6 months as an exclusion criteria for secondary CRS; hence, evidence to support the use of surgery in these patients is scarce. Moreover, patients are not stratified as platinum refractory and platinum resistant which makes it difficult to determine the exact benefit or the selection criteria.

In a retrospective review of 18 patients by Musella et al., the 5-year overall survival was significantly longer in CRS group (57%) when compared with the control group of patients who received only systemic therapy (23.5%; $p = 0.035$). However, the peritoneum was the site of relapse in only 33% of these patients [39]. In another study of six patients with isolated peritoneal relapse and isolated lymph nodal recurrence treated with secondary cytoreductive surgery, secondary CRS significantly prolonged median time to first progression (12 vs 3 months; p-value = 0.016), median time to second progression (8 vs 3 months; p-value = 0.037) and post-relapse survival (PRS) (32 vs 8 months; p-value = 0.002). Residual tumour at the first surgery (p = 0.017), the PFI ($p = 0.020$) and complete cytoreduction ($p = 0.039$) were the independent prognostic factors on multivariate analysis [16]. In selected patients with platinum-resistant disease, secondary CRS could be attempted after second-line chemotherapy provided a complete cytoreduction can be attained. Such procedures are performed in patients with a good performance status and after controlling the disease with systemic chemotherapy.

11.4.2 Detection of Recurrence

In patients who have had a complete remission, an elevated CA 125 level is usually the first indication of disease recurrence. Some of these patients may have no clinical symptoms (pelvic pain, bloating, obstruction) or evidence of dis-

ease on imaging studies. The tumour marker elevation usually precedes the clinical manifestation of recurrence. A patient with platinum-refractory disease may have persistent marker elevation after completion of frontline therapy and/or radiological evidence of residual disease.

According to the Gynecologic Cancer InterGroup definition, CA 125 progression is defined by a progressive serial increase in serum CA 125 level as follows: patients with pretreatment CA 125 elevation normalizing during or after therapy or patients with pretreatment normal CA 125 who show a CA 125 value of at least two times the upper limit of the normal level on two measurements taken at least 1 week apart [40]. Patients with increased pretreatment CA 125 who never normalize must have a CA 125 value of at least two times the nadir value on two measurements at least 1 week apart [40]. This definition is now used in many clinical trials, together with Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

11.4.3 Early Versus Delayed Treatment of Recurrence

Since recurrent ovarian cancer is not curable in most cases, the role of early treatment based on tumour marker elevation alone has been questioned. In a randomized trial (MRC OV05/EORTC 55955), 529 of the 1442 registered patients were randomized to either receive immediate chemotherapy or chemotherapy at clinical progression following a rise in CA 125 levels [41].

In all, 94% of the patients randomized to immediate treatment received salvage therapy versus 88% of the patients in the delayed treatment arm. The median time to starting salvage therapy was significantly shorter in the immediate treatment arm (0.8 vs 5.6 months; HR: 0.29; $p < 0.00001$). At a median follow-up of 49 months, no differences in survival were observed between the two groups (HR: 1.0; $p = 0.98$). However, the evaluation of quality of life, which is of paramount importance given the palliative role of second-line therapy for the majority of relapsing patients, showed that it was significantly better in the delayed treatment arm. Median time spent with a good global health score was 7.2 months in the early versus 9.2 months in the delayed treatment arm, and time from randomization to first deterioration in global health score or death was shorter in the early compared with delayed group (3.2 vs 5.8 months; $p = 0.002$). The authors concluded that there was no role of starting second-line therapy in asymptomatic patients based on a rise in CA 125 alone [41]. The limitations of this trial which would preclude the use of such a strategy in clinical practice are the use of nonuniform salvage therapy across the participating centres, the diversity in the study population in terms of the PFI, the role of secondary CRS that was not explored and, in particular, the differences between optimal and suboptimal primary CRS in the two arms that were not evaluated [40]. Some of the patients who have resectable recurrences and could benefit from early treatment may be denied the benefit if such a strategy is applied uniformly.

Tanner et al. retrospectively evaluated outcomes in 121 patients who had a complete clinical response after first-line therapy and developed recurrent disease [42]. Twenty two (18.2%) were diagnosed with a symptomatic recurrence. Though the median time to first recurrence was similar for asymptomatic and symptomatic patients (24.8 vs 22.6 months, $p = 0.36$), the post-recurrence survival was significantly longer in asymptomatic patients (45.0 vs 29.4 months, $p = 0.006$). Though secondary CRS was attempted equally in both groups (41% vs 32%, p = NS), the rate of complete CRS (optimal residual disease (<or = 5 mm)) was higher in patients with asymptomatic disease (90 vs 57%, $p = 0.053$). On multivariate analysis, detection of asymptomatic recurrence was a significant and independent predictor of improved overall survival ($p = 0.001$). Median OS was significantly greater for asymptomatic patients (71.9 vs 50.7 months, $p = 0.004$). This difference did not appear to be attributable to a discrepancy in the timing of diagnosis as a lead time bias would suggest, but, rather, to the location of these recurrences, to their earlier amenability to salvage chemotherapy and to more successful secondary CRS due to decreased volume of disease [42].

The authors pointed out several limitations in the study—small size, retrospective nature, and exclusion of a large number of patients during the study period due to either inadequate follow-up information or transfer of the patient care to another provider.

In another retrospective review by Gadducci et al., no difference in survival was observed in asymptomatic patients versus symptomatic patients although the rate of attempted secondary CRS (15%) was significantly lower than the current series. However, patients undergoing secondary CRS and chemotherapy experienced a significantly better overall survival than those who did not undergo surgery [43].

Thus, there seems to be a clear benefit of detection and early treatment of asymptomatic recurrence though it may need further evaluation in randomized trials.

11.4.4 Investigations: Evaluation of Disease Extent

11.4.4.1 CT Scan

The most commonly performed investigation is a contrast enhanced CT scan of the thorax, abdomen and pelvis [44]. The typical CT findings in recurrent ovarian cancer are similar to that of peritoneal metastases arising from other primary sites:

- Thickened peritoneum
- Ascites
- Pelvic mass
- Pelvic/retroperitoneal lymphadenopathy
- Bowel surface/mesenteric deposits
- Omental involvement
- Pelvic sidewall involvement and/or hydroureter
- Diaphragmatic involvement

A CT scan determines not only the extent of the disease but also the involvement of certain areas that would preclude a complete CRS—like involvement of the porta hepatis, extensive involvement of the small bowel/mesentery, extensive diaphragmatic involvement and upper abdominal lymphadenopathy (suprarenal) [44]. Several CT-based scores and algorithms have been developed to predict the probability of complete CRS in advanced ovarian cancer, and the same can be used to predict the probability in case of recurrent disease [45–47]. The sensitivity of CT for peritoneal tumours less than 1 cm was found to be only 25–50% compared with 85–95% for larger tumour deposits [48]. A CT scan has been shown to underestimate the extent of carcinomatosis in 33% of patients [49].

11.4.4.2 PET Scan/PET-CT Scan

Several studies demonstrated a benefit of fluorine-18-fluorodeoxyglucose positive emission tomography (FDG-PET) and FDG-PET/computed tomography (FDG-PET/CT) in the early detection of recurrent disease in ovarian cancer [50–53]. In a prospective multicentric study, Fulham et al. found a higher rate of detection of nodal, peritoneal and subcapsular liver disease as well as the total number of sites of disease with PET-CT as compared to CT [54]. They found that FDG-PET/CT altered the management in about 60% of the patients. In another study the accuracy of PET-CT for predicting optimal cytoreduction was found to be 78.6%. Like CT scan the main limitation is in the inability to detect small tumour nodules [55].

11.4.4.3 Staging Laparoscopy

Laparoscopy allows direct visualization of the peritoneal surfaces, the small bowel and its mesentery and can pick up small nodules that are missed on imaging. The disadvantages are its inability to evaluate retroperitoneal structures like the ureters and pancreas, the omental bursa near the celiac axis and the depth of involvement of the hepatic pedicle and the diaphragm [56]. Fagotti et al. evaluated the role of staging laparoscopy for selecting patients for secondary CRS. The negative predictive value, specificity, positive predictive value, sensitivity and accuracy rate of staging laparoscopy were 88.9, 64.0, 80.8, 95.0 and 83.1%, respectively [57]. A combined radiological (PET-CT) and laparoscopic evaluation showed a negative predictive value of 88.9%, a specificity of 59.3%, a positive predic-

tive value of 78.8%, a sensitivity of 95.3% and an accuracy rate of 81.4%. The authors suggested that a combination of these two modalities could optimize patient selection [57].

11.4.5 Surgical Strategies for Secondary Cytoreductive Surgery

The goal of secondary CRS should be to attain a complete/optimal cytoreduction. Many surgeons/institutions still use cut-offs of residual tumour measuring <0.5 or <1 cm as the criteria for optimal CRS though there is evidence that complete removal of macroscopic disease (completeness of cytoreduction score, 0, i.e. CC-0) results in superior outcomes as compared to leaving behind any amount of residual disease [15, 19, 27].

To attain a complete cytoreduction, a combination of peritonectomy procedures and visceral resections needs to be performed as for peritoneal metastases from other tumours [58]. The visceral resections include small and large bowel resection, cholecystectomy, partial gastrectomy, full-thickness diaphragm resection, splenectomy, distal pancreatectomy, partial ureteric resection, partial cystectomy and resection of pelvic sidewall [59–61]. A detailed description is provided elsewhere [62]. Such procedures have a survival benefit if complete CRS can be obtained [63]. Though the goal is complete removal of macroscopic disease, it should not impair the gastrointestinal and urinary function to the extent that the quality of life is significantly impaired. Extensive intestinal resections that impair digestion and nutrition and lead to dependence of parenteral nutrition (extensive small bowel resection with or without total gastrectomy or colectomy) should not be performed. Posterior pelvic exenteration is often necessary; however, the vesical trigone must be left intact because, in this context, a total cystectomy should never be performed [64].

If a pelvic and/or retroperitoneal lymphadenectomy was not performed during primary CRS, it should be performed irrespective of the presence or absence of nodal metastases in patients undergoing complete CRS. This is performed even in patients with no evidence of lymph node involvement on preoperative imaging. Nodal recurrence can be isolated or present with peritoneal disease [65, 66]. Retroperitoneal lymphadenectomy is performed till the level of the renal veins. There is a survival benefit of surgery for nodal recurrence even if it is bulky (>2 cm maximum diameter of the largest lymph node is considered bulky nodal disease) [67–69]. In case of disease involving the suprarenal nodes, lymphadenectomy can be performed in this region also if the disease is not bulky and limited [63].

Hepatic resection can be performed synchronously with secondary CRS for solitary or multiple parenchymal liver metastases. The goal of such resections should be to resect the liver lesions with a negative margin. Several retrospective studies have reported an acceptable morbidity and mortality for such combined resections [70]. The common prognostic factors reported in these studies were optimal CRS <1 cm residual disease, negative resection margins, disease-free interval >12 months, fewer number of liver metastases and fewer sites of disease. The surgical and oncological outcomes from various studies on resection of hepatic metastases in recurrent ovarian cancer are described in Table 11.3.

11.4.6 Minimally Invasive Secondary CRS

Several studies have reported the feasibility of a minimally invasive approach for secondary CRS [78–81]. These studies include patients with localized recurrence (1–3 nodules), good performance status and long platinum-free interval. The reported morbidity and mortality is similar to that of open surgery and conversion rates are low (Table 11.4). One series reported the use of loop electrosurgical excision and argon beam coagulator to ablate the metastases [79]. Such methods cannot replace a formal peritonectomy and/or resection of the viscera where indicated. Though there is no head to head comparison, it has been suggested that such an approach could shorten the postoperative recovery times, leading to a better psychological state and quality of life

Table 11.3 Surgical and oncological outcomes in patients undergoing secondary CRS with resection of liver metastases (adapted from reference [70])

Ref. no./year	No. of patients	Optimal CRS	Type of liver resection	Negative resection margins	OS (months)	Prognostic factors
[71] 2003	26	80.8%	Segmentectomy 69.2% Trisegmentectomy 3% Left hepatectomy 3.8% Right hepatectomy 15.4%	NA	26.3 optimal; CRS 27.3 suboptimal; CRS 8.6 ($p = 0.031$)	Residual disease, <1 vs >1 cm; DFI, <12 vs >12 months; distribution of disease, abdomen > pelvis or pelvis ≥ abdomen
[72] 2003	24	66.7	Wedge resection 12.5 Segmentectomy 70.9 Trisegmentectomy 8.3% Lobectomy 8.3%	54.1%	62 (95% CI, 41–83)	No significant prognostic factors found
[73] 2005	29	NA	NA	NA	Hepatic disease alone 25 (9–44); multi-organ recurrence 8 ($p = 0.033$)	Number of hepatic lesions; presence of other sites of disease; treatment with platinum-based chemotherapy
[74] 2008	10	100%	Bisegmentectomy 10% Trisegmentectomy 40% Lobectomy 50%	50%	33 (95% CI, 19–56)	Size of largest tumour ≥5 cm; negative resection margin ($p = 0.024$)
[75, 76] 2010	8	NA	Wedge resection 25% Segmentectomy 37.5% Sectorectomy 37.5%	NA	24	
[77] 2011	18	66.7%	Wedge resection 22.7% Segmentectomy 72.2% Bisegmentectomy 5.6%	66.7%	38 (3–78)	Distribution of disease: pelvis > abdomen or abdomen > pelvis; residual disease < or >1 cm; negative resection margins

[78]. The minimally invasive approach has an important limitation. A preoperative CT scan combined with a staging laparoscopy should be used to determine the extent of disease, though the extent of disease is usually underestimated. Moreover, the laparoscopic assessment is often limited by the presence of adhesions, and this should be kept in mind when taking up patients for such procedures.

11.4.7 Prognostic Factors

In a retrospective review of 153 patients with platinum-sensitive disease undergoing secondary cytoreductive surgery, Chi et al. reported that those with carcinomatosis had a poorer outcome compared to those patients with isolated disease or multiple nodules (<20) [15]. Similarly, patients recurring within 6–12

Table 11.4 Outcomes of minimally invasive surgical approach for secondary CRS (adapted from reference [78])

Ref. no./ year	No. of patients/ conversions	Recurrence	Surgical approach	Mean operating time (min)	Optimal CRS	Postoperative complications	Median disease-free survival (months)
[79] 2004	36 (2)	First	LPS	126	94%	2/34	13
[80] 2012	23 (1)	19 first	LPS	200	81.8%	1/22	71.9
		4 second					
[81] 2013	9 (0)	First	LPS robotic	177	88.9%	3/9	34.1
	10 (0)			220	70%	2/10	
[78] 2014	29 (2)	First	LPS	188	96.2%	1/27	14

LPS laparoscopic surgery, *CRS* cytoreductive surgery

months of completion of frontline therapy fared worse than those recurring from 13 to 30 months or >30 months [15]. It is important to have a reproducible quantification of the disease extent—the disease extent is one of the strongest prognostic factors determining the outcome of second-line surgical therapy—and having a uniform method of quantifying it enables comparison of treatment outcomes. The most commonly used score for this is the 'peritoneal cancer index' (PCI) developed by Paul Sugarbaker [19]. Other poor prognostic factors are mucinous or clear cell histology and more than one route of metastasis (e.g. peritoneal metastases with haematogenous or lymphatic spread) [15]. In a meta-analysis that included 2019 patients, Bristow et al. evaluated the impact of residual tumour size ranging from 0 to 2 cm on overall survival. The only statistically significant clinical variable independently associated with post-recurrence survival was the proportion of patients undergoing complete CRS ($p = 0.019$). When each study was analysed individually also, there was a survival benefit that was significant in patients who had complete CRS as compared to those who had any size of residual disease. The presence of any size of residual disease was associated with a greater risk of dying due to disease. After controlling for all other factors, each 10% increase in the proportion of patients undergoing complete CRS was associated with a 3.0-month increase in median cohort survival time [27].

11.4.8 Systemic Chemotherapy in Addition to Secondary Cytoreductive Surgery

The role of systemic chemotherapy in addition to secondary CRS has not been evaluated. Most studies have used systemic chemotherapy either before or after secondary CRS. All ongoing clinical trials have incorporated chemotherapy in the surgical arm as well. Though the best treatment strategy for such patients is not known, a logical approach is as follows. In patients with disease resectable upfront, secondary surgery could be performed first followed by chemotherapy. It is important in such cases that postoperative chemotherapy is not delayed due to complications. In patients who recur within 6 months of first-line therapy or have disease not amenable to a complete cytoreduction, second-line chemotherapy can be administered before secondary/salvage CRS.

11.5 Rational for Intraperitoneal Chemotherapy for Recurrent Ovarian Cancer

Recurrent ovarian cancer remains confined to the peritoneal cavity for prolonged periods which is the basis of using intraperitoneal chemotherapy as part of locoregional therapy. Intraperitoneal (IP) drug therapy offers the potential to increase the therapeutic index by enhanced local drug concentration and at the same time limiting systemic absorption and toxicity [82]. It exposes the

poorly vascularized tumour tissue to high concentrations of cytotoxic agents. The efficacy of IP drug therapy depends on the extent of drug penetration in tumour tissue, which is driven by diffusion and convection [82]. Obstacles to drug transport include elevated interstitial fluid pressure and the density of the interstitial matrix which are characteristic of tumour stroma [82]. In optimally resected stage III ovarian cancer, large randomized trials have shown that the addition of IP chemotherapy to adjuvant regimens significantly improved survival [83–86]. This type of chemotherapy is repeatedly administered through an implanted catheter and access port. Adverse events and catheter-related problems were more common in the IP chemotherapy group and often led to discontinuation of therapy [87, 88]. IP chemotherapy can be administered by direct abdominal wall puncture as well [89]. Benedetti-Panici reported the use of ultrasound-guided direct puncture and administration of chemotherapy in 38 patients with recurrent ovarian cancer. A total of 402 IP procedures were performed, with a mean of 10.5 procedures per patient. The feasibility rate was 97.4% [90]. In a retrospective study of 33 patients, Nicoletto et al. used IP chemotherapy administered in this manner for recurrent ovarian cancer [91]. This treatment was used as an alternative to systemic chemotherapy in patients who had received multiple lines of chemotherapy and no CRS was performed. IP cisplatin was administered on day 1 and paclitaxel on day 8 every 21–28 days for a total of 3–4 cycles. Twenty-seven patients had ascites and 14 patients had peritoneal carcinomatosis only. Fourteen (51.8%) out of 27 patients had a clinical response, with disappearance or significant reduction of ascites for more than 45 days after IP chemotherapy. These patients were compared to matched controls who received only systemic chemotherapy. In patients with less than three previous lines of treatment, IP chemotherapy conferred a survival advantage of about 2.2 months (IP = 10.0 vs IV = 7.8 months, $p = 0.011$). However, the survival advantage in heavily pretreated patients (with three or more previous treatments) was not significant [91]. There is not much evidence for this type of intraperitoneal chemotherapy in recurrent ovarian cancer. Hyperthermic intraperitoneal chemotherapy (HIPEC) is more commonly used in combination with CRS for recurrent ovarian cancer.

11.6 Rationale for Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The rationale for using HIPEC as part of second-line therapy for ovarian cancer is the same as that for CRS—recurrent ovarian cancer remains confined to the peritoneal cavity for a prolonged period. This is further supported by the benefit CRS and HIPEC have shown in the treatment of gastrointestinal peritoneal metastases. CRS and HIPEC are now the standard of care of pseudomyxoma peritonei and peritoneal mesothelioma and for colorectal peritoneal metastases with a limited peritoneal spread [92–95]. It is still the only treatment modality that has shown to prolong survival in patients with peritoneal metastases from gastric cancer [96, 97].

HIPEC is administered immediately after CRS which reduces tumour cell entrapment that is common after surgery. HIPEC has the added advantage of using heat which itself is cytotoxic to cancer cells and enhances the cytotoxicity of various chemotherapeutic drugs like platinum compounds, alkylating agents, mitomycin C and doxorubicin that is enhanced by hyperthermia [98–101]. Hyperthermia enhances tissue perfusion and oxygenation and may improve drug penetration [102].

11.7 HIPEC Methodology and Drugs

HIPEC can be performed by the open (coliseum) or closed technique maintaining an intra-abdominal temperature of 41–43° C throughout the procedure. HIPEC is performed only in those patients in whom complete cytoreduction is attained (CC-0 or CC-1) since the treatment is ineffective on residual disease more than 2–3 mm

in size [103]. Any drug that is used for HIPEC should be retained in the peritoneal cavity with a limited systemic absorption [104].

One of the most commonly used drugs in this setting is cisplatin. Cisplatin is a drug that is retained in the peritoneal cavity, and its penetration into the adjacent tissues is potentiated by heat in both platinum-sensitive and platinum-resistant cell lines [105].

Hyperthermia can modify the cellular resistance to cisplatin as demonstrated by Hettinga et al. [106]. Relatively high doses of heat 43° for 60 min can interfere with cisplatin resistance by several mechanisms like drug penetration, adduct formation and repair [105]. These are further elaborated in Table 11.5. Hyperthermia can increase the cytotoxicity of cisplatin in both platinum-sensitive and platinum-resistant cell lines [107].

Van de Vaart et al. showed that cisplatin in combination with hyperthermia in vitro leads to a higher cisplatin ± DNA adduct formation which was a good predictor of the cytotoxic effect. The level of cisplatin-DNA adduct formation which is needed for a cytotoxic effect was observed in tumour nodules up to a depth of 5 mm. Hence, the effect HIPEC is useful for patients who are cytoreduced to minimal residual disease (CC-0/1) [108].

The ideal dose of cisplatin has been evaluated in the CHIPASTIN trial. This phase 1–2 escalating dose trial established that 70 mg/m^2 of cisplatin for 1 h at 42 °C was the most appropriate protocol [109]. However, another phase 1 study concluded that a 100 mg/m^2 dose of cisplatin for HIPEC in recurrent platinum-sensitive ovarian cancer has an acceptable safety profile [110].

Table 11.5 Cellular effect of hyperthermia related to cytotoxicity of cisplatin [107]

Effect of hyperthermia	Resistance mechanism that could be affected
Increase in membrane fluidity	Cisplatin accumulation
Membrane protein denaturation	Cisplatin accumulation
Cytoplasmic protein denaturation	Detoxification
Altered DNA conformation	DNA accessibility
Inhibition of DNA repair	Repair of cisplatin-DNA adducts
Disturbance of normal cellular functions	Altered signal transduction and others
Gene expression, signalling	Response of cells to cisplatin-DNA damage

Oxaliplatin that is commonly used for HIPEC in colorectal and appendiceal tumours has been used in recurrent ovarian cancer as well [111–113]. There is no direct comparison of oxaliplatin with platinum agents or taxols though preclinical data have shown a role in recurrent and platinum-resistant ovarian cancer [114]. Oxaliplatin has only moderate cross-resistance with cisplatin or carboplatin [115].

Carboplatin has a favourable toxicity profile compared to cisplatin and has replaced it in many of the intravenous regimens [102]. When nephrotoxicity is a concern, it can be administered in full dose for HIPEC as opposed to cisplatin which requires a dose reduction [116]. When a high dose of carboplatin is used for HIPEC, the drug concentration achieved in the tumour tissue is similar or superior to that achieved by an equitoxic dose of cisplatin [117]. Carboplatin undergoes hyperthermic enhancement of cytotoxicity and has been shown to have a more homogenous distribution of platinum as compared to cisplatin [117, 118]. Phase 1 trials for HIPEC as first-line and second-line therapy found that carboplatin doses up to 800–1000 mg/m^2 were tolerable and did not preclude additional systemic therapy [119–121]. The duration of treatment is 90 min.

Paclitaxel (175 mg/m^2) alone or in combination with cisplatin (100 mg/m^2) at 41–43° C for 90 min has been used by some investigators for HIPEC in patients with platinum-sensitive recurrent ovarian cancer [122, 123]. The morbidity was acceptable and the drugs achieved high concentrations in the peritoneal tissue with low systemic absorption. The tissue penetration of paclitaxel was only 0.5 mm, compared to 2–3 mm for cisplatin [122, 124, 125]. The numbers in these studies are small, and further evaluation of toxicity and efficacy of such a regimen is needed. Unlike cisplatin, hyperthermia does not augment the cytotoxicity of paclitaxel [126].

Table 11.6 Various drug regimens for HIPEC in recurrent ovarian cancer

Regimen	IP drugs	IV drugs	Carrier solution	Duration
Sugarbaker regimen [136]	Cisplatin (50 mg/m^2)	Ifosfamide 1300 mg/m^2	Peritoneal dialysis solution	90 min
	Adriamycin (15 mg/m^2)	Mesna 260 mg/m^2		
National Cancer Institute Milan regimen [137]	Doxorubicin 15.25 mg/L, cisplatin 43 mg/L			90 min
Sugarbaker gemcitabine-based regimen for platinum-resistant ovarian cancer [138]	Gemcitabine 1000 mg/m^2		Peritoneal dialysis solution	90 min
Sugarbaker melphalan-based regimen for platinum-resistant ovarian cancer [127]	Melphalan 50–70 mg/m^2		Peritoneal dialysis solution	90 min
Sugarbaker liposomal doxorubicin-based regimen for platinum-resistant ovarian cancer	Liposomal doxorubicin 50–100 mg/m^2		Peritoneal dialysis solution	180 min

Melphalan has been used for HIPEC in patients with recurrent tumours arising from various primary sites including recurrent and platinum-resistant ovarian cancer [127, 128]. The use of melphalan has been prompted by responses produced in regional chemoperfusion in soft tissue sarcomas and extremity melanomas [129, 130]. Melphalan undergoes cytotoxic enhancement with hyperthermia and has a favourable peritoneal fluid to plasma ratio [131–134]. Bijelic et al. first reported the use of 50–70 mg/m^2 of melphalan at 41–43° C for 60–90 min in 34 patients [127]. The grade 3–4 morbidity was 43% and there was no mortality in this series. They recommended the use of 60 mg/m^2 for 60 min for future evaluation of the role of melphalan.

The other agents that have been used are mitomycin C, doxorubicin, gemcitabine and irinotecan.

There is no study that has performed a head to head comparison between various agents/regimens.

Helm et al. analysed the effect of chemotherapy agents on survival in relation to the time point at which they were used. In patients with platinum-sensitive recurrence, the OS was superior with carboplatin as compared to cisplatin ($p = 0.012$) and mitomycin ($p = 0.011$), but there was no significant difference between agents in platinum-resistant disease. However, the numbers in the carboplatin group were small [135].

Some of the common regimens for HIPEC are listed in Table 11.6.

11.8 Evidence for HIPEC in Recurrent Ovarian Cancer

Salvage CRS and HIPEC is performed in patients who have recurred after an initial complete response to first-line therapy, and secondary CRS and HIPEC is performed in patients who have had an incomplete CRS with chemotherapy resulting in a partial response or stable disease [139]. Investigators have compared outcomes in patients who received HIPEC during secondary CRS with those who only received SCS and postoperative chemotherapy and those who only received IV chemotherapy without SCS [140]. Most of the available evidence comes from retrospective single and multi-institutional studies (Table 11.7). These studies have reported a median DFS ranging from 10 to 7 months, median OS ranging from 24 to 51 months and a 5 year OS ranging from 15 to 63%.

Petrillo et al. in a study of 70 patients treated with secondary CRS and HIPEC reported a longer second remission than the first in 52% of the patients. This is higher than that reported by most chemotherapy trials in a similar patient population as the second and subsequent remissions are usually shorter than the first [159, 160]. In a French

Table 11.7 CRS and HIPEC as second-line therapy for ovarian cancer (Adapted from reference [141] with permission)

Ref no./year	Type of study	N	PS/PR	Method	Drug(s)	Median PCI	CC-0/1	Median DFS (months)	Median OS (months)	3-year OS	5-year OS
[142] 2000	Pilot	5	+/−		Cisplatin			3	16		
[143] 2004	SI Pros	30	+/−		Cisplatin		77%	17.1 [CC-0: 24.4]	28.1 [CC-0: 37.8]		
[144] 2004	SI Pros	11	+/−		Cisplatin/mitoxantrone		50%		30 ± 6		15%
[145] 2006	SI Pros	14	+/−		Paclitaxel						63%
[146] 2007	SI Pros	81	+/+	Closed	Cisplatin		55.5%	19.2 [CC-0: 26.9]	28.4 [CC-0: 54.9]		
[147] 2008	SI Pro	18	+/−	Closed	Cisplatin	14.9	87.3		24		16.7%
[148] 2009	SI Pros	25	+/−		Doxorubicin	13.4	92.8%	26.2	40		
[112] 2009	SI Pros	42	+/−		Cisplatin		77%	13	37		
					Oxaliplatin						
[149] 2010	SI Pros	10	+/−		Oxaliplatin	6	100%	10		83%	
[150] 2010	SI Pros	8	+/−	Closed	Cisplatin and mitomycin		70%				55%
[135] 2010	MI Pros	83	+/+	Open/closed	Platinum/mitomycin/combination				30.43		25.4%
[151] 2011	SI Pros	31	+/−				65%	13.3			
[113] 2011	Pilot	12	+/−		Oxaliplatin		100%	14.3			

(continued)

Table 11.7 (continued)

Ref no./year	Type of study	N	PS/PR	Method	Drug(s)	Median PCI	CC-0/1	Median DFS (months)	Median OS (months)	3-year OS	5-year OS
[152] 2012	MI Retro	474	+/+	Open/closed	Cisplatin	10.6	92.1%		45.7	59%	37%
					Oxaliplatin						
					Mitomycin						
					Doxorubicin						
					Cisplatin+						
					Doxorubicin						
					Cisplatin+						
					Mitomycin						
[153] 2014	SI Retro	90	+/+	Open	Cisplatin		69%		35.0		
[154] 2014	SI Retro	25	+/−	Closed	Cisplatin + lipodox Paclitaxel + lipodox	12.63	88%	27	11.9		
[155] 2015	SI Pros	54	+/+	Open/closed	Cisplatin+	10	100%	12.4	32.9		
					Paclitaxel						
[156] 2015	SI Pros	23	+/−	Closed	Mitomycin Cisplatin		76%				
					Oxaliplatin						
					Carboplatin						
[157] 2015	MI Retro	70	+/−	Closed	Cisplatin	7	88%	27			52.8%
					Oxaliplatin						44.7% (7 years)
[9] 2015	MI Retro	314	+/+	Open/closed	Cisplatin [114]	7	79% (CC-0)	13 (PS) 14 (PR)	42 (PS) 51 (PR)		38%
					Other agents						
[158] 2016	MI Retro	24	+/−	Closed	Cisplatin, carboplatin, oxaliplatin, doxorubicin, combination						

SI single institution, *MI* multi-institutional, *Pros* prospective, *Retro* retrospective, *PS* platinum sensitive, *PR* platinum resistant, *DFS* disease-free survival, *OS* overall survival

retrospective multicentric study of 474 patients, the median OS was 45.7 months, and in patients who had complete CRS, it was 47.2 months in patients with platinum-sensitive disease and 51.6 months in those with platinum-resistant disease [152]. This difference was not statistically significant and showed that patients with platinum-resistant disease could have a survival similar to those with platinum-sensitive disease (Fig. 11.1).

A PCI of >8 was found to be a significant factor affecting both disease-free and overall survival. The patients in this series included those with second and third recurrences as well. In 2015, the same group published the outcomes of secondary CRS and HIPEC in patients with first recurrence comprising of 314 patients from 13 institutions [9]. The CRS performed during first-line therapy was complete in 33.8% (101/314) patients, there was macroscopic residual disease in 66.2% (98/314) patients and this information was unknown for 15 patients. Treatment strategy was secondary chemotherapy followed by secondary surgery and HIPEC for 85.6% (269/314) of patients; the remaining patients were treated with secondary surgery and HIPEC before secondary chemotherapy. At a median follow-up of 50 months, the 5-year overall survival was 38.0%, with no difference between platinum-sensitive ($n = 148$) and platinum-resistant ($n = 161$) patients, and 5-year disease-free survival was 14%. Considering patients treated with second-line chemotherapy followed by secondary surgery and HIPEC, patients who had a pathological complete response to chemotherapy experienced a better DFS and OS both (Fig. 11.2). Median OS was not

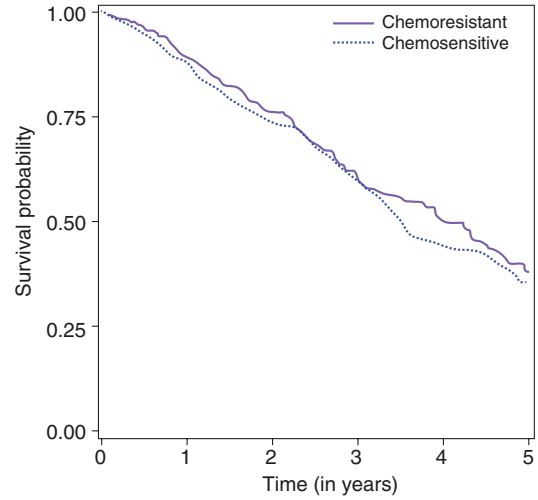

Fig. 11.1 Overall survival in platinum-sensitive (chemosensitive) and platinum-resistant (chemoresistant) recurrent epithelial ovarian cancer treated with cytoreductive surgery and HIPEC (log rank p-value = 0.799) (From ref. [152] with permission)

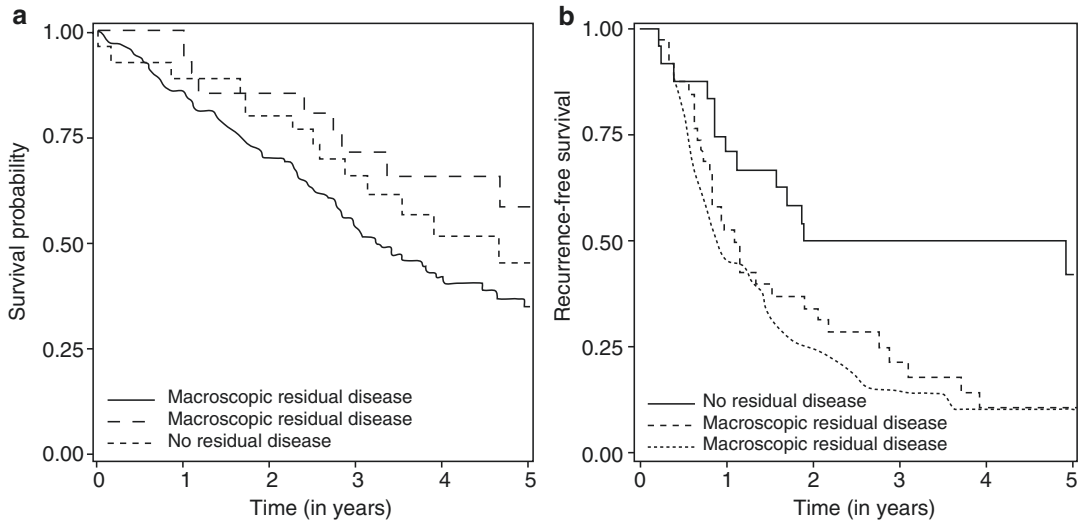

Fig. 11.2 Overall (**a**) and disease-free survival (**b**) according to pathological residual disease at the time of secondary CRS and HIPEC (From ref. [9] with permission)

reached for patients with no pathological residual disease, while for patients with microscopic residual disease it was 56 months and for patients with a macroscopic residual disease 39 months ($p = 0.073$). The median DFS was 41 months for patients with no pathological residual disease, 13 months for patients with microscopic residual disease and 10 months for those with a macroscopic residual disease ($p = 0.0019$). The residual disease distribution was similar in the platinum-sensitive and platinum-resistant cases [9].

Four other studies treated patients with platinum-resistant disease with CRS and HIPEC, two of these did not report the outcomes in patients with platinum-resistant disease separately. In a single institution series of 81 patients, the OS and DFS in patients with platinum-sensitive and platinum-resistant disease were similar. However, 58% of the patients had more than two disease recurrences and more than two surgical explorations leading to an inaccurate assessment of the PFI [146]. In another multi-institutional series of 83 patients, those with platinum-sensitive recurrence experienced a significantly better OS compared to patients with platinum-resistant disease [135]. However, patients with advanced and recurrent ovarian cancer were pooled together in this analysis due to which the impact of secondary CRS and HIPEC in platinum-resistant disease cannot be determined from this series.

In a meta-analysis of 9 comparative and 28 other studies evaluating the role of CRS and HIPEC in advanced and recurrent ovarian cancer, CRS and HIPEC with systemic chemotherapy appeared to significantly improve 1- and 3-year overall survival compared with CRS + chemotherapy alone (OR 3.48, 95% CI 1.44–8.44, $p = 0.006$; OR 7.39, 95% CI 2.29–23.86, $p < 0.001$, respectively). However, the 2-, 4- and 5-year overall survival benefit was not statistically significant (OR 2.84, 95% CI 1.01–7.89, $p = 0.05$; OR 2.82, 95% CI 0.71–11.2, $p = 0.14$; OR 2.37, 95% CI 0.4–14.12, $p = 0.34$, respectively) [161]. The first published randomized controlled trial for HIPEC in recurrent ovarian cancer randomized 120 women undergoing secondary CRS to receive HIPEC or not. They included both platinum-sensitive and platinum-resistant cases, using cisplatin and paclitaxel for the platinum-sensitive patients and a doxorubicin/paclitaxel regimen for the platinum-resistant cohort. The OS for the HIPEC group was significantly longer than that of the control group (26.7 vs 13.4 months). Patients with a complete cytoreduction experienced a better survival compared to those with residual disease, and a PCI > 15 had a negative impact on survival. There was no difference in the OS in patients with platinum-sensitive and platinum-resistant disease. Chi et al. pointed out several weaknesses in the reporting of this trial—lack of information on the DFS, median follow-up, postoperative first-line treatment and complication rates [140].

Several case-control studies have compared secondary CRS and HIPEC with CRS alone [123, 162–166]. In four of these, there was a statistically significant benefit of CRS and HIPEC over CRS alone. These studies are listed in Table 11.8. One case-control study showed a sur-

Table 11.8 Case-control studies comparing CRS and HIPEC with CRS alone as second-line therapy

Ref. no.	Year of publication	Type of recurrence	N	CRS+ HIPEC	CRS	Survival for CRS+ HIPEC	Survival for CRS alone	*p* Value
[162]	2009		26	14	12	58% (5 yrs OS)	17 (5 yrs OS)	0.011
[163]	2011		48	24	24	50% (3 yrs OS)	18% (3 yrs OS)	<0.01
[164]	2012	PS	67	30	37	68% (5 yrs OS)	42% (5 yrs OS)	0.017
[167]	2014	PS	111	27	81	79 M (median OS)	45 M (median OS)	0.016
[123]	2014	PS	54	32	22	45 (3 yrs DFS)	23 (3 yrs DFS)	0.078
[165]	2014	PS	42	23	19	75.6% (4 yr OS)	19.4% (4 yr OS)	0.013
[166]	2016	PS	79	29	50	59.3 M (median OS)	58.3 M (median OS)	0.95

PS platinum sensitive, *DFS* disease-free survival, *OS* overall survival, *M* months, *yrs* years

vival benefit of secondary CRS and HIPEC over systemic chemotherapy alone in patients with platinum-sensitive recurrence [167]. Most of these studies have a small number of patients.

Thus, CRS and HIPEC appear to be a beneficial option for patients with recurrent ovarian cancer where currently there is no standard therapy. Though there are case-control studies demonstrating its benefit over CRS alone, the numbers in these studies are small, and further evaluation is needed in randomized controlled trials. Selecting patients is the key—patients with a limited PCI derive the maximum benefit from this procedure [152]. Other important variables are the completeness of cytoreduction and time to recurrence.

11.9 Clinical Trials Evaluating the Role of HIPEC in Recurrent Ovarian Cancer

Four clinical trials are underway to evaluate the role of HIPEC in recurrent ovarian cancer (Table 11.9). The HORSE trial (NCT01539785)—CRS with or without HIPEC in Ovarian cancer recurrence—is underway in Italy and is expected to complete accrual in 2018. Patients with platinum-sensitive ovarian cancer (PFI > 6 months) are randomized to secondary CRS with or without HIPEC followed by systemic chemotherapy in both arms. The primary end point is progression-free survival, and the secondary end points are post-recurrence overall survival, quality of life, morbidity and mortality and pattern of recurrence. Patients will be stratified according to PCI and PFI. HIPEC is expected to result in a >6 months benefit in the PFI. A similar trial CHIPOR (NCT01376752) is underway in Europe. At the first recurrence (PFI > 6 months), all patient receive three cycles of second-line chemotherapy followed by CRS with or without HIPEC. HIPEC is performed by the open or closed method using 75 mg/m^2 of cisplatin for 60 min. The primary end point is overall survival (HIPEC should provide a 12-month benefit in overall survival), and the secondary objectives are improvement in DFS post-recurrence, morbidity and mortality, quality of life and cost-effectiveness. In addition, the pathological response to chemotherapy will be assessed, and a pharmacokinetic study comparing the open and closed methods will be performed. A similar phase 2 multi-institutional trial is being carried out in the United States using HIPEC with carboplatin for 90 min. The primary end point is progression-free survival. The fourth trial is being carried out at the Loma Linda University in the United States (NCT02672098). This is a phase 1 prospective study with the primary objective of comparing the efficacy and safety of CRS and HIPEC in treatment of recurrent ovarian, primary peritoneal or fallopian tube cancers. All patients with residual disease ≤2.5 mm after CRS will receive HIPEC for 90 min with carboplatin (800 mg/m^2) using the closed abdomen technique. The primary objective is progression-free survival. Historical controls will be used for comparison.

Table 11.9 Ongoing clinical trials evaluating the role of HIPEC in recurrent ovarian, fallopian tube and primary peritoneal cancer

ClinicalTrials.gov ID	Phase	Type of recurrence	Primary Institution/Group	HIPEC drugs	Control arm	Experimental arm
NCT01539785 (HORSE/MITO 18)	3	PS	Catholic University of the Sacred Heart, Italy	Cisplatin	CRS+ SC	CRS+ HIPEC+ SC
NCT01376752 (CHIPOR)	3	PS	UNICANCER Europe	Cisplatin	SC+CRS	SC+CRS+HIPEC
NCT02672098	1	PS	Loma Linda University Cancer Center, US	Carboplatin		CRS+ HIPEC+ SC
NCT01767675	2	PS	Memorial Sloan Kettering Cancer Centre + others, US	Carboplatin	CRS+ SC	CRS+ HIPEC+ SC

PS platinum sensitive, *SC* systemic chemotherapy

Most of these trials are lagging behind in recruiting the expected number of patients over a given time period. The probable reasons for this as mentioned by the investigators are patients wanting treatment with HIPEC and to not undergo randomization and physician preference for newer systemic therapies instead of HIPEC. None of these trials evaluate the role of CRS and HIPEC in platinum-resistant patients.

These trials will help in clarifying the role of HIPEC in recurrent ovarian cancer. The drug regimens used have been validated in phase 1–2 trials [109, 110, 168]. However, given the multitude of regimens in use in clinical practice and in absence of a head to head comparison, future evaluation will continue to determine the best drugs and protocols.

Preclinical studies provide a strong basis for applying this therapy in clinical practice [169]. HIPEC in addition to secondary CRS has shown promising results in the data available so far. The challenge is to optimize HIPEC methodology and drug regimens and integrate CRS and HIPEC with systemic therapies to provide a meaningful benefit of this treatment to patients—in terms of survival, cost-effectiveness and quality of life.

11.10 Morbidity and Mortality

Reported mortality rates of secondary CRS and HIPEC range from 0 to 4.2%. Large series have reported a major morbidity (grade 3–4 complications) in 30–34.8% and a reoperation rate of 8% [9, 152, 157]. The meta-analysis by Huo et al. reported a pooled median 30-day post-HIPEC mortality rate in 1.8% (range, 0–13.6%) and major (grade 3–4) morbidities in 26.2% (1.8–55.6%) of the patients. The pooled rate of minor (grade 1–2) morbidities was 27.5% (16–60.2%) [161]. These reports are similar to the morbidity and mortality rates reported in patients undergoing CRS alone for advanced ovarian cancer [18, 170]. Major complications include anastomotic leakage, bowel perforation, intraperitoneal haemorrhage, acute renal failure and wound dehiscence. Complication specific to the administration of chemotherapy is neutropenia which is caused by systemic absorption of the drug. Over the years there has been a decline in the morbidity and mortality from this procedure which is due to the increase in experience of high volume centres [171]. In these expert centres, the reduction in mortality is not just due to lower complication rates but also due to their ability to rescue patients with complications [172]. Morbidity and mortality should no longer preclude the use of this treatment where it is indicated.

11.11 Management of Subsequent Recurrences

Recurrent ovarian cancer that has been rendered disease-free after second-line therapy will recur in almost all cases. Ovarian cancer can be considered a chronic disease with majority of the patients developing multiple recurrences that can be induced into a remission with surgery and or chemotherapy [173]. The second, third and subsequent recurrences have been treated with a combination of CRS with or without HIPEC and systemic chemotherapy. In one of the first reports on tertiary CRS, Leitao et al. reported a median disease-specific survival (DSS) of 34.4 months (range 20.4–46.4 months) in 26 patients. The outcome was better in patients who had optimal cytoreduction (residual disease <0.5 cm) and a long disease-free interval >12 months (median DSS-60 months). Patients with platinum-resistant disease also experience a prolonged survival after optimal CRS [173]. In another series of 77 patients, the same authors reported a median DSS of 47.7 months [174]. Residual disease after surgery remained the only independent prognostic factor. The survival in both these series was similar to that reported for secondary CRS and was superior to that reported with chemotherapy alone [173, 174]. Similar results have been reported by other investigators [175, 176]. In another series of 159 patients, the platinum-free interval after second-line therapy, presence of mesenteric lymph node metastases at secondary CRS and tertiary CRS (as opposed to systemic chemotherapy) were predictors of survival [177]. However, the strongest predictor of survival was complete tumour removal, and patients with residual disease had a survival similar to those receiving chemotherapy alone. Patients with

ascites and disease and recurrence outside the pelvis have a poor outcome [177, 178].

HIPEC has been used along with tertiary and subsequent cytoreductive procedures. Most of these studies have a mixture of patients with first, second and subsequent relapses, and its role in third- and fourth-line therapy has not been evaluated separately [112, 146, 152].

Cytoreductive surgery with or without HIPEC can provide a survival benefit in selected patients with recurrence after second-line therapy. There are no randomized trials comparing surgical treatment with chemotherapy.

Conclusion

Recurrent ovarian cancer is a chronic disease. Secondary/salvage cytoreductive surgery can be considered the standard of care for first recurrence in platinum-sensitive disease though the results of randomized controlled trials are awaited. Early detection and treatment of recurrence has a survival benefit. HIPEC in addition to CRS and systemic chemotherapy has shown promising results in retrospective and case-control studies in both platinum-sensitive and platinum-resistant disease and has acceptable rates of morbidity and mortality. The results of randomized controlled trials are awaited which will clarify its role in this situation. The patient selection for CRS and HIPEC, drugs and protocols need standardization. An optimization of clinical strategies is needed to provide the maximal benefit of CRS and HIPEC to patients—in terms of survival, cost-effectiveness and quality of life. Such treatment requires multidisciplinary management and should be carried out at expert centres.

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12 Multimodality Treatment for Colorectal Peritoneal Metastases

Aditi Bhatt, Sanket Mehta, and François Quénet

12.1 Introduction

Peritoneal metastases (PM) of colorectal cancer are present in 5–10% of patients at the time of presentation for primary cancer treatment and in about 15–30% of patients with recurrent disease [1–3]. About 4–8% of these present with isolated peritoneal metastases with no evidence of other visceral metastases [4]. Though PM have poorer prognosis than other sites of metastases like the liver, over the past two decades the use of an aggressive locoregional strategy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has shown a significant benefit in overall survival as compared to systemic chemotherapy alone in selected patients. The role of HIPEC is currently being evaluated in randomized controlled trials (PRODIGE 7-ACCORD 15 trial (NCT00769405)). Moreover, the patients who are candidates for such treatment are a small percentage of all patients with colorectal PM (CPM). Newer treatment strategies are being investigated to improve the outcomes in other patients. Since the patients who benefit most from such treatment are those with limited disease, the focus has been on more proactive approaches for prevention and early detection of colorectal PM (CPM). This chapter provides an approach to management of patients with CPM based on the current evidence and an update on the ongoing research in this field.

12.1.1 Approach to a Patient with CPM

Management of CPM requires a multidisciplinary team and is best carried out in centers experienced in delivering this form of treatment.

12.2 Pathophysiology of Peritoneal Dissemination

Understanding the disease biology forms the basis of treating CPM. The most common mechanism of dissemination of peritoneal metastases is by direct extension of the primary malignancy into the free peritoneal space. This can occur due to full-thickness involvement of the bowel wall (local peritoneal involvement) or due to spillage caused during surgery [5]. Once a viable, free cancer cell is present in the peritoneal cavity,

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adhesion to the peritoneal surface is required in order to ultimately invade the peritoneum, proliferate, and produce peritoneal deposits. In the postoperative period, production of reactive oxygen species and inflammatory cytokines leads to upregulation of specific cell surface adhesion molecules leading to increased adhesiveness of cancer cells. Surgical trauma caused to the peritoneum is also known to increase the adhesiveness and metastatic potential of free intraperitoneal cells [6]. This creates a milieu that favors the development of PM. The adhesion molecules that have been implicated in this process are CD44, integrin α2β1, and mucin 16 (MUC 16) [7].

In cases of full-thickness involvement of the bowel wall, PM are seen in the vicinity of the primary malignancy, layered out under the right hemidiaphragm or involving the pelvic peritoneum. Despite the fact that PM are present, cytological study of the peritoneal fluid is often negative. In women, a frequent site of the progression of peritoneal metastases is the ovaries, especially in the premenopausal women [8].

The most common site of metastatic spread from colorectal primary tumors is the liver. However, liver metastases have a more protracted course as compared to CPM which are more aggressive; Sugarbaker pointed out several differences in the biology of CPM and colorectal liver metastases (Table 12.1). Liver metastases arise as a result of portal dissemination and have a lower metastatic potential as compared to PM which spread more rapidly.

Franko et al. analyzed individual patient data for previously untreated patients enrolled in 14 phase III randomized trials done between 1997 and 2008. This analysis concluded that patients with colorectal PM have a significantly shorter overall survival than those with other isolated sites of metastases. In patients with several sites of metastasis, poor survival is a function of both increased number of metastatic sites and peritoneal involvement. The pattern of metastasis and, in particular, peritoneal involvement results in prognostic heterogeneity of metastatic colorectal cancer [9].

Table 12.1 Comparison and contrast of liver metastases with peritoneal metastases from colorectal cancer [Adapted with permission from Ref. 8]

	Liver metastases	Peritoneal metastases
Mechanism of dissemination	Portal vein	Peritoneal space
Mode of progression	Expansion of a parenchymal mass	Exfoliation
Metastatic efficiency	Low	High
Incidence with primary resection	20%	10%
Incidence with diagnosis of recurrence	50%	60%
Response to modern systemic chemotherapy	60%	30%
Benefit from reoperative surgery requires R-0 resection	Yes	Yes
Preventive strategies in existence	No	Yes

Apart from full-thickness bowel wall involvement which is associated with PM in 50% of the cases, the risk of metachronous PM in patients with mucinous or signet ring cell carcinoma is 11–36% and 9–36% in patients with a positive peritoneal cytology [10–13]. Mucinous histology is associated with a poorer overall and disease-free survival regardless of the presence of peritoneal dissemination.

Honore et al. performed a systematic review of the literature that included 16 clinical studies, all nonrandomized, 3 prospective and 13 retrospective, including 4395 patients. There were three situations that could result in a real higher risk of recurrent PM: synchronous PM, synchronous isolated ovarian metastases, and a perforated primary tumor [14]. The risk was similar in patients with spontaneous and iatrogenic tumor rupture.

Patients with BRAF mutation have a higher risk of developing PM though the prognosis of patients of CPM with or without this mutation is similar [15].

12.3 Clinical Presentation

Early peritoneal dissemination does not produce any symptoms. Symptoms occur when the disease is advanced and are usually nonspecific [16, 17]. Ascites is seen at presentation in 28–30% of the patients with synchronous metastases and small bowel obstruction in 8–20% of the patients [3]. Hence, the use of imaging studies and diagnostic laparoscopy should be made in patients with a high risk for peritoneal dissemination to detect it early.

12.3.1 Evaluating the Extent of Disease Spread

CT scan is the most commonly used imaging modality for evaluating the disease extent though its sensitivity is only 23–76%, and it has a limited value in detecting low-volume disease and small tumor nodules [18, 19]. In general, the use of contrast-enhanced CT scan assists in identifying primary lesions of bowel, solid organ metastases, and nodal metastases. Visible cardiophrenic angle lymph nodes on CT scan are strongly associated with the presence of peritoneal metastases. In a study of 114 patients, Elias et al. showed that the presence of these nodes had no prognostic impact after optimal cytoreductive surgery plus HIPEC [20].

Jacquet et al. compared the PCI predicted on preoperative CT scan with the surgical PCI and found that the accuracy of the CT scan was dependent on the lesion size. Small peritoneal nodules or masses less than 0.5 cm were detected in 28% of the patients preoperatively, moderate-sized nodules 0.5–5.0 cm were detected in 72%, and gross nodules greater than 5 cm were detected in 90% [21]. When the nine abdominopelvic regions were compared, the pelvic region was the least accurate. Similarly, other investigators have reported a sensitivity of 11% for nodules less than 0.5 cm, 37% for nodules 0.5–5.0 cm, and 94% for nodules greater than 5 cm [22]. Since here is such a strong relationship of extent of disease to outcomes, it is important to diagnose limited extent PM to improve outcomes [23–25]. Other imaging modalities have been investigated in an attempt to accurately predict the extent of PM, including diffusion-weighted MRI and PET-CT scan [25–30]. In a study by Low et al., MRI correctly categorized the tumor volume in 20 of 22 patients, with an overall sensitivity and specificity of 88% and 74% [28]. Espada et al. developed a scoring system with a diagnostic accuracy of 91% by evaluating DWI for detection of PM [31]. However, the sample size was small for both these studies, and other studies have not been able to replicate these results. In a recent meta-analysis based on 22 studies, MRI and PET-CT were shown to have similar per-patient diagnostic accuracy to CT scan in predicting the PCI, but the data was more robust for CT scan [32]. MRI requires 6 h of fasting and a stringent protocol and is more accurate when used by experienced radiologists. It has shown a greater accuracy in detecting small-volume disease [33, 34]. The use of these investigations needs to be individualized, keeping in mind that PM is usually more extensive than predicted by any one investigation [35].

The BIG-RENAPE and RENAPE working groups have developed the PeRitOneal MalIgnancy Stage Evaluation (PROMISE) Internet application (www.e-promise.org) to facilitate tabulation and automatically calculate the peritoneal cancer index (PCI) [36]. This application offers computer assistance to produce simple, quick, but precise and standardized pre-, intra-, and postoperative reports of the extent of peritoneal metastases. In addition to the radiological score, pathological and surgical scores can be generated as well. Not only the peritoneal metastases but other aspects like peritoneal thickening, involvement of adipose tissue, and fluid density are taken into consideration in this application. It can be used by less experienced centers as well and can help in research and multicentric studies related to peritoneal metastases [36].

CT scan may be required in the postoperative period for the management of complications.

Dromain et al. reported CT findings in 51 patients in the first 15 days of CRS and HIPEC and found all the scans to have some abnormal findings. They concluded that findings like bowel and peritoneal thickening, increased intraperitoneal fat density, and compartmentalized ascites result from an inflammatory mesenteric reaction or inflammation of the small bowel or the peritoneum and do not require specific treatment. A knowledge of these findings is essential for appropriate management of these patients [37].

12.3.2 Diagnostic/Staging Laparoscopy

A diagnostic/staging laparoscopy allows direct visualization of the peritoneal surfaces and can pick up small peritoneal nodules that cannot be detected by imaging studies. Laparoscopy can be used for early diagnosis of PM as well as selection of patients for CRS and HIPEC. Laparoscopy has been shown to prevent an unnecessary laparotomy in 7–41% of the cases [38, 39]. The preferred site of port placement is the midline to facilitate resection of the port sites in future CRS. Laparoscopy allows sampling of the peritoneal fluid for cytology and biopsy of suspicious areas in evaluating response to chemotherapy [40]. It may be challenging to perform this procedure in patients with multiple prior surgeries. Extensive adhesions may preclude a thorough evaluation. Certain areas where a laparoscopic evaluation may be suboptimal are infiltration of the diaphragm muscle, involvement of the porta hepatis and pancreas, and in the region of the celiac axis. In addition, involvement of the ureters and pelvic sidewall may also be inaccurate. Iversen et al. reported that laparoscopy correctly predicted complete cytoreduction in only 29% of patients with recurrent colorectal cancers, compared to 33, 80, and 87.5% of patients with mesothelioma, PMP, and synchronous colorectal PC, respectively [41]. This has been attributed to the fact that recurrent CRC often tends to infiltrate retroperitoneal structures like the ureters or pancreas. However, these areas are more accurately assessed on imaging, and a combination of imaging techniques with laparoscopy should be used to select patients most likely to benefit from CRS and HIPEC [42].

12.4 Multimodality Treatment of Colorectal PM

The conventional treatment for colorectal PM is systemic chemotherapy. In the absence of definitive treatment, patients are administered systemic chemotherapy with the goal of obtaining some prolongation in survival and symptomatic relief or both. The treatment of colorectal PM with CRS and HIPEC has significantly improved the survival of these patients though this is possible only in selected patients who are in good general health and have no extra-abdominal disease, and the extent of PM is limited. This treatment may not be a replacement for systemic therapies, and majority of the patients require systemic chemotherapy in addition to CRS and HIPEC. The optimal treatment strategy needs to be individualized for each patient, and such decisions are best made by multidisciplinary teams at centers experienced in delivering this treatment.

12.4.1 Outcomes of Systemic Therapy as the Sole Treatment for CPM

Combination chemotherapy with or without targeted therapy is the cornerstone of treatment for colorectal PM. With the introduction of new agent like oxaliplatin and irinotecan, the overall survival which was rarely more than 12 months with 5-fluourouracil and leucovorin improved to almost 20 months (15.6 months with FOLFIRI regimen and 19.5 months with the FOLFOX regimen) [42, 43]. It improved further with the addition of targeted agents like bevacizumab to 20.3 months with FOLFIRI and 21.3 months with FOLFOX [44, 45]. Similarly, the addition of cetuximab to FOLFIRI increased the median survival to 19.9 months and 22.8 months with FOLFOX. This benefit was seen only in KRAS non-mutated tumors [46, 47]. However, these

studies were not carried out exclusively for patients with colorectal PM, and a large proportion of the patients in these studies had liver only metastases which is a more favorable prognostic group.

Franko et al. reported the outcome of patients with colorectal PM from a pooled analysis of two large phase III trials from the North Central Cancer Treatment Group (NCCTG) that included 2101 patients treated with systemic chemotherapy, out of which 1646 patients were undergoing evaluation of first-line therapy and 455 for second-line therapy [48]. Only 44 patients (2.1%) had PM which is a significantly low rate as compared to the expected incidence of 15–20%. Patients with PM had 30% reduction in overall survival as compared to those with other metastatic sites, with a median survival of 12.7 months compared to 17.6 months when patients had no PM (HR = 1.32, 95% CI, 1.15–1.50; $P < 0.001$). The authors opined that the presence of PM should not affect the choice of the chemotherapeutic regimen.

Klaver et al. reported the results of two similar studies from the Dutch Colorectal Cancer Group (DCCG) and came to the same conclusion as the North American group, both of which had a small percentage of patients with PM (4% and 6%, respectively) [49]. The proportion of patients with isolated PM were even lower—only 4/850 in the CAIRO study and 5/755 in the CAIRO 2 study [50, 51]. The studies analyzed the efficacy of different chemotherapy regimens in the first and subsequent lines of therapy in the metastatic setting. In the CAIRO study, median OS was 10.4 months for patients with PM vs. 17.3 months for patients with no PM, ($P < 0.001$), and in CAIRO 2, this was 15.2 months vs. 20.7 months, respectively ($P < 0.001$). These studies once again demonstrated the poor efficacy of modern chemotherapy regimens in patients with colorectal PM. There was no dose reduction in these patients or problem of tolerance, and the authors attributed the poor results to a biologically more aggressive nature of PM and a relative resistance to therapy.

Thus, although systemic chemotherapy is widely used to treat colorectal PM, there is no strong evidence showing its efficacy in this pattern of spread of colorectal cancer, and there is a need for a more aggressive locoregional therapy that could address PM [52].

12.4.2 CRS and HIPEC for CPM: Current Evidence

In comparison to only systemic therapy, patients with PM treated with CRS and HIPEC can reach a median survival of 63 months and 2- and 5-year survival rates of 81% and 51%, respectively [53]. The aim of CRS is to achieve a complete resection of all macroscopic disease within the peritoneal cavity so that the residual microscopic disease can then be treated with HIPEC. Two retrospective and one prospective studies have looked at the role of cytoreductive surgery only, without adding any intraperitoneal chemotherapy treatment. In the patients that received complete resection of peritoneal disease, the 5-year survival ranged from 24 to 36% [54–56]. However, these studies included a heterogeneous group of patients, including 40–66% patients with the presence of distant metastases at the time of treatment of peritoneal metastases; the absolute numbers were quite small, ranging from 31 to 125 patients, and the data was collected over long periods ranging from 9 to 16 years [55, 57]. Considering these drawbacks and the nonrandomized nature of the studies, it is difficult to draw inferences, but these studies do show the beneficial effect of CRS in PM.

Several single-institution and multicentric studies have been published regarding the outcomes of this combined modality treatment, but few studies have compared CRS and HIPEC to systemic chemotherapy. Verwaal et al. conducted a phase III randomized trial comparing CRS and HIPEC to the then existing systemic chemotherapy 5-FU and leucovorin [58]. One hundred and five patients were randomized to either systemic chemotherapy with palliative surgery for prevention or treatment of complications, which was the standard treatment at the time of the study, or CRS and HIPEC with mitomycin C. The median overall survival was significantly better in the HIPEC group (22.2 months vs. 12.6 months;

$P = 0.028$). This benefit was despite the fact that over half the patients in the HIPEC group did not receive a CC-0/CC-1 resection due to extensive disease, indicating that they were not good candidates for HIPEC. For the patients receiving CC-0 resection, the 5-year survival was 45%, and these findings were confirmed even after an 8-year follow-up, when more than 90% of the events had occurred [59]. The main criticism of this study is that although this was a randomized trial, it was performed in the era of 5-FU-leucovorin, and chemotherapy and targeted therapy for colorectal cancer have evolved since then with good long-term survival. To address this issue, Elias et al. compared 48 PM patients treated at various centers in France receiving palliative systemic oxaliplatin- and/or irinotecan-based chemotherapy to 48 patients who underwent additional CRS and HIPEC with oxaliplatin [53]. Both groups received a mean of 2.3 lines of chemotherapy. Two-year and 5-year overall survival rates were 81% and 51% for the HIPEC group versus 65% and 13% for the standard group, respectively. The median survival was 62.7 months in the HIPEC group, which compared favorably to 23.9 months in the standard group ($P < 0.05$). The results of this study showed that a median survival of 63 months and a 5-year survival of 51% could be achieved in patients with isolated colorectal PM which was significantly longer than the 24-month median survival achieved with systemic chemotherapy alone in patients with a similar disease extent.

Franko et al. performed a case-control study comparing 67 patients undergoing CRS and HIPEC in addition to systemic chemotherapy to 38 others receiving systemic chemotherapy alone and reported a significantly longer median survival in the CRS and HIPEC group (34.7 months vs. 16.8 months; $P < 0.001$) [60]. In another study by Franko et al., they performed a pooled analysis of the survival data of patients with PM from two phase III chemotherapy trials (N9741 and N9841) and compared the outcomes to non-PM metastatic colorectal cancer [48]. The median OS (12.7 vs. 17.6 months, hazard ratio [HR] = 1.3; $P < 0.001$) and PFS (5.8 vs. 7.2 months, HR = 1.2; $P = 0.001$) were shorter for PM versus non-PM patients, and this unfavorable prognostic influence of PM remained even after adjusting for other factors.

Cavaliere et al. reported the results of 120 patients treated with the Italian Society of Locoregional Treatment in Oncology (SITILO) protocol at six Italian centers. Patients were treated with CRS and HIPEC with cisplatin (CDDP) and mitomycin C (MMC), and only 11 underwent HIPEC with an oxaliplatin-based regimen [61]. A complete cytoreduction CC-0 was achieved in 85.2% of the patients. The 3-year survival was 25.8% and increased to 33.5% in patients who had an optimal cytoreduction (CC-0) ($P < 0001$). In a multicentric study of 523 patients from 23 French-speaking centers, Elias et al. reported a median overall survival of 30.1 months, 5-year overall survival of 27%, and a 5-year disease-free survival of 10% with CRS and HIPEC in PM [62]. The 5-year survival was 29% in patients with no residual disease and 14% in patients with residual disease <2.5 mm, and the group of patients with residual disease >2.5 mm had no 5-year survivors. On multivariate analysis, the independent variables for survival were completeness of CRS, extent of PM evaluated by PCI, lymph node positivity, and the use of adjuvant chemotherapy. This study showed that CRS and HIPEC could be performed with a low morbidity and mortality and resulted in a prolonged survival in patients with a PCI of <20. In another bi-institutional French study of 146 patients by Quenet et al., where they included only those patients who had completely resected PM and PCI < 25 treated with either oxaliplatin or oxaliplatin with irinotecan as the HIPEC agents, the median overall survival (OS) was 41 months and median relapse-free survival was 15.7 months, with a 5-year overall survival rate of 42% and 5-year relapse-free survival of 16% [63]. Lymph node metastases and PCI were the only independent prognostic variables, and there was no difference in the survival outcomes between the two HIPEC regimes [63]. Sugarbaker et al. presented their experience of CRS and HIPEC for PM in 318 patients [64].

The median survival was 21.5 months for the whole cohort, but in patients receiving CC-0/CC-1 resections, the median survival was 36.6 months, compared to 18.3 months and 7.6 months for CC-2 and CC-3 resections, again emphasizing the effect of completeness of CRS. This prognostic impact of completeness of CRS was maintained on multivariate analysis. The 3- and 5-year survival rates were 35% and 25%, which are quite encouraging considering the fact that the mean PCI was 15.2, which is quite high compared to other studies in colorectal PM. In another national patient cohort from Norway, Froysnes et al. reported a median survival of 47 months and a 5-year overall survival of 36% for their 118 patients; >95% of their patients had a CC-0 resection which further confirms the significant prognostic impact of a complete cytoreduction [65].

In a systematic review of CRS and HIPEC in colorectal PM, Baratti et al. reported that in the eight studies where patients underwent CC-0 or CC-1 cytoreduction, the median survival period ranged from 16 to 51 months (weighted average, 31.6 ± 10.3 months). The 5-year survival rates reported in nine series ranged from 22 to 50.5% (weighted average, 31.0 ± 9.4%) [66].

The results of all these studies (summarized in Table 12.2) suggest that CRS and HIPEC as a combined modality definitely offers a potential benefit in the scenario of PM, and possibly a major part of the benefit seems to be because of the cytoreduction. The role of HIPEC has been questioned for several reasons—a lack of uniformity of HIPEC protocols, drugs, and carrier solutions used, different methods of HIPEC administration (open, semi-open, closed techniques), heterogeneity of patient populations treated, and lack of randomized trials in the era of modern chemotherapy and targeted therapy. Future clinical trials will also have to address these concerns to establish the position of this promising treatment in the treatment of colorectal PM. Whether HIPEC adds a benefit over and above the CRS will be further clarified by the results of the hugely anticipated PRODIGE 7 trial (NCT00769405).

12.4.3 Role for HIPEC

Studies evaluating the drugs used during HIPEC have shown that the drug penetration is limited to a few cell layers and hence complete resection of all macroscopic disease is essential to have a beneficial effect of HIPEC. HIPEC has several theoretical benefits. HIPEC is performed immediately after the surgery which ensures free dispersion of the hyperthermia and chemotherapy prior to formation of peritoneal adhesions in which cancer cells may be trapped [67–69, 71]. Heat itself is cytotoxic and potentiates the cytotoxicity of chemotherapeutic agents. Animal studies have shown the additive effect of combining hyperthermia with intraperitoneal chemotherapy compared to either of them alone [71, 72].

However, its additive effect in humans with colorectal PM has not been conclusively proven. There is a lack of fundamental research on intraperitoneal chemotherapy which has moved very rapidly from the laboratory bench to the bedside [73].

Very few prospective clinical trials have been set up to determine the ideal parameters in terms of time, temperature, perfusion technique, and cytotoxic drug dose or type. There are no definitive guidelines for surgeons, and choice of technique is often determined by personal preference and experience [73]. However, for colorectal cancer, the protocol for oxaliplatin- and mitomycin C-based HIPEC has been standardized through consensus meetings and is widely adhered to (described later).

Conducting clinical trials in CRS and HIPEC is not only expensive, but the outcomes are difficult to evaluate, as pointed out by David Bartlett [74]. Unlike systemic therapy, the dose can be limited by a complication unrelated to the systemic effects of the drug in phase I studies which makes drawing conclusions difficult. In phase II and III studies, the concerns are patient accrual, funding, lack of endpoints other than DFS and OS, and comparison with the outcomes of systemic therapies which represents a “moving target” [74].

Table 12.2 Outcomes of cytoreductive surgery and HIPEC in patients with colorectal PM

Ref. no.	Type of study	No. of patients	PM alone	CC-0/CC-1	HIPEC	Drug	5-year disease-free survival	3-year OS	5-year OS	Median OS	*P*-value	Survival in CC-0/CC-1
55 (2011)	Prospective	125	41	24.8%	–	–	–	–	4.8%	12 M	–	22%
56 (2012)	Retrospective	153	–	31%	–	–	–	–	–	–	–	36%
57 (2015)	Retrospective	50	27	–	–	–	–	45.5%	29.64%	32.4 M	–	–
61 (2006)	Prospective	122	122	85.2%	Yes	CDDP MMC OX	–	25.8%	–	–	–	33.5 (3-year OS)
53 (2008)	Prospective Comparative	48 (96)	48	100%	Yes	OX	–	–	51%	62.7 M	<0.05	51%
62 (2010)	Retrospective	523	523	84%	Yes (86%)	MMC OX	10%	41%	27%	30.1 M	–	29%
60 (2010)	Prospective Case control	67	67	–	Yes	MMC	–	–	–	34.7 M	0.001	–
58 (2003)	Prospective RCT	52 (105)	52		Yes	MMC	–	–	–	22.3 M	–	45%
59 (2008)	Prospective RCT	52 (105)	52		Yes	MMC	–	–	45%	22.2 M (CC-0/1)	0.028	–
63 (2011)	Retrospective	146	146	90.4%	Yes	OX	14.2%	–	42.4%	41 M	–	–
654 (2016)	Retrospective	318	318	61.6%	Yes	MMC MMC + A	–	35%	25%	–	–	36.6
665 (2016)	Retrospective	119	119	95%	Yes	MMC	14%	–	36%	–	–	–

CDDP cisplatin, *MMC* mitomycin C, *OX* oxaliplatin, *A* adriamycin, *OS* overall survival

Since all aspects of intraperitoneal chemotherapy cannot be evaluated in clinical trials, researchers develop innovative animal experiments to study distinct aspects of HIPEC and other forms of intraperitoneal chemotherapy. Peritoneal metastases similar to that in humans can be induced in animals, and several small and large animal models have been developed and used for experimental purposes. Surgical techniques as well as various aspects of intraperitoneal chemotherapy have been studied [75, 76].

Most studies have successfully developed a clinically relevant model, and the focus of experimental research has now shifted toward enhancing and refining intraperitoneal chemotherapy [74]. Pelz et al. showed that HIPEC is an effective treatment for peritoneal metastases in animal models and reduced macroscopic and microscopic intraperitoneal tumor spread [73]. Another study showed that raised intra-abdominal pressure combined with hyperthermia increased the tissue concentration of oxaliplatin [77].

Klaver et al. compared CRS with CRS and heated saline perfusion, CRS and normothermic intraperitoneal chemotherapy, and CRS and HIPEC in a syngeneic rat CRC model. Every group consisted of 20 animals with a comparable PCI and surgical resection score. The primary endpoint was survival. The temperature for hyperthermia was set at 41–42°C as in the trial by Verwaal et al. [56]. A significant survival benefit was reported in both the HIPEC and the normothermic intraperitoneal chemotherapy groups, but with the latter achieving the best result [78].

These animal studies provide a proof of principle for both CRS and HIPEC. These studies do not evaluate pharmacokinetic aspects and tissue drug concentrations which are important.

The PRODIGE 7-ACCORD 15 trial (NCT00769405) has finished accrual, and the results will be available at the end of this year. Two hundred and sixty-four patients with CPM have been randomized to undergo CRS alone or CRS and HIPEC with oxaliplatin. The trial hypothesized that the addition of HIPEC to CRS should produce an overall survival benefit of 18 months over CRS alone. The secondary endpoints are recurrence-free survival, treatment toxicity, surgical morbidity, and factors influencing survival.

There are two concerns in the surgical community treating CPM.

1. Should HIPEC be used in the treatment of CPM with CRS pending the results of PRODIGE 7?

   Based on the above evidence, there seems to be a benefit of adding HIPEC to CRS as compared to performing CRS without HIPEC, since the reported survival in studies in which CRS and HIPEC both were used is longer. It is considered the standard of care in several countries for treating CPM with limited peritoneal spread. Hence, in the current scenario, when CRS is being performed for CPM, it should be coupled with HIPEC.
2. How will the results of PRODIGE 7 influence current practice?

If the results of PRODIGE 7 favor the use of HIPEC, its role will be clearly established; however, if the result is negative, efforts will continue to determine the optimal drugs and regimens and methodology and to optimize other aspects to provide a clinical benefit of this therapeutic strategy which, in selected patients, has dramatically changed the prognosis of this disease.

At the same time, it is important to keep in mind that the role of CRS is already established and cannot be undermined even though the importance of HIPEC is reduced. Patients should continue to be treated in specialized centers in order to give them the benefit of a high quality of cytoreduction which deeply influences the prognosis of the disease in terms of disease-free and overall survival.

12.4.4 Systemic Chemotherapy in Addition to CRS and HIPEC: Before or After?

Both CRS + HIPEC and systemic therapy are increasingly used for the treatment of colorectal PM. Subsequently, combined treatment strategies have been introduced. However, there is a

worldwide controversy on the indication, effectiveness, timing, and risks of perioperative systemic therapy as adjunct to CRS + HIPEC for PM. The rationale for using systemic therapy is the prevention of hematogenous spread as more than 50% of the patients treated with CRS and HIPEC develop extraperitoneal recurrence [79]. Several large studies have shown a benefit of adding systemic chemotherapy to CRS and HIPEC, whereas some others have not [18, 80–83]. In a study comprising of 231 patients with limited peritoneal disease treated with CRS and HIPEC at four expert French centers, patients who received early adjuvant systemic chemotherapy (within 3 months of surgery) experience a better DFS and OS compared to those who did not though this difference did not reach statistical significance [84]. The reasons for not administering adjuvant chemotherapy were a lack of evidence, delayed recovery from surgery, patient refusal, and early disease progression [84].

The use of perioperative systemic therapy in the neoadjuvant (neoadjuvant chemotherapy—NACT) or adjuvant setting has not been prospectively investigated for patients undergoing CRS + HIPEC [80]. A neoadjuvant treatment strategy in order to downstage intraperitoneal tumor load, limit extensiveness of CRS, and predict the biological behavior of the tumor may be of potential benefit in these patients. Additionally, in patients who proved to respond to neoadjuvant treatment, adjuvant systemic therapy in the same regimen may be of value by treating systemic micrometastases. In a systematic review of the role of neoadjuvant and adjuvant systemic chemotherapy as an adjunct to CRS + HIPEC, Waite et al. found seven eligible studies related to neoadjuvant chemotherapy, none of which showed strong evidence in favor of neoadjuvant systemic therapy [85].

A lack of response to NACT should not be considered an absolute contraindication to surgery, and patients with limited disease amenable to a complete cytoreduction and no extraperitoneal spread can still be treated with CRS and HIPEC with good long-term outcomes [86].

Ongoing clinical trials may provide more insight into patient selection and outcomes of neoadjuvant and adjuvant systemic chemotherapy with targeted therapy combined with CRS and HIPEC. The COMBATAC study (NCT01540344) is a phase II study that evaluates the effect as assessed by progression-free survival of perioperative systemic chemotherapy including cetuximab, combined with CRS and HIPEC in RAS wild-type colorectal PM patients.

The CAIRO 6 study (NCT02758951) is a prospective multicenter randomized parallel group study in which colorectal PM patients of non-signet histology, with PCI < 20 and in whom CC-0/CC-1 CRS seems likely, will be randomized to neoadjuvant combination chemotherapy plus bevacizumab and CRS + HIPEC followed by adjuvant combination chemotherapy (experimental arm) or CRS + HIPEC alone (control arm). The study will start as a randomized phase II study, and if the criteria of feasibility and safety are met, the study will continue as a phase III study with 3-year overall survival as primary endpoint. Clinical trials evaluating various aspects of treatment with CRS and HIPEC for CPM are listed in Table 12.3.

12.4.5 Long-Term Survival with CRS and HIPEC: Is There a Possibility of Cure?

Few patients undergoing CRS and HIPEC experience a prolonged DFS and OS. Goéré et al. analyzed the outcomes in 107 patients treated from 1995 to 2005 who had a follow-up of more than 5 years [87]. The median follow-up was 77 months, and the 5-year and 10-year survival rates were 35% and 15%, respectively. Patients who were disease-free for 5 years after treatment of colorectal PM or its recurrence were considered cured, and 17 patients (16%) belonged to this group; 14 of these 17 patients never developed recurrence. The analysis excluded patients who died in the perioperative period or due to other causes. Cured patients had a significantly lower median PCI than patients who were not cured, 4 (3–16) and 12 (2–36) ($P = 0.0002$), respectively. On multivariate analysis, a PCI of 10 or less was the only independent factor predicting cure. A similar cure rate has

Table 12.3 Ongoing clinical trials for CPM

ClinicalTrials.gov ID	Phase	Country	Primary institution/group	Number of patients	Primary outcome measure	Treatment arms
Clinical trials evaluating various aspects of CRS and HIPEC in the treatment of CPM						
NCT00769405 (PRODIGE 7)	3	France	Unicancer	264	Overall survival	CRS and systemic chemotherapy vs. CRS + HIPEC with oxaliplatin and systemic chemotherapy in PM
NCT01815359 (ICARuS)	2	US	Memorial Sloan Kettering Cancer Center	220	Disease-free survival	CRS and HIPEC vs. CRS and EPIC in PM of colorectal and appendiceal origin
NCT02830139	2	China	Wuhan University	100	Overall survival	Surgery vs. surgery and HIPEC for locally advanced colorectal cancer, both groups under systemic therapy
NCT02758951 (CAIRO 6)	2/3	Netherlands	Catharina Ziekenhuis Eindhoven	340	1. Major postop complications (gr 3/4) 2. Overall survival	CRS/HIPEC with preop systemic + bevacizumab and postoperative systemic therapy vs. CRS/HIPEC alone
NCT02399410 (Bev-IP)	2	Belgium	University Hospital, Ghent	45	Surgical morbidity and mortality (at 3 months postop)	CRS and HIPEC with perioperative systemic bevacizumab
NCT02866903 (IPOXA)	1/2	France	Hospices Civils de Lyon	47	1. Adverse events up to 14 days of each administration 2. Dose-limiting toxicity up to 14 days of each administration	Administration of IP oxaliplatin (normothermic port-directed) with systemic FOLFIRI and bevacizumab in PM of uncertain resectability
NCT02614534	3	Spain	Maimónides Biomedical Research Institute of Córdoba	Not provided	Locoregional control at 3 years	Study design not provided but objective to study the role of HIPEC in prevention of PM in high-risk T3/T4 tumors
NCT02949791 (HIPEC-IAP)	2	Italy	Fondazione IRCCS Istituto Nazionale dei Tumori, Milano	38	Tumor and normal tissue concentration of cisplatin	Low intra-abdominal pressure HIPEC vs. high intra-abdominal pressure HIPEC with mitomycin C + cisplatin in colorectal PM and pseudomyxoma peritonei

(continued)

Table 12.3 (continued)

ClinicalTrials.gov ID	Phase	Country	Primary institution/group	Number of patients	Primary outcome measure	Treatment arms
Trials evaluating the role of HIPEC in prevention of CPM						
NCT02965248 (APEC)	2	China	Fudan University	147	Peritoneal metastases rate at 3 years	Surgery alone, surgery and HIPEC with raltitrexed, or surgery and HIPEC with oxaliplatin
NCT02179489	3	China	Zhejiang University	300	Disease-free survival	Surgery vs. surgery and HIPEC for patients at high risk of PM
NCT02974556 (promenade)	3	Italy	University of Roma la Sapienza	140	Incidence of peritoneal metastases at 36 months	Prophylactic target-organ resection (along with primary resection) + HIPEC and systemic therapy vs. systemic therapy only after primary resection for prevention of PM for high-risk T3/T4 tumors
NCT02231086 (COLOPEC)	3	Netherlands	Academisch Medisch Centrum—Universiteit van Amsterdam (AMC-UvA)	176	Peritoneal recurrence-free survival at 18 months	Adjuvant systemic therapy only vs. adjuvant HIPEC and systemic therapy for the prevention of PM in high-risk patients
NCT01226394 (ProphyloCHIP)	3	France	Gustave Roussy, Cancer Campus, Grand Paris	130	Increase in 3-year disease-free survival	Surveillance vs. follow-up laparotomy with HIPEC with oxaliplatin after primary resection
NCT02614534	3	Spain	Maimónides Biomedical Research Institute of Córdoba	Not provided	Locoregional control at 3 years	Study design not provided but objective to study the role of HIPEC in prevention of PM in high-risk T3/T4 tumors

been reported in patients undergoing surgical resection of colorectal liver metastases [88–90]. Another study by the same authors confirmed these findings—the 5-year OS in patients undergoing CRS and HIPEC was not significantly different from those undergoing resection of liver metastases (36.5% and 38.5%, respectively) [91].

12.4.6 Role of Early Postoperative Intraperitoneal Chemotherapy (EPIC)

EPIC comprises of multiple intraperitoneal chemotherapy applications administered through drains placed during surgery. Typically, three to five instillations are performed starting on postoperative day 1. Some centers give multiple cycles of intraperitoneal chemotherapy combined with systemic chemotherapy, and this treatment continues for a few months after surgery—it is termed as sequenced intraperitoneal chemotherapy (SIPC). 5-Fluorouracil (5-FU) alone or in combination with mitomycin C (MMC) is used. MMC 10–12 mg/m^2 is administered on day 1 followed by 5-FU based on body surface area (500 mg/m^2 and 800 mg/m^2) or on body mass (15 mg/kg) from days 2 to 5 [92, 93]. Alternatively, only 5-FU is used for 3–5 days [94].

Most of the evidence comes from small retrospective studies that include patients with PM from various primary sites, and the role of EPIC has not been evaluated separately in those. Elias et al. performed a retrospective study of 64 patients who had PC arising from CRC; 19 (29.6%) of whom also had systemic metastases [79]. Seven patients were treated with CRS and EPIC and 27 patients with CRS and HIPEC. OS was lower in the EPIC group than in the HIPEC group, but not significantly.

They subsequently compared 23 patients undergoing CRS and HIPEC with oxaliplatin to 23 others receiving EPIC following CRS which showed similar results though the morbidity with EPIC was more [95].

Mahteme et al. compared 18 patients who underwent CRS with SIPC to historical controls with similar features treated with systemic chemotherapy alone [96]. The 2- and 5-year survivals in the SIPC group were 60 and 28%, respectively, whereas corresponding values in the control group were 10 and 5%, respectively. In all, 11 patients who were considered macroscopically tumor-free after CRS had a longer survival (34.5 months, 95% CI 28.7–75.7) than those who did not undergo CRS (10 months, 95% CI 15.7–70.0) (P = 0.02). Five patients in the CRS and SIPC group experienced long-term survival after surgery (median 8.3 years, range 6.8–9.1) [96].

In 1996, Elias et al. initiated a study comparing CRS and EPIC to CRS alone that had to be closed prematurely due to poor accrual and patient dissatisfaction in the control arm. The 2-year survival in this study was 60% in patients who underwent a complete cytoreduction compared to 10% in patients who received palliative therapy, demonstrating the benefit of a surgical intervention [97].

Glehen et al. reported results of a multi-institutional study of 506 patients who underwent CRS and HIPEC with or without EPIC from 28 institutions, in which 76% of the patients had HIPEC, 46% had EPIC, and 22% had both HIPEC and EPIC. A complete cytoreduction was obtained in 75%; HIPEC was commonly performed using mitomycin C (71%), mitomycin C and cisplatin (13%), and oxaliplatin (8%). EPIC was performed with 5-FU with or without mitomycin C (96%). With a median follow-up of 53 months, the median overall survival was 19.2 months and was 32.4 months in patients with a CC-0 resection and 34.8 months in patients with a low PCI. Moreover, no statistically significant difference was seen among patients treated with HIPEC, EPIC, or combined HIPEC/EPIC (overall survival, 19.2, 19.2, and 21.6 months, respectively) [98]. Cashin et al. performed a case-control study comparing 16 patients treated with CRS and HIPEC to 16 others treated with CRS and SIPC. The HIPEC group had a significantly better DFS and OS with a similar morbidity, and the authors recommended that it should be the preferred treatment for patients with CPM [99].

In another study comparing CRS and HIPEC with EPIC with CRS and HIPEC alone that

included 69 patients with CPM, there was no difference in the two groups though the morbidity was higher in the group receiving EPIC [100].

The above evidence does not answer any of the questions pertaining to the use of EPIC.

Is EPIC an alternative to HIPEC?
Is there a role of EPIC in addition to HIPEC?

Currently the ICARuS trial (NCT01815359) which is a phase II trial is accruing patients in the United States at the Memorial Sloan Kettering Cancer Center. In this trial HIPEC with mitomycin C will be compared to EPIC with FUDR in patients with colorectal and appendiceal primary tumors following complete cytoreduction. The main caveat will be EPIC with FUDR which is not used at most centers.

Currently, several "expert" centers used EPIC in addition to HIPEC routinely; other centers don't advocate its use.

12.5 Practical Concerns with CRS and HIPEC

12.5.1 Patient Selection for CRS and HIPEC

12.5.1.1 Patient-Related Factors

The two most important factors in selecting patients for the combined modality treatment are disease-specific factors (extent, histology) and the ability of the patients to withstand the procedure. Recently, there has been a lot of attention being paid to patient factors that can influence outcomes, and these need to be considered while selecting patients for CRS and HIPEC. The Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less has been recommended as a cutoff in a Peritoneal Surface Oncology Group International (PSOGI) consensus statement in 2007 [101]. In one of the largest single-institution series to date, Levine et al. demonstrated that compared to patients with ECOG 0 or 1, ECOG 2 patients had a HR of 2.8, and ECOG 3 or 4 had a HR of 4.3 for a poorer overall survival following CRS and HIPEC [102]. Other studies have demonstrated similar findings and confirmed its impact in multivariate analyses [103, 104]. Diabetics are more likely to develop complications compared to nondiabetics (27.5% vs. 15.3%; $P < 0.001$), as shown in a retrospective series of 977 patients of which 91 were diabetic [105]. In this cohort, although the DFS of diabetics remained similar to nondiabetics, they had a significantly higher 30-day (8.8% vs. 2.7%; $P = 0.007$) and 90-day mortality rates (13.2% vs. 5.2%; $P = 0.008$). Similarly, age > 70 seems to have a higher 30-day (13.6% vs. 3.9%; $P < 0.001$) and 90-day (27.4% vs. 10.2%; $P < 0.001$) mortality rates, although these outcomes seem to improve with increasing surgical experience of a well-established program [105]. It is estimated that up to one-third of the patients with advanced colorectal cancer are malnourished [106]. Several methods of assessment of nutritional status have been used like the Subjective Global Assessment (SGA) scale, presence or absence of sarcopenia as assessed on CT scan, and preoperative serum albumin levels. Malnourished patients as assessed by SGA had longer hospital stay and poorer survival [107]. Sarcopenic patients had a significantly higher rate of reoperation (25.6% vs. 12.1%; $P = 0.012$) and higher complication rates (OR 0.93; $P = 0.018$) compared to non-sarcopenic patients in a retrospective study of 206 patients by Vugt et al. [107]. Valle et al. showed that a serum albumin level of <35 gm/dl was associated with a significantly higher rate of complications and enterocutaneous fistulas [108]. The presence of ascites appears to be a poor prognostic factor for most disease types treated with CRS and HIPEC. In one series of 1000 patients, the 229 patients who had malignant ascites significantly reduced the possibility of a CC-0/CC-1 resection (15% vs. 59%; $P < 0.001$) and were predictive of a worse overall survival [109].

12.5.1.2 CRS and HIPEC in the Elderly

Conventionally, age > 70 years has been considered a relative contraindication for performing CRS and HIPEC. Elderly patients have a reduced

physical capacity to recover from surgery and other medical comorbidities [110, 111]. However, based on the favorable outcomes in elderly patients undergoing major oncologic procedures, experienced centers have used this treatment for selected patients over the age of 70 [112, 113]. Passot et al. reported outcomes in 188 patients over the age of 70 years undergoing CRS and HIPEC for various indications and reported a higher rate of "failure to rescue" in older patients leading to a higher mortality from surgical complications. The overall morbidity in both groups was similar. A PCI > 12 was an independent predictor of increased morbidity [114]. Another study of 85 patients over the age of 75 reported a similar morbidity and mortality compared to younger patients in carefully selected patients [115]. Selected patients over the age of 70 years with a good performance status and limited disease spread can be taken up for CRS and HIPEC in experienced centers where treatment is carried out by multidisciplinary teams.

12.5.1.3 Disease-Specific Factors

A consensus statement from representatives from the major peritoneal surface malignancy centers from around the world listed eight clinical and radiographic variables associated with increased chances of achieving a complete cytoreduction: [116]

- Eastern Cooperative Oncology Group (ECOG) performance status 1 or less
- No evidence of extra-abdominal disease
- Up to three small, resectable parenchymal hepatic metastasis
- No evidence of biliary obstruction
- No evidence of ureteral obstruction
- No evidence of intestinal obstruction at more than one site; small bowel involvement
- No evidence of gross disease in the mesentery with several segmental sites of partial obstruction
- Small-volume disease in the gastro-hepatic ligament

However, there are certain other factors that need to be considered.

12.5.1.4 Sugarbaker's Peritoneal Cancer Index (PCI)

Though CRS and HIPEC can produce long-term survival reaching up to 50% at 5 years, this is only possible in selected patients. One of the two most important prognostic factors is the PCI. Elias et al. in a retrospective study of 180 patients demonstrated that there was no benefit of CRS and HIPEC in patients with a PCI of >17 even if complete cytoreduction could be obtained. The survival was similar to patients with palliative debulking in patients with a higher PCI [117]. This may not be an absolute contraindication as some selected patients with a higher PCI may still benefit from CRS and HIPEC especially patients with mucinous tumors. In another multicentric retrospective French study comprising of 523 patients, the 5-year survival of patients with a PCI of >20 was 10%. The authors considered a PCI of >20 with other poor prognostic factors like poor performance status, lymph node involvement, and poor response to chemotherapy as absolute contraindications for CRS and HIPEC [62].

Sugarbaker et al. in their study of 380 patients performed a receiver operating characteristic (ROC) curve analysis and identified PCI >12 as a predictive marker for disease recurrence with 100% specificity [64]. Similar findings were reported by a Norwegian study of 47 patients [63]. Another study of 72 patients found no benefit of CRS and HIPEC for a PCI of >16 [118]. CRS and HIPEC is not recommended for patients with a PCI of >17–20. A combination of imaging studies and diagnostic laparoscopy should be employed to select patients with limited disease extent and avoid unnecessary laparotomy in patients with more extensive disease. Long-term survival is possible only in patients with a PCI of <10.

12.5.1.5 Completeness of Cytoreduction

The second most important predictor of survival is the completeness of tumor removal. The commonly used score for this is the completeness of cytoreduction score (CCR) as defined by Sugarbaker. Only patients in whom a complete

cytoreduction (CC-0/CC-1) is deemed possible should be taken up for surgery. The survival in patients having a CC-2/3 resection is similar to those receiving systemic therapy alone, and such procedures should not be undertaken [119]. In a large study, analysis of outcomes in 506 patients treated with CRS and HIPEC found completeness of cytoreduction to be the strongest predictor of survival on multivariate analysis ($P < 0.0001$) [98]. In the PRODIGE 7 trial, only patients who have residual disease <1 mm were considered to have a complete cytoreduction and subject to randomization.

12.5.1.6 The Peritoneal Surface Disease Severity Score (PSDSS)

The peritoneal surface disease severity score has been suggested as a method of preoperative prognostication of outcomes following CRS and HIPEC. The PSDSS incorporates clinical symptom severity, extent of disease as peritoneal cancer index (PCI) calculated on CT scan or laparoscopy, and primary tumor histology [120]. This score was validated by a study evaluating 1013 patients with PM and showed that PSDSS was capable of defining populations with a high or considerably lower likelihood of long-term survival after CRS/HIPEC [121]. However, other studies have not shown additional benefit of the PSDSS over PCI [122]. PCI continues to be used as the preferred tool in clinical practice and in clinical trials as well.

12.5.1.7 Response to Chemotherapy

Response to neoadjuvant chemotherapy (NACT) is predictive of a more favorable prognosis. In a study by Passot et al. of colorectal cancer patients receiving NACT prior to CRS and HIPEC, patients who had a complete or major response to chemotherapy had a significant improvement in survival compared to those who had a minor or no response ($P = 0.0019$). These survival differences were determined by an assessment of histopathologic specimens removed at the time of CRS and HIPEC. They concluded that histopathologic response to NACT was a new prognostic tool for the management of peritoneal metastases from colorectal cancer [123]. Paul Sugarbaker proposes a differential approach to patients depending on the response to chemotherapy [124]. Ten percent of the patients are expected to have a complete response, and in these patients, HIPEC may not add to the survival benefit that has been obtained with chemotherapy alone. CRS may be performed for staging purposes with a thorough exploration and generous biopsies. In situations where the surgeon is confident, the same can be performed laparoscopically. Seventy percent of the patients receiving neoadjuvant systemic chemotherapy have a minor response or no response. Though the probability of benefit of CRS and HIPEC is less in these patients, they should still undergo the procedure provided there is no extraperitoneal spread and a complete cytoreduction can be obtained [86]. If these patients received FOFOX as neoadjuvant therapy, then the drug for HIPEC should be mitomycin C with or without adriamycin instead of oxaliplatin. In those 20% of patients with a major response that falls short of complete response, CRS and HIPEC should be performed preferably using the same drug that was used for NACT [124].

12.5.1.8 Other Prognostic Factors

Several other factors have an impact on the outcomes of patients undergoing CRS and HIPEC.

Peritoneal lavage cytology to detect free intraperitoneal cancer cells is accepted as part of staging for ovarian epithelial cancers and has prognostic significance in gastric cancer [125–128]. In a large multicenter prospective study, EVOCAPE 2, peritoneal cytology was found to lack prognostic significance and furthermore did not predict for future development of PM in these same patients, including colorectal cancers [129]. However, it may have a role in predicting the risk of development of PM. There are currently two systematic reviews of intraoperative peritoneal lavage in colorectal cancer to determine risk of development of PM [130, 131]. Mohan et al. evaluated 18 studies (3197 patients) which evaluated the presence of free tumor cells and/or tumor-associated antigens (CEA, Ras, Ca 19-9) in peritoneal lavage, while Bosanquet et al. evaluated 12 studies (2580 patients) which used positive peri-

toneal lavage cytology, immunohistochemistry, or PCR [130, 131]. In both these studies, a positive peritoneal lavage portended a negative impact on prognosis and risk of peritoneal metastases. However, both reviews were limited by the heterogeneity of method of analysis of peritoneal lavage and therefore cannot be recommended for routine use in staging strategies.

Serum tumor markers are routinely used for surveillance in colorectal cancer patients. Pita-Fernandez et al. showed in a meta-analysis of 11 randomized studies comparing intensive follow-up compared to less intensive or no follow-up showed increased detection of asymptomatic recurrences and improved overall survival [132]. Serum carcinoembryonic antigen (CEA) is a widely used biomarker used for surveillance with sensitivity for relapse ranging from 41 to 97% [133]. Although not commonly used in the surveillance of colorectal cancer, serum Ca 19-9 has a higher specificity compared to serum CEA for peritoneal metastases [134]. Moreover, in a study of 105 patients, although CT scan was the most sensitive investigation to detect PM, about 27% of the patients had elevation of the CEA and/or Ca 19-9 as their earliest indicator of disease recurrence. In a study of over 870 Chinese patients, elevated CEA and CA 19-9 levels were risk factors for peritoneal metastases [135]. Thus, serum tumor markers can be used in surveillance for detection of PM, in particular early recurrence when imaging may be nondiagnostic.

Tumor histology seems to play an important role in outcomes. Although adenocarcinoma is the commonest histological subtype, mucinous adenocarcinoma and signet ring cell adenocarcinoma subtypes have more frequent peritoneal involvement [136]. The outcomes seem to be better for mucinous adenocarcinoma than for the other types. In a retrospective analysis of the Netherlands Cancer Registry, PM of mucinous adenocarcinoma had a median survival of 10.9 months vs. 7.4 months for adenocarcinoma vs. 6.6 months for signet ring histology ($P < 0.0001$) [137]. Multiple retrospective analyses have shown that the overall survival in signet ring histology PM patients undergoing CRS/HIPEC is dramatically worse than other subtypes, with median survival ranging 12–14 months and 5-year survival rates of 0–7% [138, 139]. In fact, in both the PSDSS and the colorectal peritoneal metastases prognostic surgical score (COMPASS), signet ring cell histology has been given special consideration signifying poorer outcomes [120, 140].

12.5.2 Surgical Strategies for Obtaining a Complete Cytoreduction

Cytoreductive surgery attempts to remove all macroscopic disease using a combination of peritonectomy procedures and visceral resections which have been described by Sugarbaker [141]. When tumor involves visceral peritoneal surfaces, organ resections (splenectomy, large bowel or small bowel resection) are needed. When tumor involves parietal peritoneal surfaces, one of the five peritonectomies or stripping of the peritoneum is required [142]. One of the major limiting factors in obtaining a complete cytoreduction is the extent of small bowel involvement as resection of large portion has nutritional consequences [142].

12.5.2.1 Synchronous Resection of CPM and Liver Metastases

The presence of simultaneous liver and peritoneal metastases has been considered a contraindication for aggressive treatment at either of the disease sites [98, 143–145]. However, with reports of better results with liver resection done even in the presence of extrahepatic disease, including PM, these contraindications have become less absolute [145]. In a study by Kianmanesh et al., 43 patients had management of PM and liver metastases, 3 with liver resection prior to CRS/HIPEC, 10 done concurrently with CRS/HIPEC, and 2 done 2 months following CRS/HIPEC [146]. The survival of patients in the CRS + HIPEC and liver resection group was similar to the CRS + HIPEC alone group (median survival 36.0 vs. 35.3 months; $P = 0.73$). Three other studies, with sample size ranging from 14 to 37 patients, have addressed the outcomes of patients undergoing CRS + HIPEC

with synchronous liver resection, in highly selected patient cohorts [147–149]. Elias et al. selected 24 young patients with good performance status, mild to moderate PM, moderate operative risk (no invasion of hilum, vena cava, hepatic veins, extensive PM), and responding or stable liver metastases after 3 months of systemic chemotherapy. At a median follow-up of 6.1 years, the only prognostic factor significant for recurrence was number of liver metastases >3 [147]. Maggiori et al. compared 37 patients with synchronous resection of liver metastases and PM with 61 patients with PM alone. CRS + HIPEC with liver resection fared worse in terms of overall survival compared to CRS + HIPEC alone (40% vs. 66%; $P = 0.04$). Moreover, patients with PCI < 12 and no liver metastases had a median OS of 76 months compared to PCI < 12 and 1–2 liver metastases (40 months) and PCI >12 or >3 liver metastases (27 months) [149]. Based on these studies, it appears that performing concurrent liver resection and CRS for more than three liver metastases does not confer a significant OS benefit and should be avoided. Elias and collaborators in a study of 287 patients with LM or PM or both found no difference in survival in the three groups of patients treated with liver resection, CRS and HIPEC, or both (Fig. 12.1) [150]. Based on this study, they developed a graphic nomogram that is simple to calculate and easy to use and can determine the prognosis of patients according to the number of LM, the PCI, or both. This nomogram needs to be validated in prospective studies.

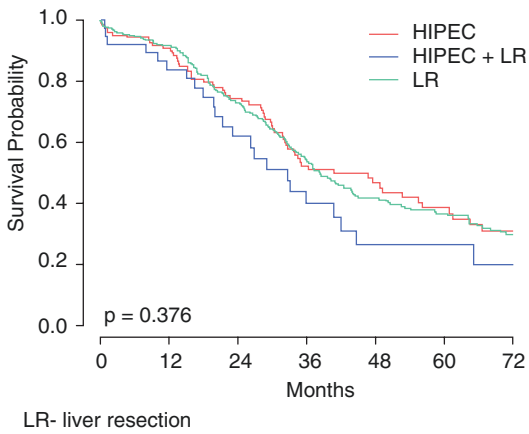


Fig. 12.1 Overall survival in patients with colorectal LM, PM, or both (From Ref. [151] with permission)

12.5.2.2 Resection of Ovaries

Synchronous ovarian metastases (OM) are reported in 1–9% of women undergoing surgical resection of a primary CRC, and metachronous OM occur in 1–7% [151, 152]. In patients with CPM, more than half of the women have OM diagnosed either before or synchronously shown in a study of 194 patients by Verwaal et al. [153]. These investigators recommended that a bilateral oophorectomy should be performed for all patients undergoing CRS and HIPEC. Patients with OM and PM have a similar OS and DFS when treated with CRS and HIPEC [154]. Women undergoing this treatment may not have completed their families and may be desirous of a future pregnancy. Of interest is the fact that in colorectal cancer, stromal involvement as opposed to capsular involvement is seen in majority of the patients as indicative to hematogenous spread [155]. Elias et al. evaluated the feasibility of ovarian preservation in 106 women aged less than 41 years undergoing CRS and HIPEC for PM [154]. Oophorectomy was done (1) when the ovary was macroscopically involved with tumor; (2) in case of clinical suspicion for tumor involvement based on intraoperative macroscopic inspection (presence of superficial tiny granulations or cysts); (3) systematically (contralateral oophorectomy) in patients who had previous unilateral oophorectomy at the time of initial surgery due to macroscopic involvement of one ovary, while the other macroscopically normal-appearing ovary was left in place; (4) when hysterectomy was needed due to tumor extent; and (5) in women who clearly did not want future pregnancy. Based on their findings, they recommend that a bilateral oophorectomy should be performed in all women who have suspicious involvement of both ovaries, when a hysterectomy is needed, and in women who do not wish to have anymore children. In women who have metastases in one ovary, the risk of contralateral ovarian metastases is 46% and a bilateral oophorectomy is recommended in these women as well. In women with grossly normal ovaries, the

risk of occult metastases is 17% and the risk of future metastases to the ovary is over 50%. They recommend conservation of ovaries in some of these patients though pregnancy following CRS and HIPEC in patients with CPM has not been reported in the literature [154, 156].

12.5.2.3 Urological Procedures

Some patients with limited disease may require a resection of the kidneys, ureters, or bladder like nephrectomy, partial cystectomy, and resection of a segment of the ureter, to attain a complete cytoreduction [157]. If complete cytoreduction can be obtained, these procedures show a survival similar to other patients with limited CPM. In this setting, resection of the ureters is very common and is never itself a contraindication to CRS; similarly, a nephrectomy is performed when required for a complete cytoreduction. However, a total cystectomy though technically feasible could be considered unethical as it is unlikely to offer any oncological benefit. At the senior author's institution, the procedure is never performed in the context of CRS/HIPEC. One small study reported increased morbidity with such procedures—the incidence of bowel fistulas and intra-abdominal abscesses was reported to be significantly higher though it was attributed to the extent of bowel resection rather than the urological procedure itself. Several other studies have reported no increase in morbidity [157–159].

12.5.3 HIPEC Methodology and Drugs

Several different HIPEC techniques have been elaborated for application in colorectal PM. Several drugs have been successfully used singly or in combination, at different concentrations, in different perfusates, for different durations, and at different effective temperatures [160]. Each modification of one of these parameters implies conducting a new pharmacokinetic study, which is not feasible. While this topic has been dealt with elsewhere, broadly the commonly used techniques are open and closed techniques. In an experimental study which compared the open to the closed technique, using intraperitoneal oxaliplatin at a temperature of 42°C, the systemic absorption and tissue concentration of oxaliplatin were higher by the open method. The closed method produced higher temperatures in the diaphragmatic cupolas, whereas the open technique performed better in other areas. Effective intraperitoneal hyperthermia could be achieved with both techniques, but systemic absorption and accumulation in the abdominal cavity were higher with the open technique [161]. There is no reported difference in the perioperative and survival outcomes between the two techniques [162]. In effect, it is very important to obtain a high and homogeneous temperature throughout the abdominal cavity, to routinely perform the same technique, which would render homogenous data for validation and analysis, as no prospective comparison of open and closed techniques of HIPEC in terms of survival, morbidity, or pharmacokinetics has ever been reported [163].

There are two commonly used regimens for HIPEC for colorectal PM: the first using mitomycin C (MCC) over 60 to 90 min at 41–43°C with a closed or open technique and the other using oxaliplatin (460 mg/m^2 of oxaliplatin in 2 L/m^2 of isoosmotic 5% dextrose) over 30 min, at a homogeneous temperature of 43°C (range, 42–44°C) with an open technique [164]. A bidirectional (intraperitoneal + systemic) intraoperative chemotherapy which combines intraperitoneal oxaliplatin preceded by an intravenous infusion of 5-FU (400 mg/m^2) with leucovorin (20 mg/m^2) is now mostly used for PM from CRC in Europe [164]. Current evidence does not show that one is superior to the other though there is a trend favoring the use of oxaliplatin. The various regimens in use of CPM are listed in Table 12.4. MMC has been used due to its high molecular weight, tissue penetration up to 5 mm, and a favorable pharmacokinetic profile that permits increased intraperitoneal concentration with limited systemic toxicity [165]. Oxaliplatin has a higher response rate when used intravenously in the metastatic setting as compared to MMC. Elias et al. have shown the efficacy and safety of intraperitoneal

Table 12.4 Various drug regimens for HIPEC for colorectal PM

Regimen	IP drugs	IV drugs	Carrier solution	Duration
Mitomycin C based				
Sugarbaker regimen [172]	Mitomycin C 15 mg/m^2 Adriamycin 15 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 liters of 1.5% dextrose peritoneal dialysis solution	90
Dutch high-dose mitomycin C regimen [173]	Mitomycin C 35 mg/m^2 17.5 mg/m^2 followed by 8.8 mg/m^2 at 30 and 60 min		3 liters of 1.5% dextrose peritoneal dialysis solution	90
ASPSM low-dose regimen: "concentration-based regimen [174]	Mitomycin C 40 mg/m^2 30 mg/m^2 followed by 10 mg/m^2 at 60 min		3 liters of 1.5% dextrose peritoneal dialysis solution	90
Oxaliplatin-based regimens				
Elias high-dose oxaliplatin regimen [175]	Oxaliplatin 460 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 liters/m2 5% dextrose solution	30
Glehen medium-dose oxaliplatin regimen	Oxaliplatin 360 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 liters/m^2 5% dextrose solution	30
Wake Forest University oxaliplatin regimen [167]	Oxaliplatin 200 mg/m^2		3 liters of 5% dextrose solution	120

oxaliplatin in pharmacological and clinical studies [166]. Its efficacy and tolerance have been demonstrated in another phase I study from the United States [167]. Three retrospective studies have tried to compare outcomes of mitomycin vs. oxaliplatin HIPEC [168–170]. The Dutch study by Homes et al. included 95 patients from two centers and did not show any difference in the survival outcomes between the two regimens [168]. In another retrospective multicentric study, 539 patients were included with stratification as per the PSDSS and survival results analyzed. For favorable histologies and low-burden patients (PSDSS I/II), the outcomes seemed to be better with mitomycin C with a median OS of 54.3 months with mitomycin C and 28.2 months for oxaliplatin [169]. However, the retrospective nature of this study and the non-standardized dose of oxaliplatin preclude definite conclusions from this study. Another Australian study of 201 patients showed a survival benefit of performing HIPEC with oxaliplatin as compared to MMC [170]. Currently, three randomized controlled trials—PRODIGE 7, PHOPHYLOCHIP, and COLOPEC—are using oxaliplatin-based HIPEC in the experimental arm. There is a high incidence of hemorrhagic complications when oxaliplatin is used, and its cautious use in patients with a high PCI is recommended [171]. In a preliminary analysis of the PRODIGE 7 trial that has completed accrual, the 30-day grades 3–5 morbidity was similar in the both the arms, whereas the 60-day grades 3–5 morbidity was higher in the HIPEC arm (unpublished data). HIPEC was performed using oxaliplatin.

12.6 Morbidity and Mortality

With an improvement in the patient selection, surgical techniques, perioperative management, and growing experience of certain "high-volume" or "expert centers," there has been a considerable reduction in the morbidity and mortality from this procedure, and it is similar to that of other major gastrointestinal surgeries. Reported morbidity and mortality rates range from 23 to 45% and 0 to 12%, respectively [147, 176, 177–179]. The surgi-

cal complications include anastomotic leakage, bleeding, and wound infection, and chemotherapy-related complications include neutropenia, cardiac arrhythmia, or renal insufficiency. Other complications common to surgical procedures in general include thrombosis, lung embolism, or pneumonia [180]. A learning curve exists for CRS plus HIPEC, and it's both the surgeon's and the institutional experience that has an impact on the morbidity and mortality [181, 182].

Several factors have been associated with an increased risk of complications. They include the duration of surgery, the age, the number of visceral resections, the need for a stoma, an increasing dose of chemotherapeutic agent, and recurrent cancer [178, 182–186]. The most widely accepted factor prognostic of morbidity and mortality is the extent of the peritoneal disease measured by PCI, with an increased risk of grade 4 morbidity (life-threatening complications) when the PCI is greater than 12 [184, 187, 188]. One study found an extensive disease involvement in the left hemidiaphragm to be the only significant predictor of severe morbidity on multivariate analysis, probably because this procedure results in respiratory complications, and in a higher risk of pancreatic leak, bleeding, and intra-abdominal abscess, due to the dissection of the hilum of the spleen [188]. There is a high incidence of hemorrhagic complications when oxaliplatin is used and its cautious use in patients with a high PCI is recommended [171]. In an interim analysis of the PRODIGE 7, male sex, transverse colon primary tumors, ureteral anastomosis, two or more bowel anastomosis, and two or more sites of bowel suturing were associated with a greater 30-day grades 3–5 morbidity. This analysis which is at present under review for publication highlighted two important points. Firstly, the rate of gastrointestinal fistulas was higher in the HIPEC group as compared to the non-HIPEC group. Though this difference did not reach statistical significance, fistulas occurred even in the presence of a diverting ostomy. The presence of a stoma did not prevent fistulas but reduced the incidence of peritonitis. Hence, the authors recommend that a protective ostomy should be performed in case of more than two areas of intestinal stiches, of more than two bowel anastomoses, or in case of rectal resection (unpublished data). Secondly, adding HIPEC with oxaliplatin to CRS did not significantly increase the overall rate of postoperative complications, and at 30 days it resulted in a mortality rate similar to that of CRS alone. The dose of oxaliplatin used in this study was 460 mg/m^2 for the open procedure and adapted to 360 mg/m^2 for the closed procedure. However, it increased significantly the rate of grades 3–4 complications at 60 days. However, the authors suggest that this should be interpreted with caution since the actual number of patients experiencing such complications was small and other studies have not reported similar findings. In this study, the grades 3–4 hematological toxicity was higher in the HIPEC arm. It was not of and consequence as most of these patients were managed without any clinical consequences. Passot et al. have suggested that a better indicator of the quality of surgery is "failure to rescue" rather than the morbidity [189]. In experienced centers, patients with complications are managed better, leading to a reduction in the mortality from the procedure.

12.7 Reiterative Procedures

Though CRS and HIPEC are performed with the intent of cure, around 70–80% of the patients will develop recurrent disease, and about half of these recurrences are confined to the peritoneal cavity [190–193].

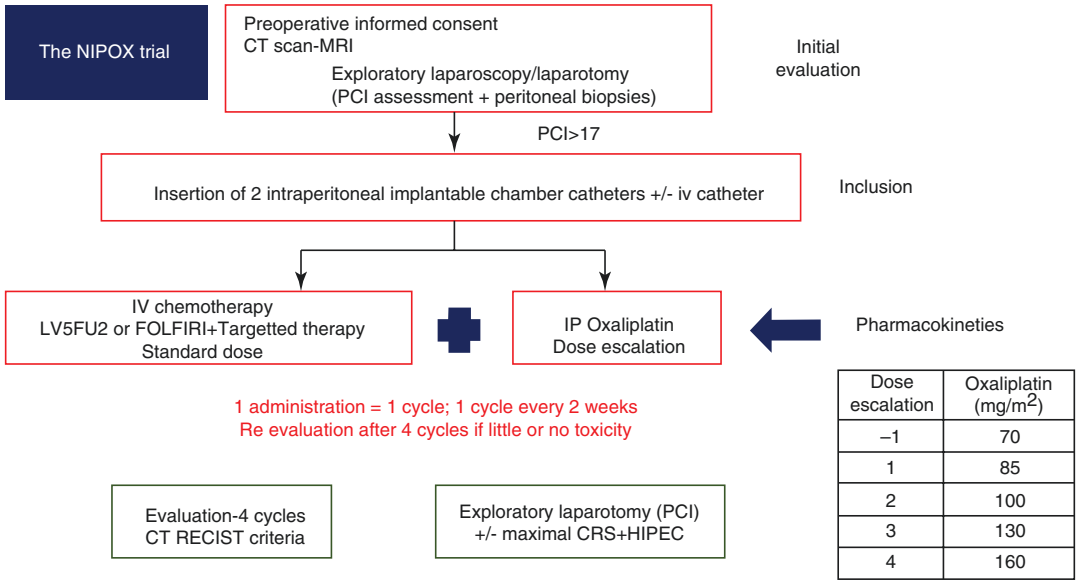
Over the years, evidence has accumulated showing the feasibility and survival benefit of a repeat CRS and HIPEC in selected patients [194, 195]. Bijelic et al. reported recurrent disease in 49 out of 70 patients with complete cytoreduction and perioperative intraperitoneal chemotherapy [193]. The median survival of patients who underwent a second surgery was significantly longer than that of patients who did not have a second operation (39 vs. 20 months; $P = 0.0003$). Diffuse peritoneal recurrence, isolated distant metastases, and diagnosis of recurrence within 6 months after CRS were associated with a worse prognosis. Median survival in complete

secondary CRS was 42 months as compared to 30 months for the whole cohort [193]. In another small study by de Simone et al., the survival after the second procedure was similar to that after the procedure. However, patients with PM from other primary sites were included in this study [196]. The morbidity and mortality of such procedures are similar to that of the first procedure in high-volume centers [197]. In the largest multi-institutional study from 11 institutions across the world comprising of 189 patients, the reported median survival was 26.4 months, disease-free survival 10.1 months, and 5-year overall survival 20% following a repeat CRS and HIPEC [198]. The median PCI was 6.9 and 81% of the patients had a complete cytoreduction. A PCI of <10 during the second procedure, a complete cytoreduction, and absence of grades 3–5 morbidity were associated with a favorable prognosis. Patients who had positive nodes during the first procedure had poorer outcomes. Though this study had limitations like the lack of a control group, and its retrospective nature, it showed that long-term survival is possible with a repeat procedure in selected patients.

12.8 New Treatment Strategies for Patients with Extensive CPM

There are still a large proportion of patients with CPM that are not candidates for CRS and HIPEC. Systemic chemotherapy leads to a favorable response only in a small percentage of patients.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an innovative intraperitoneal chemotherapy concept that seems to enhance the effectivity of IPC by taking advantage of the physical properties of gas and pressure [199]. PIPAC pharmacokinetics permit the use of a minimal drug dose which reaches a higher intraperitoneal concentration than in HIPEC. Increased intra-abdominal pressure is known to increase tissue uptake and intra-tumoral drug concentration [200, 201]. In addition, there is micronization of the cytostatic agent which creates a thin film of microdroplets over the entire peritoneal cavity, increasing the contact surface area between drugs and tissues. It is given in multiple sittings usually at three-weekly intervals through a laparoscopic approach. Systemic chemotherapy is used with it. The reported toxicity profile is acceptable in preliminary studies [202]. In patients pretreated with surgery and multiple lines of chemotherapy, it has produced symptom control, clinical response, and a prolongation of survival [203]. Prospective studies are needed to further define and expand its role [203]. A new bidirectional chemotherapy (neoadjuvant intraperitoneal-systemic chemotherapy protocol (NIPS)) was developed by Yonemura and his collaborators from Japan to induce a reduction of the peritoneal cancer index of patients with gastric PM [204]. NIPS can attack PM from both sides of peritoneum, not only from the peritoneal cavity but also from the subperitoneal blood vessels, and is considered a bidirectional chemotherapy [204]. Following a response to NIPS, selected patients become candidates for CRS and HIPEC. This treatment which has produced response rates of over 70% in patients with gastric PM is being investigated by Francois Quenet from Montpellier for CPM in the NIPOX trial (Fig. 12.2) [205]. In a pilot study, six patients with unresectable peritoneal disease of colorectal origin were included in the study. An intraperitoneal implantable chamber catheter was inserted during the laparotomy that evaluated the extent of the peritoneal disease (peritoneal cancer index 25 to 39). Patients then underwent intraperitoneal chemotherapy with oxaliplatin 85 mg/m^2 in combination with systemic chemotherapy (FOLFIRI or simplified LV/5-FU) and a targeted therapy every 2 weeks. Two patients completed the four intraperitoneal (IP) chemotherapy cycles without major toxicity. Two catheter perfusion incidents were reported due to the abdominal wall thickness. For one patient with aggressive disease, best supportive care was initiated after the first course of chemotherapy. The tolerance was acceptable for 85 mg/m^2 IP oxaliplatin combined with systemic therapy



Dose escalation	Oxaliplatin (mg/m^2)
–1	70
1	85
2	100
3	130
4	160

Fig. 12.2 The NIPOX trial

in these patients. This study formed the basis for the NIPOX trial [206].

Patients with a PCI of >17 are given a combination of systemic chemotherapy and intraperitoneal chemotherapy through two intraperitoneal catheters with implantable chambers. Responders are subsequently evaluated for CRS and HIPEC. Simultaneously, a dose escalation study for intraperitoneal oxaliplatin is being performed. Along similar lines is the IPOXA trial (NCT02866903), which is a phase I/II trial studying the administration of IP oxaliplatin (normothermic port-directed) with systemic FOLFIRI and bevacizumab in CPM of uncertain respectability. Currently, this trial is looking at morbidity, dose-limiting toxicity, and overall response rates of this treatment strategy.

12.9 Preventive Strategies for CPM

Majority of the patients with PM eventually succumb to the disease. The most appropriate treatment strategy would be to prevent the occurrence of PM.

12.9.1 The Cautious and Proactive Surgeon

While surgical teams across the world have been focusing on developing the skill to perform CRS and setting up HIPEC centers, how the primary tumor is dealt with has become equally important once again, as improper surgical handling can lead to peritoneal dissemination even in patients without high-risk features (described below) for peritoneal spread [207]. Cancer spread following resection of the primary can occur in the following ways—through portal dissemination, lymph nodal recurrence, recurrence at the operative site, and peritoneal spread [207]. Whereas portal dissemination cannot be prevented, other recurrences could be minimized by proper surgical technique. Patients with colorectal have decreased local recurrence and a longer disease-free survival when the resection of the primary tumor is performed by experienced surgeons at high-volume centers [208]. Hermanek et al. reported a variation in local recurrence from 5 to 55% between different surgeons which resulted in a 5-year survival rate varying from 34 to 85% [209].

Turnbull in his publication on *No-Touch Isolation Techniques* described a mechanism of cancer dissemination that is no longer acceptable [210]. However, the results of using this technique were far superior to any others published in the same time period [210].

Sugarbaker suggested that proper surgical technique can prevent peritoneal dissemination to a certain extent. In order to limit peritoneal spread, "containment" should be one of the main goals of the gastrointestinal cancer surgeon. He described a technique called "centripetal surgery" in which one must move around the tumor mass with perfect hemostasis, adequate margins of dissection, and sufficient visualization so that the vital structures are not damaged. If all of these requirements are not met, the surgeon must approach the malignant disease from another anatomic site [211, 212].

The other important aspect of prevention is surgical handling of patients with positive peritoneal fluid cytology or with peritoneal nodules at presentation. Non-definitive procedures except those needed in the emergency setting, i.e., for perforated or obstructed tumors, should be avoided. Sugarbaker pointed out that the peritoneum itself acts as a first line of defense against carcinomatosis, and in its absence, cells become implanted wherever a raw surface is created [213]. Non-definitive surgery in these situations has some adverse consequences. These patients become poor candidates for subsequent curative approach using CRS and HIPEC, the lymph nodal clearance becomes more difficult, and there is tumor cell entrapment in avascular scar tissue which cannot be treated with chemotherapy. Retroperitoneal implantation of tumor cells can involve tubular structures like the ureters leading to obstruction. When such a situation is encountered during laparotomy or laparoscopy, further surgical intervention should stop and the patients should be referred to a center experience in treating peritoneal metastases [213].

Laparoscopic surgery minimizes surgical trauma and, compared with open surgery, has been associated with less peritoneal as well as metastatic tumor growth in several animal models [214]. The technique has raised concerns regarding the potential effect of a CO_2 pneumoperitoneum on peritoneal cancer spread [215]. However, large clinical trials comparing open surgery with laparoscopic colectomy for colorectal cancer did not identify an increased risk of peritoneal recurrence associated with the laparoscopic approach [216]. The minimally invasive approach requires considerable amount of skill and should not be performed at the risk of compromising other oncological requirements like adequate margins, lymph node yield, and avoiding intraoperative tumor rupture and spill.

One of the most important prognostic factors determining the treatment outcomes in patients with PM is the disease extent determined by the peritoneal cancer index (PCI). In general, patients with less extensive disease have better outcomes, and one of the first treatment goals is to detect PM early in the course of disease evolution. In a study evaluating the Swedish registry data, which analyzed 11,124 patients with CRC treated between 1995 and 2007, PM was diagnosed in 8.3%, the prevalence of synchronous PM being 4.3%, and that of metachronous PM was 4.2%, with median time to recurrence around 14–16 months [217]. The known risk factors for peritoneal spread in patients with colorectal cancer are female sex; patients with primary mucinous adenocarcinomas; tumor stage T4; lymph node stage N2; a colonic primary, emergency surgery; and patients with positive resection margins [217, 218]. At the time of treatment of the primary malignancy, imaging modalities may fail to pick up low-volume disease, and during an open or laparoscopic resection, PM should be searched for and the extent documented in detail, especially in patients with known risk factors for peritoneal dissemination. For patients on surveillance also, the index of suspicion should be high. An elevation in tumor markers without evidence of disease on imaging should prompt the use of diagnostic laparoscopy for detection of early peritoneal cancer spread.

12.9.2 Role of HIPEC Is Prevention and Early Treatment of Peritoneal Metastases

One of the main concerns regarding the management of colorectal PM is that the disease is detected when the PM are extensive and patients are not eligible for a curative approach [218]. As the extent of the disease (PCI) and the completeness of resection are the main prognostic factors determining survival outcomes, it is obvious that survival results are dramatically better in patient detected with a low PCI [219].

Elias et al. performed a seminal study that has formed a basis of two randomized trials. They devised a strategy of systematic second-look surgery in patients at high risk of developing PM. In a systematic review of the literature comprising 16 studies evaluating 4395 patients, the same authors concluded that the only three factors that were consistently associated with a high risk of developing PM were synchronous PM completely resected, isolated ovarian metastases, and perforated primary tumor [14]. Based on this, they devised a new strategy which evaluated the role of systematic second-look surgery in 41 patients without clinical, radiological, or biological evidence of recurrence [220]. Patients considered to have high risk of developing PM were based on the three criteria mentioned above, present at the time of surgery for the primary tumor: resected minimal synchronous macroscopic PM ($n = 25$), synchronous ovarian metastases ($n = 8$), and perforation of the colon ($n = 8$). PM was discovered and resected in 23 (55%) patients during the second-look surgery, in spite of normal investigations. The mean PCI was low (8 ± 6) and peritoneal deposits were resectable in all of the patients. Grades 3–4 morbidity rate was low (9.7%). After a median follow-up of 30 months, OS and DFS of all patients at 5 years were 90% and 44%, respectively. Peritoneal recurrences occurred in seven patients (17%), six of whom had macroscopic PM discovered during the second-look surgery (26%). Based on these encouraging results, the phase III randomized study ProphyloCHIP (NCT01226394) was initiated. In this trial, patients who are at high risk of peritoneal recurrence and are clinically disease-free after completing 6 months of adjuvant therapy are randomized to a standard follow-up comprising of a 3 monthly follow-up for 2 years and then a 6 monthly follow-up for 3 years or a systematic second-look surgery followed by HIPEC with oxaliplatin. Another similar study sponsored by the NCI was underway in the United States (NCT01095523) [221], in which patients with CRC at high risk of developing PM who underwent curative surgery and subsequently received standard of care adjuvant chemotherapy were randomized to routine surveillance or second-look surgery and HIPEC 1 year after the primary surgery. This study, however, was abandoned before recruitment was complete.

In a case-control study carried out by Sammartino et al. in patients with advanced (T3/T4, any N, M0) colonic cancer of mucinous or signet ring cell histology, or perforated primary tumor of any histology without PM or other metastases, patients were either treated with standard colectomy ($n = 50$) or with additional surgical procedures apart from a colectomy that included omentectomy, bilateral salpingo-oophorectomy, resection of the hepatic round ligament, appendectomy, and HIPEC with oxaliplatin ($n = 25$) at the time of diagnosis [222]. The study group comprised of 25 patients with mucinous or signet ring cell histology T3/T4, any N, and M0 colonic cancer who underwent hemicolectomy, omentectomy, bilateral salpingo-oophorectomy, hepatic round ligament resection, and appendectomy followed by HIPEC with oxaliplatin during the resection of the primary, while the control group of 50 patients was treated by standard surgical resection during the same time period. There was no increase in the morbidity due to the additional surgical procedures performed in the experimental group; however, the recurrence rate was significantly lower than that in the control group (4% versus 22%; $P < 0.05$). The OS was similar in both groups, but the DFS was significantly longer in the experimental group

(36.8 versus 21.9 months; $P < 0.01$). Thus, this aggressive preventive surgical approach increased the disease-free survival significantly without increasing the morbidity. Based on these results, the PROMENADE trial (NCT02974556) has been initiated, which aims to determine the oncological effectiveness, compared to standard surgical treatment, of proactive management including target organ resection (omentectomy, bilateral adnexectomy, appendectomy, hepatic round ligament resection) and preventive HIPEC (intraperitoneal oxaliplatin with concomitant i.v. 5-fluorouracil/leucovorin) during a curative resection of high-risk (>/=5 mm tumor invasion beyond the muscularis propria) T3 and T4 colon cancer in preventing the development of peritoneal metastases. The primary outcome measure is incidence of PM at 36 months. Along the same lines, a Dutch study named the COLOPEC trial (NCT02231086) is a phase III randomized trial that aims to determine the oncological effectiveness of adjuvant HIPEC, using intraperitoneal oxaliplatin with concomitant i.v. 5-FU/LV, following a curative resection of a T4 or intra-abdominally perforated colon cancer in preventing the development of PM in addition to the standard adjuvant systemic treatment. However, in this trial the adjuvant HIPEC is given without any target organ resection, and the primary outcome measure is peritoneal recurrence-free survival at 18 months. Along the same lines, a multicentric phase III study is ongoing in China (NCT02179489) that will evaluate the disease-free survival of 300 patients at high risk of developing PM after HIPEC with mitomycin C after primary surgery (without target organ resection). Another study, the APEC trial (NCT02965248), is a phase II randomized study that plans to randomize 147 patients with colon cancer having T4NanyM0 or T3NanyM0 mucinous or signet ring adenocarcinoma undergoing an R0 resection into three arms, viz., (1) standard adjuvant chemotherapy only (control group), (2) HIPEC with raltitrexed (3 mg/m^2) intraperitoneally for 60 min during surgery or within 10 days after the operation, or (3) HIPEC comprising oxaliplatin (130 mg/m^2) during surgery for 30 min. The primary outcome measure is the incidence of PM at 3 years.

The above studies highlight the fact that the best way to deal with PM is to treat it early or prevent it and can potentially form the basis of future treatment for PM from CRC.

Conclusion

PM from colorectal cancer represents a subgroup of patients who are often diagnosed with advanced disease and have poor outcomes in spite of advances in modern chemotherapy and targeted therapy. The combined modality treatment of CRS and HIPEC offers a promising strategy especially if offered when the extent of peritoneal involvement is limited. Adequate patient selection is paramount in ensuring good results. Future strategies for prevention or early treatment of PM seem promising but require validation in the ongoing randomized trials. At the same time, new therapies for patients with extensive disease that is not amenable to aggressive therapy need to be further developed.

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13 Pseudomyxoma Peritonei Arising from Epithelial Appendiceal Tumours

Aditi Bhatt, Guillaume Passot, and Olivier Glehen

13.1 Introduction

Appendiceal tumours and pseudomyxoma peritonei (PMP), two rare entities, are often described in conjunction because of their close association. PMP is a clinical condition characterized by mucinous ascites and peritoneal implants, generally originating from a perforated mucinous tumour of the appendix. Mucinous appendiceal tumours are the cause of PMP in over 90% of the cases.

PMP represents a disease spectrum ranging from mucinous ascites with a benign mucinous tumour of the appendix at its origin to a high-grade mucinous adenocarcinoma. With cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), these patients experience a prolonged survival. Selecting appropriate patients for this treatment is necessary for achieving optimal results. The completeness of cytoreductive surgery and the disease biology are two major factors influencing the outcome.

13.2 Mucinous Appendiceal Tumours

A wide variety of tumours arise from the appendix, but the mucinous tumours are of particular concern due to their propensity for peritoneal dissemination. More specifically, it is the low-grade mucinous tumours that have generated a lot of debate. Despite having bland histopathological features, these tumours can invade through the appendiceal wall, cause rupture of the appendix and produce peritoneal implants.

Appendiceal tumours constitute 1% of all the intestinal neoplasms and 2% of colorectal cancers [1]. They are broadly classified as epithelial and non-epithelial tumours [2]. Carcinoid tumours are the commonest epithelial tumours followed by mucinous tumours. This chapter focuses on mucinous appendiceal tumours and some other tumours that have potential for peritoneal spread. There are several classifications that have been used to classify mucinous appendiceal tumours [3–5]. The first was proposed by Woodruff and Macdonald in 1940; the authors classified these tumours as benign mucocoeles and cystadenocarcinomas [3]. Currently, the two most popular classifications are the WHO classification (Table 13.1)

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Table 13.1 WHO classification of epithelial appendiceal tumours (Adapted from Ref. [6])

Epithelial tumours of the appendix	*Non-epithelial tumours*
Adenoma	Neuroma
• Tubular	Lipoma
• Villous	Leiomyoma
• Tubulovillous	Gastrointestinal stromal tumour
• Serrated	Leiomyosarcoma
Carcinoma	Kaposi's sarcoma
• Adenocarcinoma	Others
• Mucinous adenocarcinoma	Malignant lymphoma
• Signet ring cell carcinoma	*Secondary tumours*
• Small cell carcinoma	*Hyperplastic polyps*
• Undifferentiated carcinoma	
Tubular carcinoid	
Goblet cell carcinoid (mucinous carcinoid)	
Mixed adenoneuroendocrine carcinoma	
Others	

Table 13.2 PSOGI expert consensus classification of appendiceal epithelial tumours (Adapted from Ref. [7])

Classification of non-carcinoid epithelial neoplasia of the appendix	
Lesion	Terminology
Adenoma resembling traditional colorectal type, confined to mucosa, muscularis mucosa intact	Tubular, tubulovillous or villous adenoma with low- or high-grade dysplasia
Tumour with serrated features, confined to the mucosa, muscularis mucosa intact	Serrated polyp with or without dysplasia (low- or high-grade)
Mucinous neoplasia with low-grade cytological features and any of	Low-grade appendiceal mucinous neoplasm
• Loss of muscularis mucosa	
• Fibrosis of submucosa	
• Pushing invasion	
• Dissection of acellular mucin	
• Undulating or flattened epithelial growth	
• Rupture of the appendix	
• Mucin and/or cells outside the appendix	
Mucinous neoplasm with architectural features of LAMN and no infiltrative invasion but high-grade cytological atypia	High-grade appendiceal mucinous neoplasm
Mucinous neoplasm with infiltrative invasion	Mucinous adenocarcinoma: well, moderately or poorly differentiated
Neoplasm with signet ring cells (<50% of cells)	Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
Neoplasm with signet ring cells (>50% of cells)	(Mucinous) signet ring cell carcinoma
Non-mucinous adenocarcinoma resembling the traditional colorectal type	Adenocarcinoma, well, moderately or poorly differentiated

and the PSOGI expert consensus classification (Table 13.2).

In both these systems, a tumour in which the muscularis mucosa has not been breached is termed as an adenoma. Controversy exists when there is a breach of the muscularis mucosa. While the WHO classification considers any invasion beyond the muscularis mucosa as an adenocarcinoma, the PSOGI expert committee has classified these tumours based on the type of invasion (pushing or infiltrative) [6, 7]. In 'pushing' invasion, a broad front of cells expands into surrounding tissue without destructive features. Desmoplasia is not seen in these tumours. Features of infiltrative invasion include tumour budding (discohesive single cells or clusters of up to five cells) and/or small, irregular glands, typically within a desmoplastic stroma characterized by a proteoglycan-rich extracellular matrix with myofibroblasts with vesicular nuclei. Tumours showing the pushing type of invasion have been given the term 'low-grade appendiceal mucinous neoplasm (LAMN)'. These tumours have fibrosis but no desmoplastic response. Desmoplastic reaction is essential for classifying the tumour as an adenocarcinoma. There is another subgroup of tumours which have low-grade architectural features and high-grade cytological features. These are termed as 'high-grade appendiceal mucinous

neoplasm' (HAMN) [7]. Both LAMN and HAMN were grouped together by Carr et al. as tumours of uncertain malignant potential (TUMP); this term is not used anymore. The term 'mucinous adenocarcinoma' is used for mucinous tumours with infiltrative invasion. They are further classified as well, moderately or poorly differentiated.

According to the WHO classification, the diagnosis of an adenocarcinoma is made when the tumour invades beyond the muscularis mucosa. Adenocarcinomas are further classified as adenocarcinoma, not otherwise specified (NOS), mucinous adenocarcinoma, signet ring adenocarcinoma and an undifferentiated carcinoma [6].

The term 'mucocoele' is no longer used for neoplastic lesions of the appendix. It is used as a descriptive term and not a pathological diagnosis. Distension of the appendix with mucous ensuing from an inflammatory process with no evidence of hyperplasia or neoplasia is a mucocoele [4]. Similarly, the terms cystadenoma and cystadenocarcinoma are no longer used as pathological diagnosis.

In both the classifications, the term signet ring cell carcinoma is used for tumours in which >50% of all cells show signet ring morphology and >50% extracellular mucin defines a lesion as mucinous.

Most primary appendiceal adenocarcinomas arise from an adenomatous polyp or serrated adenoma. The non-mucinous tumours are also termed as 'intestinal type' or colonic type of appendiceal adenocarcinoma. The adenoma-carcinoma sequence seen in colorectal cancers is seen in appendiceal tumours as well.

13.3 Other Epithelial Appendiceal Tumours

Of the other appendiceal tumours, those that require special mention are the mixed exocrine and endocrine tumours that show features of both glandular and endocrine differentiation, because of their propensity for peritoneal spread and the potential for treatment with CRS and HIPEC.

13.3.1 Goblet Cell Carcinoids (GCC)

These are rare endocrine tumours that have various names, such as adenocarcinoid, mucinous carcinoid, crypt cell carcinoma and mucin-producing neuroendocrine tumour, but were first termed goblet cell carcinoid, in 1974 by Subbuswamy et al. [8]. GCCs are believed to be amphicrine tumours which originate from a single undifferentiated pluripotent intestinal epithelial crypt base progenitor stem cell that has dual neuroendocrine and mucinous differentiation. The natural history of these tumours is intermediate between carcinoids and classical adenocarcinomas. There is characteristic sparing of the mucosa. These tumours express CEA, CDX2, CK7 and CK20, but unlike adenocarcinomas, KRAS and b-catenin expression is absent. Most GCCs have been shown to stain inconsistently with neuroendocrine markers and contain very few endocrine cells (APUD cells).

Metastatic disease at presentation is seen in 14–63% of the patients, the commonest sites being the peritoneum and the ovaries [9]. Peritoneal metastases from these tumours have a poor prognosis than those form mucinous adenocarcinomas and similar to adenocarcinomas signet ring cells [10].

13.3.2 Mixed Adenoneuroendocrine Carcinoma (MANEC)

This term is used for carcinomas arising in a pre-existing goblet cell carcinoid. The other name used is adenocarcinoma ex-goblet cell carcinoid [7]. These carcinomas occur in apparent absence of neoplastic change in the mucosal epithelium.

13.4 Management

13.4.1 Clinical Presentation

Appendiceal tumours can be incidental, investigational or surgical findings or present with a wide variety of symptoms which may make them difficult to diagnose correctly at the first instance.

Some of the common presentations are as an incidental finding in the appendectomy specimen or, in a case of suspected appendicitis, as a pelvic or ovarian mass or during hernia surgery [11]. Patients with peritoneal dissemination can present with abdominal distension, increasing abdominal girth, fatigue, weight gain, shortness of breath and early satiety.

13.4.2 Surgical Treatment

An appendiceal tumour may be an incidental finding during an open or laparoscopic surgery performed for another indication, most commonly acute appendicitis, and the operating surgeon must be careful and well versed in dealing with it. If the tumour has not perforated or ruptured, every attempt must be made to avoid an iatrogenic rupture [12]. For benign non-carcinoid epithelial tumours, an appendectomy is sufficient provided the margin is free. For malignant tumours, conventionally, a right hemicolectomy is performed to clear the regional lymph nodes that could harbour occult metastases. For the intestinal type of adenocarcinomas, the reported incidence of lymph node metastases is high, 66.7% reported by Moreno et al. in an analysis of 501 patients. A right hemicolectomy is recommended for these patients. However, the same authors reported that, for mucinous appendiceal tumours, the incidence of lymph node metastases was only 4.2% and had no impact on survival [13]. There was no survival benefit of performing a right hemicolectomy over appendectomy if the tumour can be resected with clear margins. Similar results have been reported by other authors subsequently [14]. Sugarbaker et al. recommend the use of the sentinel node concept to decide if a right hemicolectomy is needed for a mucinous appendiceal tumour. At the time of the initial surgery or reoperation, the appendiceal nodes are dissected away from the posterior aspect of the caecum. Four to seven nodes lie in and along the appendiceal artery. This en bloc resection of the mesoappendix is submitted for frozen section. A right hemicolectomy is performed only if the nodes show metastases. To obtain a negative margin, a caecectomy can be performed instead of a hemicolectomy. Preserving the right colon is beneficial since many of these patients require a resection of the left colon/rectum [12]. In a recent report, Sugarbaker found low incidence (6.0%) of positive lymph nodes in patients with well or moderately differentiated peritoneal mucinous carcinomatosis (PMCA). In patients with high-grade disease, lymph node involvement was seen in 29.0%, and a right colectomy is advocated. For the mixed exocrine and endocrine tumours, a right hemicolectomy is recommended [15].

Sugarbaker also recommends that for both benign and malignant tumours, a thorough examination of the periappendiceal region and peritoneal spaces should be done for the presence of mucous, free fluid and/or tumour nodules, and if found, these should be sampled and sent for cytological examination. This practice helps in taking appropriate treatment-related decisions at a later stage. In female patients, the ovaries should be examined for the presence of metastases.

About 20% of patients with a mucinous neoplasm of the appendix develop PMP [16].

13.4.3 Proactive Management of Appendiceal Tumours

Fifty percent of the appendiceal tumours present with peritoneal dissemination [17] and 75% with acute appendicitis. A proactive approach can lead to early diagnosis and/or prevention of PMP leading to an improvement in the long-term outcomes.

Misdraji et al. found in a retrospective analysis of 107 patients with low-grade mucinous neoplasms that tumours confined to the appendix behaved in a benign manner with no recurrence after 6 years of follow-up, while the low-grade tumours with mucin and/or cells on the serosal surface had a 5-year and 10-year survival of 86 and 45%, respectively [5]. Macdonald et al. identified two subtypes of LAMN: LAMN I (disease confined to the appendiceal lumen) and LAMN II (mucin or neoplastic epithelium or in the appendiceal submucosa, wall or periappendiceal tissue

or both with and without perforation). Patients with LAMN II lesions were found to have an increased risk of developing peritoneal dissemination [18, 19]. When an appendiceal tumour presents as acute appendicitis, the patients are usually treated by general surgeons who may not be well versed in the management of these tumours and/or may not have the set-up to perform CRS and HIPEC. Moreover, the final diagnosis is usually made only after the surgical exploration and pathological diagnosis [17]. It is important that all tumours submitted for pathological examination are evaluated thoroughly for the presence of epithelial cells or mucin on the surface. For patients with a non-invasive mucinous tumour with mucin and/or epithelial cells on the serosal surface and no peritoneal spread, active surveillance with tumour marker evaluation and a CT scan every 6–12 months for 5–10 years is recommended [12, 18]. Peritoneal spread develops in 23–52% of patients with appendiceal neoplasms on surveillance after the initial surgery [20, 21]. Honore et al. in a retrospective study of 25 patients only 64% could undergo a complete cytoreductive surgery for PMP arising in patients who had undergone removal of a mucinous appendiceal tumour [21]. Hence, all efforts should be made to detect disease progression at the earliest. If peritoneal metastases are present, the patient should undergo CRS and HIPEC in an expert centre.

For an adenocarcinoma of the appendix, the approach is more aggressive. Sugarbaker recommends the following strategy: a second-look open surgery with a thorough exploration of all the peritoneal surfaces. If no peritoneal spread is found, a prophylactic surgery comprising of greater and lesser omentectomy, sampling of the appendiceal nodes (and a right hemicolectomy if they are positive) and bilateral oophorectomy with HIPEC should be performed. The ideal timing of such a procedure would be 6 months after the first procedure. If peritoneal spread is found during the second-look surgery, a complete CRS is performed in addition to the procedures listed above along with HIPEC. The rationale for such treatment is that for adenocarcinomas, the long-term outcome depends on the extent of the disease, and early disease could be missed by CT scans and tumour marker surveillance (CEA and CA-19-9) [11].

13.5 Pseudomyxoma Peritonei

PMP refers to the accumulation of mucin within the peritoneal cavity secondary to mucinous epithelial neoplasia.

It is defined as a clinical syndrome characterized by the presence of free or organized mucin with or without neoplastic cells in the peritoneal cavity and the typical pattern of redistribution [7].

It is considered a misnomer, and many authors do not use it anymore; however, in the absence of a more acceptable alternative, the term continues to be used widely [7]. Around 94% of cases of PMP develop from a mucinous tumour of the appendix [22, 23]. The less common sites of origin are a primary mucinous carcinoma of the ovary and adenocarcinomas of the gall bladder, stomach, colorectum, pancreas, fallopian tubes, urachus, lung and breast [23, 24]. When PMP develops from an ovarian tumour, it generally does so from a mature teratoma within which a mucinous neoplasm has developed [25, 26]. Primary ovarian mucinous tumours can closely mimic appendiceal metastases histologically, although there are some morphologic features in the ovary that may point to the appendix as the source [27]. PMP is now considered a malignant condition [7].

13.6 The Genesis of PMP

To begin with, there is neoplastic transformation of the appendiceal goblet cells resulting in a mucinous tumour. The tumour cells proliferate and secrete mucin leading to mucin accumulation. When the pressure within the tumour rises, it ruptures releasing mucin and tumour cells into the peritoneal cavity [28]. These tumour cells lack cell surface adhesion molecules and circulate passively with the peritoneal fluid. They get redistributed throughout the peritoneal cavity. This leads to mucinous tumour implants at the

sites of reabsorption of peritoneal fluid and dependent portions of the abdomen and pelvis which is characteristic of PMP and is known as the 'redistribution phenomenon'. Tumour deposits are commonly found in the pelvis/pouch of Douglas, right retrohepatic space, paracolic gutters, greater omentum, lesser omentum, ligamentum teres and the undersurface of the right hemidiaphragm [29, 30]. There is sparing of the peritoneal surfaces of the small bowel and its mesentery due to continuous peristaltic activity. Extensive tumour seeding may be seen around the antrum and the pylorus, the ileocaecal region and the rectosigmoid region; these areas are retroperitoneal and have limited mobility. Tumour deposits comprise of acellular mucin or mucin with cells with varying degrees of atypia with or without invasion. Fibrosis and/or a desmoplastic reaction is often present.

13.7 Classification of PMP

PMP has generally been classified according to the histology of the peritoneal disease rather than the primary tumour, since the outcome depends on the grade of the peritoneal disease and not the primary tumour; this is unusual in oncology [5, 31]. The classification has been confusing and a source of constant debate for several reasons. PMP is essentially the proliferation of mucin with varying amounts of epithelium which is usually bland, in the peritoneal cavity, yet it pursues a relentless course and if left untreated leads to death. However, unlike other malignant tumours, the disease remains confined to the peritoneal cavity for prolonged periods, and hematogenous spread which is characteristic of malignant disease is seldom seen. Organ invasion is uncommon except for the ovarian and splenic surfaces. This raises the question as to whether it should be considered benign or malignant [32]. The pathological classification is important as it provides an indication of prognosis following CRS and HIPEC and thus useful for selecting patients for this procedure. Patients with low-grade PMP appear to gain maximal benefit.

There are several classifications that have been used for the past few decades. The first and most popular is the classification proposed by Ronnet et al. in 1995 that divides PMP into three groups—disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) and an intermediate group called PMCA-I. According to this classification, DPAM represents the classic PMP with paucicellular mucinous ascites on the surface of the peritoneum without invasion, and an indolent clinical course, whereas PMCA has a higher percentage of overtly malignant cells/cell groups invading the tissue and a poorer prognosis. Peritoneal mucinous adenocarcinoma with intermediate features (hybrid tumours) has both features with PMCA representing at least 5% of the tumour [33]. Subsequently, Ronnet regrouped hybrid tumours with PMCA based on prognostic similarity [34].

Conversely, others like Bradley grouped the DPAM and hybrid tumours together [35].

The main pitfall of the Ronnet classification is that DPAM was considered benign, though it has a malignant behaviour. In 2010, the American Joint Committee on Cancer (AJCC) and WHO proposed a two-tiered classification for PMP:

- Low-grade PMP that is characterized by mucin pools with low cellularity (<10%), bland cytology and non-stratified cuboidal epithelium
- High-grade PMP that is characterized by mucin pools with high cellularity, moderate/severe cytological atypia and cribriform/signet ring morphology with desmoplastic stroma [36]

Though PMP is a clinical entity and not a pathological diagnosis, the WHO retains this term as a histological diagnosis [36].

Participants of the PSOGI expert consensus meeting have proposed a similar classification (Table 13.3); however, they recommend that the spread of mucin and epithelial cells should both be described separately. They also concluded that PMP should be regarded as a malignant condition

Table 13.3 PSOGI expert consensus classification of PMP (Adapted from Ref. [7])

Lesion	Terminology
Mucin without epithelial cells	Acellular mucin
PMP with low-grade histologic features*	Low-grade mucinous carcinoma peritonei OR disseminated peritoneal adenomucinosis (DPAM)
PMP with high-grade histologic features*	High-grade mucinous carcinoma peritonei OR peritoneal mucinous carcinomatosis (PMCA)
PMP with signet ring cells	High-grade mucinous carcinoma peritonei with signet ring cells OR peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)

* Omental cake and ovarian involvement can be consistent with a diagnosis of either low-grade or high-grade disease

and recommended the use of the term 'mucinous carcinoma peritonei' in favour of PMP.

The classification of PMP into low- or high-grade depends essentially on the epithelial component. Invasion of PMP through the peritoneum into the parenchyma of abdominal viscera can be seen in both low-grade and high-grade lesions as demonstrated by Carr et al. in their retrospective study of 274 patients [31]. They found no association between the grade and the frequency of organ invasion. Invasion was seen to spread inwards from the serosa and exhibited a rounded rather than infiltrative edge. It appeared to be due to direct spread and not blood-borne metastases. As opposed to this 'infiltrative' invasion of single cells or complex small glands, a desmoplastic stroma was associated with high-grade lesions. Thus, low-grade peritoneal deposits could have acellular mucin alone, mucin with non-invasive epithelium or mucin with non-infiltrative invasive epithelium. High-grade lesions showed infiltrative invasion with or without signet ring cells. The authors found a concordance between the degree of atypia in the primary lesion and the PMP except in two cases where high-grade appendiceal adenocarcinomas were associated with bland, low-grade PMP. Thus, in general, low-grade PMP is usually associated with LAMN, high-grade PMP with mucinous adenocarcinoma or signet ring cell carcinoma [31].

These classifications still do not clarify how the hybrid tumours (PMCA-I) are to be classified. The presence of epithelium with infiltrative invasion would warrant grouping them with high-grade PMP or high-grade mucinous carcinoma peritonei (Fig. 13.1).

13.8 The Importance of Signet Ring Cells

According to the Ronnet classification, even PMCA-I tumours can have signet ring cells, and some researchers classify PMCA-I with low-grade tumours which raises the question whether low-grade tumours can have signet ring cells. However, both the WHO and the PSOGI classification classify tumours with any percentage of signet ring cells as high-grade. In a retrospective study of 55 patients, Sirintrapun et al. demonstrated that the behaviour of tumours with signet ring cells floating freely in mucin pools was similar to high-grade adenocarcinomas with signet ring cells, whereas tumours in which the signet ring cells invaded the tissue had a poorer prognosis. Free-floating signet ring cells were usually present focally in their study [37]. Shetty et al. used a three-tiered grading system for PMP [38]. In their system, PMP1 was analogous to DPAM; tumours with any amount of signet ring cell morphology were classified as PMP3; and PMP2 was reserved for tumours that did not meet the criteria for PMP1 or PMP3 [38]. Tumours with any percentage of signet ring cells are considered to be of 'high-grade' though those with a smaller percentage may have a better outcome.

13.9 The Mucin in PMP

The mucin that is seen in PMP has certain characteristic features that differentiate it from mucinous peritoneal deposits arising from mucinous adenocarcinomas. Acellular mucin is seen in patients with PMP. The mucin in PMP is associ-

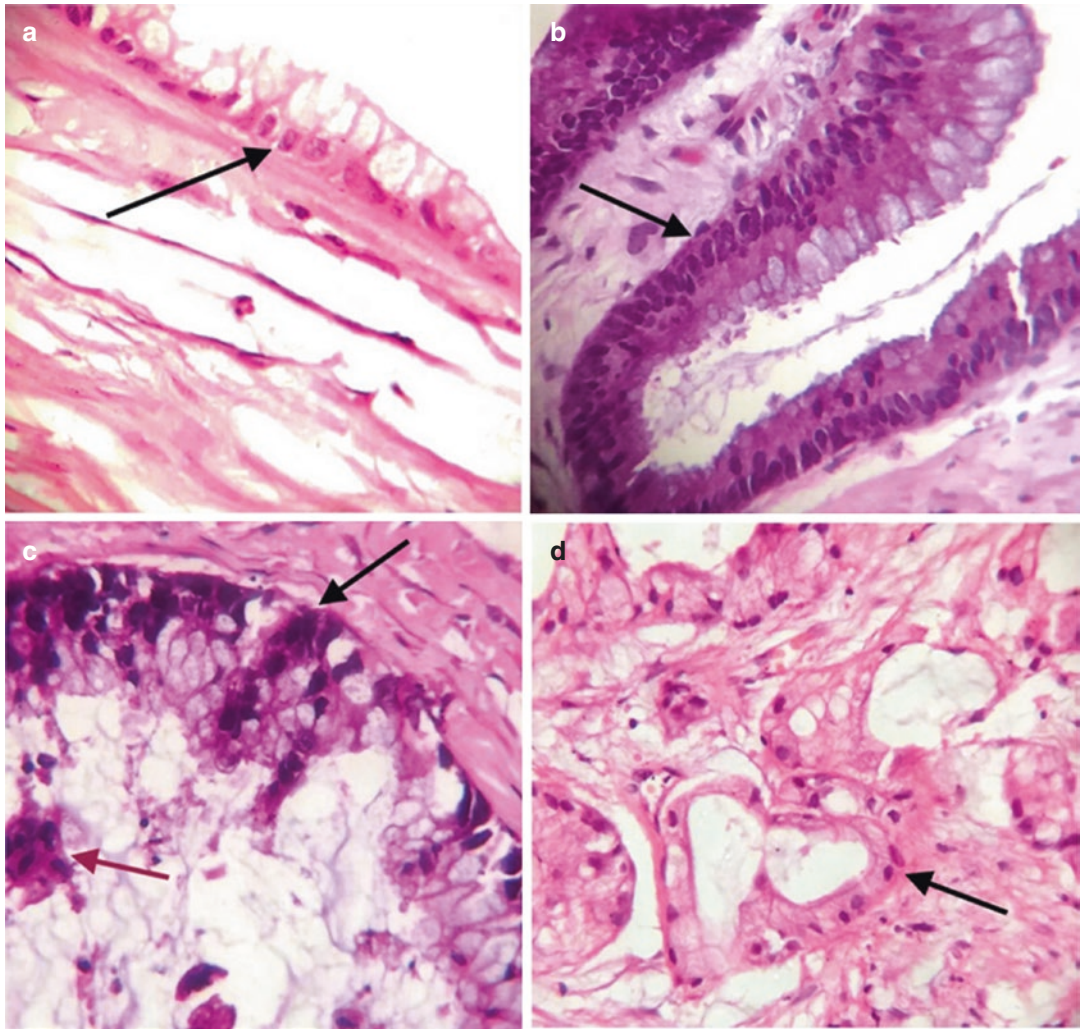

Fig. 13.1 Pathological spectrum of PMP. (**a**) Low-grade PMP with a single layer of cuboidal epithelium with basal nuclei. (**b**) Low-grade PMP-pseudostratified columnar epithelium with basal nuclei and apical mucin, without desmoplasia. (**c**) Low-grade tumour with high-grade cytological atypia—area of epithelium with high-grade cytological features and foci of necrosis (red arrow); however, no infiltrative invasion/organ invasion was seen. (**d**) High-grade PMP epit, characteristic of infiltrative invasion

ated with an inflammatory reaction and has fibrosis and ingrowth of blood vessels [39].

Mucins are secreted by normal epithelial cells in the body and line the mucosal surfaces. They are a group of high molecular weight heavily glycosylated proteins also called MUC proteins. There are two types of mucins—membrane-associated mucins and secreted mucins. There are two types of secreted mucins—gel-forming and non-gel-forming [40, 41]. Colonic mucin is a gel-forming mucin, and this is the mucin that is secreted in PMP. There are various gel-forming mucins of which MUC2 is specifically secreted in the small intestine and colon [42].

MUC2 is more extensively glycosylated and more voluminous, and hence there is abundant mucin collection with an average mucin/cell ratio of >10:1. O Connell showed that primary ovarian mucinous tumours express MUC5AC, while solitary appendiceal mucinous tumours express MUC2 and MUC5B. MUC2 is a molecular marker for PMP [43, 44].

The mucin in PMP is ectopically secreted and increasingly deposited in the peritoneal cavity where it is unable to degrade or drain away forming voluminous gels over months and years. Most of the tumour cells are surrounded by the mucin coat that allows them to move freely, disseminate and redistribute within the peritoneal cavity. This coating also acts as a protective shield against immune recognition and chemotherapy [42].

13.10 Management

13.10.1 Presentation: Symptoms and Signs

PMP tends to be an incidental finding either on imaging or during exploratory surgery performed for other indications, most commonly acute appendicitis or evaluation of a pelvic mass, less commonly during hernia surgery. Intraperitoneal accumulation of mucin itself produces almost no symptoms till there is gross distention resulting in abdominal discomfort and breathlessness. These patients are usually well preserved till very late in the course of the disease when obstruction sets in and oral intake is compromised. Typically, the symptoms are out of proportion with the clinical findings.

13.10.2 Establishing a Diagnosis

A history of appendectomy with subsequent development of peritoneal metastases/ascites may point towards the diagnosis. PMP has certain classical imaging features like scalloping of the liver, spleen, etc. which also help in the diagnosis. In less advanced cases, the density (high attenuation due to mucin) of the ascitic fluid on CT scan is suggestive of mucinous ascites and PMP [45]. When a complete cytoreduction is deemed possible and the clinical picture befits PMP, a biopsy may not be necessary. When the diagnosis is in doubt or a non-surgical intervention is planned, it is prudent to perform a biopsy for confirmation of the diagnosis and to determine the grade of PMP. An ultrasound-guided aspiration of the mucinous fluid which is often the first test to be performed may yield only fluid without cells and may be inadequate [46]. A peritoneal or omental biopsy performed laparoscopically or at open surgery is ideal. For paracentesis and laparoscopy both, no lateral puncture or port sites should be used as this may result in abdominal wall tumour seeding, reducing the probability of disease eradication. Many times, laparoscopic access and visualization may be compromised by disease extent, in particular a large omental cake, rendering accurate laparoscopic assessment impossible [47].

13.10.3 Investigations

13.10.3.1 Tumour Markers: CEA, CA125, and CA19.9

These should be performed for all patients undergoing CRS and HIPEC. Several studies have found that preoperative marker elevation correlated with an inferior survival. Patients with one or more marker elevations are less likely to have a complete cytoreduction, have a propensity to recur and have a poor survival compared to those that have normal markers [47–49]. These markers can be used for follow-up as well, and rising markers post-surgery are indicative of disease recurrence [50].

13.10.3.2 Imaging for PMP

CT scan The most commonly performed investigation is a contrast enhanced CT scan of the thorax, abdomen and pelvis. Mucinous disease is typically represented by areas of low attenuation with islands of high attenuation due to solid material within the mucinous ascites.

Some of the findings characteristic of PMP are (Fig. 13.2):

- Scalloping of the surfaces of the liver and spleen by the mucinous deposits
- Sparing of the small bowel serosa
- Extensive omental involvement
- Loculated intraperitoneal collections
- Curvilinear calcifications
- Fluid around the appendix or a mass in the appendiceal region [51]

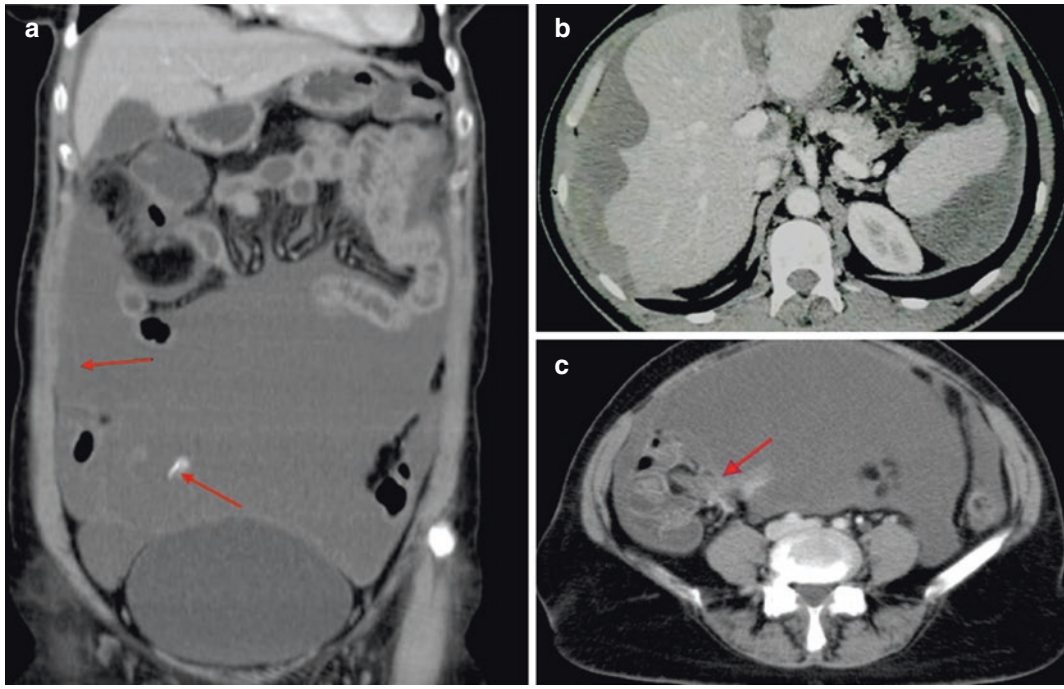

Fig. 13.2 Characteristic CT findings in PMP. (**a**) Loculated fluid collections with areas of calcification, sparing of the small bowel; (**b**) scalloping of the surfaces of the liver and the spleen; (**C**) mass in the region of the appendix

A CT scan is also used to evaluate the extent of the disease and determine the peritoneal cancer index (CT-PCI). The accuracy of a CT in predicting the PCI is dependent on the lesion size. For lesions <0.5 cm, it is 11% as opposed to 37 and 94% for lesions measuring 0.5–5.0 cm and those >5 cm, respectively [52]. The BIG-RENAPE and RENAPE working groups have developed the PeRitOneal MalIgnancy Stage Evaluation (PROMISE) Internet application (www.e-promise.org) to facilitate tabulation and automatically calculate the peritoneal cancer index (PCI). This application offers computer assistance to produce simple, quick but precise and standardized pre-, intra- and postoperative reports of the extent of peritoneal metastases [53].

In contrast to colorectal and gastric cancer, there is no cut-off for PCI beyond which a CRS should not be performed provided a complete tumour removal is possible. However, it does have prognostic significance as patients with lower PCI have a longer survival [12].

The small bowel and its mesentery are the areas that are most difficult to clear of all the disease, and predicting the extent of disease in this area is an important part of the preoperative evaluation. Sugarbaker et al. defined two kinds of small bowel involvement:

1. Compartmentalization: In this situation, a large volume of mucinous tumour surrounds a compartmentalized small bowel. The bowel loops may be pushed to one side of the peritoneal cavity. However, the contour of the bowel loops is normal, and the patient has no gastrointestinal symptoms. Such a patient would have a high probability of a complete cytoreduction (Fig. 13.3).
2. Diffuse involvement of the small bowel: In this situation, there is diffuse infiltration of the spaces between the small bowel with mucinous tumour, and the patient has a low likelihood of a complete cytoreduction (Fig. 13.4) [12].

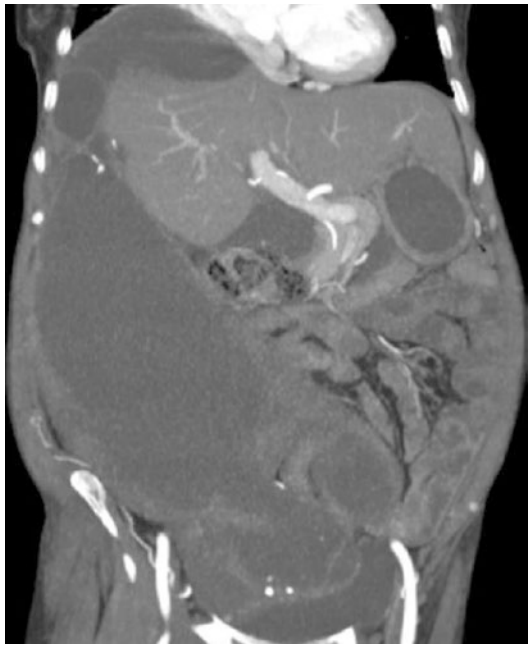

Fig. 13.3 Compartmentalization of the small bowel on CT scan—the small bowel is pushed to the left upper quadrant of the abdomen but is uninvolved by tumour

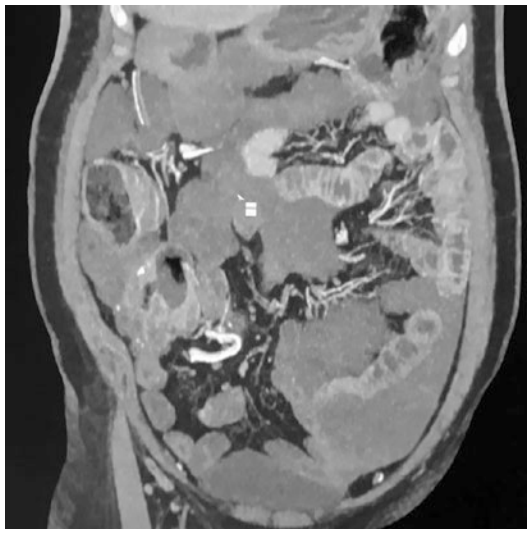

Fig. 13.4 CT scan showing mucinous tumour involving the serosa of the small bowel at multiple sites

Other adverse radiological features associated with small bowel involvement include segmental obstruction and tumour masses greater than 5 cm on the small bowel and its mesentery. When both features are present, there is an 88% probability of incomplete resection compared with a 92% probability of complete resection when both are absent [54].

Other adverse features of CT scan which would preclude a complete cytoreduction are:

- Involvement of the bladder trigone, pancreatic head and porta hepatis
- Massive or diffuse involvement of the pleural space [55]

A simplified preoperative assessment for appendix tumour (SPAAT) score has been developed by Fournier et al. based on computed tomography scan findings thought to predict incomplete cytoreduction. This score is based on scalloping on organs by mucinous deposits and the degree of small bowel mesentery foreshortening. A score of >3 is a predictor of inoperability [56]. However, it is possible to attain a complete cytoreduction even in the presence of organ indentation, and hence the value of such a score is questionable.

MRI

MRI is being increasingly used for assessment of peritoneal metastases, and some have reported a greater accuracy in predicting the PCI [57]. However, it requires a stringent protocol: bowel preparation, 6 h of fasting and prolonged scan time. In the hands of experienced radiologists, it has been found to be more accurate in predicting small bowel involvement as compared to a CT scan. MRI may be better for detecting small volume disease as compared to CT [58]. Both CT and MRI can be used in conjunction to accurately predict operability.

FDG-PET Scan

FDG-PET is used by some in patients with appendiceal adenocarcinoma for detecting distant metastases, whereas most would prefer a CT scan of the thorax, abdomen and pelvis [59]. In a prospective study of 34 patients, Passot et al. found that though CT was more accurate in predicting the extent of peritoneal spread, preoperative 18F-FDG-PET distinguished DPAM from

PMCA or hybrid forms, with a sensitivity of 90% and a specificity of 77%. The authors concluded that preoperative 18F-FDG-PET may be useful in differentiating between pathological grades based on uptake of 18F-FDG and that the combination of 18F-FDG-PET with CT scan improves evaluation of peritoneal spread [60].

13.10.4 Patient Selection

Two issues need to be addressed while selecting patients for the procedure: the patient's ability to withstand the procedure and the ability of the surgeon to completely remove the tumour. Patients with a good performance status (ECOG 0-1) fare better and those with a poor performance status and these patients should be excluded. Similarly, patients with a serum albumin level of less than 3 g per decilitre have a poor outcome. A complete blood count and biochemistry and anaesthesia evaluation is done for all patients. For both high- and low-grade tumours provided that a complete cytoreduction is possible, a surgery is warranted irrespective of the PCI. For high-grade tumours, preoperative chemotherapy may be considered for patients in whom the surgeon is not confident of a CC-0/1 [12]. There is no cut-off of PCI beyond which a complete cytoreduction cannot be achieved. Similarly, a poor general condition does not always preclude an aggressive surgical approach. However, such decisions are best made by a multidisciplinary team in an expert centre. Evaluation of patients at expert centres ensures that no patient is denied the opportunity to undergo a curative resection.

13.10.5 Treatment

Compared to colon cancer, mucinous appendiceal tumours with peritoneal spread tend to remain confined to the peritoneal cavity with a low incidence of spread to the lymph nodes, liver and other distant sites of metastases. This unique tumour biology makes them candidates for aggressive loco-regional therapy. Recurrences outside the abdomen and pelvis are uncommon.

The standard of care for PMP is aggressive loco-regional therapy comprising of complete cytoreductive surgery and HIPEC [61–63]. The conventional treatment used to be repeated is drainage of mucin or debulking surgery comprising of removal of the primary tumour and the omentum. In two publications from the Mayo Clinic, reporting the results of debulking surgery for low-grade appendiceal mucinous tumours, the 10-year survival was 32% in one series and 5-year survival 6% in another [64, 65]. In 2005, Miner et al. reported a 10-year survival of 21% (12% disease-free) in 97 patients treated by serial debulking, systemic chemotherapy and/or delayed intermittent intraperitoneal 5-fluorouracil over a 22-year period at Memorial Sloan Kettering Cancer Center [66].

Contrary to this, Sugarbaker reported a 5-year survival of 86% in patients with low-grade tumours undergoing a complete cytoreduction in a series of 385 patients [67]. An expert consensus panel discussion at the Fifth International Workshop on Peritoneal Surface Malignancy in Milan, Italy, concluded that there was a survival benefit of the procedure compared with historical controls [62]. Subsequently, 2298 patients from 16 specialized institutions around the world treated with cytoreductive surgery and HIPEC experienced a median survival rate of 196 months (16.3 years) and the median progression-free survival rate of 98 months (8.2 years), with 10- and 15-year survival rates of 63 and 59%, respectively [68]. In the largest single institution series of 1000 patients, Moran et al. reported a 5- and 10-year overall survival of 87.4 and 70.3%, respectively, in the 738 patients who had CC-0/1 compared with 39.2 and 8.1%, respectively, in patients who had a CC-2/3 resection [69].

Though the reports from expert centres report a mortality of 2% and a grade 3–4 morbidity of 24%, these could be significantly higher when the procedure is undertaken by less experienced teams [68]. Selecting patients is crucial, and only those patients who will derive benefit from the procedure should be subjected to it. The goal of CRS should be complete removal of macroscopic disease. Several prognostic indicators have been identified for patient selection.

13.10.6 Surgical Interventions

The goal of cytoreductive surgery is to attain a complete cytoreduction (cc0, no residual tumour; or CC-1, residual tumour <2.5 mm). A midline incision from the xiphoid to the pubis is required with resection of all the previous scars.

For this one or more of the five peritonectomies with resection of adjacent viscera are required. Only the areas of disease involvement are resected. Normal peritoneal surfaces are not resected. The only exception is a total omentectomy which is performed even with no macroscopic tumour deposits in the omentum. A detailed description is provided elsewhere [70]. When the disease is extensive, a thorough exploration is performed to look for contraindication for CRS, and no bowel should be resected till the surgical plan is finalized. Sugarbaker advocates the use a ball-tipped cautery at high voltage that leaves a margin of heat necrosis and devoid of tumour cells [71]. However, several surgeons have their preferences, including the use of bipolar scissors, the ultrasonic scalpel or a combination of any of the above.

Of particular mention is the technique of resection of Glisson's capsule that is frequently involved in PMP.

Conventionally, the tumour is destroyed using high-voltage pure-cut electro-evaporation. But complete tumour removal like that of a peritoneal resection may not be achieved by this method. Glehen and his collaborators have described the technique of digital glissonectomy using blunt finger dissection and a bipolar scissors by which a fast and bloodless Glisson's capsulectomy can be performed [72]. The procedure can be combined with an atypical liver resection if required. In their institutional experience of 91 procedures, the authors reported that it did not add to either the morbidity or mortality of CRS significantly [73].

13.10.7 Multi-visceral Resection for Achieving Complete Cytoreduction

Approximately one third of the patients with PMP present with extensive disease. While there is no standard definition of what constitutes extensive disease, Elias et al. have defined it as a PCI of >28 as 'huge PMP' [74]. Patients with extensive disease usually require resection of multiple viscera and one or more segments of the bowel.

Sacrificing large segments of the small bowel that leads to a remnant 2 m is often the limiting factor for achieving a complete CRS. When the remnant is smaller than 2 m, patients require total parenteral nutrition. When the total colectomy is required, at least 3 m of small bowel needs to be preserved, and if the colonic remnant is less than 30–50 cm, at least 2.5 m should be preserved [74].

Mucinous tumour that enters the lesser sac through the foramen of Winslow will accumulate by gravity in the sub-pyloric space which is a cul-de-sac beneath the pylorus [74]. For complete cytoreduction, mucinous tumour accumulation in the sub-pyloric space must be cleared.

If there is tumour accumulation in the sub-pyloric space and the left gastric artery can be preserved, a complete cytoreduction can be achieved without gastrectomy. In other cases, complete tumour clearance requires a partial or total gastrectomy [75] (Fig. 13.5).

Sugarbaker initially used a staged procedure performing a high jejunostomy to drain the enteric secretions followed by a Roux-en-Y anastomosis few months later in patients who required a total gastrectomy for achieving a complete cytoreduction [76]. Recent studies have shown

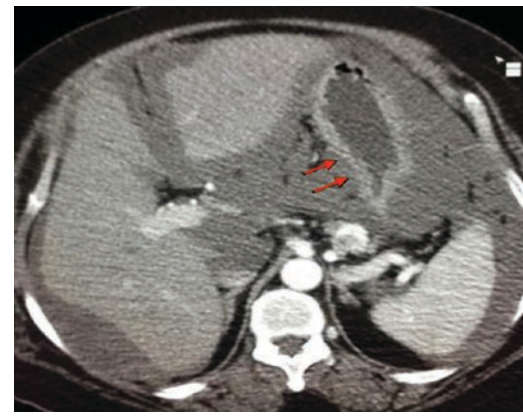

Fig. 13.5 CT scan showing extensive upper abdominal disease with encasement of the antrum of the stomach and serosal involvement—the patient will require at least a partial gastrectomy to clear the disease around the stomach

that in experienced centres, immediate restoration of gastrointestinal continuity is feasible and safe [77, 78]. In a review of 1014 patients of PMP by Moran et al., 12% of the patients received a total or partial gastrectomy. The morbidity was significantly higher in patients undergoing a gastrectomy (31 vs 13%, $p = 0.001$), but there was no difference in the mortality. Patients requiring a gastrectomy experienced a good long-term survival (5-year DFS of 48% and 5-year OS of 77%) though this was significantly inferior to that in patients not requiring a gastrectomy [79].

Contrary to these reports, Elias et al. do not recommend a total gastrectomy for patients with PMP, stating that these patients require extensive small bowel resection that precludes maintaining a good nutritional status and quality of life [74]. A total gastrectomy should not be performed in patients who have undergone extensive small bowel resection.

Yonemura et al. reported the results of performing a total gastrectomy and total colectomy in 48 patients with a median PCI of 33. Grade 3–5 complications were seen in 18 (37.5%) patients, and the mortality was 2.1% [80]. Patients who had staged resections had an acceptable quality of life.

For tumour seeding in the pelvis, resection of the pelvic peritoneum along with the prevesical peritoneum, pouch of Douglas and the rectosigmoid may be needed to attain a complete cytoreduction. Pelvic peritonectomy begins in a centripetal fashion from the pelvic and prevesical peritoneum towards the rectum and the mesorectum preserving the retroperitoneal structures like the ureters, gonadal vessels and iliac vessels [81]. The plane of dissection is anterior to these structures and is largely an avascular plane. The inferior limit of the dissection is the seminal vesicles in males (and the uterine cervix in females). Once the anterior wall of the rectum is completely freed and the cul-de-sac dissected en bloc with the pelvic peritoneum, the rectum is transacted in its mid portion after clearing the mesorectum [81]. A stapled end-to-end tension-free anastomosis is performed. When the anastomosis is above the peritoneal reflection, a temporary ileostomy can be avoided. Sugarbaker has described the technique of inverting the stapled anastomosis with a layer of interrupted silk sutures and avoiding a temporary ileostomy provided 10–15 cm of the rectum is preserved [82]. In a series of 958 patients undergoing CRS and HIPEC from Basingstoke, 34.5% of the patients required a stoma for achieving complete CRS of which 25% of the patients had a permanent stoma. All temporary stomas in this series were subsequently reversed [83].

13.10.8 Laparoscopic CRS and HIPEC

For selected patients with limited disease extent (PCI < 10) and low PMP, laparoscopic CRS and HIPEC have been used with the goal of reducing the morbidity and hospital stay [84–86]. The reported conversion rates were low and improved with experience. Patient selection is important. The drawbacks of this approach are difficulty in properly assessing certain areas like the small bowel mesentery, technical difficulty in obese patients and those with extensive prior surgery, the potential for dissemination of malignant cells (debatable) and prolonged operative times [86]. With growing experience, the utility of such procedures could increase specifically in patients with more extensive disease.

13.10.9 Small Bowel Transplant

The peritoneal surface malignancy team from Basingstoke in conjunction with an organ transplant team has performed small bowel and multivisceral transplant for four patients of PMP with end-stage disease and intestinal failure over a period of 2 years. Two patients died of postoperative complications. The two patients who survived were independent of TPN for over a year and experienced a good quality of life [87]. The long-term outcomes of such procedures need to be looked into to determine their role in the treatment of PMP.

13.10.10 HIPEC

HIPEC is performed after complete tumour removal by the open, semiopen or closed technique for a duration of 30–120 min using a mitomycin C or oxaliplatin-based regimen. There are various protocols used in clinical practice, and current evidence does not show the superiority of one over the other (Table 13.4). Oxaliplatin is cleared rapidly from the peritoneal cavity (80% in 60 min); hence, HIPEC is performed for 30 min, while mitomycin C takes a longer time (80% in 90 min) to clear; hence, the HIPEC duration is 90 min [93]. A simultaneous intravenous infusion of 5FU is included in some protocols.

The mechanism is enhanced concentration of the drug in the heated peritoneal surfaces leading to prolonged exposure of the tumour to the drug [93]. There is a variation in the toxicity profile of the two drugs, but a head-to-head comparison in terms of efficacy is not available. The carrier solution for oxaliplatin is 5% dextrose which can result in hyperglycaemia, hyponatremia and metabolic acidosis in the postoperative period [94]. These effects become more pronounced at a perfusion temperature of 42–43° C [95]. In a recent report by Verwaal et al., using Dianeal instead of 5% glucose leads to a significant reduction in the electrolyte imbalance and hyperglycaemia in the perioperative period [96]. HIPEC with oxaliplatin is also associated with a greater reduction in the neutrophil and platelet count in the postoperative period as compared to a mitomycin-based protocol [97]. There is a significant increase in the haemorrhagic complications following HIPEC with oxaliplatin as reported by the retrospective multicentric French study of 771 patients. The incidence of postoperative haemorrhage was 14.3%, and a PCI of >12 was an independent risk factor for haemorrhagic complications ($p = 0.040$) [98]. The dose of oxaliplatin is according to the Elias protocol of 460 mg/m^2 which is several times higher than that for intravenous administration [91]. Currently, two other regimens that use a lower dose of oxaliplatin are in clinical use.

Table 13.4 Various drug regimens for HIPEC for appendiceal tumours

Regimen	IP drugs	IV drugs	Carrier solution	Duration
Mitomycin C based				
Sugarbaker regimen [88]	Mitomycin C 15 mg/m^2 Adriamycin 15 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 L of 1.5% dextrose peritoneal dialysis solution	90
Dutch high-dose mitomycin C regimen [89]	Mitomycin C 35 mg/m^2 17.5 mg/m^2 followed by 8.8 mg/m^2 at 30 and 60 min		3 L of 1.5% dextrose peritoneal dialysis solution	90
ASPSM low-dose regimen: 'concentration-based regimen' [90]	Mitomycin C 40 mg/m^2 30 mg/m^2 followed by 10 mg/m^2 at 60 min		3 L of 1.5% dextrose peritoneal dialysis solution	90
Oxaliplatin-based regimens				
Elias high-dose oxaliplatin regimen [91]	Oxaliplatin 460 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 L/m^2 5% dextrose solution	30
Glehen medium-dose oxaliplatin regimen	Oxaliplatin 360 mg/m^2	5-Fluorouracil 400 mg/m^2 Leucovorin 25 mg/m^2	2 L/m^2 5% dextrose solution	30
Wake Forest University oxaliplatin regimen [92]	Oxaliplatin 200 mg/m^2		3 L 5% dextrose solution	120

13.10.11 EPIC and Postoperative Intraperitoneal Chemotherapy

Some surgeons administer early postoperative chemotherapy in addition of HIPEC or as an alternative. Many others do not administer it because of the probability of a prolonged hospital stay and complications and uncertain benefit. The most commonly used regimen of EPIC is the one by Sugarbaker in which 5-fluorouracil is given for 4 days as an intraperitoneal instillation in 1.5% peritoneal dialysis fluid at 400 mg/m^2 [12]. The total dose should not exceed 2 g/m^2 including what has been given as part of the bidirectional chemotherapy. Patients who have had systemic chemotherapy previously may not tolerate the full dose. EPIC should be avoided in patients who are at a high risk of developing bowel fistula in the postoperative period—patients who have had extensive surgery over the bowel or bowel damage fall into this category [12].

In the largest multi-institutional study by Chua et al., EPIC had a favourable impact on the overall survival, but less than half the patients received it [68]. In a retrospective study of 250 patients, Morris et al. demonstrated that the combination of HIPEC + EPIC leads to a significant benefit in overall survival for patients with LAMNs with PMP compared with HIPEC alone without increasing postoperative morbidity and mortality [99]. In another retrospective study of 93 patients, no difference in OS and DFS was observed between patients with high-grade appendiceal adenocarcinoma treated with CRS and HIPEC + EPIC versus HIPEC alone. However, HIPEC + EPIC patients experienced a greater morbidity [100].

At Memorial Sloan Kettering Cancer Center, patients are given multiple cycles of postoperative intraperitoneal chemotherapy through an intraperitoneal catheter: intraperitoneal 5-fluoro-2′-deoxyuridine (1000 mg/m daily for 3 days) plus leucovorin (240 mg/m^2) during each cycle. The number of such cycles is variable and depends on the tolerance of the patient. In a retrospective study of 50 patients who received 1–9 cycles of such treatment, the authors reported a 5-year DFS of 43% and a median OS of 9.8 years [101].

Another retrospective study in Norway of 93 patients compared EPIC and HIPEC following complete cytoreduction and showed no difference in 10-year OS and DFS [102]. However, both these are small retrospective studies, and the survival is inferior to that shown by CRS and HIPEC in larger studies. A randomized, non-blinded, phase II clinical trial is currently ongoing at MSK—'Intraperitoneal Chemotherapy After cytoreductive Surgery' (ICaRuS). It is the first head-to-head comparison between HIPEC and EPIC after complete cytoreduction in patients with neoplasms of the appendix, colon or rectum with isolated peritoneal metastases (https://clinicaltrials.gov/ct2/show/NCT01815359).

13.11 Prognostic Indicators

Proper selection of patients for treatment is important to ensure that only those patients who actually benefit from the procedure are subjected to it. Quantitative prognostic indicators have been established that allow the surgeon to predict the likelihood of long-term benefit. Apart from the general health and fitness for the procedure, these indicators should be taken into consideration before taking up a patient for surgery [103].

The most important prognostic indicator is the completeness of cytoreduction (CC) score; a complete cytoreduction indicates that either there is no visible residual disease (CC-0) or the residual tumour deposits measure less than 2.5 mm in size and can be eradicated by the HIPEC (CC-1). Any residual disease >2.5 mm (CC-2 residual disease measuring 2.5 mm–5 cm or CC-3 residual disease measuring >5 cm) is considered debulking. Chua et al. reported a 5-year survival of 85% in patients with CC-0 and 80% in patients with a CC-1 resection as opposed to only 24% in patients with gross residual disease (CC-2/3) in the largest multi-institutional study published so far. The difference was statistically significant and was not influenced either by the tumour grade or PCI [68]. Similarly in the largest single institutional study of 1000 patients, the 5- and 10-year overall survival was 87.4 and 70.3%, respectively, in the 738 patients who had a complete CRS compared with 39.2 and 8.1%, respectively, in patients with

CC-2/3 resections [69]. Achieving a complete cytoreduction especially in patients with a high tumour burden requires a considerable amount of skill and is associated with a prolonged learning curve (90 procedures for the surgeon and 100 procedures for the centre) [104]. Hence, such procedures should be taken up by surgeons and centres that have the necessary expertise and experience, baring which referral to someone more experienced is warranted.

This is reiterated by the fact that patients with low-grade mucinous carcinoma peritonei (DPAM) and high-grade mucinous carcinoma peritonei (PMCA) experience a 5-year and 10-year survival of 73 and 68% (for DPAM), respectively, and 56 and 46% (for PMCA), respectively, for PCI >31–39 [68]. In another series of 48 patients with a median PCI of 33, Yonemura et al. reported a 5-year overall survival of 48.6% [80]. PCI is still an important prognostic variable for patients with DPAM and PMCA both. However, unlike colorectal and gastric cancers, there is no cut-off of the PCI level beyond which a complete cytoreduction should not be attempted. For some patients, rather than the actual PCI, it is the anatomical location of the disease which is important. Especially in cases of small bowel involvement where despite a PCI that is not very high, it may be impossible to clear the entire tumour from the bowel surface and its mesentery. Another group of patients is those who have had multiple prior attempts at cytoreduction and have unresectable disease at crucial anatomic sites like the common bile duct, the base of the bladder or pelvic sidewall. The presence of residual unresectable disease at these crucial anatomic sites overrides the favourable effect on the prognosis of low PCI score [105].

The other important prognostic factor is the tumour grade or the histologic subtype. Ronnet and colleagues originally described diffuse peritoneal adenomucinosis (DPAM, median survival 112 months) and the more aggressive peritoneal mucinous carcinomatosis (PMCA, median survival 24 months).

Chua et al. reported a significantly better 5- and 10-year overall survival for patients with DPAM and hybrid tumours as compared to PMCA (81 and 70%, respectively, for DPAM; 78 and 63%, respectively, for hybrid tumours; and 59 and 49% for PMCA) [68]. In contrast to this, Levine et al. reported a median OS of only 18 months in 110 patients with high-grade tumours which increased to 36 months in patients who had a complete removal of macroscopic disease (CC-0). However, included in this analysis were non-mucinous tumours, and neuroendocrine tumours with or without goblet cell differentiation were included as well [106]. For both high- and low-grade tumours, where a complete CRS is possible, it should be the first line of treatment.

13.12 Other Prognostic Factors

13.12.1 Prior Surgical Score

The prior surgical score quantifies the extent of non-definitive surgery that was performed prior to CRS and HIPEC. Prior surgical score (PSS) ranged from 0 to 3 and looks at abdominal regions 0–8. PSS-0 indicates no prior surgery or only a biopsy, PSS-1 for surgery in one abdominal region only, PSS-2 for surgery in two to five regions and PSS-3 for surgery in more than five regions [12]. The biopsy could be an open or laparoscopic biopsy, a CT-guided biopsy or a paracentesis with cytology. The number of abdominopelvic regions is additive for all prior surgical procedures; hence, the PSS is a composite of all prior surgeries [105].

Sugarbaker has demonstrated that in most areas, the peritoneum serves as the first line of defence against peritoneal metastases and cancer does not spread to the connective tissue below the peritoneum at least in early stages of the disease [107]. The exceptions are the milky spots in the omenta, at the junction of the small bowel and its mesentery, the lacuna in the diaphragm and naturally occurring raw areas on the surface of the ovary due to corpus haemorrhagic. The commonest cause of breach in the peritoneum is prior debulking surgery that leads to the implantation of intraperitoneal tumour cells at the surgical resection sites, deep to the peritoneum. Tumour implanted in the scar tissue deep to the peritoneum may be impossible or difficult to remove by peritonectomy or eradicate by intraperitoneal

chemotherapy [107]. Moreover there is formation of intra-abdominal adhesions that makes subsequent cytoreduction technically challenging. In a retrospective study of 83 patients, Chua et al. demonstrated that upfront treatment conferred a superior 5-year recurrence-free survival rate (77 vs 37%, $p = 0.011$) and 10-year overall survival benefit (67 vs 35%, $p = 0.054$) [10]. A prior surgical score of >2 has a negative impact on both DFS and OS [68].

13.12.2 Lymph Node Involvement

Chua et al. demonstrated an inferior survival in patients with lymph node involvement both in low-grade and high-grade PMP. The 5-year survival was similar in node-positive patients in both these subgroups (50% for DPAM, 43% for PMCA) [68]. In another retrospective study of 250 patients, patients with positive lymph node involvement had a greater risk of death than those without (HR = 2.87, $p = 0.009$) [108].

Wagner et al. identified three high-risk features: high tumour grade, lymph node involvement and incomplete cytoreduction. They found that the presence of one or more of these features was associated with an inferior survival, and subsequently they came up with a prognostic staging system and nomograms [109].

13.12.3 Prior Chemotherapy

Prior chemotherapy has been associated with a poorer overall and disease-free survival. This is probably due to the fact that patients with either high tumour burden or PMCA would be the ones receiving chemotherapy [68, 108].

13.13 Debulking Surgery

Patients with extensive disease may be declared inoperable before the procedure. Without treatment, these patients experience worsening of symptoms, bowel obstruction and death. They might obtain some symptom relief and prolongation of life by a debulking surgery. The likelihood of benefit from surgical treatment in such cases has to be balanced against the risk of postoperative complication and the ensuing deterioration in the quality of life. Some patients planned for a complete cytoreduction are found to have unresectable disease during surgery and end up with a CC-2/3 resection.

There is no consensus on what is the most appropriate treatment for such patients.

The questions that arise in this situation are:

- Should a debulking surgery be performed in patients that seem inoperable?
- Which patients benefit from debulking surgery?
- What should be the extent of surgery?
- Should such procedures be combined with perioperative chemotherapy?

Moran et al. in their study of 1000 patients reported a 5- and 10-year overall survival of 39.2 and 8.1%, respectively, in 242 patients who had a major tumour debulking [69]. Major debulking in their series comprised of an extended right hemicolectomy, greater omentectomy and splenectomy with an ileocolic anastomosis or a total colectomy with an end ileostomy [69].

Another strategy as proposed by Delhorme et al. is to perform maximal tumour debulking, leaving less than 20% of the disease in areas where it is not likely to cause symptoms, with the goal of obtaining prolonged OS and long-lasting relief of the symptoms, thus ensuring a good quality of life [110]. The visceral resections mostly performed comprise the distal portion of the stomach, a total or subtotal colectomy and a part of the small bowel preserving at least 2.5 m. The areas on which tumour may be left behind are the undersurfaces of the diaphragms, Glisson's capsule, the whole rectum (if there is no stenosis) and the nonobstructive nodules measuring less than 10 mm on the small bowel. The authors recommend that all efforts should be made to avoid creating a stoma as stomas created in such situations have a greater likelihood of

being permanent. Use of any form of intraperitoneal chemotherapy is not recommended by them in view of the higher risk of major morbidity. The 5-year overall survival was 46% in this series compared to 15 and 30% in other series [66, 110].

Glehen et al. reported 3-year and 5-year survival rates of 34% and 15%, respectively, in 174 patients who had incomplete cytoreductive surgery with or without perioperative intraperitoneal chemotherapy [111]. Thirty-seven patients who did not receive any form of intraperitoneal chemotherapy due to inter-bowel adhesions had an inferior survival than those who received either HIPEC or EPIC or both ($p < 0.001$). Sixty-one patients had HIPEC, and these patients had a better survival that those who did not ($p < 0.001$). The authors also mentioned that there was a selection bias in favour of patients who had perioperative chemotherapy (POC). No patients with lymph node involvement were alive at 2 years, and the 2-year survival of patients with signet ring cells was less than 30%. The authors did not recommend an incomplete CRS and POC for these patients [111].

Thus, there is enough evidence to suggest that such procedures may provide a prolongation of life and symptomatic relief in selected patients. However, such decisions should be made by multidisciplinary teams and the treatment executed in experienced centres, to ensure that no patient is deprived of a complete cytoreduction where it is possible. Whereas the use of HIPEC is recommended by some, others do not advocate it.

13.14 Morbidity and Mortality

The crux of the combined modality treatment has been the morbidity. It has been demonstrated quite clearly that an increase in the experience leads to a reduction in the morbidity and mortality both, this being attributed to an improvement in patient selection, perioperative management and surgical expertise [112]. According to recent reports, the grade 3 and 4 complication rate ranges from 22 to 34% and mortality from 0.8 to 4.1% [68, 113–115]. Some of the factors associated with increased morbidity are increasing number of prior surgeries, prior surgical score of 3 and a PCI > 20 [66]. Several studies have shown that two or more bowel anastomosis have a significant impact on morbidity of patients undergoing CRS and HIPEC [116–118]. Increasing number of peritonectomies also increases the morbidity. Only the number of anastomoses seems to have an impact on morbidity, not the number of organs resected [119].

13.15 Role of Chemotherapy

Though peritoneal dissemination from mucinous appendiceal tumours is a stage 4 disease, the standard of care is CRS and HIPEC irrespective of the tumour grade. The role of chemotherapy is not clear in these patients. It may be used as adjuvant therapy in patients with high-grade disease or with other poor prognostic factors. It may also be of use in patients deemed unresectable or those having a recurrence after CRS and HIPEC.

Evidence to support the use of systemic chemotherapy after complete CRS and HIPEC in patients with high-grade PMP is scarce. Though some authors still claim that chemotherapy is the standard of care for high-grade PMP, the evidence to support such a recommendation is even more scarce [120].

Analysis of a national cancer database showed that the use of chemotherapy did not improve the OS in patients with mucinous histology, while there was a benefit in patients with non-mucinous histology. The surgical details were not available, but patients who had some kind of surgery in addition to chemotherapy had better outcomes. Stratification according to grade is not available either [121].

Some small retrospective studies have shown a benefit of adjuvant chemotherapy for high-grade tumours; others have not [122].

FOLFOX 4 has shown to be active in patients who are deemed unresectable or have relapsed after CRS and HIPEC [123]. The addition of bevacizumab to chemotherapy in such patients has shown to improve both the progression-free and overall survival [124]. An older study showed a

benefit in 38% of patients with unresectable disease receiving mitomycin C and capecitabine [125]. FOLFIRI has also shown activity in these tumours [126].

In a prospective study of 34 patients, Sugarbaker et al. concluded that CRS may be facilitated in 20% of the patients. There was no difference in outcomes between 3 and 6 months of FOLFOX. There was less toxicity if the treatment was given for 3 months and disease progression is minimized in nonresponders. An accurate assessment of response was possible only by exploratory laparotomy. Three patients experienced downstaging to DPAM from PMCA, and 29% had a complete or near-complete histopathologic response [127]. In another series of 26 patients receiving systemic chemotherapy ± bevacizumab, 58% had a response based on improvement in imaging, biomarkers or both, and 34% had stable disease [128]. Another study showed a benefit only in signet ring cell tumours [129].

13.16 Lysis of Mucin as a Therapeutic Option for PMP

Recurrence is common in patients with PMP. The progressive accumulation of mucin is debilitating. There is a theoretical possibility to using a mucolytic agent in addition to CRS and HIPEC to reduce the risk of recurrence. Similarly, it can be used to dissolve mucinous masses and aid surgery or be used as a palliative option. Dextrose has been proposed as mucolytic agent, but its clinical benefit is unproven [130–133]. There are case reports showing benefit of other agents like sodium bicarbonate [134]. Other in vitro studies showed a benefit of agents like ascorbic acid and hydrogen peroxide used in combination [135]. Morris et al. have demonstrated the mucin-lysing effects of a combination of N-acetyl cysteine and bromelain in in vitro studies as well as in in vivo studies in animal models without significant adverse effects [136, 137]. In in vitro models, this combination has also shown to limit tumour growth [138]. This approach appears to be promising in preclinical studies.

13.17 Follow-Up of Patients

Following definitive treatment, patients are followed up with tumour markers CEA and CA19-9. A CT scan of the thorax, abdomen and pelvis is performed every 6 months for 5 years. The rationale for active follow-up is the ability to detect and treat recurrent disease. Elective reoperation for recurrent disease is beneficial for selected patients.

13.18 Recurrence and Its Management

Approximately one in four patients develops recurrence after complete CRS and HIPEC for PMP of appendiceal origin [139]. Recurrence can be diffused or localized. A diffuse recurrence represents an aggressive disease biology or insensitivity of the tumour to intraperitoneal chemotherapy especially if the recurrence-free interval is short. This type of recurrence is associated with a poorer survival. Localized recurrence is probably due to tumour cell entrapment at the suture line or in adhesions and has a better prognosis [140]. In some cases, the cause of recurrence is technical failure as in the subhepatic region which is a very difficult area to clear [141].

The rationale of a repeat CRS and HIPEC is the probability of infrequent metastasis outside the peritoneal cavity, compressive rather than invasive behaviour of the recurrent disease, relative sparing of small bowel and a good response to intraperitoneal chemotherapy as shown by Sugarbaker et al. in one of the first published series of second-look surgery [142]. A repeat CRS+ HIPEC was performed in 79/111 in their series resulting in a 3-year survival of 73.6%. Subsequently many other series have shown favourable outcomes with repeat CRS and HIPEC not just for the first but also for subsequent recurrences (Table 13.5) [143].

Some of the factors associated with an increased incidence of recurrence are a high PCI at initial surgery, higher tumour grade and those who have received preoperative chemotherapy [149].

Table 13.5 Outcomes of repeat CRS and HIPEC (Adapted from Ref. [143])

Ref	Year	N	PCI	High-grade	Overall survival	PFS	Median follow-up (months)	Grade 3 and 4 morbidity	Mortality	CC-0/1
[142]	2001	98	NA	NA	5-year 73.6%	NA	NA	NA	NA	68.4% (Second CRS)
[140]	2007	98	19.0 (mean)	38.0%	5-year 90%	5-year 70%	66.0	NA	NA	78.0% (Second CRS)
[144]	2003	45	NA	5.0%	5-year 70%	NA	NA	11.0%	4.4%	57.8% (Third CRS)
[145]	2005	38/97	NA	48.0%	Median survival 9.8 years	NA	BA	16% (of all operations)	4.0% (entire population)	35.% (Overall)
[146]	2013	26	>20 (65%)	61.5%	5-year 33.9 months	NA	28.0	27.0%	0.0%	96.0%
[147]	2012	33/62	9.2 (mean)	15.2%	Median survival 52.1 months	NA	60.8	14.5%	3.2%	R0-R1 43.5%
[148][a]	2017	66	NA	66%	5-year 68% 10-year 61%	5 years 39% 10 years 19%	85	38%	NA	83%

N number of patients, *PCI* peritoneal cancer index, *PFS* progression-free survival, *NA* not available
[a]Study included ten patients with isolated extraperitoneal recurrence

Patients with elevated tumour markers before surgery are more likely to have a recurrence. Dubreil et al. found a SUV max on preoperative FDG-PET/CT of >2.02, an independent predictive factor for PFS in PMP [149].

Patient selection is important and should be discussed in a multidisciplinary meeting. Some of the factors to be considered are the performance status, the extent of the peritoneal disease, recurrence-free interval from the first surgery, the completeness of primary surgery and the grade of the PMP [149]. The commonest sites of recurrence are the small bowel and the pelvis [139]. Elias et al. have suggested that if HIPEC has failed, a second attempt would not be successful as well. For localized recurrence, they recommend a CRS alone especially if the time interval from the first procedure is less than 1 year. If the relapse is diffuse and develops after a long disease-free interval, but is amenable to a complete CRS, they recommend intraperitoneal chemotherapy with a different drug [150]. The role of systemic chemotherapy in such patients is not clear. For a diffuse relapse occurring at a short interval from the first procedure, with dedifferentiation to a more aggressive tumour, a surgical intervention is unlikely to be useful, and these patients are candidate for systemic chemotherapy [150].

Sugarbaker et al. reported the results in patients with three or more operative procedures. The 5- and 10-year survival rates reported were 60 and 48% for 3 interventions, 78% and 36% for 4 and 100 and 80% for 5 or more interventions, respectively [144]. Complete cytoreduction, especially at the subsequent procedures, was associated with improvement in survival. The authors noted a change in histologic type in subsequent procedures in 47% of the patients. In 14

patients, a more aggressive histologic type was noted, whereas the remaining had less aggressive pathologic type noted on repeat CRS; however, survival was not statistically impacted by change in tumour histology [144].

Thus, repeat CRS/HIPEC for appendiceal primaries results in long-term survival in appropriately selected patients not just at the first recurrence but for the subsequent recurrences as well.

13.19 Molecular Profile of Appendiceal Tumours and PMP

The long-term outcomes of CRS and HIPEC for PMP are heterogeneous even in subgroups based on clinical and pathological variables. The identification of additional prognostic and predictive biomarkers is an unmet clinical need [151]. Some mutations have been found to occur in a high proportion of these patients. *KRAS* mutations are the commonest, in both appendiceal tumours (53–100%) and PMP (57–100%) [152–156]. It is more frequently seen than in colorectal cancers. Some series report a higher incidence of these mutations in patients with PMCAs, whereas others have reported a similar incidence in both DPAM and PMCA. Most of mutations are found on codons 12 and 13 of exon 2. The difference between the lowest and highest frequencies could be due to a variation in the sensitivity of the detection method and the tumour cell percentages in the samples; most of these tumours have a low cellularity which makes analysis difficult [157]. The second commonest mutation is the *GNAS* codon 201 mutation which has been found in 40–70% of the patients with PMP and 40–77% of the patients with LAMN [156–158].

GNAS encodes the α-subunit of a stimulatory G-protein (Gαs) responsible for the production of adenylyl cyclase. *GNAS* mutations cause the constitutive activation of adenylyl cyclase and an elevated cAMP level, regardless of the presence or absence of receptor agonists [159, 160]. *GNAS* mutation promotes tumorigenesis only, not cell growth, thus leading to the indolent behaviour of mucinous tumours. But it increases the expression of MUC2 and MUC5AC implying the role of this pathway in mucin overproduction. However, this is not the only pathway responsible for mucin overproduction [161]. *GNAS* mutations are also seen in other tumours of the gastrointestinal tract like villous adenomas of the colorectum, pyloric gland adenomas of the stomach and duodenum and intra-pancreatic mucinous neoplasms suggesting a preferential association with tumours having a benign or indolent behaviour [162–165]. They are rare or absent in adenocarcinomas arising from these organs [163, 165].

Both *KRAS* and *GNAS* mutations have been shown to have a negative impact on the progression-free survival [151, 166].

BRAF V600E, *PIK3CA*, *AKT1*, *SMAD4* and *APC* mutations are rare in PMP tumours, and they express mismatch repair enzymes.

BRAF V600E, *PIK3CA*, *AKT1*, *SMAD4* and *APC* mutations are relatively uncommon in PMP tumours [157, 166, 167].

Microsatellite instability and p53 overexpression are reported to be infrequent [161]. However, p53 has been associated with high-grade histology and a reduced survival [168, 169]. Deregulation of PI3K-AKT pathway has also been implicated in the progression to PMCA [169].

Conclusion

Cytoreductive surgery and HIPEC substantially prolong the disease-free and overall survival in patients with PMP arising from mucinous appendiceal tumours. The best results are obtained when such treatment is carried out at expert centres. An accurate diagnosis and classification, institution early definitive surgical treatment and aggressive surgical efforts to achieve complete tumour removal yield the best results. Even patients with recurrent disease benefit from CRS and HIPEC and experience a prolonged survival. About one fourth of the patients have disease that is not completely resectable, and other treatment modalities need to be employed. An increase in the knowledge about the molecular biology of these tumours has led to the identification of

molecular targets for drug therapy. New therapeutic approaches like small bowel and multivisceral transplant and mucin-lysing therapy are currently being investigated and developed for the management of these patients.

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14 Intraperitoneal Chemotherapy for Gastric Cancer

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14.1 Introduction

Gastric cancer (GC) is the world's fourth fastest growing cancer [1]. It is an aggressive cancer with poor prognosis. Peritoneal metastasis (PM) is present synchronously in 14–40% of cases [2, 3], and metachronous PM is present in 10–46% of patients after curative surgery [4]. Almost 60% of deaths occur due to PM. The peritoneum is the sole site of recurrence in 12–40% of patients with a median survival of only 6 months [2, 4]. Both neoadjuvant and adjuvant chemotherapy protocols have marginally improved the survival without decreasing the incidence of PM. With all modern chemotherapeutic agents like S1 and docetaxel, the survival for PM is only 8–14 months [5, 6]. Risk factors for peritoneal recurrence following curative surgery are advanced T and N stage, female gender, young age, positive cytology with no macroscopic evidence of metastasis, and signet ring histology [2, 7, 8].

Gastric cancer usually spreads by three methods—hematogenous, lymphatic, or peritoneal. Peritoneal metastasis (PM) is usually considered as a locoregional disease. Free cancer cells first exfoliate from primary tumor, then attach to the peritoneal surface invading into the subperitoneal space, and thus form tumor nodules [9, 10]. Incidence of free cancer cells increases with the thickness of the primary tumor and presence of lymph nodes. It can be seen in up to 24% in stage I and 40% in stage II [11]. Another way of free cancer cell dissemination in the abdomen is due to iatrogenic spread during surgery of primary tumor. Tumor cells spread from transected lymphatics, tissues at narrow margin, and tumor-contaminated blood lost from the cancer specimen [12–14].

This concept of locoregional spread of PM from GC and poor outcome of systemic chemotherapy has led to interest in regional therapies for GC especially cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The peritoneum is poorly supplied by blood vessels. As a result, systemic chemotherapy reaches in very low concentrations in peritoneal deposits. Thus, in order to achieve adequate chemotherapy concentration in tumor nodules, very high doses need to be administered systemically which might not be tolerated by the patient. On the other hand, chemotherapy delivered intraperitoneally has higher intraperitoneal bioavailability leading to higher concentrations in tumor deposits [15]. Another benefit of intraperitoneal chemotherapy is that it is absorbed via portal vein thus passing through liver and may have higher antitumor effect on liver micrometastasis [16].

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Intraperitoneal chemotherapy plays a role in three different situations in gastric cancer—prophylactic HIPEC/intraperitoneal chemotherapy in advanced gastric cancer to prevent PM after curative surgery, in established cases of PM, and lastly in management of intractable ascites due to extensive PM.

14.2 Prophylactic HIPEC/ Intraperitoneal Chemotherapy

Positive peritoneal lavage is considered to be a poor prognostic factor in the outcome of gastric cancer surgery. Despite curative resection, the disease tends to recur with the 5-year survival being less than 2% [17]. In patients with a positive peritoneal fluid cytology, despite a curative resection, the peritoneal failure rate is around 80% compared to 45% in cytology-negative patients [18–20]. This implies that patients with a positive peritoneal cytology without evidence of visible peritoneal disease (Cy+/P0) should be treated differently. In this scenario, intraperitoneal chemotherapy/HIPEC has been used to destroy the free intraperitoneal cancer cell [21–23]. Yonemura et al. have shown a significantly better survival after HIPEC in Cy+/P0 with 5-year survival reaching up to 42% [9/78].

Advanced gastric cancers have shown poor outcome after curative surgery especially tumors with serosal involvement. Literature is replete with the outcome favoring HIPEC in these with level 1 evidence in its favor [24–30]. There are several randomized controlled trials comparing radical surgery with adjuvant HIPEC to radical surgery alone. Most of them have used serosal involvement and nodal involvement as inclusion criteria. Ikeguchi et al. in 1995 randomized 174 patients with serosal involvement in two treatment arms (those receiving HIPEC and those undergoing only curative surgery). Five-year survival was 51% compared to 45% in HIPEC arm [26]. In the meta-analysis conducted by Coccolini et al. [31], comprising over 2000 patients, there was significant improvement in the overall survival in the HIPEC group at 1, 2, and 3 years. HIPEC also demonstrated a significantly lower overall and peritoneal recurrence rate with no difference in the rate of nodal recurrence. There was, however, some increase in the morbidity. The choice of chemotherapy also remains unclear. Larger well-designed studies are required to clear the issue.

Prophylactic HIPEC is hence indicated in patients with serosal involvement, extensive nodal involvement, and positive peritoneal wash cytology. Table 14.1 shows the studies done for gastric cancer with serosal involvement treated with HIPEC. The role of adjuvant HIPEC is being prospectively evaluated in two randomized controlled trials.

The GASTRICHIP study is a phase III randomized European multicenter study evaluating the role of HIPEC with oxaliplatin in patients undergoing curative gastrectomy and showing high-risk features for developing PM like serosal involvement, regional lymph node involvement, or positive peritoneal fluid cytology [32]. The primary end point is the 5-year overall survival and the secondary end points include disease-free survival, morbidity, pattern of recurrence, and quality of life. In another ongoing trial in Europe, patients with high-risk GC who have received neoadjuvant chemotherapy are randomized to have a curative gastrectomy with or without HIPEC [33].

Apart from HIPEC, normothermic intraperitoneal chemotherapy has also been used and adjuvant treatment in high-risk gastric cancer. Takahashi et al. randomized patients to receive mitomycin C bound to activated carbon particles in addition to gastrectomy or no intraperitoneal therapy and demonstrated a significant survival benefit [34]. The 3-year survival was 66% in the experimental group versus 20% in the control group ($P < 0.01$). HIPEC was proven to be superior to normothermic intraperitoneal chemotherapy (NIIC) in two studies resulting in a significantly longer disease-free and overall survival in patients with high risk of developing PM [27, 35].

Table 14.1 Prophylactic HIPEC in management of gastric cancer

Reference	Country	Study design	Treatment given [no. of patients]	Drug used	Curative surgery	Postoperative morbidity	Postoperative mortality	Survival	Peritoneal recurrence
Koga et al. [60]	Japan	RCT	Surgery + HIPEC (26) vs. surgery alone (21)	MMC 64–100 mg	100% vs. 100%	Leak 3.1% vs. 7.1%	NR	30-month OS rate: 83% vs. 67%	NR
Hamazoe et al. [71]	Japan	RCT	Surgery + HIPEC (41) vs. surgery alone (39)	MMC 10 mg/mL	95% vs. 88%	Leak 4.8% vs. 7.5%	0% vs. 0%	Median OS: 77 vs. 66 months; 5-year 64% vs. 52%	39% vs. 59%
Ikeguchi et al. [26]	Japan	RCT	Surgery + HIPEC (75) vs. surgery alone (96)	MMC 80–100 mg/m^2	100% vs. 100%	1.2% vs. 2.08%	NR	5-year OS: 51% vs. 46%	35% vs. 40%
Fujimoto et al. [25]	Japan	RCT	Surgery + HIPEC (69) vs. surgery alone (68)	MMC 10 mg/mL	94.3% vs. 92.8%	2.8% vs. 2.8%	0% vs. 0%	2-year OS: 88% vs. 77%; 4-year OS: 76% vs. 58%; 8-year OS: 62% vs. 49%	1.4% vs. 23%
Hirose et al. [24]	Japan	Prospective case-control	Surgery + HIPEC (15) vs. surgery alone (39)	MMC 20 mg + CDDP 100 mg + VP16 100 mg	NR	60% vs. 42.5%	0% vs. 12.5%	Median OS: 33 vs. 22 months; 3-year OS: 48.9% vs. 28.8%; 5-year OS: 39.1% vs. 17.3%	26.7% vs. 45%
Kim et al. [29]	Korea	Prospective case-control	Surgery + HIPEC (51) vs. surgery alone (50)	MMC 40 mg	NR	36.5% vs. 33.3%	NR	5-year OS: 32.7% vs. 27.1%	7.6% vs. 25%
Zhu et al. [72]	China	Prospective case-control	Surgery + HIPEC (41) vs. surgery alone (53)	MMC 30 mg + CDDP 300 mg	73.8% vs. 66.7%	23.1% vs.12.1%	0%	Mean OS: 61 vs. 43 months; 2-year OS: 83.0% vs. 63.7%; 4-year OS: 70.5% vs. 52.1%; 6-year OS: 67.9% vs. 37.7%	10.3% vs. 34.7%

MMC mitomycin C, *CDDP* cisplatin, *VP16* etoposide

A similar benefit in overall survival was shown with the use of EPIC in patients with high risk of developing PM. In a randomized controlled trial, 248 patients were randomized to either undergo surgery alone or surgery followed by EPIC from days 1–5 [36]. The 5-year survival was significantly higher in the EPIC group compared to the surgery-only group (54% vs. 38%, $P = 0.02$). Patients with serosal invasion (5-year survival 52% vs. 25%, $P = 0.004$) and those with nodal metastasis (5-year survival 46% vs. 22%, $P = 0.02$) were benefited most by EPIC.

14.3 Established Peritoneal Metastases

In the management of established PM, two approaches have been described.

14.3.1 As an Adjunct to Cytoreductive Surgery

Various studies have been published after Fujimoto first published their experience of HIPEC in established cases of gastric PM in which they showed 2-year survival of up to 45% after HIPEC with CRS compared to 0% with CRS alone (Table 14.2) [37, 38]. Such dismal results were improved for the first time by Yonemura et al. who reported 5-year survival of 11% [39].

Glehen et al. reported an overall median survival of 10.3 months with 5-year survival reaching up to 16% in a single institution study from France [40]. Subsequently, the same investigators reported the outcomes of a multi-institutional study involving 159 patients. Patients had a median PCI score of 9.4. It also showed overall median survival of 9.2 months with 5-year survival of 13%, while patients having complete cytoreduction had a median survival of 15 months with 5-year survival of 23% [41]. The first randomized controlled trial was reported by Yang et al. who showed a significantly higher median survival of 11 months for CRS and HIPEC group compared to 6.5 months for CRS alone group [42]. The 3-year survival in the CRS with HIPEC arm was 5.9% compared to 0% in the CRS alone arm.

Median PCI score was 15 in this study. The authors concluded that compared to CRS alone, CRS with HIPEC is likely to increase survival by 2.6 times. The most important prognostic factor in patients undergoing this treatment is the disease extent as determined by the peritoneal cancer index (PCI).

However, selection criteria in most of the studies have varied considerably. Also the drugs used have also varied although most have used the combination of cisplatin and mitomycin.

14.3.2 Neoadjuvant Therapy

A recent introduction is neoadjuvant intraperitoneal chemotherapy plus systemic chemotherapy (NIPS) in established cases of PM. The goal is to reduce the disease burden, eradicate the free intraperitoneal cells, and thus enable a complete CRS. Yonemura et al. first published their criteria regarding the use of NIPS in 2006 [43]. The intra-abdominal catheter was placed in the pouch of Douglas. Both intraperitoneal chemotherapy (docetaxel and carboplatin) and systemic chemotherapy (methotrexate and 5-FU) were administered simultaneously. This treatment resulted in a negative peritoneal cytology in 56% of patients. Those who received complete resection had a median survival of 20 months.

In another study by Yonemura et al. [44] involving 96 patients having PM, intraperitoneal Taxotere and cisplatin were instilled together with oral S-1. Patients with nonprogressive disease were taken for CRS, and those achieving complete cytoreduction underwent HIPEC. Negative peritoneal cytology was achieved in 69% of patients and complete cytoreduction (CC-0) in 70%. CC-0 of 96% was achieved in those with PCI ≤ 6. Patients with CC-0 had a median survival of 21 months, and those with PCI ≤ 6 had a median survival of 20 months. Because of high morbidity and mortality, strict selection criteria are required.

Table 14.2 Therapeutic HIPEC for peritoneal carcinomatosis for gastric cancer

Reference	Country	Study design	Treatment arms	Drug used	Duration	Complete cytoreduction	Morbidity	Mortality	Outcome
Fujimoto et al. [37]	Japan	Prospective	Surgery +HIPEC (20) vs. surgery alone (7)	MMC 10 μg/mL	120	NA	NA	NA	6-month survival: 94% vs. 57% 2-year: 45%
Yonemura et al. [39]	Japan	Prospective	Surgery + HIPEC (40)	MMC 5 μg/mL + CDDP 30 μg/mL	40–60	NR	12.0%	0%	Median OS: 14.5 months; 3-year: 28.5%
Yonemura et al. [39]	Japan	Prospective	Surgery + HIPEC (83)	MMC 30 mg + CDDP 300 mg	60	33.7%	NR	NR	1-year OS: 43.0%; 5-year OS: 11.0%
Fujimoto et al. [38]	Japan	Prospective case-control	Surgery + HIPEC (47) vs. surgery alone (18)	VP16 150 mg + MMC 10 μg/mL	120	NR	NR	NR	1-year OS: 54.0% vs. 11.0%; 3-year OS: 42.0% vs. 0%; 5-year OS: 31.0% vs. 0%; 8-year OS: 25.0% vs. 0%
Hirose et al. [24]	Japan	Prospective case-control	CRS + HIPEC (17) vs. CRS alone (20)	MMC 20 mg + CDDP 100 mg + VP16 100 mg	50	35.2% vs. 20%	35.2% vs. 20.0%	5.8% vs. 0%	Median OS: 11 vs. 6 months; 1-year OS: 44.4% vs. 15.8%
Glehen et al. [40]	France	Prospective	CRS + HIPEC (48)	MMC 40–60 mg	90	10.2%	27.0%	4.0%	Median OS: 10.3 months; 5-year OS: 16.0%
Hall et al. [73]	USA	Prospective case-control	CRS + HIPEC (34) vs. surgery alone (39)	MMC 40 mg	120	21%	35.0%	0%	Median OS: 8 months; 1-year OS: 36.0%; 2-year OS: 26.0%; 5-year OS: 12.0% (all patients)
Yonemura et al. [61]	Japan	Retrospective	Peritonectomy + HIPEC (41) vs. conventional surgery + HIPEC (63)	MMC 30 mg + CDDP 300 mg + VP16 150 mg	60	69% vs. 28%	43.0% vs. 8.0%	7.0% vs. 0%	Median OS: 11 months; 5-year OS: 6.7% (all patients)

(Continued)

Table 14.2 (Continued)

Reference	Country	Study design	Treatment arms	Drug used	Duration	Complete cytoreduction	Morbidity	Mortality	Outcome
Zhu et al. [72]	China	Prospective case-control	Surgery + HIPEC (10) vs. surgery alone (12)	CDDP 50 μg/mL + MMC 5 μg/mL	60		NR	0%	Median OS: 10 vs. 5 months
Scaringi et al. [74]	France	Retrospective	CRS + HIPEC (26)	MMC 120 mg + CDDP 200 mg/m^2	60–90	30.7%	27.0%	3.8%	Median OS: 6.6 months (all patients); CC0 vs. CC ≥1: 15 vs. 3.9 months
Glehen et al. [41]	France	Retrospective	CRS + HIPEC and/or EPIC (159)	HIPEC: MMC 30–50 mg/m^2 + CDDP 50–100 mg/m^2; or OX 360–460 mg/m^2 ± irinotecan 100–200 mg/m^2 ± i.v. 5-FU and leucovorin; EPIC: MMC 10 mg/m^2 + 5-FU 600 mg/m^2	60–120	56.0%	27.8%	6.5%	Median OS: 9.2 months; 5-year OS: 13%
Yang et al. [75]	China	Prospective	CRS + HIPEC (28)	MMC 30 mg + CDDP 120 mg	90–120	CC0, 39.2%; CC1, 21.4%	14.3%	0%	1-year OS: 78.6%; 2-year OS: 42.8%
Yang et al. [42]	China	RCT	CRS + HIPEC (34) vs. CRS alone (34)	MMC 30 mg + CDDP 120 mg	60–90	58.8% vs. 58.8%	14.7% vs. 11.7%	NR	Median OS: 11.0 vs. 6.5 months; 1-year OS: 41.2% vs. 29.4%; 2-year OS: 14.7% vs. 5.9%; 3-year OS: 5.9% vs. 0%
Magge et al. [76]	USA	Prospective	CRS + HIPEC (23)	MMC 40 mg	100	95.6%	52.0%	4.3%	Median OS: 9.5 months; 3-year OS: 18%
Rudloff et al. [77]	USA	RCT	CRS + HIPEC (9) vs. chemotherapy alone (8)	OX 460 mg/m^2	30		11.0%	NR	Median OS: 11.3 vs. 4.3 months

14.3.2.1 Prognostic Factors for Patients with Gastric PM

One of the most important prognostic factors in patients with gastric PM undergoing CRS and HIPEC is the disease extent as determined by the PCI. Yonemura et al. reported complete cytoreduction in 86%, 39%, and 7% of patients with GCPC if the PCI score was ≤6, >7, and >13, respectively [45]. In the multi-institutional French study, the PCI was the only independent factor predicting survival; in patients with a PCI >19, no patients survived for more than 6 months, and in those with a PCI >12, none survived for more than 3 years [41]. Yang et al. reported a significant difference in the median survival if the PCI score was ≤20 or >20 (27.7 months vs. 6.4 months, $P = 0.0001$) [42]. Canbay et al. found a PCI of ≤6 to be an independent prognostic factor for survival in patients treated by NIPS followed by CRS and HIPEC (HR = 2.16; 95% CI, 1.17–3.98; $P = 0.013$) [46].

The presence of preoperative ascites seems to be a poor prognostic factor, with a median survival of only 5 months in the presence of ascites compared to 15.6 months in its absence [40]. Using a scoring system for ascites, Randle et al. found that each point increase in ascites score conferred 33% greater odds of incomplete macroscopic resection (OR = 1.33; 95% CI, 1.14–1.55; $P < 0.001$) [47].

The survival also improves with institutional experience—one study showed a 5-year survival of 8% in institutes with less than 3 years of experience and 16% in those with >11 years of experience [41]. The learning curve for the procedure is long with surgeons requiring 70–180 cases to achieve operative proficiency, reduce complications, and achieve good oncological outcomes [48–50].

14.3.2.2 Possibility of Cure in Patients Undergoing CRS and HIPEC for Gastric PM

A small percentage of patients undergoing CRS and HIPEC for gastric PM remain disease-free for >5 years and are considered to be cured. This was demonstrated in the BIG-RENAPE study of 81 patients treated from 1989 to 2009 [51]. Fifty-nine patients had no macroscopic and the median PCI was 6. Mitomycin C was the most commonly used drug during HIPEC (88%). The 5-year overall survival (OS) rate was 18%, with nine patients still disease-free at 5 years, for a cure rate of 11%. All "cured" patients had a PCI score below 7 and a CC-0. Factors associated with improved OS on multivariate analysis were synchronous resection ($P = 0.02$), a lower PCI score ($P = 0.12$), and the completeness of cytoreduction ($P = 0.09$). The authors concluded that the cure rate of 11% for patients with gastric PM who are deemed terminal emphasizes that CRS and HIPEC should be considered in highly selected patients (low disease extent and complete CRS).

14.3.2.3 C-Palliative HIPEC

PM may be complicated by malignant ascites which may be debilitating. Control of ascites will improve quality of life. HIPEC has been used to palliate ascites due to PC. Fujimoto et al. and Yonemura et al. initially reported complete resolution of ascites with HIPEC [44]. The procedure may be done laparoscopically as well [52–54]. In a systemic review involving 76 patients, ascites control was achieved in 95% patients with no major complications [53]. Ultrasound-guided HIPEC has also been reported, showing comparable ascites control with shorter hospitalization and reduced costs [55].

CRS with HIPEC has also been used in patients with malignant ascites with ascites control in 93% of patients, but survival was improved only when CRS was complete. Because of associated morbidity, the procedure is advisable only if complete cytoreduction seems possible [47].

14.3.2.4 Other Palliative Therapies

Pressurized intraperitoneal chemotherapy (PIPAC) is a new method of intraperitoneal drug delivery that uses aerosolized chemotherapy in the setting of a capnoperitoneum to produce a high tumor drug concentration [56]. It has shown good response rates in metachronous gastric PM

where the results are much worse than that for synchronous PM for gastric cancer.

Reymond et al. evaluated the role of PIPAC in gastric PM retrospectively. Sixty PIPAC were applied in 24 consecutive patients with PM from gastric cancer. Sixty-seven percent of patients had previous surgery, and 79% had previous platinum-based systemic chemotherapy. Mean PCI was 16 ± 10 and 18/24 patients had tumors with signet ring cells. Cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2 were given for 30 min at 37°C and 12 mmHg at 6-week intervals. Median follow-up was 248 days (range 105–748), and median survival time was 15.4 months. Seventeen patients had >1 PIPAC. Objective tumor response was documented in half of the patients after PIPAC, including complete histological regression in six patients. This study showed that there was a benefit of PIPAC in patients with recurrent platinum-resistant gastric PM, and it needed further prospective evaluation. Though the selection criteria for PIPAC could not be defined based on this study, the authors suggested using PIPAC soon after development of recurrence would be most beneficial [57].

Clinical trials are currently underway to further evaluate the role of PIPAC in gastric PM. The PIPAC-GAO1 (ClinicalTrials.gov Identifier: NCT01854255) a phase II study has completed accrual. This study will evaluate the role of PIPAC in patients with recurrent gastric cancer in terms of clinical benefit rate and objective response at 3 months after treatment completion and overall survival at 1 year after treatment completion. PIPAC is performed using cisplatin and doxorubicin, and three procedures should be performed for each patient.

The PIPAC EstoK 01 is a prospective, multicentric, randomized, open-label, controlled, parallel-group, phase II trial designed to evaluate the effect of PIPAC with oxaliplatin combined with systemic chemotherapy in patients with gastric PM with a PCI >8. The primary end point of this trial is the progression-free survival at 24 months. The secondary end points are the 24-month OS, safety, tolerability, and quality of life. It will also evaluate the feasibility of three successive PIPAC procedure and secondary resectability rate in these patients. Six specialized centers target to recruit 2 × 47 patients over 36 months.

PIPOX 01 is a phase I/II multicentric study in which a dose escalation study for oxaliplatin will be performed to treat patients with unresectable gastric, colorectal, and small bowel peritoneal metastases. The primary end point of the phase I study is the dose-limiting toxicity and that of the phase II study is the secondary resectability rate. Four centers in France will recruit 6 and 50 patients for the 2 studies.

14.3.2.5 Drugs Used in HIPEC

Multiple drugs have been used in HIPEC for gastric cancer including mitomycin C, cisplatin, and taxanes. The characteristics of an ideal drug include proven systemic activity, favorable pharmacokinetics, concentration-related cytotoxicity, adequate tissue penetration, acceptable local toxicity, synergistic activity with hyperthermia, and safety of hospital personnel. Whether to use them as monotherapy or as a combination is not yet clear, and which combination is best is yet to be determined.

Mitomycin C was the first drug used based on the experience from pseudomyxoma peritonei and PM from colorectal carcinoma [58]. It is usually given in a dose of 15 mg/m^2 for duration of 90 min. However, both dose and duration have varied in literature [25, 26, 39, 58]. It was initially used alone, but more recently, it is used in combination of cisplatin or cisplatin and etoposide both [29, 58–61].

Platinum-based agents both cisplatin and oxaliplatin have been used in HIPEC. Cisplatin has been used in combination with mitomycin C in dose ranging from 50 to 200 mg/m^2 with perfusion time between 60 and 90 min [60].

Oxaliplatin has been used recently in a dose of 460 mg/m^2 for duration of either 30 or 60 min [35]. Due to synergistic effect of oxaliplatin with 5 FU, 5 FU and leucovorin are given intravenously either just prior to or during HIPEC to

increase the cytotoxic effect of oxaliplatin. Both have acceptable hematological toxicity, but cisplatin is more nephrotoxic compared to oxaliplatin. Oxaliplatin is degraded in sodium-based solutions and, hence, is given in 5% dextrose, which may cause severe electrolyte disturbance [62, 63].

Taxanes both paclictaxel and docetaxel have been used as systemic agents for gastric cancers. They have mainly been studied in ovarian malignancies with limited utility in gastric cancer.

Epirubicin and doxorubicin have also been used for PM from appendiceal cancer and peritoneal sarcomatosis but have not been used in gastric cancer. Intraperitoneal doxorubicin is used in dose of 15 mg/m^2. It is toxic at dose of 30 mg/m^2 causing peritoneal inflammation leading to fibrosis and obstruction [64].

In a consensus statement on peritoneal surface malignancy, 5-fluorouracil is not considered an appropriate drug for intraperitoneal chemotherapy [65]. It is, however, used as bidirectional therapy in HIPEC.

Catumaxomab, a monoclonal antibody, binds to EpCAM-positive cells causing tumor killing. Its intraperitoneal infusions have been used in malignant ascites with high efficacy and have shown improvement in paracentesis-free survival [66]. Its role in peritoneal carcinomatosis of gastric cancer is not known, while its safety has been shown in a phase II trial [67].

At present various trials are going on in Europe and China using oxaliplatin, oxaliplatin and paclitaxel, and mitomycin and cisplatin for peritoneal carcinomatosis or prophylactic HIPEC for locally advanced tumors.

14.3.2.6 Morbidity of HIPEC

HIPEC seems promising in the management of advanced gastric cancer, but is not free from complications. These can be either related to surgery or the chemotherapeutic agent.

Chemotherapy impairs wound healing and increases the infections. HIPEC is therefore associated with increased abscess, wound infection, and anastomotic leak. Other associated morbidity includes postoperative ileus, bleeding, and thrombosis. However, Mizumoto found a reduced postoperative complication rate [59]. In addition, the chemotherapeutic agent is absorbed from the peritoneum into systemic circulation leading to leukopenia, anemia, thrombocytopenia, and organ failure (heart, liver, or renal).

The initial reported morbidity was 50% with re-exploration rate of 33% [60]. The results have improved with time with a current morbidity of 20%. The reported mortality has varied from 0% to 14.3% with a median of 4.8% [68]. Chua et al. have opined that such high morbidity and mortality may be acceptable owing to the fatal nature of the disease [69]. Age >60 years, poor performance status, neoadjuvant therapy, and duration of procedure have been identified as the risk factors for high morbidity, but the "independent" reported risk factor is institution [35, 49, 70].

To improve on the results, institutional and surgical awareness and willingness are paramount. Feingold et al. suggested few technical tips like complete drainage and lavage before reconstruction, freshening of the bowel edges before reconstruction, and avoidance of excessive peritoneal stripping to improve the morbidity.

Conclusion

Prophylactic HIPEC against peritoneal carcinomatosis in advanced gastric cancer is safe, significantly improves survival, and reduces peritoneal recurrence. CRS+ HIPEC is the optimal treatment in selected patients of gastric cancer with peritoneal carcinomatosis which has been shown to prolong survival. There is very limited role of HIPEC in malignant ascites from gastric cancer.

However, some issues still remain unresolved like the chemotherapeutic agent, dose, and duration of therapy. Apart from this, surgeon and institution sensitization are lacking with the unavailability of the required equipment.

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15 Malignant Peritoneal Mesothelioma

Elizabeth Poli, Ashvin Rangole, and Kiran K. Turaga

15.1 Introduction

One of the first descriptions of malignant peritoneal mesothelioma (MPM) was in a case report published 100 years ago [1]. In 1972, Moertel published a review of MPM and described the clinical presentation, histological features, and biological behavior of 169 patients [2].

Today, MPM accounts for approximately 10–30% of all mesothelioma diagnosed, with the majority being the pleural variant [3, 4]. Men are affected more frequently than women, likely because of higher occupational exposure to asbestos in men [5]. Until recently, treatment options were limited, and a diagnosis of MPM predicted a survival of less than a year. However, new advances in therapy are beginning to change the course of this disease, and now more than 50% of patients survive in the past 5 years [6].

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15.2 Epidemiology and Risk Factors

MPM is a rare disease [5]. Incidence data is now available through European registries and the SEER database from the United States. Currently, standardized incidence rates among men range from 0.5 to about 3 cases per million population, while rates among women are in the range of 0.2–2 per million [7]. However, data on incidence of MPM is not available from non-industrialized countries.

The relationship between cancer and exposure to asbestos, a silicate mineral fiber used as a building textile, was originally suspected in the 1930s. In 1960, Dr. J Christopher Wagner described a large group of patients in South Africa with peritoneal and pleural mesothelioma. It was suspected that they had been exposed to a blue type of asbestos, named crocidolite [8]. There are now several retrospective case-control studies, which have elucidated the important role of occupational and non-occupational asbestos exposure in the development of peritoneal and pleural mesothelioma [9, 10]. Further research has determined that the crocidolite type of asbestos offers the highest risk compared to other types, such as chrysotile and amosite. Furthermore, the risk for developing peritoneal mesothelioma is proportional to the square of cumulative exposure to asbestos, and the interval between exposure and disease is around 20–40 years [11, 12]. The risk

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of peritoneal mesothelioma is 2.2-fold increased per kg of asbestos exposure per year according to ecological studies on international populations [13]. However, others have argued that the relationship between peritoneal mesothelioma and asbestos exposure is not as clear—Sugarbaker et al. suggested that in their study of 40 patients with MPM and their matched controls, there only appeared to be a strong relationship between exposure to asbestos and the development of the disease in men [5].

It has been hypothesized that the incidence of mesothelioma in several countries has reached its peak, given that the use of hazardous asbestos declined several decades ago. It is postulated, however, that the incidence of mesothelioma is yet to reach its peak in India, China, Russia, and Brazil since the use of asbestos has been increased and the latency period is yet to be completed. However, there is a large range in the literature of the percentage of cases of MPM that are thought to be due to asbestos exposure, but it is likely around 50–60% [12, 14]. Other risk factors that have been reported through animal studies, case reports, and case series include prior radiation therapy, various other mineral fibers, organic chemicals, simian virus 40, and pancreatitis [12, 15–18].

Although there is a well-documented relationship between asbestos exposure and MPM, asbestos is not the only risk factor implicated in the pathophysiology of the disease. Therefore, one should not allow a history of exposure or non-exposure to bias the diagnosis.

15.3 Genetics of Peritoneal Mesothelioma

Recent studies have suggested a deletion in the germline and somatic BRCA-associated protein (BAP)-1 gene with an increased incidence of peritoneal mesothelioma [19]. While germline mutations can be associated with other malignancies such as uveal melanomas and renal cell carcinomas, the significance of a somatic mutation is unclear. Current epidemiological studies are investigating this association, and patients with family history or the absence of clear exposure must be considered for BAP-1 testing.

15.4 Diagnosis and Evaluation

Much like other peritoneal neoplasms, MPM can present with vague abdominal symptoms, including pain, loss of appetite, increasing abdominal girth and bloating, weight loss, and a decrease in energy [20, 21]. These symptoms are frequently the result of a large tumor burden and ascites. In up to one-third of patients, a mass may be palpated on physical exam [22]. The lack of overt symptoms can often delay the diagnosis, and the disease is often discovered when it is already very advanced. One key feature of MPM is that it rarely spreads beyond the peritoneal cavity. However, long-standing disease can extend into the pleural space or metastasize to extra-abdominal lymph nodes [23]. Despite the rarity of the development of metastases in MPM, the progression of the disease in the peritoneal cavity is terminal.

Although ultrasound is not the gold standard for the diagnosis of MPM, patients with vague abdominal symptoms may undergo a screening abdominal ultrasound. Under this modality, MPM may be seen as sheet-like hypoechoic to echogenic masses, omental thickening, or ascites. A computed tomography (CT) scan is frequently the first-line imaging modality when a peritoneal neoplasm is suspected. A CT scan can be useful in distinguishing MPM from other peritoneal malignancies, such as ovarian cancer or carcinomatosis from gastrointestinal cancers. CT scan findings can range from just a few soft tissue and omental masses or a thickened peritoneum with ascites to diffuse nodular thickening of greater than a few centimeters, loss of the normal architecture of the bowel,

and segmental obstruction [21, 24, 25]. The clinical presentation and CT findings of MPM can be subgrouped into the "dry type," which presents with abdominal pain and has CT features of localized peritoneal masses with little or no ascites; the "wet type," which presents with abdominal distension and CT features of ascites with widespread nodules and plaques; and the "mixed type," which presents with ascites and pain [5, 26].

For peritoneal tumors that are less than 1 cm, CT scans only have a sensitivity of 25–33%. Therefore, some centers are starting to use magnetic resonance imaging (MRI) to help determine a patient's burden of disease prior to surgery [27]. Figure 15.1 shows examples of peritoneal mesothelioma seen on different imaging modalities.

Potentially useful serum markers for patients with peritoneal mesothelioma include mesothelin, which has been found to be elevated in 71% of patients, and CA-125, which is elevated in 53% of patients. However, both of these markers are also elevated in patients with ovarian cancer, making them more useful for disease surveillance, rather than diagnosis [28, 29].

Cytologic analysis of ascites has a low diagnostic potential due to an absence of large quantities of malignant cells in the fluid [21, 28]. Ultimately, the diagnosis of MPM relies on a tissue diagnosis, either from a core needle biopsy or surgery.

15.5 Pathology

On gross pathologic analysis, the peritoneum in MPM can be thickened and studded with tumor nodules or covered in a diffuse plaque. The omentum can be caked with tumors (Fig. 15.2). In the advanced stage, tumors can invade and encase bowel, which results in obstruction.

The pathologic diagnosis of MPM is complex, as there have been seven described histologic subtypes: epithelioid, which makes up 75% of cases, sarcomatoid, biphasic/mixed, papillary well differentiated, low-grade (tubulopapillary) mesothelioma, multicystic, and deciduoid [5, 30]. Patients with the epithelial subtype typically have a better prognosis, with a reported median survival of 55 months compared to a 13-month

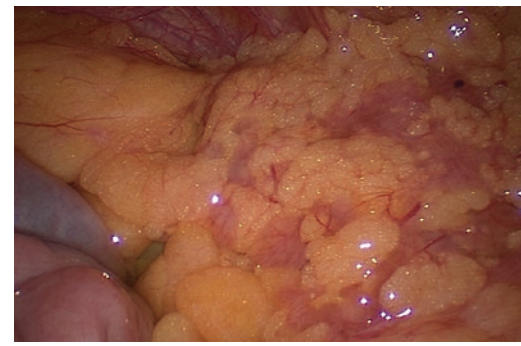

Fig. 15.2 Intraoperative image showing tumor caking of the omentum

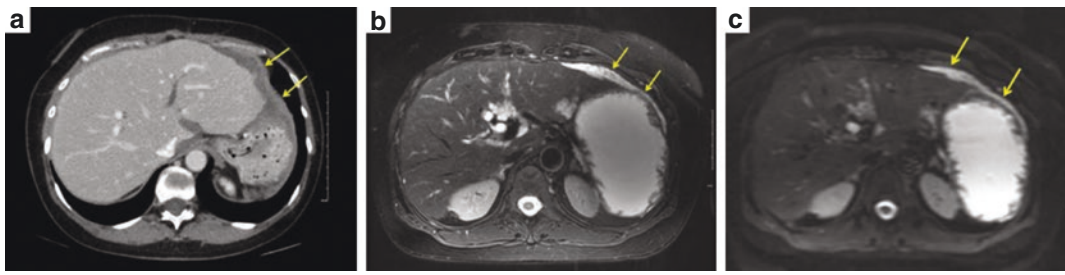

Fig. 15.1 (**a**) Contrast-enhanced computed tomography—(arrows) low-attenuation material along the perihepatic, lesser sac, and perigastric regions representing mucinous ascites; (**b**) axial, T2-weighted magnetic resonance imaging; (**c**) diffusion-weighted magnetic resonance imaging (used with permission from Rajeev R, Turaga KK, Cancer Control 2016;23(1):36–46)

median survival for mixed, sarcomatoid, and deciduoid tumors [21]. Multicystic mesotheliomas and well-differentiated papillary mesothelioma have also been described and should be included in the differential diagnosis of peritoneal lesions, but they are benign and associated with a long survival [31].

The definitive diagnosis of MPM is made with immunohistochemistry, especially to distinguish it from papillary serous carcinoma or adenocarcinoma of the gastrointestinal organs. However, there does not exist one specific marker that can make the diagnosis by itself; rather, at least two or more markers should be stained for. Markers which are positive in MPM include calretinin, D2-40, cytokeratin, and WT-1. MPM is also characterized by the absence of certain antigens, such as BG8, Ber-EP4, B72.3, CEA, estrogen receptor, and MOC-31 [31, 32]. Synoptic reporting of the Ki-67, necrosis, mitosis, and grade and histological subtype is essential in the pathological reporting of mesothelioma [33].

Distinguishing malignant mesothelioma from mesothelial hyperplasia and reactive mesothelium can also be challenging. MPM tumors typically stain positive for cytokeratins and demonstrate stromal and fat invasion. In a study by Kato et al., GLUT-1 reactivity was found in 40/40 malignant mesothelioma cases, whereas all 40 cases of reactive mesothelium were negative [34]. Similarly, a study done at the University of Chicago showed all benign mesothelial tissues to be negative for GLUT-1. Of the malignant mesotheliomas, 20% were negative, 53% were weakly positive, and 27% were strongly positive for GLUT-1 [35]. This data suggests that GLUT-1 positivity in biopsy samples can be an adjunct to other IHC studies for the diagnosis of malignant mesothelioma. BAP-1 deletion strongly supports the diagnosis of a malignant peritoneal mesothelioma versus reactive mesothelium.

15.6 Staging

Currently, there is no universally accepted staging system for MPM. The peritoneal cancer index (PCI) has been used to standardize the description of the burden of disease in patients with cancer of the peritoneum, including MPM. To calculate the PCI, the abdomen is divided into 13 regions, and each region is given a score of 0–3, depending on the size and appearance of the tumors in that region. Those scores are summed to give a total score between 0 and 29 [36]. Yan et al. combined data on MPM patients from eight institutions in the Peritoneal Surface Oncology Group International (PSOGI) to determine a clinicopathologic staging system. In this system, PCI is grouped into T categories: T1 is PCI 1–10, T2 is PCI 11–20, T3 is PCI 21–30, and T4 is 30–39. Although nodes are not typically involved in MPM, if there is nodal disease, it is classified as N1. Systematic sampling of retroperitoneal nodes is often essential for nodal staging. M1 represents disease that has extended past the peritoneal cavity. Using these categories, a staging classification was described that correlated with outcomes. Stage I included T1N0M0 disease and had an 87% 5-year survival rate. Stage II included T2-3N0M0 tumors and had a 53% 5-year survival. Stage III included patients with T4 tumors or evidence of nodal or distant metastasis, which had a 5-year survival. This staging system has not been formally standardized by the American Joint Committee on Cancer [37, 38].

15.7 Treatment

Prior to 2000, treatment for peritoneal mesothelioma included a combination of systemic chemotherapy, and palliative surgical procedures, which offered a modest survival benefit, ranging between 6 and 16 months with median survival of approximately 1 year [6, 39].

Operative therapies were largely focused on palliative cytoreduction. The addition of debulking procedures to the treatment of MPM initially only offered a survival benefit of 7 months [40].

The use of conventional systemic chemotherapy has also not significantly impacted the course of peritoneal mesothelioma. Cisplatin- and pemetrexed-based chemotherapies are the drugs most frequently used and typically have good response rates for pleural mesothelioma.

However, when they are used for the treatment of MPM, these drugs have response rates between 11 and 28% and median OS 10–26.8 months. Monotherapy with intraperitoneal chemoperfusion has also not resulted in any significant benefit with a median survival of 9–12 months [6].

More recently, aggressive locoregional treatment strategies, such as cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), have proven to offer a significant survival benefit. The aim of cytoreductive surgery is to remove as much tumor as possible with an optimal cytoreduction defined as residual disease <2.5 mm in thickness (CC-1). Depending on the burden of disease, the operation can consist of a greater omentectomy with splenectomy, right upper quadrant peritonectomy, left upper quadrant peritonectomy, lesser omentectomy with removal of the gallbladder, and/or pelvic peritonectomy with resection of the rectosigmoid colon [25].

The completeness of cytoreduction is scored depending on the residual peritoneal seeding within the abdomen as CC-0, no residual tumors; CC-1, residual tumor size less than 0.25 cm; CC-2, residual tumor between 0.25 and 2.5 cm; and CC-3, residual tumor >2.5 cm [21]. Direct exposure of antitumor agent to the peritoneal surface is considered to be the most effective treatment modality against malignant peritoneal mesothelioma. Intraperitoneal chemotherapy instilled at the time of surgery gives maximum advantage by exposing a larger area of tumor to the chemotherapy drug solution and can greatly enhance drug concentrations in the peritoneal cavity while having decreased systemic toxicity. During HIPEC, a preheated (42.5 °C) perfusate with two or three drugs (cisplatin, mitomycin C, fluorouracil, doxorubicin, and/or paclitaxel) is infused continuously into the closed or open abdomen after surgery. Earliest reports of use of cytoreduction with HIPEC had varied results. Yan et al. published the largest early studies with 405 patients. Overall median survival was 53 month, and 5-year survival was 47% [41].

Recent meta-analysis by Helm et al. reports that survival after cytoreductive surgery and intraperitoneal chemotherapy is 34–100 months and that 67% of patients were able to have a CC-0 or CC-1 resection. The pooled 1- and 5-year survival rates were 84 and 42%, respectively. Epithelioid histology, the extent of disease (PCI score), and completeness of cytoreduction were found to be favorable prognostic factors [3]. This review confirmed the safety of CRS and HIPEC for MPM; the reported operative mortality was between 0 and 5%.

A study from NCI Milan reported outcomes in MPM using neoadjuvant or adjuvant systemic chemotherapy in addition to HIPEC. They did not find any association between the use of neoadjuvant or perioperative chemotherapy and operative morbidity or improved survival [42].

A recent analysis of patients with MPM in the SEER database identified parameters associated with increased risk of shortened survival to be advancing age, male gender, histology, and extent of disease. The study also found that surgical resection was associated with improved overall survival and that survival after surgical resection improved over time. However, the authors stated that currently almost 57% of individuals with a diagnosis of MPM do not undergo any type of surgical resection [43]. This result is striking and points to the need for further dissemination of successful surgical treatment modalities for MPM.

Recent reports in the use of long-term intraperitoneal pemetrexed with intravenous cisplatin have been shown to have encouraging long-term survival. The consideration of adjuvant therapy, either intraperitoneal or systemic, is controversial and is currently being investigated. Additionally, for patients with good biology, recurrence can be treated safely with iterative cytoreductive surgery and HIPEC with low mortality rates and acceptable morbidity and long-term survival [44]. A proposed algorithm for the management of MPM from Sugarbaker et al. is shown in Fig. 15.3 [45].

15.8 Novel Agents

While cytoreductive surgery and HIPEC remain the standard of care for patients with peritoneal mesothelioma, there are several novel agents that are being considered in the management of patients. Some of the ongoing clinical trials for

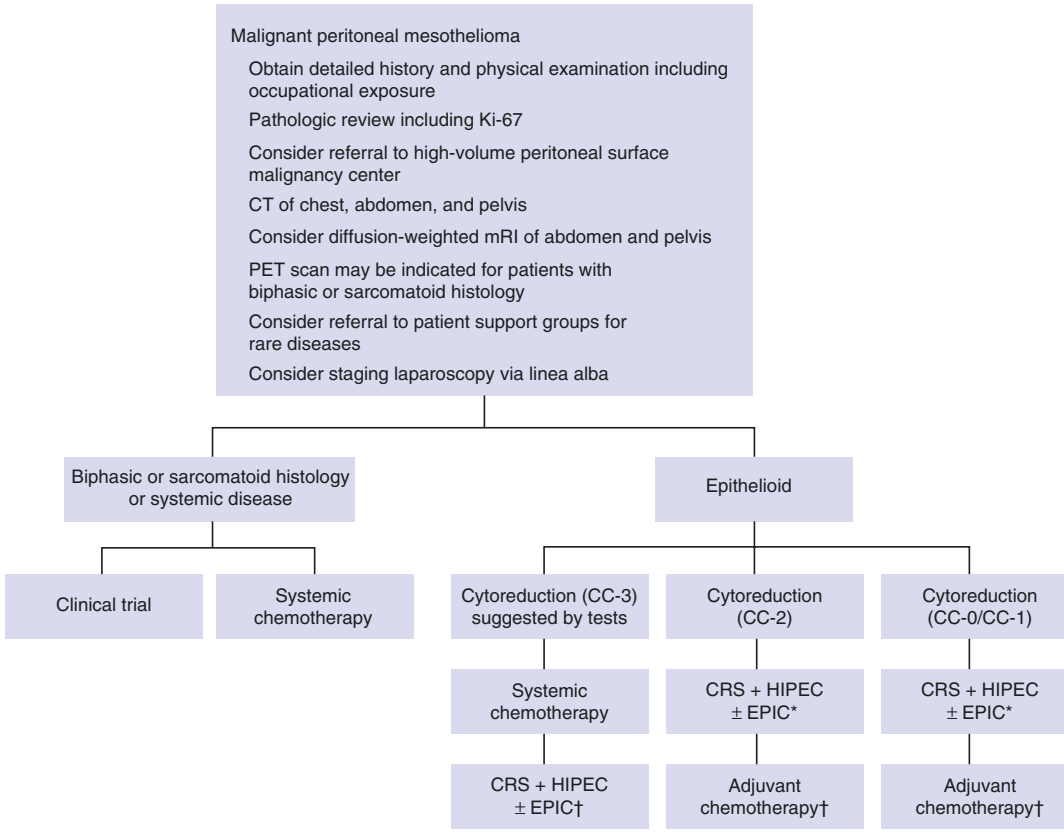

Fig. 15.3 Treatment algorithm for malignant peritoneal mesothelioma. *CRS* cytoreductive surgery, *CT* computed tomography, *EPIC* early postoperative intraperitoneal chemotherapy, *HIPEC* hyperthermic perioperative chemotherapy, *MRI* magnetic resonance imaging, *PET* positron emission tomography. *Consider second-look laparoscopy in 6 months to 1 year. †No adjuvant chemotherapy regimen has been studied extensively. Maintenance intraperitoneal pemetrexed plus intravenous cisplatin may be considered after CRS plus HIPEC. ‡HIPEC for palliation of ascites, which can be performed laparoscopically, may be considered

patients with peritoneal mesothelioma include trials with the anti-mesothelin antibody (anetumab) and with the PD-L1 checkpoint inhibitor (pembrolizumab). A current listing of peritoneal mesothelioma trials is included in Table 15.1.

15.9 Special Considerations

While the majority of patients diagnosed with MPM are treated with cytoreductive surgery and HIPEC first, patients in whom complete cytoreduction is not possible may be treated with neoadjuvant chemotherapy, which has been reported to have response rates as high as 60%. In addition, patients with wet dominant mesothelioma (ascites) can also be treated with laparoscopic HIPEC to control the ascites while they undergo neoadjuvant therapy in order to make a more complete cytoreduction possible.

Patients with bicavitary disease pose a difficult problem since a diaphragmatic resection at the time of CRS + HIPEC is difficult for postoperative recovery. Such patients can undergo either a perfusion of the chest and abdomen at the same time with a higher volume of perfusate or undergo sequential treatment with the peritoneum first followed by the pleural cytoreduction.

Table 15.1 List of selective current ongoing clinical trials that include patients with MPM

Trial	Study title	Phase
NCT02535312	Methoxyamine, cisplatin, and pemetrexed disodium in treating patients with advanced solid tumors or mesothelioma that cannot be removed by surgery or mesothelioma that is refractory to cisplatin and pemetrexed	Phase 1/ phase 2
NCT03102320	Phase 1b multi-indication study of anetumab ravtansine in mesothelin expressing advanced solid tumors	Phase 1b
NCT01655225	A study of LY3023414 in participants with advanced cancer	Phase 1
NCT02399371	Pembrolizumab in treating patients with malignant mesothelioma	Phase 2
NCT01583686	CART T cell receptor immunotherapy targeting mesothelin for patient with metastatic cancer	Phase 1/ phase 2
NCT02798536	Reduced immunogenicity mesothelin-targeted immunotoxin LMB-100 in people with malignant mesothelioma	Phase 1

Conclusion

Recent advances in the understanding of the biology of malignant peritoneal mesothelioma and in treatment options have significantly improved the outcomes from this previously devastating diagnosis. There is growing evidence that aggressive local-regional strategies, including CRS and HIPEC, will likely become the standard of care for these patients.

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16 Rare Indications for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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16.1 Introduction

There are some rare primary and secondary tumors involving the peritoneum that have been treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [1–5]. The incidence of these tumors is rare with a limited number of cases reported in literature. Some tumors arise from the peritoneum itself, and some others are rare histologies arising from various primary sites and metastasizing to the peritoneum. Some common cancers that metastasize to the peritoneum like hepatobiliary, pancreatic, cervical, and breast cancers are generally treated with systemic chemotherapy alone. However, in the rare situation when there is limited disease confined to the peritoneal cavity alone, patients with PM from these primary sites have been treated with CRS and HIPEC. Put together, all these cases form "rare indications" for CRS and HIPEC. CRS and HIPEC in these situations has been used on the basis of logic rather than evidence with the hope of providing a survival benefit to these patients. The only other treatment for such patients would be systemic chemotherapy, which has a poor response rate in most of these cases.

Several aspects need to be considered when treating these patients. The natural history may not be properly known in case of rare histologies. Similarly, the benefits of various treatments are difficult to quantify since most published reports comprise of retrospective case series comprising of a small number of patients treated over prolonged periods and from case reports. However, in a recent undertaking by the peritoneal surface oncology group international and the BIG-RENAPE, data pertaining to the outcomes of CRS and HIPEC for rare indications from 53 centers across the world were pooled together and published which has provided evidence and insights into the treatment of some of these tumors [6]. A review of the rare indications for CRS and HIPEC, their natural history as is known, and the results of various treatments are provided here.

16.2 Classification

The rare indications for CRS and HIPEC can be divided into three broad categories—primary peritoneal tumors, rare secondary peritoneal tumors, and peritoneal metastases from common primary

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sites, which are not usually treated with CRS and HIPEC (Table 16.1). This classification is not exhaustive and includes the common subtypes in each group treated with CRS and HIPEC. The role of cytoreductive surgery and HIPEC in these tumors is described separately for each tumor.

Table 16.1 Rare indications for CRS and HIPEC

Primary peritoneal tumors
Mesothelial tumors
• Peritoneal malignant mesothelioma • Well-differentiated papillary mesothelioma • Multicystic mesothelioma • Adenomatoid tumor
Epithelial tumors
• Primary peritoneal serous carcinoma • Primary peritoneal serous borderline tumor
Smooth muscle tumor
• Leiomyomatosis peritonealis disseminata
Tumors of uncertain origin
• Desmoplatic small round cell tumor • Fibromatous tumor
Rare secondary peritoneal tumors (*PM from rare tumors*)
Uncommon histologies of ovarian cancer
• Mucinous ovarian tumors • Granulosa cell tumors • Malignant germ cell tumors
Sarcomas
• Uterine leiomyosarcoma • Liposarcoma • Others
Neuroendocrine tumors
Small bowel adenocarcinoma
Fibrolamellar hepatocellular cancer
Papillary serous carcinoma of the endometrium
Mucinous urachal tumors
Gastrointestinal stromal tumors
Miscellaneous tumors
Peritoneal metastases from common primary tumors
Hepatobiliary and pancreatic tumors
• Gallbladder carcinoma • Hepatocellular carcinoma • Cholangiocarcinoma • Pancreatic tumors
Gynecological primary sites
• Uterine cervical carcinoma • Endometrial adenocarcinoma
Extra-abdominal primary sites
• Breast cancer • Lung cancer

16.3 Primary Peritoneal Tumors

16.3.1 Peritoneal Desmoplastic Small Round Cell Tumors

Desmoplastic small round cell tumor (DSRCT) is a malignant neoplasm that usually arises from the peritoneal surface of the abdomen and pelvis. The disease entity was first described in 1989 by Gerald and Rosai and Ordonez and Zirkin [7, 8]. Other primary sites have been reported, including the paratesticular region, the pleural serosa, the posterior cranial fossa, soft tissues and bone, the ovary, and the parotid gland [9–20]. DSRCT has a highly aggressive clinical course with multiple local recurrences but few distant metastases.

No large population data exists regarding the epidemiology of this tumor due to its rarity. Previous studies reported that DSRCT was found to be more prevalent in males, more specifically young Caucasian boys. Presenting symptoms include abdominal pain, constipation, and abdominal distension with ascites.

This tumor type has a strong tendency to spread within the peritoneum but can also give rise to extraperitoneal metastases, mainly in the liver and lungs [21].

16.3.1.1 Pathology

The tumor usually forms a large intra-abdominal mass consisting of nests or strands of small round cells embedded in a dense desmoplastic stroma. The cells show polyphenotypic differentiation, typically a mixture of epithelial, mesenchymal, and neural features. The immunohistochemical profile of DSRCT shows reactivity for epithelial (keratin, epithelial membrane antigen), mesenchymal (vimentin), neural (neuron-specific enolase and CD56), and myogenic (desmin) markers.

Less than 500 cases have been reported in the medical literature. Its histological and clinical attributes do, however, overlap with other primitive tumor types including Ewing sarcoma, primitive neuroectodermal tumor (PNET), rhadomyosarcoma, rhabdoid tumor, and Wilms tumor [22]. The cell of origin and molecular pathogenesis of DSRCT remain unknown. The concept of DSRCT as a separate entity is supported by

the identification of a specific recurrent chromosomal abnormality. A specific translocation, t (11; 22) (p13; q12), is seen in almost all cases, juxtaposing the Ewing sarcoma (EWS) gene to the Wilms tumor (WT)-WT1 tumor suppressor gene [22–24].

DSRCT, WT, and EWS share a chimeric relationship with one another. DSRCT is caused by the translocation of the *EWSR1* gene from chromosome 22 to chromosome 11, resulting in a fusion product *EWSR1/WT1* [25]. EWS is caused by the translocation of the *EWSR1* gene from chromosome 22 to chromosome 11 in most cases (*EWSR1-FLI1*) and chromosome 21 to chromosome 7 in rare cases (*EWSR1-ERG* and *EWSR1-ETV1*) [26–28]. Mutation of the *WT1* gene on chromosome 11 is observed in 20% of WT cases [29, 30]. Thus, DSRCT, ES, and WT seem to be genetically related and present in young adults. These genes code for transcription factors and tumor-specific translocations result in oncogenicity of chimeric transcription factors [31, 32]. This phenomenon of pairing of the EWS gene with other genes is similar to such pairings that are found more commonly in hematological malignancies and are used for diagnosis [33–35].

16.3.1.2 Clinical Manifestations

DSRCT typically affects men in 5–25-year age group [36]. The commonest presentation is a large intra-abdominal mass with other smaller deposits over the visceral and parietal peritoneum. The peritoneal deposits interfere with the absorption of peritoneal fluid leading to ascites formation, which is another common presentation. The symptoms are nonspecific and include abdominal pain, distension, loss of appetite, and nausea and vomiting [36]. Common sites of metastases are the liver, lungs, and lymph nodes (retroperitoneal, groin, mediastinum, and neck) [36].

16.3.1.3 Diagnostic Evaluation

Imaging of the abdomen with ultrasound, computed tomography (CT), or magnetic resonance imaging reveals multiple tumor nodules "studding" the peritoneal cavity (almost always more than one nodule) [37, 38]. Nodules on the subphrenic peritoneum produce indentation of the liver surface (scalloping). Large pelvic masses are a common finding. Less common nonspecific clinical findings that should raise a suspicion of DSRCT in a young male are retroperitoneal lymphadenopathy, hydronephrosis, bowel obstruction, calcifications, and nodular peritoneal thickening, especially when these findings are supported by radiographic evidence of a disseminated intra-abdominal neoplasm [38, 39].

Table 16.2 Staging of desmoplastic small round cell tumors (From Ref. [41] with permission)

Stage	PCI	Liver metastases	Extra-abdominal metastases
I	<12	Absent	Absent
II	≥12	Absent	Absent
III	Any PCI	Present	Absent
IV	Any PCI	Present/ absent	Present

A histopathologic and cytogenic diagnosis is needed for all cases. A CT thorax abdomen pelvis or a PET CT is performed to determine the extent of disease [39, 40].

A staging system (Table 16.2) has been proposed by Jordan et al. from the MD Anderson Cancer Center that incorporates abdominal disease burden (stage I or II) and sites of metastasis such as the liver (stage III) or lung (stage IV) [41]. The authors demonstrated a trend toward stage-specific survival in their patients. An important inference is that a patient with extensive intra-abdominal disease (peritoneal metastases) with no liver and extraperitoneal metastases can experience a prolonged disease-free survival after CRS with or without HIPEC.

16.3.1.4 Treatment

Patients with DSRCT require aggressive multimodal therapy. The treatment protocol introduced by Kushner is commonly used. It comprises an intensive chemotherapy regimen based on alkylating agents (P6 regimen). Seven cycles of doxorubicin and vincristine alternating with ifosfamide and etoposide were administered to 12 patients in the initial study. In addition, debulking surgery, radiotherapy, autologous stem cell rescue, or a combination of these was

used. In the initial publication, the median overall survival (OS) was 19 months for all patients and 22 months for the 7 achieving complete response to chemotherapy [42, 43].

As DSRCT is a tumor arising from the peritoneum itself and is chemosensitive, hyperthermic intraperitoneal chemotherapy (HIPEC) has been used in addition to surgery. The results of multimodality treatment including cytoreductive surgery with or without HIPEC are described in Table 16.3.

La Quaglia and Brennan treated 66 patients with a median age of 19 years (range, 7–58) with multimodality therapy [42, 43]. In 96% of the patients, the primary tumor site was intra-abdominal; 50% had lymph node involvement and 41% had distant organ metastases at diagnosis. The 3- and 5-year overall survival was 44% and 15%, respectively. Twenty-nine of these patients (44%) underwent induction chemotherapy (P6), surgical debulking, and radiotherapy. Surgical debulking was carried out in an attempt to achieve greater than 90% resection of the gross tumor burden. Attempts were not made to achieve microscopic negative margins. Three-year survival was 55% in those receiving chemotherapy, surgery, and radiotherapy vs 27% when all three modalities were not used ($p < 0.02$). The 3-year survival was 58% in patients treated with gross tumor resection compared to no survivors past 3 years in the non-resection cohort ($p < 0.00001$). Ten patients (15%) had no evidence of disease with a median follow-up of 2.4 years (range, 0.4–11.2 years).

Jordan et al. first reported the use of HIPEC in addition to debulking surgery in eight patients and compared the outcomes with 16 historical controls who received chemotherapy ± radiation therapy or

Table 16.3 Outcomes of CRS and HIPEC/CRS alone as part of multimodality treatment for DSRCT

Ref no. year	No.	HIPEC (no)	Drugs	CC-0/1	Morbidity	Peritoneal recurrence	Prognostic factors	Survival
[43] 2005	66	0		NR	NR	NR	>90 tumor debulking, use of P6 protocol; multimodal therapy	3 year OS 44% 5-year OS 15%
[41] 2010	8	8	Cisplatin	NR	27.5%		Extra-abdominal metastases	3 year OS 71%
[3] 2014	26	26	Cisplatin	24	Wound dehiscence 19% Renal toxicity 23%		Complete CRS (CC-0/1); extra-abdominal disease; RT	Median OS 63 months
[44] 2010	3	3	Cisplatin	2	1/3	2 within 12 months		
[45] 2015	23	5	Oxaliplatin	52%			No extraperitoneal metastases complete tumor removal, post op radiotherapy, post op chemotherapy	Median OS 37.7 months Median DFS 15.5 months
[46] 2017	48	11	Cisplatin Mitomycin + Cisplatin Oxaliplatin Oxaliplatin + irinotecan	48	1/3 grade 3–4	69% (median time to recurrence 13 months)	No prognostic factor identified	5 year DFS 12% Median OS 42 months 5 year OS 19%

surgery alone. HIPEC was performed with cisplatin at 100 or 150 mg/m^2, for 90 min at 40–41 °C [41]. There was no mortality in the series, and major morbidity included renal insufficiency and gastroparesis. Comparisons were made between three groups: (1) those who received no surgery, (2) those who received debulking surgery, and (3) those who received cytoreductive surgery with HIPEC. The projected 3-year survival was 71% in patients who had HIPEC and 26% in patients who did not undergo surgery with or without HIPEC. Extra-abdominal metastasis correlated with poor survival ($p = 0.021$) [41].

The same group reported outcomes in 26 pediatric and adult patients treated with CRS and HIPEC, most of whom received postoperative radiotherapy as well, as part of a phase I trial. All patients received neoadjuvant and adjuvant chemotherapy. Five patients (19%) were less than 12 years of age at surgery. A median survival of 63.1 months and 100% survival at 4 years was reported in a subset of DSRCT patients receiving HIPEC. The role of HIPEC was assessed even in patients who did not have a complete cyoreduction [3].

The absence of extra-abdominal metastases and CC-0/1 resection had a favorable impact on survival [3]. The authors stated that, technically, cytoreduction was easier to perform in patients with DSRCT as compared to other tumors with a similar tumor burden as it is less invasive leading to a lesser degree of organ invasion.

Of importance is the fact that Jordan et al. performed CRS and HIPEC in patients with liver metastases and/or extra-abdominal disease as well.

Msika et al. reported on three patients of DSRCT treated with CRS and HIPEC who had received multiple cycles of chemotherapy, and the procedure was only palliative in two patients [44]. There was no perioperative mortality. Complete cytoreduction (CCR-0/CCR-1) was obtained in two patients. One patient died 14 months after initial diagnosis of recurrent disease; the other patient had a CC-0 and was disease-free for 10 months after the procedure. One patient had a complete response to chemotherapy, and the only residual lesions were intraperitoneal calcified nodules after chemotherapy. The probable role of CRS was as a second look staging procedure in the patient. The third patient died of disease progression within 6 months of the surgery. The authors concluded that calcified nodules following chemotherapy could be considered sterile lesions, yet a systematic second look should be performed for staging purposes [44].

In another series of 38 patients, 47.4% has extraperitoneal metastases (78% in the liver and 11% in the lungs). The median survival was 21.1 months in 14 patients (37%) who were treated with chemotherapy alone [45]. 23 patients underwent surgery, in 52% complete removal of macroscopic disease was achieved, 5 received intraperitoneal chemotherapy, and 7 received postoperative whole abdominopelvic radiotherapy (WAP-RT). The median follow-up was 59.9 months, the median OS was 37.7 months, and the median DFS was 15.5 months. Absence of extraperitoneal disease, complete tumor removal, use of post-op WAP-RT, and postoperative systemic chemotherapy were independent predictors of survival, while intraperitoneal chemotherapy had no impact.

Honore et al. carried out a retrospective nationwide survey of the prospective and retrospective databases of the French Network for Rare Peritoneal Malignancies, French Reference Network in Sarcoma Pathology, French Sarcoma Clinical Network, and French Pediatric Cancer Society [46].

Among the 107 patients with DSRCT, 48 had no extraperitoneal metastases (EPM) and underwent a complete CRS. The median peritoneal cancer index (PCI) was 9 (range, 2–27). Among these 48 patients, 38 (79%) had pre- and/or postoperative chemotherapy and 23 (48%) postoperative whole abdominopelvic radiotherapy (WAP-RT). Intraperitoneal chemotherapy was administered to 11 patients (23%): two received early postoperative intraperitoneal chemotherapy (EPIC) and nine HIPEC. The drugs used during HIPEC were oxaliplatin alone, cisplatin alone, oxaliplatin and irinotecan, and mitomycin and cisplatin with or without irinotecan in combination. After a median follow-up of 30 months, the median overall survival (OS) of the entire cohort was 42 months. The 2- and 5-year OS were 72 and 19%. The 2- and

5-year disease-free survival (DFS) were 30 and 12%. Thirty-seven patients (77%) had a recurrence, and the median time to recurrence was 12 months (range, 5–73 months). The first recurrence was located in the peritoneum in 23 patients (62%), outside the peritoneum in six patients (16%), or synchronously in and outside the peritoneum in seven patients (19%). The authors stated that with a 5-year DFS of 12% despite an optimal locoregional treatment, a prolonged adjuvant treatment could be evaluated in a prospective trial [46].

Whole abdominopelvic radiotherapy was the only variable associated with longer peritoneal recurrence-free survival and DFS after complete CRS. The influence of HIPEC/EPIC on OS and DFS was not statistically conclusive. The probable reasons for this were the lack of statistical power in the study to determine this difference, the significantly higher PCI in the HIPEC group, the benefit of HIPEC/EPIC undermined by another locoregional treatment (radiotherapy), and the heterogeneity of drug regimens with some drug inappropriate for mesenchymal tumors.

Several case reports have shown a variable benefit of multimodality treatment in patients with DSRCT with few reports of long-term survivors as well [47–51].

Fan et al. reported outcomes in three patients with CRS and HIPEC. Two of these recurred at 6 months following surgery, and one patient was disease-free 6 months after treatment completion [52].

16.3.1.5 Summary

- DSRCT is an aggressive tumor that needs multimodality treatment. With nonsurgical treatment complete remission is uncommon.
- Surgical debulking has a survival benefit in patients who do not have extraperitoneal disease. There is also a survival benefit of complete tumor removal (residual disease <2.5 mm, CC-0/1 resections). However, even patients having CC-2/3 resections have experienced a benefit in survival compared to no surgical treatment. The criteria for patient selection for CRS need to be defined.
- There is no PCI cutoff for surgery in these patients though patients with PCI > 12 have an inferior survival.
- The role of intraperitoneal chemotherapy is not known and needs further prospective evaluation.
- Other treatments like targeted therapies and whole abdominopelvic radiotherapy are being evaluated as well and may be used as a replacement for/in addition to intraperitoneal chemotherapy (IPC).
- Prognostic factors like response to chemotherapy need to be identified.
- Despite optimal locoregional and systemic therapy, the recurrence rates are high.

16.3.2 Primary Peritoneal Serous Carcinoma

Extraovarian peritoneal serous papillary carcinoma (EPSPC) was recognized as a clinical entity in 1959 [53]. Subsequently the terms primary peritoneal cancer (PPC) or primary peritoneal serous cancer (PPSC) have been used for it [53, 54]. The histological characteristics and clinical behavior of this tumor are similar to that of epithelial ovarian cancer though it is much rarer (6.78 cases per million vs 120.5 cases per million, respectively) [55, 56].

16.3.2.1 Origin of Ovarian Tumors and PPSC

The similarities between ovarian serious carcinomas, fallopian tube carcinomas, and primary peritoneal serous carcinoma and their resemblance to tumors of Mullerian origin have led to the suggestion that both these cancers develop from the embryonic Mullerian system [57].

The hypothesis that ovarian cancer does not arise from ovarian tissue is supported by clinical findings, indirect evidence, and logic, and concrete evidence to support the cell of origin is lacking.

- The three most common subtypes of these tumors, referred to as serous, endometrioid, and mucinous, are morphologically identical to carcinomas of the fallopian tube, endometrium, and endocervix, respectively.
- A cystic component comprising of epithelial cells of non-ovarian origin is often seen in

serous epithelial tumors, and both benign and mucinous epithelial tumors form cystic lesions.
- Benign ovarian epithelial-like tumors are at least as frequent outside the ovary (para-tubal and para-ovarian cystadenomas) as they are within this organ.
- Primary peritoneal cancers that are histologically and clinically identical to ovarian carcinomas may be seen outside the ovary and may develop in individuals in whom the ovaries were removed several years previously and for reasons other than cancer [58–61].
- Women with familial ovarian carcinoma predisposition due to germline mutations in either BRCA1 or BRCA2 continue to be at an increased risk of developing serous extra-ovarian carcinomas (usually referred to as primary peritoneal carcinomas) after undergoing prophylactic salpingo-oophorectomies [62–64].
- Serous, endometrioid, and mucinous ovarian carcinomas express the same set of HOX genes as epithelial cells from normal fallopian tube, endometrium, and endocervix, respectively [65]. HOX genes are specific for different body parts.

The various tissues to which ovarian epithelial tumors resemble, including the lining of fallopian tubes, endometrium, and endocervix, share a common embryological origin, unrelated to that of the ovary, which is the paramesonephric or Mullerian duct.

There are two hypotheses for the origin of epithelial ovarian cancer and that of PPSC.

The coelomic theory (no longer accepted) proposed that coelomic epithelium that is present on the surface of the ovaries first undergoes Mullerian metaplasia and then malignant change.

The Mullerian theory (widely accepted) proposes that Mullerian epithelium is present on the ovarian surface or within its substance and around it as well and these Mullerian cells undergo malignant degeneration.

16.3.2.2 Diagnostic Criteria

The following criteria to discriminate PPSC from ovarian papillary serous carcinoma have been suggested by Gynecologic Oncology Group in 1993:

- Both ovaries must be normal in size or enlarged by a benign process.
- The involvement in extra-ovarian sites must be greater than the involvement on the surface of either ovary.
- Microscopically, the ovarian component must be nonexistent and confined to ovarian surface epithelium with no evidence of cortical invasion, or involving ovarian surface epithelium and underlying cortical stroma but with tumor size less than 5 × 5 mm.
- Histological and cytological characteristics of the tumor must be predominantly of the serous type that is similar or identical to ovarian serous adenocarcinoma of any grade [54].

The tumors are histologically similar to papillary serous ovarian cancer, being composed of irregular, interconnecting clusters of malignant cells that show solid, cribriform, or cystic architecture [66]. Due to the frequent and abundant presence of psammoma bodies, some authors have called this tumor psammomacarcinoma [67].

The immunohistochemistry (IHC) expression by PPSC is used to distinguish it from other secondary peritoneal tumors. PPSCs express CD15, CK7, S-100, and CA12, have a variable expression of ER and PR, and do not express CK20 and CEA [56]. PPSC and ESOC both exhibit similar histological features and have a tendency to involve the peritoneum, mimicking both clinically and morphologically, diffuse peritoneal mesothelioma. PAX8 and claudin-4 have been being investigated as IHC markers for discriminating peritoneal papillary serous carcinomas and peritoneal epithelioid mesotheliomas [68].

PAX8 is usually absent in peritoneal epithelioid mesotheliomas and is expressed in ESOC and PPSC.

When the appropriate IHC markers have not been tested, other tumors like peritoneal mesothelioma or benign conditions may be difficult to distinguish from PPSC [69].

The staging of PPSC is similar to that of ESOC. PPSC is likened to stage II–IV ESOC depending on the disease extent and sites.

16.3.2.3 Difference Between PPSC and ESOC

Some of the risk factors for EOC also increase the risk of PPSC like BRCA-1 mutations, hysterectomy, and age > 35 at last pregnancy. Tubal ligation is known to have a protective effect for both cancers, though there are some conflicting reports suggesting an increased risk of PPSC after tubal ligation [70–72].

A distinct pattern of diffuse micronodular involvement of the upper abdomen and diaphragmatic surfaces by serous peritoneal cancer with the presence of dense adhesions is a finding specific to this tumor. Deposits are seldom large in size [73].

PPSCs are more anaplastic and proliferative tumors overexpressing HER2 more often than serous ovarian carcinomas, which points toward a more aggressive biology and distinct pathogenesis [72, 74, 75].

There are reports that have shown that PPSC is multifocal in origin, and that is also a possible explanation for its more aggressive behavior [76–79].

Recent studies have shown altered expression of β-catenin, E-cadherin, vimentin, VEGF, p53, EGFR, Ber-EP4, mesothelin, MOC31, and Ki-67 in these patients [80, 81].

16.3.2.4 Presentation

Primary peritoneal serous carcinoma almost always occurs in women (mean age, 56–62 years). Nevertheless, PPSC in male patients occurs in rare cases and is a known entity [82]. PPSC is uncommon and is usually diagnosed when the disease is advanced [82, 83]. According to recent reports, PPSC is more common than previously thought, with 15% of epithelial ovarian carcinomas actually being PPSC, though this may just be due to increased reporting of these tumors [84].

The presentation is similar to that of ovarian cancer with abdominal discomfort, distension, loss of appetite, and an alteration in the bowel habits [84]. Imaging reveals ascites, peritoneal nodules, and omental thickening/nodularity/caking, but no primary site can be identified. CT scan usually demonstrates ascites, peritoneal nodules, and omental thickening but seldom identifies origin of the tumor. The majority of patients have an elevated level of serum CA-125, but the preoperative serum CA-125 levels have no significant predictive value for OS [84].

16.3.2.5 Treatment of PPSC

PPSC has been treated in a similar manner as epithelial ovarian cancer. Though epidemiological data describing the natural history of the disease is lacking, since PPC arises from the peritoneum and like ovarian cancer remains confined to the peritoneal cavity, locoregional therapy comprising of CRS with or without HIPEC in addition to systemic chemotherapy is used for treatment. The studies reporting outcomes in PPSC are heterogeneous. Some have reported response to chemotherapy regimens used for ESOC, others have reported clinicopathological features and outcomes of CRS and systemic chemotherapy, there are case-matched studies comparing clinical features and treatment outcomes in patients with PPSC and EOC, and some reports of the use of CRS and HIPEC in addition to systemic chemotherapy in these patients.

16.3.2.6 Response to Systemic Chemotherapy in PPSC

The reported response rates to platinum-based chemotherapy are similar to those obtained in patients with EOC [85]. Bloss et al. compared the response to a combination of cyclophosphamide and cisplatin in women with ESOC and PPC in a phase II trial [86]. The estimated probability of clinical response (complete and partial) to the treatment regimen for PPC was 65% (95% confidence interval [CI], 41–85%) compared with 59% (95% CI, 47–71%) for women with EOC. Surgical complete responses were similar (20% vs 19%) in the two patient groups. The authors concluded that since results of ovarian cancer trials are extrapolated to patients with PPSC, and the outcomes of treatment with systemic chemotherapy are similar, these patients should be included in trials involving advanced ESOC [86].

16.3.2.7 Outcomes of CRS and Systemic Chemotherapy

Some of the studies reporting outcomes of CRS and systemic chemotherapy in patients with PPSC are listed in Table 16.4.

Nah et al. treated 27 patients of PPSC (stages III–IV) with a combination of cytoreductive surgery and platinum-based chemotherapy. Optimal CRS was obtained in 70.4% and all patients received adjuvant chemotherapy. The median overall survival time was 41 months, and the overall 5-year survival rate was 18.1%. Patients who had optimal cytoreduction had a longer median survival (42 months) than those who had suboptimal cytoreduction (10 months; $p < 0.05$) [98].

Iavazzo reported a median disease-free survival of only 7 months and median OS of 2.5 years in nine patients treated with CRS and Taxol-platinum combination chemotherapy. This may be attributed to an optimal debulking rate of 33% and complete response only in one patient [84].

Similarly, Roh et al. reported a median OS of 23.1 months in 22 patients of PPSC treated with CRS and platinum-based chemotherapy. The estimated 3-year survival rate was 29% (SE, 13%). The response rate to first-line platinum-based chemotherapy was 79%, and the median time to treatment failure was 9.9 months (95% confidence interval, 1.38–18.4 months). The only independent predictor of survival was the performance status. Once again, optimal CRS was obtained in 6/17 (28.3%) patients undergoing CRS upfront which may be the cause of the poor results [95].

Currently, the results of PPSC are reported with ESOC and hence it can be presumed that the outcomes are also the same. Whether the prognosis and long-term survival are similar or inferior to ESOC is not known; there are no reports that have shown a better prognosis compared to ESOC.

16.3.2.8 Case-Matched Studies

Several studies have compared outcomes of PPSC with matched cases of ESOC treated along the same lines. The outcomes of these studies are provided in Table 16.5.

Killackey et al. compared 29 patients with PPSC to 170 with ESOC undergoing debulking surgery with systemic chemotherapy treated from 1984 to 1991 and found a higher rate of suboptimal debulking ($p = 0.04$), a poorer response to chemotherapy, and a shorter DFS (3.4 vs 11.7 months; $p = 0.005$) and shorter OS (19 vs 31 months; $p = 0.12$) in patients with PPSC compared to ESOC, though the shorter DFS did not produce a significant difference between the OS between the two groups [99].

Eisenhauer et al. evaluated the difference between chemotherapy response, platinum resistance, DFS, and OS between 43 patients with PPSC and 129 matched patients with ESOC, stages III–IV treated at their institution from 1998 to 2004. They reported similar rates of response to initial platinum-based chemotherapy but a higher rate of platinum resistance and a shorter DFS and OS [104].

Ben-Baruch found no significant difference in 22 patients with PPSC compared to 63 others with ESOC in terms of clinical characteristics, DFS, or OS. The factor influencing survival in both groups was optimal cytoreduction which was defined as residual disease <2 cm in size. The authors concluded that patients with PPC should be treated like other patients with stages II–IV ESOC [101].

Halperin et al. reported a higher rate of incomplete cytoreduction ($p = 0.0087$) and a lower 3-year survival ($p = 0.017$) in patients with PPSC as compared ESOC. A significant increase in the prevalence of PPSC compared with ESOC was observed during the study years ($p = 0.00001$). The authors concluded that PPSC and ESOC might be two distinct cancers, presenting a new epidemiologic trend regarding the increased incidence of PPSC [84].

Most of these studies were carried out before the use of radical surgical procedures, and intraperitoneal chemotherapy became more widely adopted and some of them have not used platinum-Taxol regimens which are now the standard of care for treatment of ESOC. Moreover they have a small number of patients with PPSC and are

Table 16.4 Outcomes of CRS and systemic chemotherapy in patients with PPSC

Ref year	No.	Optimal CRS	Chemotherapy regimen	Median OS (months)	DFS (months)	Prognostic factors	Conclusions
[87] 1990	33	69%	P + alkyl or A	17			No difference in natural history, response to treatment or outcome
[83] 1990	22	90%	P and alkyl	14.7			Worse outcome for PPSC compared to ESOC
[88] 1995	10	60%	CAP	27			Similar behavior and management
[89] 1996	10		P and alkyl	15			Similar behavior and outcome as in suboptimally debulked ESOC
[90] 1997	18	33%	P and alkyl	10		Optimal debulking	Debulking problematic in PPSC due to diffuse upper abdominal disease
[91] 1997	46	70%	CAP in 25, TP in 21	23		Optimal debulking	Optimal debulking feasible in PPSC. Trend for better outcome with taxol and P
[92] 1998	38	34%	P + taxol	40		Optimal debullking	Low rate of optimal debulking in PPSC, outcome similar to suboptimally debulked ESOC patients
[93] 2004	11	45.4%	P + taxol P + cyclophosphamide	22	NA		
[94] 2005	47	35%	P + taxol	15		High CA125, normal CA19-9	SPPC patient outcome similar to optimally debulked ESOC
[95] 2007	22	17	Platinum based	23.1	13.8	Performance status	Long-term survival is possible in patients with PPSC
[96] 2007	20	55%	P + taxol	Not reached			Similar outcome to ESOC
[84] 2008	9	33.3%	P + Taxol	30	NA		PPSC mimics ESOC but has a poorer survival
[97] 2008	24	13%	P + taxol or CAP	42		Platinum/taxane chemo, low grade. Optimal cytoreduction NS	Platinum/taxane combo very effective, while the impact of aggressive cytoreduction remains unproven
[67] 2011	22	81.8%	Platinum based	21	NA		CRS and systemic chemotherapy may be effective in patients with PPSC
[69] 2014	10	80%	P + Taxol		22		PPSC presents in advanced stages and may be misdiagnosed as tuberculosis in tropical countries. Survival is inferior to ESOC

P Cisplatin, *A* Adriamycin, *C* cyclophosphamide

Table 16.5 Comparison of outcomes of CRS and systemic chemotherapy in patients with PPSC and ESOC

Ref/year	No. of patients[a]	Optimal CRS	Chemotherapy regimen	Median OS (months)	Prognostic factors	Conclusions
[61] 1990	74 vs 743	41%	Platinum + alkyl combinations in 71%	24 vs 27	Combination chemo, low grade. Optimal debulking	Management and outcomes similar in both PPSC and ESOC
[99] 1993	29 vs 170	65% vs 79%	P + alkyl ± doxorubicin	19 vs 31	Low ascites volume, optimal debulking	Poorer outcome in PPSC which could be due to disease biology or suboptimal CRS
[54] 1993	33 vs 33	33% vs 36%	Cyclophosphamide + P	20 vs 27.8		Debulking often suboptimal in SPPC. Behavior and outcome similar to suboptimally debulked SOC
[100] 1994	34 vs 70	44%	P + cyclophosphamide	18 s vs 22	Platinum. Optimal debulking	Similar behavior and outcomes in PPSC and ESOC
[101] 1996	25 vs 71	28% vs 22%	P + cyclophosphamide ± A	21 vs 26	Optimal debulking	Similar behavior, management and outcome
[86] 2003	36 vs 130		P + cyclophosphamide	22 vs 27	–	When confounding covariates are matched, there is no difference between PPSC and EOC
[102] 1998	15 vs 52	67% vs 52%	P + taxol or cyclophosphamide	36 vs 30 s	–	Similar surgical and chemotherapeutic management result in similar outcomes in PPSC and ESOC
[103] 2000	38 vs 38	79% vs 76%	P + taxol	40 vs 34	–	Similar outcomes in PPSC and ESOC
[84] 2001	28 vs 35	39% vs 60%	P + taxol	17 vs 40	–	Inferior outcome in patients with PPSC due to aggressive biology and suboptimal debulking ($p = 0.02$)

P cisplatin, *A* adriamycin
[a]PPSC versus ESOC

retrospective in nature. Most clinical trials have pooled patients of PPSC with ESOC, and the outcomes of PPSC have not been reported separately [105, 106]. PPSC is treated on the same lines as ESOC with a combination of complete cytoreductive surgery and systemic chemotherapy with or without intraperitoneal chemotherapy.

16.3.2.9 Should PPSC Be Considered a Variant of ESOC or a Separate Entity?

Pentheroudakis et al. systematically reviewed all articles studying molecular biology, pathophysiology, clinical presentation, management, and outcomes of at least ten patients with PPSC from 1980

to 2008 in English medical journals and critically analyzed the data [73]. Based on their exhaustive review, the authors recommended that patients with PPSC should be evaluated as a predefined subgroup in ESOC clinical trials and outcome analysis and basic translational research should be performed separately in these patients to determine if a difference exists between ESOC and PPSC which seems to be a more aggressive phenotype.

They based this conclusion on the following findings:

- Patterns of loss of heterozygosity at several chromosomal loci in PPSC differ from those seen in ESOC. The overexpression of the HER2 oncogene is encountered more often.
- PPSC affects older patients, tends to be multifocal, and exhibits a more aggressive genotype at metastatic sites.
- The disease tends to be more extensive and diffuse, making it difficult to achieve a complete CRS if the surgical expertise is not available.
- The overall survival tends to be inferior in these patients despite a complete response to frontline therapy [73].

Despite a good response to chemotherapy and few prolonged remissions, patients with PPSC survive a few months less than ovarian cancer patients.

16.3.2.10 Role of HIPEC in Addition to CRS

The role of HIPEC is less clear in these patients because of its rarity and also because the results are often reported with those of patients with ESOC. Look et al. reported outcomes of CRS with intraperitoneal chemotherapy in 28 patients in epithelial ovarian cancer of which 10 patients had PPSC. Some patients received HIPEC, others EPIC and/or systemic chemotherapy alone. A complete cytoreduction (residual disease <2.5 mm) was obtained in 57.1% if the patients. Outcomes in patients with PPSC were not reported separately. The prognostic indicators associated with a statistically significant impact on survival were the prior surgery score ($p < 0.001$), the completeness of cytoreduction score (CC; $p = 0.037$), and response to chemotherapy prior to surgery ($p = 0.012$) [107].

Bakrin et al. reported outcomes in 36 patients with PPSC from nine institutions treated with CRS and HIPEC. A complete cytoreduction was obtained in 89.1% of the patients. Survival analyses were performed in 32 patients. One-, three-, and five-year survival was 93.6%, 71.5%, and 57.4%, respectively. Median disease-free survival was 16.7 months, and disease-free survival at 1, 3, and 5 years were 59.5%, 40%, and 24%, respectively. By univariate analysis, the only factor that had prognostic value was PCI ($p = 0.03$) [108].

In a recent publication on outcomes of CRS and HIPEC for rare indications by the PSOGI and BIG-RENAPE working groups, of 850 procedures performed in 781 patients, PPSC was not listed separately as a rare tumor and outcomes were not reported, most likely due to a small number [6].

There are several case reports of patients treated with CRS and HIPEC [109, 110].

The above results are obtained in centers that specialize in the management of peritoneal surface malignancies, and therefore the quality of surgery and rates of complete CRS are high, which may be one of the factors for the comparatively high survival rates. One conclusion that can be drawn is that a complete CRS leads to a survival benefit. Whether HIPEC is of benefit cannot be concluded from the above data.

16.3.2.11 Summary

- Primary peritoneal serous cancer is a rare primary tumor that is clinically and histologically similar to epithelial serous ovarian cancer.
- It may be a biologically more aggressive tumor, but further evidence is needed to prove or disprove this notion.
- Cytoreductive surgery and systemic chemotherapy can be considered the standard treatment for these patients.
- There is a potential for treating these patients with intraperitoneal chemotherapy/HIPEC; in addition, this needs further prospective evaluation.

- Clinical trials for ovarian cancer should evaluate the results of this subgroup of patients separately to better understand it biology and develop future treatment strategies accordingly.

16.3.2.12 Primary Peritoneal Serous Borderline

Primary peritoneal serous borderline tumor (also known as peritoneal serous micropapillomatosis) is a rare lesion of low malignant potential that is histologically identical to borderline surface epithelial stromal tumors of the ovary [111]. The tumor does not invade the submesothelium or omental fat which distinguishes these tumors from PPSC. These tumors are commonly seen in female patients aged 16–67 years (mean, 33 years) and are most often discovered incidentally during laparotomy or laparoscopy as focal or diffuse miliary nodules on the peritoneal and omental surfaces [112]. Surgical staging similar to that for ovarian cancer is performed in these patients. A systematic lymphadenectomy is not indicated in these patients [84, 113].

16.3.3 Diffuse Peritoneal Leiomyomatosis

In 1952, diffuse peritoneal leiomyomatosis (DPL) was discovered by Wilson and Peale; however, the first scientific description was attributed to H.D. Taubert in 1971 [114].

Diffuse peritoneal leiomyomatosis (DPL) is characterized by the proliferation of multiple benign nodules comprising of smooth muscle cells in the peritoneal cavity. Fewer than 150 cases have been reported in history. The exact etiology is not known though several theories have been proposed [115, 116]. Its presentation in adult women, response to hormonal therapies, and possibility of degeneration into malignancy pose need to be taken into account while planning treatment for these women which usually comprises of CRS. Only one case of DPL has been reported in male patients as well [117–119].

16.3.3.1 Etiology of DPL

The pelvic peritoneum in females retains its ability to differentiate into specialized epithelia and stroma producing various pathologic conditions even in adult life. This is also referred to as the "secondary Mullerian system" or "Mullerianosis" [120–122]. Smooth muscle cells that are present in the subperitoneal stroma are a part of this system, and this has been demonstrated in peritoneal biopsies taken from patients with endometriosis and pelvic pain [122]. These muscles cells express estrogen receptors (ER) and progesterone receptors (PR) [123]. LPD is a nodular proliferation of smooth muscle cells in the subperitoneal mesenchyme. The expression of ER and PR distinguishes it from other retroperitoneal smooth muscle tumors that do not arise from this secondary Mullerian system and therefore do not express these receptors. There are several theories about the pathogenesis of DPL.

Parmley et al. proposed that DPL is a benign reparative process in which benign smooth muscle cells replace decidual cells, also called the "fibrosing deciduosis" theory. This theory is not accepted anymore [124, 125].

The second theory that is widely accepted is that DPL results from Mullerianosis development of multipotent Mullerian stem cells in the subperitoneal mesenchyme [126, 127]. This development can be triggered by various stimuli, the most common being the hormonal stimulus.

16.3.3.2 Hormonal Stimulus

DPL can be stimulated and aggravated by high estrogen states like pregnancy, long-term use of oral contraceptives, use of hormone replacement therapy, adjuvant tamoxifen for breast cancer, and estrogen-producing ovarian tumors [128–135]. An association between endometriosis and DPL has been described as well. The changes taking place in the subperitoneal mesenchyme due to endometriosis make the tissue more sensitive to hormonal stimuli and thus the development of leiomyomata [136, 137].

There is a rare possibility that DPL is brought on by increased levels of luteinizing hormone in postmenopausal women, and the presence of LH

receptors has been demonstrated in postmenopausal women [138].

16.3.3.3 Iatrogenic Implantation/ Spontaneous Dissemination

Another theory is that DPL arises form implantation and proliferation of benign smooth muscles or cells from a uterine leiomyoma which typically occurs during a laparoscopic morcellation [7]. The tumor cells can get implanted during surgery, and the pneumoperitoneum facilitates the distribution throughout the peritoneal cavity. Miyake et al. in a case report proved the occurrence of iatrogenic dissemination [139, 140]. It is also possible that cells are shed from a leiomyoma as in the case of borderline ovarian tumors.

16.3.3.4 Genetic Alterations

DPL has molecular, genetic, and cytogenetic features that suggest individual tumorlets are monoclonal and may have a pathogenesis similar to that of uterine leiomyoma. DPL can arise from a single uterine leiomyoma. Quade et al. analyzed multiple nodules of DPL from four patients and found the same pattern of X chromosome inactivation in all patients, which was contrary to the expectation that the inactivation would be random and polyclonal. It is uncertain at present whether DPL tumorlets are metastatic deposits of unicentric disease or multicentric deposits having inactivation of the same X chromosome [139]. Similar findings were reported by Miyake et al. [140].

16.3.3.5 Presentation

DPL is commonly seen in women in the reproductive age group though it has been diagnosed in postmenopausal women as well. Patients are asymptomatic, and DPL is an incidental finding on imaging or is diagnosed during a surgical exploration. It may present with nonspecific symptoms like abdominal pain and discomfort, nausea and vomiting, pelvic pain, and discomfort.

16.3.3.6 Diagnosis

Cross-sectional imaging studies show numerous well-circumscribed solid masses in the peritoneal cavity that vary in size from several millimeters to many centimeters that have heterogenous attenuation and enhance like uterine leiomyomas [141, 142]. Typical MR findings show masses that are isointense with muscle on T1-weighted sequences, enhance heterogeneously after gadolinium contrast, and have low signal intensity on T2-weighted images (Figs. 16.1 and 16.2) [143].

The diagnosis needs to be confirmed by performing a biopsy and immunohistochemistry where required. The nodules are histologically composed of spindle cells that are bland and have few or no mitosis [66]. The mitotic index is less than 3/10 HPF. High-grade features are absent. The nodules may contain fibroblasts, myofibroblasts, decidual cells, and, sporadically, endometrial stromal cells in addition to smooth muscle

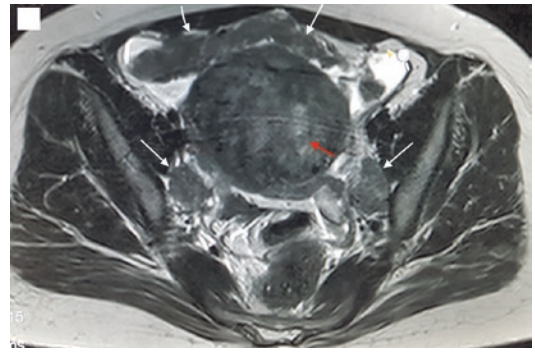

Fig. 16.1 T2-weighted MRI of a patient with DPL and a large uterine fibroid; white arrows point to the peritoneal leiomyomata; red arrow, uterine fibroid

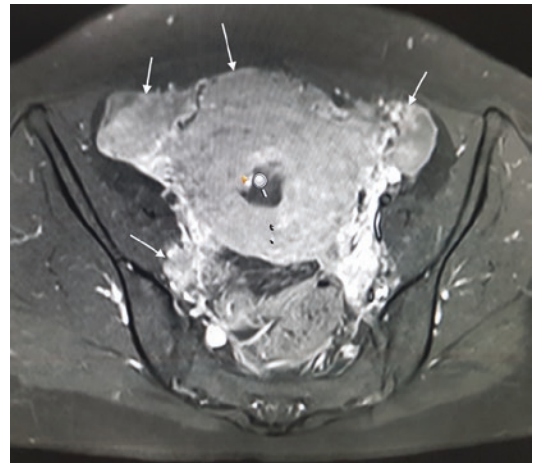

Fig. 16.2 Post-contrast mild enhancement of the lesions (white arrows)

cells. Evaluation of the ER and PR receptor status should be performed in all patients.

Differential diagnoses for multiple peritoneal nodules include peritoneal carcinomatosis, peritoneal leiomyosarcomatosis, mesothelioma, tuberculosis, and lymphoma [142, 144–146].

A benign metastasizing leiomyoma is characterized by fewer nodules and often presents with metastases in the lungs, and a gastrointestinal stromal tumor does not have smooth muscle cells in the nodules [118, 147].

16.3.3.7 Treatment

Spontaneous regression has often been described in LPD, mostly when the estrogen stimulus is removed (stopping oral contraceptive pills, hormone replacement therapy, postpartum). A conservative approach is recommended when DPL is diagnosed in association with pregnancy, due to exogenous estrogen exposure, or uterine leiomyomas and the nodules express ER and PR receptors. GnRH analogues or surgical castration with or without a total abdominal hysterectomy can be used for patients with progressive disease, recurrence, or those who are symptomatic. A conservative approach is preferred in benign cases when a hormonal excess is the underlying cause [126, 148–151]. TAH with unilateral or bilateral salpingo-oophorectomy is recommended only in cases when the family is complete for control of symptoms or in patients who do not respond.

Gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors, and danazol are the other drugs that have been used for treating DPL [152].

In nonresponders to the above therapy, a complete tumor removal is advocated that may require one or more of the peritonectomy procedures and visceral resections. Even when the response is partial and there is incomplete resolution of the tumor nodules, CRS is advocated [153]. As described below, nonresponders to therapy are the ones who are at risk of developing metastatic disease and should be subjected to radical surgery.

The role of HIPEC in DPL is undefined. It has been performed in patients with sarcomatosis but not those with DPL.

16.3.3.8 Does a Malignant Change Occur in Patients with DPL?

Patients with DPL without exogenous or endogenous estrogen exposure, without uterine leiomyomas, and without ER and PR expression on the tumor nodules are considered to be at high risk of developing malignancy. Often the malignant change develops within months or a year of diagnosis of DPL [142, 154, 155]. In some cases, a low-grade leiomyosarcoma may be misdiagnosed as DPL or is already present in one of the nodules that was not biopsied. In 1196, Raspagleisi et al. reviewed the published literature and reported a 10% incidence of progression to sarcomatosis in patients with DPL (5/49 cases) [156].

Hence women, who do not respond to therapy, should undergo radical surgery with removal of all the tumor. Another alternative would be active surveillance with periodic laparoscopic evaluation and biopsies of suspicious lesions. However, the benefit of such procedures and progression rates has not been reported [156].

16.3.3.9 Summary

- Diffuse peritoneal leiomyomatosis is a benign disease with malignant potential.
- In most instances, increased exposure to endogenous or exogenous estrogens is the underlying cause. ER and PR receptor status should be evaluated in all patients. In case of hormonal excess, withdrawal of the hormonal stimulus leads to disease regression. Medical management involving the use of GnRH analogues or aromatase inhibitors can be used in those who do not respond to hormonal withdrawal.
- In patients developing DPL in the absence of increased estrogen exposure or without ER/PR receptor positivity, surgical resection of the tumors is recommended, and this may require peritonectomy and visceral resections to be performed depending on the extent of the disease.
- DPL is known to occur after morcellation of uterine fibroids and myomectomy as well. Patients who have undergone morcellation should be kept on surveillance.

16.4 Secondary Peritoneal Metastases

16.4.1 Peritoneal Metastases from Sarcomas

Soft tissue sarcomas consist of approximately 100 distinct pathological, biological, and clinical diagnoses, many of which may cause PM [157]. Thirty percent of all patients with soft tissue sarcomas have intra-abdominal disease. Fifty to seventy percent of the intra-abdominal sarcomas recur and majority of them will develop peritoneal metastases. Intra-abdominal sarcomas include the retroperitoneal sarcomas, as well as those arising from intraperitoneal structures and the pelvic sidewall. Retroperitoneal sarcomas are more common than intraperitoneal sarcomas. In rare instances, sarcomas arise from intraperitoneal structures. Figure 16.3 shows the CT image of an epithelioid leiomyosarcoma arising from the omentum.

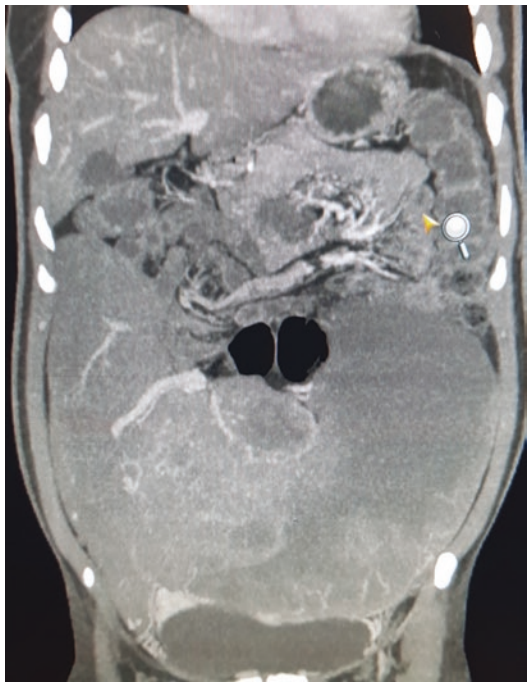

Fig. 16.3 CT scan showing a huge epithelial leiomyosarcoma arising from the omentum. The tumour shows increased vascularity with areas of necrosis

Pelvic sidewall and retroperitoneal sarcomas tend to be large and follow a clinical course that differs from that of adenocarcinomas and visceral sarcomas [158–162]. These tumors are fleshy and have pushing edges; because of their deep location, they grow to a considerable size before a diagnosis is made [163]. All the patients with recurrent disease have local recurrence, and it's the only site of recurrence in 50% of the patients [164, 165].

Peritoneal metastases from sarcomas can be present at the time of diagnosis but usually occur in the recurrent setting and are largely due to tumor spillage during surgery.

Intraperitoneal sarcoma emboli may occur because of the following:

- Spontaneous tumor emboli leading to involvement of the peritoneum before surgery
- Tumor embolization that takes place during surgery in the venous blood that is shed
- Surgical trauma leading to intraperitoneal spillage of tumor cells [165]

Local recurrence after resection of a retroperitoneal or pelvic sidewall recurrence has a fusiform recurrence. There are heavy deposits of tumor cells at the site of resection of the primary and low-density seeding on peritoneal surfaces caused by tumor emboli. The low-density deposits are seen within adhesions as the tumor emboli get covered with fibrin [165].

In addition, extra-abdominal sarcomas can metastasize to the peritoneum. Sarcomas that spread or recur by seeding nearby peritoneal surfaces represent a particularly ominous moiety [163]. Peritoneal metastases in sarcomas have a dismal prognosis largely due to their propensity for hematogenous spread.

The commonest sarcomas that give rise to PM are gastrointestinal stromal tumors (GIST), liposarcomas, and leiomyosarcomas. GIST is discussed separately. Some of the common sarcomas producing PM are described here.

16.4.1.1 Liposarcoma

Liposarcoma accounts for 20% of all soft tissue sarcomas in adults and is the most common

retroperitoneal sarcoma [166, 167]. Five histological subtypes of liposarcoma in order of increasing malignant behavior are well-differentiated, dedifferentiated, myxoid, round cell, and pleomorphic. Most retroperitoneal liposarcomas are well-differentiated and dedifferentiated subtypes [168]. Liposarcomas can also arise intraperitoneally from the omentum and mesentery and present as large intraperitoneal masses [169]. Retroperitoneal liposarcoma is known to recur frequently with multiple intra-abdominal masses after resection [170].

16.4.1.2 Leiomyosarcoma

Leiomyosarcoma is a malignant neoplasm of smooth muscle origin arising most commonly from the genitourinary tract, usually the uterus, retroperitoneum, and gastrointestinal tract [171]. Primary involvement of the peritoneum by leiomyosarcoma occurs in rare instances, and late recurrences have been reported [172].

16.4.1.3 Uterine Leiomyosarcomas

Uterine leiomyosarcoma (ULMS) is an uncommon mesenchymal neoplasm accounting for 1.3% of all uterine malignancies and 30–40% of all uterine sarcomas. ULMS have a high propensity for hematogenous spread most commonly to the lungs. The peritoneum is the next common site of metastases [173]. Uterine sarcomas can arise in patients who have undergone morcellation of a fibroid as an early tumor may be missed in some of these patients, and the surgical procedure can lead to peritoneal tumor dissemination. Current estimates are that approximately 1 in 350 patients will be exposed to this risk of widespread sarcomatosis [173]. Sugarbaker et al. based on their experience proposed that a prophylactic CRS and HIPEC should be performed in patients who have undergone morcellation of a ULMS since most of these patients will eventually develop sarcomatosis [174]. A similar strategy has been recommended by other investigators as well [175].

16.4.1.4 Other Uterine Sarcomas

The other uterine sarcomas are endometrial stromal sarcomas and carcinosarcomas. Endometrial stromal sarcomas can be high grade or low grade, the former pursuing a more aggressive course. Metastases to the peritoneum are common in these tumors though they are often associated with other sites of metastases especially the lung [176].

16.4.1.5 Imaging Findings

Some of these tumors have characteristic radiologic findings leading to the diagnosis. The amount of macroscopic fat within the tumor decreases with more aggressive histological subtypes. Myxoid liposarcoma is a distinct subtype characterized by homogeneous low-density masses with a propensity for spread to the peritoneum, mesentery, retroperitoneum, spine, and paraspinal soft tissues [177]. Retroperitoneal liposarcoma is known to recur frequently with multiple intra-abdominal masses after resection [170]. The peritoneal masses are often heterogeneous in density, with variable proportions of fat and soft tissue and with occasional calcification. The soft tissue component tends to show mild to moderate enhancement. Ascites is typically not seen.

In leiomyosarcomas, peritoneal spread may be seen as diffuse peritoneal thickening or focal masses. Tumor implants are often large, heterogeneous, and intensely enhancing and may show calcification. Ascites is not a dominant finding. Complications include bowel obstruction or hemoperitoneum [172].

16.4.1.6 Management of Peritoneal Metastases from Sarcomas

Peritoneal sarcomatosis has traditionally been viewed as a terminal disease with median survival of less than 1 year, with surgery only reserved for associated complications such as intestinal obstruction and ureteral obstruction [178–180]. Bilimoria et al. found the median survival of patients with sarcomatosis treated with palliative surgery and/or chemotherapy to be 13 months with the only negative prognostic factor being tumor volume [178]. An overall survival of 7–15 months has been reported in patients undergoing palliative procedures [178–181]. Except for imatinib that has shown a significant benefit in patients with GIST, for other patients with PM

from sarcomas, the outcomes of systemic therapies remain poor.

The radical approach of complete cytoreductive surgery (CRS) combined with perioperative chemotherapy comprising of either HIPEC or early postoperative intraperitoneal chemotherapy (EPIC) that had yielded a significant survival benefit in other PM was used to treat sarcomas as well. Most of these investigators have reported the outcomes of a variety of sarcomas pooled together making interpretation difficult. Some authors have reported just the retroperitoneal versus visceral source of PS, and others only the site of origin, or the histological diagnosis [163, 182–184].

In a study of 43 patients with recurrent sarcomatosis undergoing CRS, Berthet et al. were able to achieve a complete cytoreduction in 30 patients and used EPIC with doxorubicin or cisplatin and doxorubicin in these patients. The median OS of the whole group was 20 months.

A significant survival benefit was seen in patients who had involvement of less than six abdominopelvic regions ($p = 0.0009$), less than ten anatomic sites ($p = 0.0002$), complete cytoreduction (CC-0/1) ($p = 0.005$), and PCI less than 13 ($p = 0.01$). Histological type and grade of recurrent sarcoma did not have an impact on the prognosis.

This shows that selected patients with recurrent sarcomas can be treated with CRS and intraperitoneal chemotherapy and outcomes largely depend on the volume and distribution of disease at the commencement of therapy [182].

Baratti et al. reported outcomes in 37 patients who underwent CRS and HIPEC with cisplatin and doxorubicin or mitomycin C and included patients with GIST (pre-imatinib era), uterine leiomyosarcomas, and retroperitoneal liposarcomas [157]. Complete CRS was achieved in 28 patients (75.7%). After median follow-up of 104 (range, 1–131) months, peritoneal recurrence was seen in 16 patients, distant metastases in 5, and both in 13. For all patients, median OS was 26.2 months; seven patients were alive at 46–130 months.

Retroperitoneal liposarcomas had the best OS (median, 34 months) but a peritoneal relapse in 100% of the cases; GIST had a dismal overall survival and high rate of local and distant failures; ULMS had the higher proportion of long-term survivors and lowest rate of local recurrence. Patients who had low-grade tumors, a complete cytoreduction, and had received systemic chemotherapy had a better OS; the only independent predictor of a better OS was tumor grade. Patients with low-grade tumors had a significantly better DFS as well [157].

Bonvalot et al. randomized 38 patients with PM sarcomas undergoing CRS to receive EPIC or not after complete cytoreduction (CC-0). EPIC was performed with five postoperative days with doxorubicin 0.1 mg/kg and cisplatin 15 mg/m^2 diluted in 2 L of Ringer's lactate every day. Histological grade, Sugarbaker's score, and mean number of resected organs were similar in both groups. There was no mortality and morbidity was similar in both groups. The median follow-up is 60 months. The median local relapse-free, metastatic relapse-free survival, and overall survival were identical in both groups (12.5, 18, and 29 months, respectively), with no difference in patients with retroperitoneal and visceral sarcomas. There were ten patients with GIST (pre-imatinib era) of whom three received imatinib subsequently [184].

In another study of 17 patients with PM from sarcomas of different varieties, the median simplified PCI was 6 (range 3–9) and a complete cytoreduction was obtained in all the patients. HIPEC was performed with mitomycin C, cisplatin, or doxorubicin [185]. The median intra-abdominal disease-free and overall survival after CRS/HIPEC was 17.2 months (95% CI, 2.4–19.7) and 22.6 months (95% CI, 6.1–62.6 months), respectively. Since all the patients had a CRS before without HIPEC, the authors compared the DFS after the first and second surgeries and found that there was a trend toward delayed recurrence after combined CRS/HIPEC than after prior CRS alone (17.2 months vs 10.7 months, respectively; $p = 0.52$). The study was underpowered to detect this difference. The median OS varied according to the histology; it was 38.5 months for leiomyosarcomas, 23.9 months for GISTs, 22.6 months

for synovial cell sarcomas, 17.7 months for liposarcomas, and 6.2 months for other sarcomas, though these differences also did not reach statistical significance ($p = 0.56$).

The authors concluded that CRS and HIPEC could improve the locoregional control in these patients though the benefit of HIPEC could not be clearly defined given the lack of studies comparing outcomes between CRS and HIPEC and CRS alone [185].

In an analysis of 850 procedures for unusual cases performed in 781 patients, in 53 centers worldwide, nearly two-thirds of the procedures were performed for three indications: rare ovarian carcinoma ($n = 224$), sarcoma ($n = 189$), and neuroendocrine tumors ($n = 127$). For the three main indications, 5-year OS was significantly greater in patients with PM from rare ovarian carcinoma (57.7%), than that of patients with PM from neuroendocrine tumors (39.9%), and from sarcoma (29.3%; $p < 0.0001$) and not significantly inferior to that in PM from neuroendocrine tumors (39.9%). The authors concluded that the respective roles of CRS and HIPEC in prolonging survival were difficult to determine in these patients. Outcomes in patients with GIST were analyzed separately [6].

Outcomes of CRS and perioperative chemotherapy in patients with PM from sarcomas are described in Table 16.6.

16.4.1.7 Summary

- Soft tissue sarcomas represent a biologically aggressive group of tumors with a propensity for hematogenous spread.
- CRS has shown to be effective in producing disease control and prolonging survival in selected patients with peritoneal metastases though the role of HIPEC remains undefined. The evidence comes from retrospective studies and one randomized controlled trial all having a limited number of patients. The patient population in these studies included a mixture of patients with tumors of various histologies, anatomic sites of origin, and some with synchronous liver and peritoneal metastases which makes it even more difficult to derive meaningful conclusions.
- Patients with a limited disease spread as indicated by the PCI < 10–14, a complete cytoreduction (CC-0/1), low-grade tumors, and certain primaries like uterine leiomyosarcomas have a better overall survival.
- Some centers have stopped performing HIPEC given the lack of demonstrable benefit and added morbidity of the procedure.
- The results of CRS and HIPEC have to be compared with those obtained with systemic therapies alone with the availability of new targeted therapies and different and more effective regimens for some histologies.
- A multidisciplinary evaluation and decision making is the preferred way of treating these patients.
- The role of targeted therapies in STS is evolving and future studies in this direction will probably yield improved outcomes. These should be incorporated into the treatment plan where indicated [194].

16.4.2 Neuroendocrine Tumors

Peritoneal metastases from neuroendocrine tumors (NET) are often considered part of widespread metastatic disease and treated with systemic therapies. PM are not uncommon in patients with carcinoid tumors and other endocrine tumors of gastroenteropancreatic origin [195].

16.4.2.1 Incidence

Data from a prospective French National Registry found the incidence of PM to be 17.5% in 508 patients with gastrointestinal NET [196]. The incidence was 17% in 603 patients with small intestinal NET treated at Uppsala from 1985 to 2010 [197]. In this report which analyzed the outcomes of surgery, the presence of PM had a negative impact on survival. According to the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) report in 2013 in 13,715 patients with NET, metastatic disease was present in 13.5% [198]. In patients with metastatic disease, PM are present in 33% of the patients [199].

Table 16.6 Outcomes of CRS and perioperative chemotherapy in patients with PM from sarcomas

Ref year	No. of patients	Commonest histology	Grade	PCI	CC-0/1	HIPEC	Drugs used	Morbidity	Prognostic factors	Survival
[186] 1997	28		NR		79%	EPIC	Cisplatin	NR	NR	5 year OS—7%
[182] 1998	43	Leiomyosarcoma Liposarcoma, fibrous sarcoma	I-10 II-11 III-22	<13–9 >13–34	62.7%	HIPEC-16 EPIC-27	Cisplatin Cisplatin and doxorubicin	19%	PCI < 13; CC-0/1 resection, involvement of <4 abdominopelvic regions	Median OS—20 months
[187] 1999	54	GIST Leiomyosarcoma Liposarcoma Hepatic metastases in 35%	High grade 72% Low grade 18%	NR	100%	Normothermic postoperative intraperitoneal chemotherapy	Mitoxantrone	9%	Stage, grade	Median DFS—9 m Median OS—18 m 5-year OS—31% Peritoneal recurrence—48% hepatic recurrence 69%
[183] 2004	60	GIST Retroperitoneal sarcoma Uterine sarcoma	High grade 48% Low grade 52%	7.7	100%	HIPEC	Cisplatin and doxorubicin	33%	Grade Completeness of cytoreduction	Median DFS—22 m Median OS—34 m 5-year OS–38% Peritoneal recurrence 71%
[188] 2005	10			NR	90%	HIPEC	Cisplatin and doxorubicin Cisplatin and Mitomycin C	0%		Median DFS 15 months 5-year OS 65% Peritoneal recurrence 60%
[184] 2005	38	Retroperitoneal sarcomas Visceral sarcomas GIST (pre-imatinib)		13.7	100%	EPIC 19 None 19	Cisplatin and doxorubicin	21%		Median DFS—12.5 months Median OS—29 months 5-year OS—40%

[189] 2007	6					HIPEC	Mitomycin C ± Mitoxantrone	43%		Median OS 28.1 m
[163] 2007	28	Leiomyosarcoma/ GIST DSRCT Liposarcoma			94.7/100%	HIPEC	HIPEC cisplatin	16/44%		5-year OS 15%
[190] 2008	9					HIPEC/EPIC	Cisplatin Cisplatin and mitoxantrone	29.8%		Median OS 39.5 m 3-year OS—50%
[157] 2010	37	GIST (pre-imatinib) Uterine leiomyosarcoma Retroperitoneal sarcoma		14.7 (2–34)	75.7%	HIPEC	CIS + adria Mitomycin	21.6%	Tumor grade, CC-0/1, systemic chemotherapy	Median OS 26.3 m 5-year OS—24.3%
[4] 2012	13	Liposarcoma pleomorphic sarcoma		12.1	70%	HIPEC	Cisplatin and doxorubicin	38.5%	CC-0/1 PCI > 10 Low grade tumors had a better DFS not OS	Median DFS—10 m Median OS—12 M
[185] 2013	17	Synovial sarcoma liposarcoma leiomyosarcoma	High 71% Low 6% Unknown 24%	Mean—6	100%	HIPEC-16 delayed HIPEC 1		24%	Intra-abdominal disease free interval	Median DFS— 17.2 months Median OS—22.6 months
[191] 2013	10	Hemangiopericytoma Leiomyosarcoma Spindle cell sarcoma			60%	HIPEC	Mitomycin C Mitomycin C and mitoxantrone	50%		Median OS 21.6 m 5-year OS 43% Recurrent disease in 71%
[192] 2014	3	Uterine leiomyosarcoma Uterine adenosarcoma	High grade 100%			HIPEC	Doxorubicin and cisplatin Melphalan			2 alive and disease free; 1 alive with disease
[193] 2016	8	Liposarcoma			62.2%	HIPEC	Mitomycin, Cisplatin Doxorubicin	35%	PCI < 20	

16.4.2.2 Site of Origin

PM are more commonly seen in patients with NET arising from the midgut and those with large pancreatic NET, and they are infrequently the only site of metastases [200]. Vasseur et al. studied 116 consecutive patients with gastroenteropancreatic NET treated over a 3-year period of which 15 were gastrinomas, 30 carcinoid tumors, and 27 other endocrines, the majority being nonfunctioning tumors [195]. Diagnosis of PM was based on clinical symptoms (ascites and König's syndrome), findings of computed tomography scans that were performed at least yearly, and pathologic confirmation of tumor nodules or positive cytology in the peritoneal fluid. PM was found in 11 patients (overall prevalence of PM, 10%, with 27% in patients with carcinoid tumors, 11% in those with non-gastrinoma pancreatic endocrine tumors, and 0% in patients with gastrinomas). Nine of 11 patients with PM also had liver metastases [195].

NET-derived PM arise mainly from midgut tumors and usually are associated with other sites of distant metastases, notably liver metastases, and usually represent only a small part of the tumor load. Elias et al. observed that the focus was surgical treatment of liver metastases, while the PM were neglected, and this led to progressive peritoneal disease and its consequences [199]. This provides a rationale for treating NET-PM with CRS similar to PM from other sites. The presence of the liver and lymph node metastases which is a common occurrence makes it mandatory to resect those metastases as well.

NET arising from the small intestine tend to develop PM and lymph node metastases early in course of the disease [201]. The peritoneal spread has been attributed to the proximity of the peritoneum.

16.4.2.3 Presentation

PM may produce no symptoms themselves and may be an incidental finding during surgery or during preoperative imaging [202]. The patients may be symptomatic from the primary tumor. Nonspecific symptoms include abdominal pain and discomfort [203–205]. In advanced cases, there may be abdominal distension due to ascites. Some patients may present with acute or subacute intestinal obstruction. Carcinoid syndrome may be present especially in patients with liver metastases [206, 207].

16.4.2.4 Diagnosis

The presence of PM should be confirmed on histopathology. The specimen can be procured during a diagnostic laparoscopy or surgical exploration. Immunohistochemistry should be performed for chromogranin A, synaptophysin, and the Ki-67 proliferation index. WHO tumor staging and TNM staging/grading should be performed. A positive peritoneal fluid cytology may also confirm the presence of PM.

Standard imaging is performed to detect and determine the extent of PM. There are some points regarding the biological behavior of neuroendocrine tumors that should be borne in mind especially those arising from the midgut.

- Even in patients with tumors that have a low Ki-67 proliferative index and are grade I tumors, lymph node metastases are present in nearly half the patients.
- Mesenteric tumor deposits (defined as nodules >1 mm in size that are distinct from lymph nodes) are present, often along the large blood vessels and are not diagnosed on imaging. Palpation may be required to determine the exact extent of the disease [208–210].
- The average size of the metastatic nodules is <2 mm which cannot be picked up on imaging [211].

The common imaging modalities used are CT, MRI, and/or somatostatin receptor scintigraphy which will detect nodules >1 cm [212].

Somatostatin receptor-based PET/CT technology is clearly superior to standard cross-sectional imaging in the detection of grade I and grade II NET in many aspects and bears influence on therapeutic strategies [213–215]. ^{68}Ga-DOTATOC PET/CT can detect primary tumor recurrence, lymph node metastases, bone metastases, and lung metastases more frequently than standard imaging [215].

The physiological uptake of the tracer by the normal liver parenchyma and the small bowel loops increases both the false-negative and false-positive findings [215].

Thus, it is likely that preoperative evaluation will underestimate the extent of disease.

The presence of ascites requires cytological confirmation for the presence of malignant cells. A negative fluid cytology does not rule out the presence of PM [4].

In patients with small bowel obstruction, which may be secondary to the primary tumor, peritoneal nodules and/or associated mesenteric retraction, a CT or MRI enteroclysis may be useful both for diagnosis and planning of treatment.

16.4.2.5 Treatment of NET-PM

The evidence supporting or disfavoring surgical resection of NET-PM is limited. Elias found that patients with PM from NET become symptomatic of them and hence proposed performing complete cytoreductive surgery for patients with NET-PM similar to other patients with PM. Kianmanesh et al. listed the potential benefits of surgical resection:

- Prevention of luminal obstruction or invagination
- Prevention of the consequences of fibrosis due to mesenteric or vascular involvement
- Prevention of hemorrhage [216]

PM from NET have a tendency to infiltrate surrounding structures early in the course of disease. PM from other sites increase in volume first and compress surrounding structures before they invade the underlying organs. Hence, in NET-PM, a wider resection with resection of underlying structures is required more often even in cases with a low tumor burden [199].

Moreover, most cases require extensive surgery comprising of resection of the primary, regional nodes, PM, and LM since metastases are present at multiple sites in most patients.

In a consensus statement by the ENETS published in 2010, the authors recommended surgical resection without adequate referential data of both PM and LM in specialized centers when the surgical risk was acceptable and patients had a good performance status [216]. In patients requiring major liver resection, such as for bilobar liver metastases, staged resections should be employed. In females >55 years, it is usually recommended to remove both ovaries (after preoperative discussion and consent); in younger patients, the ovaries are removed only if involved by metastases. In patients whom CC-0/1 resections are not possible, palliative procedures can be performed to avoid complications later. Where resection of multiple segments of bowel is required, the risk of short bowel syndrome versus the benefit of complete resection should be considered [216]. A grading system was developed based on the extent of the peritoneal disease (quantified by the Lyon prognostic index), the lymph node involvement, and extrahepatic disease (Table 16.7). Surgery is recommended for patients falling into groups A and B. The Lyon prognostic index is described in Table 16.8.

Table 16.7 European Neuroendocrine Tumor Society (ENETS) proposal of GPS grading system based on the association of PM with lymph node and liver metastases [216]

	0 points	1 point	2 points	3 points
Lymph node metastases	None or local[a]	Regional[b]	Para-aortic or hepatic pedicle	Extra-abdominal
Liver metastases	No macroscopic nodules	One lobe less than 5 nodules	Both lobes, 5–10 nodules	Both lobes, more than 10 nodules
Peritoneal metastases	No macroscopic nodules	Lyon I-II resectable	Lyon III–IV resectable	Lyon I–IV unresectable

GPS Global peritoneal carcinomatosis score
GPS Grade A = 0–3 points, Grade B = 4–6 points, Grade C = 7–9 points
[a]Local—first (adjacent to the primary tumor)
[b]Regional—second level of drainage

Table 16.8 Lyon prognostic index (Gilly's peritoneal carcinomatosis score) for quantifying the extent of PM [216]

Stage	Description
Stage 0	No macroscopic disease
Stage I	Localized nodules in one part of the abdomen <5 mm in size
Stage II	Localized nodules spread to the whole abdomen <5 mm in size
Stage III	Localized or diffuse nodules 5–20 mm in size
Stage IV	Localized or diffuse nodules or masses >20 mm in size

16.4.2.6 Evidence for CRS and HIPEC

Elias et al. performed surgery in 37 patients with NET-PM that constituted 33% of all the patients (n = 189) treated at their institute from 1993 to 2003. They divided the patients in two groups; the first comprising of 20 patients in whom complete resection of PM was not possible. Ten patients had bulky disease that was symptomatic but in the other ten, the diagnosis of PM was made during surgery being performed for resection of liver metastases. The extent of the liver disease precluded complete resection, and most of these patients had tumor debulking with palliative bypass procedures where required. In the other group, complete resection of all nodules >2 mm was performed with intraperitoneal chemotherapy (HIPEC with mitomycin C in five patients and EPIC with mitomycin C and 5-fluorouracil in 12 patients). The PCI was >10 in 14 of these patients and >20 in 4 patients. Sixty-five percent of the patients had liver resection as well. The morbidity was 47% in group 2 [217].

The 5-year survival rates were 40.9% (95% CI, 22–62) for patients in group 1 and 66.2% (95% CI, 45–85) for patients in group 2 (p = 0.0068). Seven-year survival rates were 14.6% and 55.2%, respectively. Forty-one percent of patients were disease-free just after surgery, and only 10% were disease-free 5 years later [217].

This study also provided important insights into the natural history of the disease in patients with NET-PM. In 81% of the cases with PM, the primary tumor was located in the ileum or the appendix and was of pancreatic origin only in 5.4%. Eighty-nine percent of the patients with PM had liver metastases. Those patients who did not have LM at the time of surgery for PM went on to develop metastases within 18 months of surgery. Thus, NET-PM are associated with extensive multicentric metastatic disease. In group 1, the cause of death was related to the PM in 40% of the patients. Bone marrow suppression was seen in patients who had extensive liver resection, and the authors advice a dose reduction when IPC is used in these patients [217].

The authors concluded that though resection of PM and other metastatic diseases leads to a survival benefit, cure was not possible since most of the patients developed recurrent disease.

The same group questioned the benefit of HIPEC in addition to CRS. In a subsequent publication, they compared outcomes of CRS alone (n = 13) to those of CRS and HIPEC (n = 28). Liver metastases were treated during the same operative procedure in 66% of the patients. Mortality was 2% and morbidity 56%. OS at 5 and 10 years was 69% and 52%, respectively, and DFS at 5 and 10 years was 17% and 6%, respectively. At 5 years, PM and LM recurred in 47% and in 66% of cases, respectively. Overall survival was not different between patients treated with or without HIPEC, but disease-free survival was greater in the HIPEC group (p = 0.018), mainly because of fewer lung and bone metastases. They concluded that complete CRS of peritoneal metastases from a NET is feasible in most of the patients and could increase the survival; the additional benefit of HIPEC remained undetermined.

In a series of 1001 surgical procedures performed for 800 patients with NET arising from various sites at a single center, 189 patients had PM [218]. Though the outcomes in patients with PM were not reported separately, the authors concluded that surgical resection was the only curative option for these patients. In patients with advanced disease, they performed a resection of the primary with cholecystectomy (patients who receive somatostatin analogues have a propensity to develop gallstones) and resection of as much hepatic and extrahepatic disease as possible. Ablative methods like radiofrequency ablation, microwave ablation, and tumor ablation with the

other high-energy devices were used to achieve cytoreduction. For patients with residual disease, further surgical resection was performed or staged resections were planned. Where this is not possible, liver-directed therapy, targeted therapy with radiolabeled somatostatin analogues, and/or systemic therapies were used. These authors also reported a benefit in survival when resection of 70–90% of the tumor could be resected though it is less than those that have resection of >90% of the tumor [218, 219].

In a single institutional study of 562 patients with small bowel NETs, Norlén et al. compared survival rates in surgically resected patients to non-resected patients [220]. In the surgical cytoreduction group, 5- and 10-year OS were 75% and 51%, respectively, versus 28% and 6%, respectively, in the non-resected group. Similar findings were also reported in a smaller study (n = 258) of surgically resected patients with small bowel NETs by Bergestuen et al. [221].

In the series of 850 procedures carried out at 53 centers across the world, 114 (15.5) of the patients had PM from NET. The 5-year OS in these patients was 39.9%. The DFS, which was calculated only in patients, who have CC-0/1 resection, was 40.2% at 5 years. The extent of resection performed in these patients and the selection criteria were not reported though the authors recommend surgery only in those patients where a complete CRS is possible. Once again, the role of HIPEC/EPIC was not clear these patients.

In another study, 73 patients with PM from small intestinal NET undergoing cytoreductive surgery were compared to 468 others without PM treated from 1985 to 2012. The presence of PM had a negative impact on survival. Residual peritoneal disease after surgery also had a negative impact on survival. The authors also reported genotypic differences between patients with and without PM and recommended further evaluation of this aspect [221].

16.4.2.7 Summary

- PM are common in patients with NET specifically in tumors arising from the midgut. PM are accompanied by multicentric metastatic disease in most cases involving the primarily the liver and lymph nodes. If left untreated, PM can be the cause of death in these patients.
- Aggressive surgical treatment performed with the goal of complete tumor removal at all sites has a survival benefit.
- In patients whom complete resection is not possible, staged procedures can be performed for liver metastases. Debulking surgery also has a survival benefit in these patients over systemic therapies alone if >70% of the tumor can be removed.
- Systemic therapies and liver-directed therapies should be used as adjuncts to surgery.
- Such surgeries are complex, carry a high morbidity, and should be carried out in centers having the expertise in delivering such treatment.
- In most patients, such procedures prolong survival but do not lead to a cure.
- All the above recommendations are for patients with grade I and grade II well-differentiated tumors.

16.4.3 Rare Ovarian Tumors

The World Health Organization Histological Classification for ovarian tumors separates ovarian neoplasms according to the most probable tissue of origin: surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastases (5%), and miscellaneous [222]. Of the epithelial tumors, serous tumors are common, while the other subtypes (mucinous, endometrioid, clear cell, and transitional cell tumors) are relatively rare. CRS is routinely performed for PM arising from non-serous epithelial ovarian tumors. HIPEC has been used for the treatment of some of these tumors as well.

16.4.3.1 Mucinous Ovarian Tumors

Though conventionally reported and treated on the same lines as other epithelial tumors of the ovary, mucinous borderline and invasive tumors have distinct clinical, pathological, and molecular features [223].

Collaborative phase III trials in ovarian cancer have not analyzed results according to the histological subtype, and mucinous tumors comprise

only a small percentage of the patients in these trials [224–227].

The reported incidence of these tumors varies from 2 to 4% to up to 11%. The probable reasons for these differences in various reports are:

- Misclassification of a gastrointestinal primary tumor as an ovarian primary tumor (80% of mucinous epithelial to ovarian tumors are of extra-ovarian origin).
- Misclassification of a mucinous borderline tumor as an invasive cancer.
- Classification of pseudomyxoma peritonei as being of ovarian origin—in over 90% of the cases, the primary site is the appendix.
- Most of these reports come from referral centers where complex cases get referred, and therefore they have a larger proportion of mucinous tumors [223].

16.4.3.2 Pathological and Molecular Features

Ovarian mucinous carcinoma is divided into intraepithelial (noninvasive) carcinoma and invasive carcinoma. Intraepithelial (noninvasive) mucinous carcinoma is characterized by the presence of marked epithelial atypia in the absence of stromal invasion. Invasive mucinous carcinoma is diagnosed once stromal invasion measuring more than 5 mm or more than 10 mm^2 is detected [228, 229]. Two types of invasive mucinous carcinoma are recognized: (1) expansile (confluent) type and (2) infiltrative type.

Mucinous tumors have an increased incidence of *KRAS* mutations and a significantly lower incidence of *BRCA* and p53 mutations in comparison to the serous epithelial tumors.

Serous and mucinous ovarian tumors have distinct gene expression profile and can be easily distinguished from each other [228, 229].

16.4.3.3 Clinical Features and Prognosis

Mucinous tumors are usually diagnosed in the first stage, tend to be unilateral, have a larger mean tumor diameter, have a lower incidence of occult lymph node involvement, and respond poorly to platinum-based chemotherapy [230–234].

An appendiceal primary tumor should always be ruled out in patients presenting with mucinous ovarian tumors with or without pseudomyxoma peritonei (PMP). If the appendix has not been removed, immunohistochemistry can point to the site of origin of the tumor.

Patients diagnosed with stage I disease have a significantly better OS survival compared to serous tumors presenting with stage I disease. Contrary to this, the prognosis of stage III mucinous ovarian cancer is much worse than that of serous ovarian cancer.

In a retrospective analysis of 1895 women with stage III epithelial ovarian cancer enrolled in 6 GOG phase III trials, 74% had serous ovarian cancer, while only 2% had mucinous ovarian cancer. Women with mucinous tumors had a progression-free survival of 10.5 months, compared to 16.9 months for women with serous tumors. The relative risk of progression in women with mucinous tumors was 2.18 times that of those with serous tumors ($p < 0.001$). Similarly, the median OS was only 14.8 months for women with mucinous ovarian cancer, compared to 45.2 months for women with serous ovarian cancer. The relative risk of death from mucinous cancer for mucinous cancer compared to serous cancer was 4.14 ($p < 0.001$) [235].

Kikkawa et al. reported a 5-year OS of 75% in 169 women with mucinous carcinomas of the ovary and a survival rate of about 28% for those with stage III disease [236]. Chaitin et al. reported a 7-year OS of 72% for stage I mucinous carcinoma but only 8% for patients of stage II or higher in 70 patients with mucinous ovarian carcinoma [237].

The poor survival in patients with mucinous ovarian cancer can be attributed to an intrinsic aggressiveness of the tumors, resistance to platinum-based chemotherapy, and misclassification of metastatic tumors that are primary ovarian carcinomas.

A phase III trial enrolled 4000 women with stage III or IV ovarian carcinoma, treated by surgical staging and debulking, with randomization to one of five chemotherapeutic arms. A review of patients with mucinous carcinoma was performed by three pathologists independently, and

the tumors were classified as primary or metastatic. The median OS did not differ significantly between the groups interpreted as primary or metastatic, but the OS was significantly less than that for women with serous carcinoma (14 vs 42 months, $p < 0.001$) [238].

16.4.3.4 Response to Chemotherapy

Mucinous ovarian carcinoma responds poorly to platinum and Taxol chemotherapy as compared to serous ovarian cancer [239, 240].

In an experimental study, in ovarian cell lines resistant to platinum compounds, the combinations of oxaliplatin and 5-fluorouracil were inhibitory in 4/5 cell lines [241].

This combination is being compared to the Taxol and platinum combination in a GOG trial.

16.4.3.5 Role of Cytoreductive Surgery and HIPEC

Mucinous ovarian cancer with PM has been compared to pseudomyxoma peritonei arising from mucinous appendiceal tumors and hence treated with CRS and HIPEC. In the PSOGI and BIGRENAPE study of 850 patients, 199 patients had as the primary site an uncommon histology of ovarian cancer, most of which were mucinous ovarian tumors. These patients had the longest survival rates among all patients with 5-year OS and DFS rates of 57.7% and 38.9%, respectively. The authors concluded that the prolonged survival rates obtained for mucinous ovarian carcinoma with PM confirmed that this histological type can be likened to pseudomyxoma peritonei, with mucinous peritoneal implants, and thus should be treated similarly, with complete radical surgery and HIPEC [6]. There are no other reports evaluating the role of CRS and HIPEC in advanced mucinous ovarian cancer as the results are reported with those of serous epithelial tumors. In a study of 46 patients from advanced epithelial ovarian cancer (group A) or recurrent epithelial ovarian cancer (group B) who were treated by 50 CRS + HIPEC procedures, 11 (23.9%) patients had mucinous adenocarcinomas. The median OS was 74.0 months for group A versus 57.5 months for group B. The median PFS was not reached for group A versus 8.5 months (95% CI, 0–17.5) for group B ($p = 0.034$). The impact of histology on survival outcomes was not evaluated in this study [242].

16.4.3.6 Granulosa Cell Tumors

Granulosa cell tumor (GCT) is the most common form of ovarian sex cord-stromal tumors presenting in two histopathologically different forms, as common adult granulosa cell tumor (AGCT) and as the less frequent juvenile granulosa cell tumor (JGCT) [243]. These tumors have a long natural history and tend to relapse even after more than 10 years after the initial diagnosis. Reported 5-year OS for patients with stage I disease ranges from 75 to 95%, with many studies demonstrating survival rates in excess of 90%; it drops to 55–75% for patients with stage II disease and 22–50% for patients with stage III/IV disease [244, 245]. The overall 10-year survival rate has been reported as between 85 and 95% [246].

Reported rates of recurrence after frontline therapy range from 17 to 50% [247]. One-third of recurrences develop after 5 years or treatment and one-fifth after 10 years [248–250]. A high initial stage increases the risk of relapse.

In a multi-institutional study of 97 patients with primary GCT with a median follow-up of 88 months (range, 6–498), 33 patients had at least one episode of disease recurrence, with a median time to recurrence of 53 months (range, 9–332). Forty-seven percent of recurrences occurred after 5 years from initial diagnosis. At multivariate analysis, age and stage were independent poor prognostic indicators for survival; surgical treatment outside specialized centers and incomplete surgical staging retained significant predictive value for recurrence in both univariate and multivariate analyses [244].

The standard treatment is surgery, but the extent of surgery is not clearly defined. Fertility-sparing approaches have been used for women desirous of preserving their fertility where as more radical surgery comprising of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy is performed when fertility preservation is not desired. A systematic review from the Cochrane database comprising five retrospective cohort stud-

ies with data on 535 women was performed by Gurumurthy et al. The authors found the overall quality of evidence to be low and were unable to offer clear recommendations about the type of surgery that should be offered to these patients [251]. Similarly, though one study showed a benefit of adjuvant radiotherapy, there was a high risk of bias, and the authors could not make definite conclusions on the best adjuvant therapy either, whether it was needed at all.

16.4.3.7 Role of CRS and HIPEC

Peritoneal cancer spread is more common in patients with recurrent adult GCT. Fotopoulou et al. analyzed 45 patients with adult GCT, of which 18 had primary and 27 recurrent GCT [252]. Peritoneal involvement is more common in recurrent tumors as compared to primary tumors (52% vs 15.8%; $p = 0.027$), and involvement of the middle (48.1% vs 15.8%; $p = 0.05$) and upper abdomen (33.3% vs 0%; $p = 0.006$) is also higher in recurrent tumors. A complete CRS was possible in all the patients with primary disease and only in 85.2% of the relapsed patients ($p = 0.13$). Complex procedures including multiple peritonectomies, intestinal or diaphragmatic resection, splenectomy, and partial hepatectomy/pancreatectomy had to be performed only in recurrent GCT (55.6%). Extensive peritoneal involvement is uncommon in patients with primary GCT.

Consequently, there are no studies reporting outcomes of CRS with or without HIPEC in patients with advanced primary GCT. However, it has been used to treat recurrent disease.

There are no standard guidelines for the treatment of recurrent GCT, and multiple modalities such as surgery, chemotherapy, radiotherapy, and hormonal therapy have been proposed. Despite the lack of evidence of large randomized studies, many clinicians recommend surgical resection of the recurrent disease. Complete tumor removal has a survival benefit in these patients [253].

In the event of a relapse, there is no consensus concerning adjuvant treatment after debulking surgery [254–256]. One of the chemotherapy regimens commonly used comprises a combination of bleomycin, etoposide, and cisplatin (BEP).

Since granulosa cell tumors are not chemosensitive, HIPEC has been considered as an alternative to reduce the risk of further recurrence.

Canbay et al. treated four patients with recurrent granulosa cell tumors with CRS and HIPEC with cisplatin. These patients were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy with the diagnosis of primary adult type GCT of the ovary. The median disease-free survival after primary treatment was 4.7 (range, 1–9) years. After a median follow-up of 4 (range, 1–6) years, one patient died and the other three patients were alive with no disease progression [257].

In another series of six patients with recurrent GCT, all patients achieved a complete cytoreduction (CC-0/1) and underwent HIPEC with cisplatin and doxorubicin. From 2010 to 2013, six patients underwent CRS + HIPEC. Five patients had recurrences in both the abdomen and pelvis, while one had it only in the abdomen. Chemotherapy was given to four patients who had not received it before. At their last follow-ups which were at 40, 32, 27, 24, 20, and 16 months post-surgery, all the patients were alive and disease-free [253].

In another retrospective series of seven patients, all the patients had complete cytoreduction and HIPEC with oxaliplatin and irinotecan. Two patients had recurrent disease in the pelvis alone, while the other five had disease in both the abdomen and pelvis [258]. Median follow-up after CRS plus HIPEC was 32 months (range, 25–56). Two patients were disease-free at the time of the last follow-up; three had developed peritoneal metastases and two other liver metastases. The authors did not recommend the use of HIPEC using oxaliplatin to treat recurrent GCT but suggested that other therapies like bevacizumab should be tried in addition to CRS [258, 259].

There is a role of CRS in patients with advanced and recurrent GCT. Recurrent disease can develop after >10 years of diagnosis of the primary tumor. The prognostic factors are not clearly defined and even patients with recurrence experience a prolonged survival. Once the disease recurs, subsequent recurrences are common. The role of HIPEC in these patients is undefined.

16.4.3.8 Malignant Ovarian Germ Cell Tumors

Malignant ovarian germ cell tumors are rare tumors that occur in adolescent and young females, are predominantly unilateral, are diagnosed at an early stage, are chemosensitive, and have a high cure rate [260]. For early-stage disease, the cure rate approaches 100% and is approximately 75% for those with advanced tumors [260]. Practically, it is most helpful to subdivide MOGCT into dysgerminoma—the most common type and the counterpart of the male seminoma—and non-dysgerminomatous tumors. The most common types of non-dysgerminomatous tumors are yolk sac tumor, immature teratoma, and mixed germ cell tumors, with embryonal carcinoma, nongestational choriocarcinoma, and polyembryoma being much less common [261]. In the most recent version of the WHO classification system, MOGCT are divided into three categories: primitive germ cell tumors, biphasic or triphasic teratoma, and monodermal teratoma and somatic-type tumors associated with dermoid cysts [262]. Dysgerminomas and low-grade immature teratomas have a good prognosis. Endodermal sinus tumors, choriocarcinomas, and high-grade immature teratomas are the more aggressive tumors.

16.4.3.9 Cytoreductive Surgery for Advanced Disease

The peritoneum is one of the sites of disease spread in these patients. The principle of primary cytoreductive surgery for patients with advanced-stage malignant ovarian germ cell tumors has also been extrapolated from experience with epithelial ovarian cancer [260]. Most of these tumors are very chemosensitive; when the PM are extensive, CRS can be morbid. However, studies have shown a benefit of complete tumor removal in patients treated with both platinum- and non-platinum-based regimens [263]. In a study of 76 patients, only 28% of the patients who had complete CRS recurred compared to 68% with incomplete CRS [264]. Hence, when the morbidity is acceptable, complete tumor removal should be attempted in patients with malignant germ cell tumors with PM [264].

16.4.3.10 Secondary Cytoreductive Surgery for Recurrent Disease

The treatment options for patients who have recurrent or residual disease are either second-line/salvage chemotherapy alone or a combination of chemotherapy and secondary cytoreductive surgery [265]. These tumors have lower rates of residual disease as compared to patients with testicular tumors and are commonly treated with second-line chemotherapy [265]. The rarity of the disease with the small percentage of patients who recur makes it difficult to have sufficient numbers for comparison or to conduct a randomized trial. Munkarah et al. who treated 20 patients with various subtypes of malignant ovarian germ cell tumors concluded that though the role of secondary CRS remained undefined, it could benefit patients with immature teratomas, those who had fewer sites of disease, and those to whom a complete cytoreduction was possible [266]. Once again, the patients include not just those with PM but other sites of disease as well.

16.4.3.11 Role of HIPEC

Hayes-Jordan et al. have performed CRS and HIPEC for adolescents and young adults with PM from various primary sites [267]. In their series of 50 patients, three patients had rare ovarian tumors (one PNET, one Leydig cell tumor, one yolk sac tumor). While no definite conclusions could be drawn regarding the role of HIPEC for these patients, this study showed that HIPEC could be performed safely in this patient population. In a subsequent publication, the authors reported outcomes in 101 pediatric patients treated with CRS and HIPEC of whom eight had ovarian primary tumors and multifocal peritoneal disease. There were three yolk sac tumors (germ cell, mixed teratoma), one Sertoli-Leydig, one PNET of the ovary, one choriocarcinoma, one juvenile granulosa cell tumor, and one adenocarcinoma. Age ranged 4–18 years. Three of the eight (37%) recurred and died. For the remaining 63% of the patients, the disease-free survival ranged from 2 to 6 years. Patients treated for a third or fourth relapse did not experience a survival benefit. The pediatric patients had a better outcome as compared to the adults [268].

16.4.3.12 Other Rare Ovarian Tumors

For other tumors like Sertoli-Leydig cell tumors and uncommon epithelial tumors, only case reports exist, and it's not possible to derive conclusions regarding the benefit of HIPEC in these [268]. Cytoreductive surgery is used for treating patients with advanced disease as in patients with epithelial tumors.

16.4.3.13 Summary

- Mucinous ovarian tumors with PM behave like pseudomyxoma peritonei arising from mucinous appendiceal tumors and should be treated with CRS and HIPEC.
- An appendix primary tumor should always be ruled out in these patients.
- For recurrent granulosa cell tumors, CRS should be offered when complete cytoreduction is possible; the role of HIPEC is undefined for these tumors.
- Late recurrences are common in patients with GCT, but treatment of recurrence results in a prolonged survival. The prognostic factors for these tumors are not known.
- Similarly, for malignant germ cell tumors with PM, there is a benefit of CRS, and it should be offered, whereas the role of HIPEC is uncertain.
- In all these patients, CRS should be done only for those patients where a complete cytoreduction is possible.

16.4.4 Mucinous Carcinoma of the Urachus

Most cases of pseudomyxoma peritonei arise from mucinous appendiceal tumors [269]. Mucinous tumors are known to arise in the urachus and give rise to pseudomyxoma peritonei (PMP) [270]. The urachus is an embryonic remnant resulting from involution of the allantoic duct and the ventral cloaca, which connects the bladder dome to the umbilicus and is found in one-third of adults [271]. Urachal carcinoma is rare, accounting for less than 1% of all bladder cancers [272]. The urachus is lined by transitional epithelium that undergoes glandular metaplasia to give rise to mucinous tumors [273]. The tumor presents as a cystic mass in the lower midline and may communicate with the bladder if the urachus is patent producing mucosuria (passage of mucin in the urine) which is rare but points to the diagnosis. The urachal tumor ruptures into the peritoneal cavity producing PMP.

Sometimes when the pressure inside the tumor rises, cells are shed into the peritoneal cavity producing PMP even though the primary tumor is intact. Stenhouse et al. reported a case of PMP arising from a urachal cystadenoma, which can be explained by this phenomenon [274].

The spectrum of mucinous tumors that is seen in the appendix is also seen in urachal tumors though most of the tumors tend to be of a high grade [275–277]. In some patients, the epithelial cells are described as bland, well-differentiated, and noninvasive and thought to be of borderline malignancy, whereas other may show signet ring cells. Sugarbaker et al. proposed the term "mucinous urachal neoplasms" to be used for the range of mucinous urachal tumors [273].

16.4.4.1 Treatment of Mucinous Urachal Tumors

Localized Tumors

The handling of the urachal tumor is important, and in case of an intact tumor, excision with wide margins without causing rupture should be performed. A partial cystectomy is sufficient in most cases. Performing a radical cystectomy does not increase the cure rate [277]. Moreover, most of these tumors do not infiltrate into the wall of the bladder [273].

Amin et al. studied the clinicopathological features of 55 patients with glandular tumors of the urachus and divided them into two broad categories—mucinous cystic neoplasms and invasive non-cystic adenocarcinomas [278]. The mucinous cystic neoplasms were predominantly unilocular, filled with mucin, and had mucin extravasation into the cyst walls, often with calcification or rarely ossification. The cyst lining ranged from flat to cuboidal to typical mucinous columnar to pseudostratified to papillary; scattered areas had goblet cell differentiation. Of

the 31 patients with mucinous cystic tumors, the pathological spectrum ranged from benign to malignant including mucinous cystadenomas (n = 4), mucinous cystic tumors of low malignant potential (n = 22, including two cases with intraepithelial carcinoma), and mucinous cystadenocarcinomas with microscopic (n = 4) or frank invasion (n = 1). Follow-up information was available for 13 patients with mucinous cystic tumors (mean, 41 months); no local recurrence or distant metastasis was observed [278].

PMP Arising from Mucinous Urachal Tumors

The standard approach should be to treat PMP from urachal tumors with CRS and HIPEC like PMP arising from mucinous epithelial tumors as recommended by Honore et al. though the prognosis of these tumors may be worse [279]. Of the three patients in their series, two were alive and disease-free at 20 and 37 months. The third patient developed early peritoneal recurrence and liver metastasis, demonstrating unusual tumor aggressiveness, and died after 14 months. The median PCI was 11 in these three patients [279].

The largest series reported so far comprised of nine patients treated with CRS and HIPEC with cisplatin and mitomycin C. The diagnostic criteria included:

- A MRI or CT scan showing a tumor in the lower abdomen in the midline in the region of the urachus or the presence of mucin in urine
- Tumor connected to both the posterior surface of the umbilicus and the bladder during surgery
- A pathology in the urachus without any other site of origin found on pathological examination

Six patients had low-grade mucinous carcinoma peritonei, and three had high-grade mucinous carcinoma peritonei according to the WHO classification. Four patients had signet ring cells. All tumor specimens of nine patients were diffusive positive for CK-20, CDX-2, MUC-2, and MUC-5 AC and were variant positive for CK-7. The median PCI was 10 (mean, 13.5; range, 2–33). A complete CRS was obtained in all the patients. One patient developed recurrence, while eight others were disease-free at a median follow-up of 27.5 months [280]. There are numerous case reports on PMP arising from mucinous tumors of the urachus (Table 16.9). The disease-free survival in all these reports ranges from 6 to 108 months.

16.4.4.2 Summary

- PMP arising from urachal mucinous tumors has the same spectrum as that of PMP of appendiceal origin and should be treated on the same lines with CRS and HIPEC.
- The prognostic factors are not defined, and some authors have suggested the possibility of a more aggressive tumor biology.
- Most cases do not require bladder resection.

16.4.5 Endometrial Carcinoma

Endometrial carcinoma is a common gynecological malignancy that is generally diagnosed in the early stages. Patients with advanced-stage endometrial cancer represent only 10–15% of all newly diagnosed cases but account for over half of all uterine cancer-related deaths [293, 294]. The 5-year survival rate for regional disease (FIGO stage III) is 57% and 5–20% for stage IV disease [295–297]. Cytoreductive surgery has a role to play in patients of endometrial cancer with PM. Approximately 11% of endometrial cancer patients develop a recurrence [298]. Though most of the recurrences are central pelvic recurrence managed with pelvic exenteration, patients with PM have been treated with CRS with or without HIPEC.

16.4.5.1 Endometrial Cancer with Peritoneal Metastases

The most common histology of endometrial cancer is endometrioid adenocarcinoma that presents with localized disease in majority of the cases. Papillary serous carcinomas comprise 1–10% of the endometrial tumors and are also called uterine serous carcinomas (USC) [299–301].

Table 16.9 Case reports of PMP arising from mucinous tumors of the urachus and treatment outcomes

Ref no. year	No. of patients	Pathology	CRS	Cystectomy	HIPEC	Survival (months)	Current status
[270] 1971	1	MAC	Debulking	–	–	28	DOD
[281] 1997	1	Adenoma	–	–	–	–	–
[276] 1997	1	Signet ring cell adenocarcinoma	Extensive	Yes	Mitomycin C	31	DOD
[275] 2000	1	Low grade mucinous tumor	Extensive	No	Mitomycin C	108	NED
[282] 2003	1	MAC	Oophorectomy	–	–	–	NED
[274] 2003	1	Low grade mucinous tumor	–	–	–	–	–
[274] 2004	1	MAC	Minimal	–	–	–	–
[283] 2006	1	Mucinous tumor of low malignant potential	Extensive	Partial	5-Fluorouracil	84	NED
[284] 2006	2	MAC MAC	Limited Extensive	No No	No Mitomycin C & doxorubicin	12 18	NED NED
[273] 2007	2	MAC MAC	Extensive Extensive	No No	EPIC Mitomycin C	132 20	DOD NED
[285] 2008	1	MAC	Limited	Partial		6	NED
[286] 2009	1	MAC	Extensive	–	–	–	–
[287] 2010	1	MAC	Extensive	Partial		18	DOD
[288] 2011	1	Mucinous tumor of low malignant potential	Extensive	–	–	54	NED
[289] 2012	1	MAC	Limited	–	–	36	DOD
[290] 2012	1	MAC	Extensive	Partial	Oxaliplatin	24	NED
[291] 2014	1	Low grade mucinous tumor	Extensive	–	–	–	–
[292] 2017	1	MAC	–	–	–	–	LWD

MAC mucinous adenocarcinoma, *DOD* died of disease, *NED* no evidence of disease, *LWD* living with disease

Endometrioid tumors do not produce lymph node metastases until myometrial invasion has occurred. Peritoneal spread occurs late in the course of disease and is relatively uncommon. In contrast, serous tumors have an intrinsic ability to spread through lymphatic/vascular (LV) channels without invading the myometrium. This is certainly one mechanism of spread to account for the more aggressive clinical course of serous tumors, and it has been shown that LV invasion is associated with a poor prognosis except in stage I patients [302]. In addition, to LV invasion, transtubal spread of tumor cells has been demonstrated to occur and could explain the occurrence of PM in the absence of LV or myometrial invasion [302, 303].

Most reports of cytoreductive surgery have pooled patients with endometrioid adenocarcinomas and USCs.

16.4.5.2 Advanced Endometrial Cancer

Initially, endometrial cancer was treated with radiotherapy and surgery was used as an adjunct to radiotherapy. Early studies investigating the role of radiotherapy showed that patients who underwent surgery in addition to radiotherapy and had residual disease <2 cm experienced a benefit in survival [304–306]. Several retrospective studies have demonstrated a benefit of CRS in advanced and recurrent endometrial cancer of various histological subtypes [307].

Barlin et al. performed a meta-analysis that included 14 retrospective cohorts with advanced or recurrent endometrial cancer (672 patients) [307]. The percentage of patients with stage IV disease and USCs was small. Cohort median overall survival time was positively associated with increasing proportion of patients undergoing complete surgical cytoreduction (each 10% increase improving survival by 9.3 months; $p = 0.04$) and receiving postoperative radiation therapy (each 10% increase improving survival by 11.0 months; $p = 0.004$), while an increasing proportion of patients receiving chemotherapy was negatively associated with survival (each 10% increase decreasing survival by 10.4 months; $p = 0.007$).

Optimal cytoreduction was defined as follows: ≤2 cm in three studies (140 patients or 20.8%), ≤1 cm in seven studies (375 patients or 55.8%), and no gross evidence of disease in four studies (157 patients or 23.3%). Fifty-two to seventy-five percent of the patients had an optimal cytoreduction, and 18–75% of the patients had a complete cytoreduction [307].

The conclusions drawn from this study were that:

- Complete cytoreduction leads to a statistically significant improvement in median OS, such that each 10% increase in cytoreduction to no gross evidence of disease was associated with a 9.3-month increase in survival.
- Surgical resection of all visible disease should be the goal for patients with advanced or recurrent endometrial cancer undergoing operative intervention.
- Further studies were need for defining the selection criteria for such procedures [307].

Abu-Zaid reported outcomes in two patients with advanced endometrial cancer and four with recurrent disease treated with CRS and HIPEC. Three patients had endometrioid adenocarcinomas, one USC, one clear cell carcinoma, and one mesonephric carcinoma. The median PCI was 19. Complete cytoreduction (CC-0) was achieved in five patients and CC-2 in one patient. HIPEC was performed with cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) and allowed to circulate in abdominopelvic cavity for 90 min at 41.0–42.2 °C.

Two patients developed grade IV complications and no intraoperative mortality occurred. Postoperatively, all patients received chemotherapy (carboplatin and paclitaxel). Two patients died of progressive disease, whereas four others were alive and disease-free without evidence of recurrence of follow-ups at 35, 34, 19, and 7 months [308]. Most other series have reported outcomes in patients with recurrent disease and are described below.

16.4.5.3 Recurrent Endometrial Cancer

Approximately 50% of the patients with recurrent endometrial cancer have local recurrence, while in others the recurrent disease is distant or multifocal [309–312]. Patients with recurrent disease have been treated with intravenous chemotherapy, hormonal therapy, radiotherapy, and surgery.

Although combination of paclitaxel and carboplatin produces good response rates, the benefits are short lived in most cases with a median progression-free survival of 7 months and overall survival of 14 months reported in one series. Response rates to hormonal therapy are between 21 and 31%, 26% with low-dose medroxyprogesterone acetate (39), 26% with megestrol acetate (40), and 31% with arzoxifene (41) [313–318]. For the pelvic recurrences, pelvic exenteration has been performed with a survival benefit in selected patients. Several investigators used cytoreductive surgery to treat patients with PM reported a survival benefit (Table 16.10). Some reports include a heterogeneous group comprising of patients with local pelvic recurrence and nodal recurrence as well which makes it difficult to draw conclusions for outcomes in patients with peritoneal disease alone.

Scarabelli et al. reported outcomes in 20 women at their first large pelvic or abdominal recurrence from endometrial carcinoma treated with maximal cytoreductive surgery [319].

Complete macroscopic resection of tumor was feasible in 13 women (65%), and these women experienced a significant benefit in both DFS (median, DFS −9.1 months) and OS (median, OS-11.8 months) compared to women with residual disease. In patients with a complete cytoreduction, not only was survival significantly improved, but 84.6% of the patients did not develop local recurrence [319].

Campagnutta et al. reported outcomes in 75 patients who underwent a secondary surgery for recurrent endometrial cancer [320]. This series included patients undergoing pelvic exenterations for isolated pelvic recurrences. They were able to optimally (residual disease <1 cm) cytoreduce 75% of patients and demonstrated that patients who underwent an optimal cytoreduction had a significantly improved survival compared to those with residual disease (36% vs 0%, 5-year survival). In addition, the use of chemotherapy after secondary surgery and central or pelvic recurrence was also associated with improved survival [320].

Awtrey et al. treated 27 patients with recurrence at various sites including those with PM [321]. Patients who underwent exenterative procedures were excluded from the analysis. Fifteen patients (56%) had disease limited to the retro-

Table 16.10 Outcomes of CRS with or without HIPEC for recurrent endometrial cancer

Ref no./year	No. of patients	Disease sites	Optimal CRS (% of patients)	HIPEC	Survival
[319] 1998	20	PM	Not defined (65%)	–	Median DFS—9.1 m; median OS 11.8 m for optimal CRS
[320] 2004	75	PM + others	<1 cm (75%)	–	5 year OS—36% for optimal CRS vs 0% for residual disease > 1 cm
[321] 2006	27	PM (44%)	<2 cm (67%)	–	Median DFS 14 m; median OS 35 m (43 m for residual disease <2 cm
[322] 2007	5	PM	CC-0 (80%)	+	–
[323] 2010	5	PM	CC-0/1 (100%)	+	–
[324] 2014	13	PM	CC-0/1 (61%)	+	–
[325] 2015	8	PM	–	+	–

peritoneum, ten patients (37%) had intraperitoneal disease, and two patients (7%) had both intra- and retroperitoneal disease. Cytoreduction to ≤2 cm of residual disease was achieved in 18 patients (67%), while nine patients (33%) had residual disease >2 cm. The median progression-free survival was 14 months (95% CI, 6–23), and the median disease-specific survival was 35 months (95% CI, 24–not reached). Patients with residual disease ≤2 cm had a median disease-specific survival of 43 months (95% CI, 35–not reached) compared with 10 months (95% CI, 7–29) for those with N2 cm residual ($p = 0.01$). The only prognostic factor was the size of the residual disease. The author was not certain if a biologically less aggressive disease process made a complete cytoreduction possible in certain patients leading to an improvement in the survival. Though they did not find a negative impact of either the grade or histological subtype on the probability of obtaining a complete cytoreduction, this could not be determined conclusively due the small number of patients in the study [321].

Helm et al. treated five patients with CRS and HIPEC for PM from USC ($n = 1$), endometrioid adenocarcinoma ($n = 3$), and endometrioid adenocarcinoma with clear cell features ($n = 1$) [322]. The mean interval between the first treatment and CRS and HIPEC was 47 (29–66) months. Four patients had a CC-0 resection and one patient had a CC-2 resection. Two patients were alive and disease-free at 28 and 32 months, and two were alive with disease at 12 and 36 months. There was one death unrelated to the disease. The patients who were alive with disease had a good performance status. The authors concluded that this therapy was well tolerated, could lead to prolonged survival in some patients, and needed further prospective evaluation in a phase II trial. The patients who had residual disease after CRS had a significantly shorter DFS, and the goal of surgery should be to obtain a complete CRS [322].

Bakrin et al. reported outcomes in five patients with recurrent endometrial carcinoma confined to the peritoneal cavity treated with CRS and HIPEC [323]. Four patients had endometrioid adenocarcinomas, while one had endometrioid adenocarcinoma with a pseudosarcomatoid component. The mean interval from the first surgery was 47.5 months (10–120 months); HIPEC was performed by the closed method using cisplatin 1 mg/kg and mitomycin C 0.7 mg/kg at an inflow temperature of 46–48 °C. Two patients died of progressive disease in the first year following surgery, while the remaining three were alive and disease-free at 7, 23, and 39 months from surgery with a good performance status. The authors concluded that patient selection was important for obtaining good results and only when a complete cytoreduction is possible should surgery be undertaken [323].

Deloitte et al. reported outcomes in 13 patients with primary ($n = 2$) and recurrent ($n = 11$) endometrial cancer with PM treated with CRS and HIPEC. Two patients had USC and 11 had endometrioid adenocarcinoma [324]. The average duration of tumor progression between the end of initial treatment and the HIPEC procedure was 18.5 months (range, 0–53). The median exposure to chemotherapy was of one line (mean, 1.23; range values, 0–3).

The median PCI at laparotomy was 12 (mean, 11.46; extreme values, 3–24). The CC-S after surgery was 0 for eight patients, 1 for three patients, and 2 in the last two cases. Two patients had persistent disease at the end of the procedure. The median overall survival is 19.4 months, and the median disease-free survival is 11.4 months (range values, 1.5–124.83). No complication of grade III or IV severity or perioperative deaths was recorded. The preoperative PCI was a major prognostic factor. If the PCI was greater than ten, patients all died within 48 months following the HIPEC procedure. In contrast, for patients whose PCI was less than ten, the median survival was not reached, and, for one of them, survival exceeded 120 months. The authors concluded the following:

- Complete cytoreduction was essential to obtain a survival benefit.
- Patients with PCI < 10 experienced a prolonged survival.

– Given the prolonged survival experienced by selected patients undergoing HIPEC, its role needed further evaluation in a randomized trial [324].

In a single-institution study of eight patients with USC treated with CRS and HIPEC, there were two early deaths due to disease progression. Two patients were alive with disease at 19 and 26 months, while four were alive and disease-free at 9, 14, 26, and 33 months. Various studies have identified the tumor histology, extent of disease, and completeness of cytoreduction as factors affecting survival. Since the survival with aggressive surgery was longer in the observational studies, a more aggressive approach can be justified in these patients provided complete tumor removal is possible [325].

There are two other reports of one case each treated with CRS and HIPEC [279, 326].

16.4.5.4 Summary

- Endometrial cancer with peritoneal metastases can be treated effectively with CRS with a survival benefit.
- The role of HIPEC is undefined.
- Completeness of cytoreduction is the only known prognostic factor.
- Further prospective evaluation is needed to better define the selection criteria, the prognostic factors, and the role of HIPEC.
- In the setting of recurrent disease presenting with PM, cytoreductive surgery has a role with few patients experiencing long-term survival.
- Completeness of cytoreduction (CC-0/1) and a PCI < 10 lead to a better survival.
- HIPEC may have a role to play but needs further evaluation.
- The prognostic impact of histology in outcomes of these patients is undetermined.
- Clinical trials though difficult to conduct may be helpful in filling the gaps in the existing knowledge.

16.4.6 Hepatic Cancer

Hepatic cancer included hepatocellular carcinoma (HCC) and its variants like fibrolamellar HCC and intrahepatic cholangiocarcinoma. There is no evidence regarding the incidence and treatment of these patients except few cases reported as part of larger series treated with CRS and HIPEC in which the outcomes of these patients were not described separately [325, 327, 328].

In the pooled data published by the PSOGI and BIG-RENAPE network, 23 patients had hepatic cancers, of which a survival analysis was performed in 19 (2.6% of the 761 patients in the study). These patients seemed to have a better survival (hazard ratio, 0.77 (95% CI, 0.29–2.03)) as compared to other histologies though the results were not elaborated in the publication [6].

Fibrolamellar hepatocellular carcinoma is a rare malignancy, with an estimated age-adjusted incidence of 0.02 per 100,000 in the USA and constitutes 1% of all the hepatocellular carcinomas. Despite its rarity, it is the more common liver cancer in adolescents and young adults and occurs in the absence of hepatitis or cirrhosis [329, 330]. Fibrolamellar hepatocellular carcinoma was first described by Edmondson in 1956. Fibrolamellar carcinoma is distinct from HCC in both its clinical and pathologic manifestations, often affecting younger patients and having a higher incidence in women [331, 332]. In general fibrolamellar HCC has a better prognosis as compared to HCC and has generated interest in managing this tumor more aggressively [329, 332, 333].

Using the SEER data, Mayo et al. examined differences in clinicopathologic and surgical factors associated with long-term survival in 7225 patients with fibrolamellar HCC or HCC undergoing surgical resection from 1986 to 1988 [334].

The overall median survival of patients with surgically managed fibrolamellar HCC was 75.0 months (95% CI, 52.3–97.7 months), which was longer than the median survival of 43.0 months (95% CI, 40.6–45.4 months) for patients with HCC ($p = 0.001$). Among individuals managed with a liver-directed procedure, fibrolamellar HCC and HCC patients had 1-, 3-, and 5-year survival rates of 91.0%, 65.7%, and 54.1% vs 77.1%, 53.6%, and 41.7%, respectively (all $p < 0.001$) [334].

Unlike conventional HCC, in fibrolamellar HCC, the incidence of regional lymph node

involvement was 40% which was double the incidence in patients with conventional HCC [334].

Although long-term outcomes after surgical management were better than those after conventional HCC, 5-year survival of patients with fibrolamellar HCC was only 54%. Given this background, Elias et al. treated two patients of fibrolamellar HCC with peritoneal metastases with CRS and HIPEC. In their experience, all the patients developed peritoneal recurrence with distant metastases within 2 years, and the median disease-free survival was only 13 months. The authors did not recommend CRS and HIPEC for PM arising from fibrolamellar HCC [325].

16.4.7 Small Bowel Adenocarcinoma

Small bowel tumors constitute 1–3% of all the gastrointestinal malignancies [335, 336]. Of the various tumors arising from the small bowel, adenocarcinomas are the commonest and constitute 30–45% of all the tumors [337, 338]. Small bowel adenocarcinoma (SBA) is known to have a poor prognosis with a median overall survival ranging from 12 to 20 months [339, 340].

SBA do not become symptomatic early and have vague symptoms, which makes an early diagnosis difficult. The index of suspicion for these tumors is usually low, and endoscopic non-accessibility in most cases and inability of imaging to pick up early lesions lead to diagnosis in an advanced stage [341, 342]. Consequently, by the time a diagnosis is made, the tumor has already spread to the regional nodes or to the peritoneal cavity [343]. The 5-year survival rates range from 10 to 26% [343]. PM is the most common site of metastases in patients with SBA, being present in 25–50% of the patients with metastatic disease. Patients are treated with chemotherapy alone or a combination of chemotherapy and surgery [343, 344].

16.4.7.1 Treatment of PM Arising from Small Bowel Adenocarcinoma

Systemic Chemotherapy

Conventionally, systemic chemotherapy has been used to treat PM arising from SBA like other metastatic disease sites. Since SBA share genotypic and phenotypic features with colorectal cancer, chemotherapy regimens used for the treatment of colorectal cancer have been used to treat patients with SBA [345, 346]. The evidence comes from retrospective studies and phase II trials [347–355]. There are no phase III trials, however, showing the benefit of one regimen over the other. Rovers et al. performed a review of 15 published studies that reported outcomes of first-line systemic therapy for SBA with metastatic disease [356]. The overall response rates in these studies ranged from 6 to 50%, the disease controlled rates from 50 to 90%, the median progression-free survival was 3–11 months, and the median OS was 8–20 months. The combination of oxaliplatin and 5-fluorouracil had better outcomes as compared to other regimens.

Cytoreductive Surgery and HIPEC

Sugarbaker first used cytoreductive surgery and EPIC to treat PM arising from SBA [343]. The rationale, selection criteria, methodology, and prognostic factors used to treat patients with PM from other primary sites like colorectal and appendiceal cancers were applied to these patients as well. Six patients with tumors arising from the ileum and jejunum, two of the intestinal type, and four of the mucinous type underwent cytoreductive surgery and EPIC with mitomycin C and 5-fluorouracil. Two patients required additional procedures to obtain complete tumor removal. The median survival was 12 months with one patients surviving for 4.5 years [343]. The outcomes of CRS and HIPEC in patients with SBA are described in Table 16.11.

Jacks et al. reported a median survival of 45 months in six patients with PM from SBA treated with CRS and HIPEC. All patients received chemotherapy before or after HIPEC. One patient underwent a second CRS and HIPEC for recurrence after the first procedure [344].

Chua et al. reported a median OS of 25 months and median DFS of 12 months in seven patients of PM from SBA treated with CRS and HIPEC. The 1-, 2-, and 3-year survival rates were 57%, 38%, and 20%, respectively. Patients with poorly differentiated and signet ring cell tumors, tumor histology of poorly differentiated adenocarcinoma with

Table 16.11 Outcomes of CRS and HIPEC in patients with PM from SBA

Ref no. year	N	Primary site	Median PCI	CC-0/1	IPC	HIPEC drugs	Grade 3/4 morbidity	Median DFS (months)	Median OS (months)
[343] 2002	6	Jejunum (50%) Ileum (50%)			HIPEC EPIC	Mitomycin C 5-FU			12
[344] 2005	6								45
[357] 2009	7		12 (6–22)	100%	HIPEC ± EPIC	Mitomycin C 5-FU	29%	12	25
[358] 2010	31		11	100%	HIPEC EPIC	Oxaliplatin/ Mitomycin C Mitomycin C/5-FU	35%		47
[359] 2013	17	Duodenum (6%) Jejunum (53%) Ileum (41%)		82%	HIPEC	Mitomycin C	12%		18
[360] 2015	16	Duodenum 3% Jejunum 58% Ileum 39%		94%	HIPEC	Mitomycin C	25%	10	31
[361] 2015	31	Duodenum 3% Jejunum 58% Ileum 59%	11 (1–39)	68%	HIPEC	Mitomycin C and Cisplatin	26%		36
[325] 2015	4	–	–	–	HIPEC	–	–	–	–

signet ring, lymphovascular invasion, and perineural invasion had an inferior outcome [357].

In a pooled analysis of patients with PM arising from four primary sites treated at 23 French centers from 1989 to 2007, outcomes of 440 patients who had complete cytoreductive surgery were reported by Elias et al. in 2010. Of these 31 patients had PM secondary to SBA. The median PCI was 11. Twenty-one patients underwent HIPEC and 10 EPIC. The mortality in these 31 patients was 2.9% and major morbidity 32%. The 5-year OS for all the 440 patients was 33% and the DFS was 18%. The origin of the PM was of borderline significance ($p = 0.06$), with a 15% increase in the risk of death for patients with rectal cancer, a decreasing risk of death of 44.5% for appendix cancer, and 32.5% for small bowel tumors, compared with colon cancer taken as the reference [358]. The PCI was the most significant prognostic factor; a single-point increase on this index increased the risk of death by 4.9%. The two others were the presence of positive lymph nodes ($p = 0.001$) and adjuvant systemic chemotherapy ($p = 0.002$). The presence of liver metastases, whether resected at the same time as the combined treatment, did not impact negatively ($p = 0.19$) on survival.

There was no significant difference between the survival for different primary sites [359]. Sun et al. performed 20 procedures in 17 patients with a morbidity of 47% [359]. Thirteen of 17 received chemotherapy before their HIPEC (76%); five patients received chemotherapy after HIPEC (29%). A complete cytoreduction was obtained only in 14 patients (70%). The median OS was 37 months after diagnosis and 18.4 months after HIPEC. The 1-, 2-, 3-, and 5-year overall survival was 94.1%, 75.3%, 48.3%, and 6.9%, respectively. Eight patients (47%) experienced postoperative complications, in which two patients had major postoperative complications (12%) [359].

Sixteen patients with PM from SBA underwent CRS and HIPEC at four tertiary referral centers in the Netherlands. A complete macroscopic resection was achieved in 93.8%. Serious adverse events requiring re-intervention occurred in 25%, and no in-hospital mortality was observed. Recurrent disease was observed in 50% of patients and median survival after CRS and HIPEC was 31 months. Patients who did not undergo CRS and HIPEC had a median survival of 2.3–7.1 months. The median survival was not reached in patients who did not receive chemotherapy and hence the benefit of chemotherapy could not be determined. Of the 15 patients who had a complete cytoreduction, ten survived for more than a year and eight of these developed recurrence which was intraperitoneal in seven patients [360].

The median OS in 25 patients of PM from SBA treated at a Japanese center was 36 months (range, 6–95 months), and the median survival after diagnosis was 50 months (range, 18–101 months). Multivariate analysis revealed that peritoneal cancer index <15 ($p = 0.009$) and HIPEC ($p < 0.001$) were independent predictors of better survival [361].

In four patients treated by Cardi et al., mean survival was 31.2 months, with two patients alive disease-free at 43 and 22 months and two alive with disease at 33 (pulmonary metastases) and at 27 (abdominal recurrence) months.

All the studies show better results when compared to conventional treatments [325]. CRS and HIPEC has been used a palliative treatment to relieve bowel obstruction and control ascites.

The median OS of 31–36 months in these studies similar to that obtained in the patients with CRC PM with limited peritoneal disease [56]. Rovers et al. pointed out that there is a lack of awareness about the treatment of PM from SBA with CRS and HIPEC stating the example of the Netherlands where 16 patients underwent CRS and HIPEC of the 167 diagnosed with synchronous PM during the same time frame. Sixty percent of these patients had limited peritoneal disease. The incidence of metachronous PM was not reported which would further increase the actual number of patients with PM [362].

The available data points toward a probability of improved survival with CRS and HIPEC in patients with PM from SBA. The studies are retrospective, with a small number of patients treated over prolonged periods. The selection criteria for surgery (limited vs extensive PM), the nature of surgery (complete vs incomplete),

the type of intraperitoneal chemotherapy used (HIPEC vs EPIC), and the drug regimens used were variable. The use of systemic chemotherapy before or after the procedure was not uniform. This makes it difficult to draw conclusions. However, the prognostic impact of a complete cytoreduction has been shown in most of these studies, with no long-term survivors among patients who had CC-2/3 resections. Though few patients experienced long-term survival, most of them developed recurrent disease and 5-year survivors have not been reported.

16.4.7.2 Summary

- CRS and HIPEC may be used to treat these patients though further prospective evaluation is needed.
- Only patients in whom a CC-0/1 resection can be attained should be subjected to such procedures.
- Other prognostic factors need to be defined.
- Multi-institutional studies and registries may be useful given the rarity of the disease.
- The added benefit of newer systemic therapies that include targeted therapies needs to be considered and evaluated.

16.4.8 Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumor is the most common sarcoma arising from the gastrointestinal tract [363]. A complete surgical resection can cure patients who have localized disease and adjuvant imatinib has led to an additional survival benefit [364, 365]. However, relapses do occur, and these are most common in patients with large tumors (>5 cm in size), those with a faster growth rate (as measured by mitotic counts), and in primary anatomic location outside the stomach, despite optimal frontline therapy [366].

In the metastatic setting, once again the use of imatinib and other tyrosine kinase inhibitors (TKIs) has tripled the median OS which was 18 months in the pre-imatinib (TKI) era. Some of the patients have stable disease for prolonged periods, while others eventually develop disease progression and die. However, the vast majority of patients eventually progresses and dies of their disease [367, 368].

There are two situations in metastatic disease. Treatment with TKIs is the cornerstone of therapy. The role of surgery needs to be evaluated in:

- Patients who are responsive to TKIs and will continue to receive it post-surgery
- Patients who have become unresponsive to TKIs

Metastasectomy has been performed for both liver metastases and PM with an acceptable morbidity [369–371]. In patients who developed metastases after a prolonged disease-free interval, the survival was prolonged with the combination of surgery and TKIs. A trial would be ideal to evaluate the role of surgery in such situations since TKIs has to be used even after surgery, but in the past, such a trial could not be conducted due to difficulties in recruiting patients. Randomizing patients to a surgical versus nonsurgical intervention is not acceptable to many surgeons and physicians.

In patients who had progressive disease on TKIs, the outcomes of surgery were poor with no benefit in survival.

Bauer et al. performed a retrospective analysis of 329 patients who underwent surgical resection of metastatic disease. Forty-six percent had PM and 18% had both liver metastases and PM [369]. All the patients received imatinib starting within 3 months of surgery till disease progression. Median OS was 8.7 years for patients who had complete tumor removal or microscopic residual disease (R0/R1) compared to 5.3 years in patients with gross residual disease (R2) ($p = 0.0001$). Median OS from time of metastasectomy was 3.8 years for patients in remission versus 1.5 years ($p = 0.2$) in patients progressing at the time of surgery. When patients with progressing disease (focal or general progression) at time of surgery were excluded, the median OS was not reached in the R0/R1 group and 5.1 years in the R2 arm ($p = 0.0001$).

The median OS was not reached in patients who had only liver metastases, 7 years in those

with PM and 3.7 years in those with both liver metastases and PM (p = 0.003, log-rank test). Notably, in patients who were operated in remission and in whom complete macroscopic resection was achieved, the median OS was not reached in the liver metastases group, 8.7 years in patients with PM but also 8.1 years in patients who had both liver and peritoneal disease (p = 0.018). The authors stated that there was a bias in selecting patients since patients selected for surgery are more likely to have fewer comorbidities, a lower tumor load, a better response to imatinib therapy, and have also been treated at high-volume centers which may have given them access to more salvage therapies through clinical trials. And hence, these outcomes may represent a selection of patients with a good prognosis who would have lived longer anyway. They recommended a matched-pair analysis given the difficulties in performing a randomized trial.

Bryan et al. evaluated the role of CRS and HIPEC in 16 patients with PM from GIST treated at their institution. Of a total of 18 procedures performed in these patients, nine were performed in the pre-TKI era and the remaining, thereafter. Hence, six of these patients never received targeted therapy, and the median OS in these patients was 1.04 years compared to 7.89 years in patients who received targeted therapy. Within patients with an R0/1 resection, those who never received TKI at any point before or after CRS/HIPEC had a median survival of 1.09 years versus median survival was not reached in those who received TKI (p = 0.28).

Median survival in patients who progressed on TKI preoperatively was 1.35 years post-CRS/HIPEC as compared with a median survival that was not reached in those without progression on TKIs (p = 0.007).

Based on these results, the authors recommend CRS alone without HIPEC in patients with PM from GISTs who on preoperative imaging have disease responsive or stable on TKIs. They do not recommend HIPEC based on previous reports that did not show a benefit in patients with sarcomas. The extent of the cytoreduction according to them should be based on morbidity and quality of life criteria and not necessarily by achieving negative microscopic margins, as long as macroscopic margins are obtained, while TKIs are continued indefinitely after CRS.

Contrary to these reports, Cardi et al. found a benefit of CRS and HIPEC in patients with GIST resistant to TKIs. In three patients with small bowel imatinib-resistant GIST treated with CRS and HIPEC, two patients were alive disease-free at 34 and 108 months; one patient died of disease at 38 months [325]. Other series comprising of patients with PM from various primary sites have 2–6 patients with GIST treated with CRS and HIPEC, but no definite conclusions can be drawn from these [327, 372].

In the PSOGI-BIG-RENAPE collaborative series, 47 patients (6.4%) had GISTs. These patients had a significantly inferior survival compared to patients with rare ovarian cancers and neuroendocrine PM [6].

16.4.8.1 Summary

- Based on the above evidence, CRS may be offered to patients with PM from GIST. A case-matched study would help to further define the role of CRS in addition to TKIs alone.
- The important prognostic factors are response to TKIs and complete tumor removal.
- The role of HIPEC is undefined and many do not recommend its use.
- For patients in whom removal of all macroscopic disease is not possible and in those who have progressed on TKIs, the role of CRS needs further evaluation.

16.4.9 Adrenocortical Carcinoma with PM

PM in adrenocortical carcinoma (ACC) is unusual and has been reported in 4–15% of the patients [373, 374]. Some studies have reported an incidence of local recurrence and PM as high as 50% [375]. Improper surgical technique has been recognized as one of the reasons for an increased incidence of peritoneal spread especially in patients who undergo laparoscopic resection of these tumors. Laparoscopic resection is recommended

for benign tumors less than 6 cm in size [376]. The reported incidence of locoregional failure including PM is as high as 67% with laparoscopic adrenalectomy for ACC.

The reported rates of PM after open and laparoscopic surgery range from 16 to 27% and 21 to 67%, respectively. When comparing open and laparoscopic resections performed by the same surgeons, the incidence of PM after laparoscopic resection was higher [377–379]. Amini et al. reported recurrence in two-thirds of the patients undergoing curative resection for ACC. This was local only in 36.3%, distant only in 45.1%, and combined locoregional and distant in 18.6%. Increasing T-stage was associated with locoregional recurrence ($p = 0.02$) [376]. In a study of 126 patients, the median and 5-year overall survival for patients undergoing R0 resection were 96.3 months and 64.8% as compared to 25.1 months and 33.8% for patients having an R1 resection ($p < 0.001$). The authors concluded that proper surgical techniques should be used to achieve negative margins, which is a determinant of long-term survival [380].

Currently, no strategies exist for prevention of recurrence and PM during or following surgical resection of ACC, and proper surgical exposure and technique to ensure adequate margins and avoid intraoperative tumor spillage are the only methods that can be employed by surgeons.

There is not much data regarding the management of patients with PM arising from ACC. A clinical trial evaluating the role of HIPEC after complete cytoreduction in these patients is currently on going in the USA and is expected to complete accrual in 2018 (Clinical Trials.gov Identifier: NCT01833832). HIPEC is performed with cisplatin, and the primary endpoint is disease-free survival, with secondary endpoints including the morbidity and quality of life following surgery.

There are reports on five patients treated with CRS and HIPEC for PM arising from ACC. Honore et al. reported a median disease-free survival of 12 months at a median follow-up of 40 months in four patients with PM from ACC. Three patients had localized disease, three had metachronous PM, and the median PCI was 11.

Sugarbaker reported one single case of ACC with peritoneal and pleural metastases following resection of the primary tumor infiltrating the liver that was treated with extensive CRS and HIPEC with melphalan. Within a year, the patient developed a second primary tumor and had resection of the tumor with a second look for PM and prophylactic HIPEC with melphalan again. Sugarbaker pointed out that effective strategies need to be developed for prevention of PM during surgical resection of ACC [381].

16.4.10 Peritoneal Metastases from Breast Cancer

The common sites of metastatic spread from breast cancer are the bone, liver, lungs, and brain with the peritoneum being relatively uncommon [382].

In a study including 3096 patients who underwent surgery for invasive breast cancer and had at least a 4-year follow-up, 289 (9.335) had or developed distant metastases.

Distant metastases were seen in 9.3% (289/3096); in 19.7% the metastases were synchronous, whereas in the remaining 80.3% metastases were metachronous after 83 months of median follow-up. PM had a prevalence of 0.7% (22/3096) and developed later than all other secondary sites. On multivariate analysis, high tumor grade, invasive lobular carcinoma, and a higher TNM stage emerged as risk factors for development of PM. Median OS after the detection of metastases was 28 months and was significantly lower for brain metastases and PM as compared to other disease sites [383].

Some studies have shown a poor survival of patients with PM from breast cancer. In a review of 1628 patients from a NHS trust hospital, 44 individuals (2.7% of the cohort) had PM. Of these, the majority (77%) had invasive ductal carcinomas (IDCs). While the median survival from the diagnosis of metastatic breast cancer measured 20.5 months (range, 0.1–125 months), the median survival of patients with peritoneal disease was 1.56 months (range, 0.2–27 months) [384].

PM can develop metachronously many years (5–30 years) after the diagnosis of breast cancer [385–387]. This may represent a unique feature of the disease biology of breast cancer—it is known to be one of the most slowly growing solid tumors given that metastases may appear many years, even decades, after the initial diagnosis [382].

16.4.10.1 Presentation and Diagnosis

PM may be a manifestation of widespread metastatic disease with metastases at one or more other sites. In such cases, the diagnosis is straightforward. When isolated peritoneal spread occurs, the presentation may be variable. Patients may present with ascites and its associated symptoms or other nonspecific symptoms like abdominal pain, bloating, and loss of appetite [388]. In other cases, patients may present with an ovarian mass or pelvic mass with or without peritoneal metastases [389]. In such patients, other more probable differential diagnoses need to be considered like ovarian cancer. When a woman with a history of breast cancer presents with an ovarian mass, it is three times more likely to be a primary ovarian tumor than metastases to the ovary from breast cancer [390]. This and other differential diagnoses like primary peritoneal serous carcinoma and malignant mesothelioma need to be excluded. Immunohistochemistry markers that could be performed include human epidermal growth factor receptor-2 (HER-2), Wilms tumor 1 suppressor gene (WT1), cancer antigen 125 (CA-125), cytokeratin-7 (CK7), cytokeratin-20 (CK20), estrogen receptor (ER), progesterone receptor (PR), PAX-8, and gross cystic disease fluid protein (GCDFP-15) [391]. WT1 is a tumor suppressor gene that is positive in over 90% of primary ovarian tumors and never found in primary and metastatic breast cancer [392, 393]. CA-125 is a glycoprotein expressed in up to 90% of ovarian malignancies and from 10 to 30% of primary breast cancer [394]. GCDFP-15 is a relatively specific and sensitive marker for breast cancer (expressed in about 50% of the cases) and never in ovarian malignancies [392, 394].

BRCA testing is also indicated for these patients.

16.4.10.2 Management

The conventional management of metastatic disease in breast cancer is systemic therapy. And this is the treatment for most patients with PM from breast cancer that occurs in addition to metastases at other sites. In a small percentage of patients, metastases develop late after a prolonged disease-free interval and are isolated. The role of a surgical intervention has been evaluated in such patients.

In one of the early reports comparing outcomes of various types of surgery in 168 patients with ovarian and peritoneal metastases from various primary sites, the median OS was better for patients with breast cancer as compared to colorectal cancer (28.3 vs 24 months), but the 5-year survival was worse in breast cancer patients. This was attributed to the temporary benefit obtained from oophorectomy in breast cancer. The extent of surgery ranged from just a biopsy and/or resection of the ovarian mass to more extensive procedures comprising of peritonectomies and visceral resections. There was a trend toward a better survival in patients who had more extensive surgery. This study is over 20 years old and a lot has changed since then, especially, the availability of more effective systemic therapies for different subtypes of breast cancer [395]. Other studies did not report a significant difference in survival compared to gastrointestinal tumors as well [396, 397].

Petru et al. discussed the importance of residual tumor volume in women with metastatic cancers other than ovarian to the abdomen and pelvis, reporting a higher 5-year survival rate for patients with residual disease 2 cm (16% vs 3%) [398].

Abu Rustum et al. evaluated the role of surgery in patients with PM from ovarian cancer in 40 patients treated at their institution [389]. The median interval from the diagnosis of breast cancer and a surgical intervention of pelvic tumor/PM was 80 months (range, 9–264 months). The median survival for all patients was 24.1 months. Patients who had no gross residual disease in the abdomen or pelvis after surgery had a median survival of 41.6 months, which did not significantly differ from those with gross residual < or

=2 cm (16.1 months) or >2 cm (18.4 months) (p = 0.624). Though the disease extent was not quantified, from the type of surgical procedures performed (only an adnexectomy in 82.5% of the patients) and the percentage of patients undergoing a complete cytoreduction (49%), it could be concluded that a large proportion of the patients had limited disease. The authors stated that the small numbers in the study and the heterogeneity of the salvage systemic therapies could be the reasons for a lack of significant benefit from a surgical intervention [389].

Subsequently the same authors published outcomes in 59 patients undergoing surgery for PM in patients with breast cancer [399]. The patients population comprised mainly of those presenting with a pelvic/ovarian mass with a previous history of breast cancer. The median time to surgery from the initial diagnosis of breast cancer was 5 years (range, 0–25 years). Median OS from the time of diagnosis of abdominopelvic recurrent disease was 23 months and 5-year survival was 24%. Survival was 36 months for optimally debulked patients (residual disease <2 cm) and 20 months for suboptimally debulked patients (p = 0.07). Patients diagnosed 5 or more years after initial breast cancer diagnosis had a median survival of 36 months versus 17 months if diagnosed earlier (p = 0.01). The two significant factors affecting survival were the time to abdominal recurrence and optimal debulking with the hazard ratio for dying of disease if recurring before 5 years was 2.7 (CI, 1.45–5.03) [p 0.01] and for suboptimal debulking was 2.14 (CI, 1.13–4.02) [p 0.02] [399].

16.4.10.3 The Role of CRS and HIPEC

These patients often present to surgical oncologists who specialize in the management of peritoneal surface malignancies and a more aggressive approach comprising of CRS and HIPEC has been used to treat these patients as well.

Cardi et al. reported outcomes in five patients (mean age, 59.4 years) with PM from breast cancer treated with maximal cytoreduction and HIPEC at 40 °C for 1 h with cisplatin 75 mg/m^2 [371]. The primary breast cancer was a ductal carcinoma in three patients and a lobular carcinoma in two. Mean peritoneal cancer index was 20.2. In four of the five patients, surgery achieved macroscopic complete cytoreduction. One patient died of disease at 56 months; four are alive and disease-free at 13, 45, 74, and 128 months. All patients received adjuvant hormone therapy after CRS and HIPEC [325].

Notably, the median time interval from the diagnosis of breast cancer to the development of PM in this study was 18 years (range, 10–30 years). There was one patient in whom both the primary tumor and PM did not express ER, PR, or HER-2 (triple negative breast cancer). There were two patients in whom the PM expressed HER-2. This study showed that in selected patients, CRS and HIPEC could achieve a prolonged survival (>10 years in one patient) maintaining a good quality of life.

In the PSOGI-BIG-RENAPE collaborative series, 17 patients (2.3%) had PM from breast cancer. These patients experienced an inferior survival to patients with PM from other primary sites like mucinous ovarian tumors and neuroendocrine tumors (hazard ratio, 2.26 (95% CI, 1.10–5.05)) [6]. There are other isolated reports of CRS and HIPEC for treating PM from breast cancer [327, 372].

16.4.10.4 Summary

- Isolated PM from breast cancer in general occurs metachronously and several years after the initial diagnosis of breast cancer.
- Cytoreductive surgery with or without HIPEC has the potential to provide a survival benefit to these patients in addition to systemic therapies.
- The rapid progress is development of new systemic therapies for these patients, and the survival benefit by those should be considered while planning the treatment for these patients.

16.5 Miscellaneous Indications

There are several other rare and common primary tumors for which CRS and HIPEC has been used for the treatment of PM. Few cases have been reported for each one, and it is difficult to derive any conclusions from those.

Two cases of Wilms tumor and one case of Sertoli-Leydig cell tumor have been reported

as part of a larger series, and outcomes in these patients have not been reported [268].

This series also included seven patients with rhabdomyosarcoma of unspecified histological subtype; the authors showed that this etiology was individually associated with a very poor prognosis, having an overall 1- and 2-year survival of 29% and 14%, respectively [268].

Solid pseudopapillary epithelial neoplasms occur in young women, and 11 cases of PM arising from these tumors had been reported, probably related to tumor rupture and spillage. In patients who had CRS alone, the recurrence rate is 58% at an interval of 12–228 months [400]. Honore et al. treated two patients with metachronous PM from SPEN with CRS and HIPEC. The median PCI was 13 and the median DFS was 47 months. One patient who recurred at 8 months after CRS alone was disease-free at 57 months following CRS and HIPEC.

Patients with PM from gall bladder and pancreatic adenocarcinomas have been treated with CRS and HIPEC. The numbers are few in large case series. In the PSOGI-BIG-RENAPE collaborative series, 39 (5.3%) patients had PM from cholangiocarcinoma and 30(4.1%) had PM from pancreatic tumors. The survival of these patients was inferior with a hazard ratio of 2.85 (cholangiocarcinomas) and 3.23(pancreatic tumors) as compared to rare ovarian tumors that had a more favorable prognosis [6]. Sugarbaker has listed some more rare conditions in which CRS and HIPEC could be used. These include borderline ovarian tumors, mesenteric cysts giving rise to PMP, pararectal hamartoma, nephroblastoma, cylindroma, endocervical mucinous adenocarcinoma, testicular germ cell tumor, and adenocarcinoma of unknown primary site (normal appendix identified).

16.6 Current Recommendations for CRS with or Without HIPEC in Uncommon Situations

The rare primary and secondary peritoneal tumors pose a therapeutic challenge for the surgeon treating peritoneal surface malignancies. With the increase in experience with CRS and HIPEC, the morbidity and mortality can be controlled by careful patient selection and treatment strategies and is no longer a barrier to offering this treatment to patients. The evidence to support its use in rare tumors comes from retrospective series, most of them having relatively small numbers of patients, with varied treatment protocols, treated over prolonged time periods. The patient population in these studies is heterogeneous; some include patients with different histologies or those with both primary and recurrent disease; the use of intraperitoneal chemotherapy is variable; some include patients with only CRS; others have included those treated with HIPEC and/or EPIC; the regimens for HIPEC and EPIC are variable as well. Level I/II evidence is not available as it is difficult to conduct randomized trials for a surgical intervention especially for rare conditions. Case-control studies have also not been performed for most indications. Moreover, new systemic therapies are available, and the results of CRS and HIPEC have to be compared to those obtained with these therapies. Based on the available evidence, a brief summary of the outcomes of CRS and intraperitoneal chemotherapy for rare peritoneal tumors is provided in Table 16.12.

There are some tumors for which both CRS and HIPEC may be beneficial, other in which there is an obvious benefit of CRS but that of HIPEC is uncertain and other tumors in which the benefit of both CRS and HIPEC is questionable. Sugarbaker has provided a list of rare tumors that could benefit from CRS and HIPEC (Table 16.13) [381].

Based on their vast experience with treatment of rare tumors and after performing an exhaustive review, Elias et al. categorized tumors based on the benefit derived from CRS and HIPEC (Table 16.14) [279].

The above classifications can aid in decision making as CRS and/or HIPEC may not be of benefit even if the disease is completely resectable.

Other factors that need to be considered were outlined by Goéré et al. Patients should have a good performance status, the risk of complications should be low, they should be responsive to systemic therapy if used, and they should have a prolonged disease-free interval and a limited disease extent as defined by the PCI [6]. For the

Table 16.12 Rare indications for CRS and HIPEC/intraperitoneal chemotherapy

Primary site	Level of evidence	Total no. of studies	Total no. of patients	Systemic chemotherapy	Intraperitoneal chemotherapy	Drugs	Median OS (months)	Prognostic factors	Benefit of CRS	Benefit of HIPEC
DSRCT	III/IV	6	174	Yes	HIPEC	Cisplatin Mitomycin Oxaliplatin	37–63	Complete CRS; no extra-abdominal disease; PORT; systemic chemotherapy	Yes	Uncertain
PPSC	III/IV	24 + 4[a]	702	Yes	HIPEC (48)	Cisplatin Doxorubicin	10–42	Complete/optimal CRS; PCI	Yes	Uncertain
Soft tissue sarcomas	IV	15	363	Yes	HIPEC EPIC	Cisplatin Doxorubicin Mitomycin C Mitoxantrone	12–39.5	Low grade; CC-0/1, PCI < 13–20, Leiomyosarcoma	Yes	Uncertain
Neuroendocrine tumors	IV	3	299		HIPEC (5) EPIC (10)	Mitomycin C	5-year OS 39.9%	Complete resection of tumor at all metastatic sites	Yes	Uncertain
Mucinous ovarian tumors	IV	1	199		HIPEC	Not specified	5-year OS 57.7%	Not specified	Yes	Beneficial extrapolating from PMP
Granulosa cell tumors of the ovary[a]	IV	3	56	Yes	HIPEC	Oxaliplatin Cisplatin and doxorubicin	–	–	Yes	Uncertain
Mucinous urachal tumors with PM	IV	18	32		HIPEC EPIC	Oxaliplatin Mitomycin C Doxorubicin	12–132		Yes	Beneficial extrapolating from patients with PMP of appendiceal origin
Endometrial carcinoma (including USC)	IV	8	159		HIPEC	Cisplatin	11.8–19.4	CC-0/1; PCI < 10 for recurrent tumors	Yes	Maybe beneficial—further evaluation is needed
Small bowel adenocarcinoma	IV	8	118	Yes	HIPEC EPIC	Oxaliplatin Mitomycin C 5-FU	12–47	Not defined	Yes	Maybe beneficial extrapolating from colorectal cancer

Primary site	Level of evidence	Total no. of studies	Total no. of patients	Systemic chemotherapy	Intraperitoneal chemotherapy	Drugs	Median OS (months)	Prognostic factors	Benefit of CRS	Benefit of HIPEC
GIST	IV	3	229	Yes	No		7–8 years	Response to TKI, R0/R1 resection	Uncertain	Uncertain
Breast cancer	IV	3	81	Yes	HIPEC (<50%)	Cisplatin	36–60	Time to recurrence, complete CRS	Uncertain	Uncertain

Patients received CRS and HIPEC in four studies

[a]Includes advanced and recurrent tumour both

Table 16.13 Rare disease having isolated peritoneal metastases that could possibly benefit from CRS and HIPEC (adapted from Ref. [381])

Abdominal/pelvic sarcoma	Endocervical mucinous adenocarcinoma
Neuroendocrine tumors	Hepatocellular carcinoma
Urachal adenocarinoma	Fibrolamellar hepatocellular carcinoma
Borderline ovarian tumors	Testicular germ cell tumor
Colonic polyps (traumatic resection)	Solid pseudopapillary epithelial tumor of the pancreas
Mesenteric cysts	Nephroblastoma
Pararectal hamartoma	Cylindroma
Adrenocortical carcinoma	Adenocarcinoma of unknown primary site (normal appendix identified)
Desmoplastic small round cell tumor	

Table 16.14 Categorization of rare tumors according to the probability of benefit from CRS and HIPEC (with permission from [279])

Category	Tumor origin
Probable benefit from CRS and HIPEC	PM arising from mucinous carcinoma of the urachus, solid pseudopapillary epithelial neoplasms of the pancreas, thymoma
Probable benefit of CRS but with uncertain, controversial or unverifiable benefit of HIPEC	PM from DSRCT, Sertoli-Leydig tumors, granulosa cell tumors, PPSC
Uncertain or unverifiable benefit of CRS	PM from breast cancer, endometrial cancer, non-seminomatous germ cell tumor, malignant adrenocortical carcinoma, adenoid cystic carcinoma, nephroblastoma, fibrolamellar hepatocellular carcinomas, cervical carcinoma, embryonic rhabdomyosarcoma

use of HIPEC, the authors recommended that the decision should be based on the site of origin of the tumor, on the histological subtype, and on whether extraperitoneal disease is present or not. According to them, HIPEC should be preferentially offered to young patients, in good general condition, without extraperitoneal disease, and with PM from an intra-abdominal primary site or from mucinous histology. Sugarbaker listed the clinical features that are predictive of a favorable outcome (Table 16.15) [381].

Table 16.15 Clinical features predictive of favorable/unfavorable outcome in patients undergoing CRS and HIPEC for PM (with permission from [381])

Clinical features predictive of a favorable outcome
1. Good performance status
2. Possibility of a complete or near complete CRS Sparing of the small bowel No extra-abdominal disease Few, easily resectable hepatic metastases Absence of disease at the porta hepatis
3. In patients with a high grade malignancy—the PCI is low or moderate
4. Symptomatic patients
Clinical features predictive of an unfavorable outcome
1. Poor performance status
2. Rapidly progressive high grade disease
3. Low likelihood of response to preoperative chemotherapy
4. Prior abdominal or pelvic radiotherapy
5. Asymptomatic patient

There are few other important factors that need to be considered:

1. The benefit of CRS and HIPEC should be considered separately. There are situations where there is a definite role of CRS, but HIPEC is of uncertain benefit as discussed above. In these situations, it only adds to the morbidity and should be avoided. IPC has several pharmacokinetic limitations, and there are no clear guidelines/evidence about which regimen is most suited for a particular tumor/histological subtype.
2. New systemic therapies and the results obtained with their use should be considered. A multidisciplinary approach is the best that integrates various treatments to provide the maximum survival benefit to the patient.
3. Surgery should be undertaken with the goal of performing a complete cytoreduction (CC-0/1). Patients in whom this is unlikely should not be taken up for surgery. Patients with NET-PM are an exception where debulking

has a role if >70% of the tumor can be removed and also for palliation to prevent/treat the symptoms of PM. In DSRCT, the role of debulking is undefined and needs further evaluation. Attempts should be made to achieve a CC-0/1 as far as possible.

4. PCI should be determined and reported in all cases. For some histologies, the prognostic value of PCI has been established. As indicated in the PSOGI- BIG-RENAPE series, a high PCI > 10–14 points to a poor long-term outcome.
5. The possibility of use of emerging therapies like pressurized intraperitoneal chemotherapy (PIPAC) that can be combined with systemic chemotherapy as well should be considered as a treatment option. Where the disease is extensive and the risk of morbidity is high, PIPAC could provide effective palliation, though it had not been used for many of the rare tumors yet.

Conclusions

CRS and HIPEC can be used to treat highly selected patients with certain uncommon peritoneal metastases in patients with a good performance status, limited peritoneal spread, in absence of extraperitoneal disease, in metastases from intra-abdominal primary sites, and in patients with tumors of mucinous histology. However, there is no level I evidence to support its use, and most evidence is in the form of retrospective studies or pooled data from registries. Given the rarity of these diseases, it is highly unlikely that level I evidence will ever be available. Hence, CRS with or without HIPEC for these rare tumors should be performed only in the context of a clinical trial or protocol, and the outcomes must be prospectively recorded and audited. The data should preferably be pooled into national/international registries so that a large body of evidence is obtained in the future. Surgery should be performed only in those patients where a complete cytoreduction (CC-0/1) is possible with very few exceptions. The roles of CRS and HIPEC should be considered separately and treatment decisions should be made by multidisciplinary teams in specialized centers. The prognostic impact of a PCI > 10–14 should be considered in the decision making. The use of HIPEC/intraperitoneal chemotherapy should be avoided in situations where the benefit is uncertain and the risk of morbidity is high. New therapeutic modalities like pressurized intraperitoneal chemotherapy (PIPAC) should be considered as an alternative in these situations as a palliative option with or without systemic chemotherapy.

The use of systemic therapies should be integrated in the treatment plan where such therapies have shown a benefit to provide the maximum benefit to the patient.

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17 Clinical Trials in CRS and HIPEC: Ongoing Trials and Future Directives

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17.1 Introduction

The management of peritoneal metastasis (PM) from colorectal malignancies has faced a difficult history in attempting to adapt cytoreductive surgery (CRS) and concomitant use of hyperthermic intraperitoneal chemotherapy (HIPEC). These treatment modalities have become the standard of care for pseudomyxoma peritonei (PMP) and peritoneal mesothelioma. Conducting clinical trials to validate potential treatment efficacy in PM from other gastrointestinal malignancies has proven equally difficult [1, 2]. Despite treatment efficacy shown in these peritoneal malignancies, as well as a host of retrospectively analyzed data to support use in PM of other origins, there have been few prospective, controlled clinical trials for HIPEC. Challenges include trial design, oncology-community bias, and poor patient accrual. In the USA, Stojadinovic et al., in collaboration with the US Military Cancer Institute, the American College of Surgeons Oncology Group, and the National Cancer Institute, attempted to enroll 328 patients for a randomized controlled trial (RCT) investigating the role of CRS and HIPEC for the management of colorectal PM; however, they were only able to recruit a single patient. Lack of patient accrual is a common factor in the failure of most clinical trials for CRS and HIPEC, despite a growing need for clinical evidence to validate an aggressive treatment approach toward peritoneal malignancies.

CRS and HIPEC have slowly gained acceptance in the wider oncology community, even being included in the 2017 National Cancer Comprehensive Network guidelines for colon cancer, stating that "if R0 resection can be achieved, surgical resection of isolated peritoneal disease may be considered at experienced centers [3]." This treatment paradigm appears necessary, as at the time of primary colon cancer resection, as many as 10–15% of patients may present with synchronous PM [4]. Furthermore, in patients with recurrences, the peritoneum may be the only site of disease in 10–35% [5, 6]. Limited clinical trials, as well as significant retrospective data, already published have provided a foundation from which more prospective trials have developed.

17.2 Published Clinical Trials

Few clinical trials have reached completion regarding the benefits of CRS and HIPEC in patients with PM. The current NCCN Guidelines

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for the management of PM from colon cancer highlight the significance of the only randomized controlled trial investigating the effectiveness of CRS and HIPEC specifically for CRC published by Verwaal et al. [3, 7]. Between January 1998 and August 2001, this group randomized 105 patients. Patients in the control arm received treatment with standard chemotherapy, and palliative surgery when necessary, comprised of 5-fluorouracil (FU) and leucovorin for up to 26 weeks or irinotecan for 6 months if previously treated with FU, as well as palliative surgery, when necessary. The experimental group underwent CRS and HIPEC with mitomycin-C (MMC), followed by adjuvant chemotherapy within 3 months of surgery. Ultimately, 44 patients were included in the standard therapy group and 49 patients underwent CRS and HIPEC, with 33 patients proceeding to adjuvant therapy. This study demonstrated a significant improvement in median survival, 12.6 months in the control group, compared to 22.4 months in the CRS/HIPEC group ($p = 0.032$). Importantly, survival was nearly 2 years longer in the CRS/HIPEC treatment group. Verwaal's data suggests a 20% 5-year survival rate in the patients undergoing CRS and HIPEC, compared to control. The authors also noted that patients with PM involving greater than six regions of the abdomen had worse survival compared to those with less than five regions involved, as previously reported by Sugarbaker et al. and Elias et al. [8, 9].

Furthermore, this group from the Netherlands Cancer Institute analyzed a subset of the randomized patients who underwent "standard therapy" [10]. At this time, many were pushing for clinical trials investigating the use of CRS/HIPEC for PMs from colorectal cancer, yet the full benefit of this "standard therapy" was not fully understood. The goal of this subgroup analysis was to demonstrate the effectiveness of standard therapy, including conventional surgery and systemic chemotherapy. Ultimately, 50 patients were randomized to treatment with standard therapy, with 25 completing the full 26-week treatment schedule. Fifteen patients stopped systemic therapy due to progression of disease. They demonstrated a median survival of 12.6 months (37–58 months), longer than observed by previous studies, likely due to patient selection [11]. However, the patients that underwent a more radical resection had a survival of 17.3 months, demonstrating a potential survival benefit beyond that of standard treatment.

The Verwaal group later published a follow-up to their RCT in 2008 [12]. The median follow-up time was 8 years (72–115 months). Median progression-free survival was 7.7 months for patients with standard therapy and 12.6 months after CRS and HIPEC with adjuvant chemotherapy ($p = 0.02$). Disease-specific survival was 12.6 months for control group and 22.2 months for CRS and HIPEC group ($p = 0.28$). At time of follow-up, four patients from the control arm, two with disease and two without, were still living. In the CRS and HIPEC arm, five patients were alive, two with disease and three without. Ultimately, the major impact on survival was completeness of cytoreduction. Patients who underwent a complete cytoreduction had a 5-year survival of 45%, with no treatment-related deaths occurring, as compared to those with incomplete cytoreduction.

Glehen et al. conducted an open, prospective, nonrandomized trial between 1998 and 2001 [13]. This study included 56 patients with PM of varying origins: 26 colonic adenocarcinoma, 7 PMP, 7 ovarian carcinoma, 6 gastric adenocarcinoma, 5 peritoneal mesothelioma, 3 small bowel adenocarcinoma, and 2 of unknown primary. The goal of this early study was to evaluate the outcomes of aggressive peritonectomy procedures and "intraperitoneal (IP) chemohyperthermia" in patients with these various forms of PM. In this study, the 27 patients who underwent a complete macroscopic resection (R0 and R1) had a 2-year survival rate of 79.0%, as compared to 44.7% in the 29 patients who received an R2 resection (mean survival 558.2 vs. 360.1 days, respectively, $p = 0.006$). This study demonstrated a 28.6% (16/56) morbidity rate, with seven patients suffering cutaneous fistulas. Of note, three patients were included in this study twice due to recurrence at 11, 16, and 29 months after the first surgery. These patients survived 36, 20, and 22 months, respectively, after the second proce-

dure. By August of 2002, 13 patients died from disease recurrence, with an additional mortality due to myocardial infarction. Additionally, this group monitored tolerance to hyperthermic chemotherapy, reporting a mean maximal body temperature via pulmonary artery monitoring of 38.5 °C, returning to normal values within 2–5 h.

Similar studies have been conducted investigating the impact of CRS with or without HIPEC on gastric cancer. Gastric cancer may spread via hematogenous, lymphatic, or intra-abdominal metastases; however, despite surgery and adjuvant chemotherapy, most patients recur locoregionally, as demonstrated by the MAGIC, INT-0116, and ACTS-GC trials [14–16]. Importantly, up to 30% of patients with primary gastric cancer may present with synchronous PM, demonstrating a need for a more aggressive approach toward treatment [17]. Yang et al. conducted a phase III trial in which 68 patients with PM of gastric origin were randomized to CRS alone or CRS with HIPEC [18]. Median survival in the CRS group was 6.5 months as compared to 11 months in the CRS and HIPEC cohort ($p = 0.046$), with 1-, 2-, and 3-year survival rates of 29.4, 5.9, and 0 vs. 41.2, 14.7, and 5.9%, respectively. Subgroup analysis was performed based on peritoneal carcinomatosis index (PCI) and completeness of cytoreduction (CCR) scores, to assess the impact of each on survival [19]. In the 23 patients with a high PCI (≥20), the median overall survival of the CRS and HIPEC group was 13.5 months as compared to 3-month survival in the CRS-only group ($p = 0.012$). Importantly, in patients with incomplete cytoreduction (CCR 2–3), CRS and HIPEC provided a longer median overall survival (8.2 months), as compared to the CRS-only group (4 months) ($p = 0.024$) [18].

The current standard of care for ovarian cancer involves a combination of CRS and platinum-based, systemic chemotherapy. In a comparison of retrospective studies, Chi et al. demonstrated an improved median overall survival of 54 months in patients who underwent optimal cytoreduction, including upper abdominal procedures, as compared to 43 months in patients who underwent more traditional resection, involving just the lower abdominopelvic region. Yet despite maximal treatment, most patients recurred within 2 years, many with platinum-resistant disease, leading to investigations into the oncologic benefit of intraperitoneal chemotherapy [20, 21]. A phase III RCT by the Gynecologic Oncology Group, published in 2006, randomly assigned 415 patients with stage III ovarian carcinoma or primary peritoneal carcinoma who had already undergone maximal debulking, with no residual mass greater than 1.0 cm, to treatment with adjuvant systemic paclitaxel plus cisplatin or systemic paclitaxel with intraperitoneal (IP) cisplatin and paclitaxel. While grade 3 and 4 toxicities were more common in the IP arm, the authors demonstrated a median progression-free survival of 23.8 months in this group as compared to the control arm ($p = 0.05$), with a median overall survival of 65.6 and 49.7 months, respectively ($p = 0.03$). Though patient quality of life was worse after IP therapy in the short term (3–6 weeks after treatment), by 1 year this group reported improved quality of life as compared to the systemically treated patients [21].

Spiliotis et al. later conducted a prospective randomized phase III study investigating the efficacy of HIPEC for epithelial ovarian cancer (EOC) [22]. EOC often presents at an advanced stage with spread throughout the abdominopelvic region due to its indolent pathogenesis, leading to poor overall median survival [23]. This study represented the first randomized control trial for recurrent EOC. Over 8 years, from 2006 to 2013, this group randomized 120 women, who previously underwent CRS/debulking and adjuvant chemotherapy, with stage IIIC or IV recurrent EOC. Patients were randomized to CRS and HIPEC with subsequent systemic chemotherapy or CRS with systemic chemotherapy only. For HIPEC paclitaxel and cisplatin were used in platinum-sensitive disease, while doxorubicin and paclitaxel or MMC were used for platinum-resistant disease. In the HIPEC treatment group, mean survival was 26.9 and 26.4 months in the stage IIIC and IV groups, respectively. In those treated with CRS and systemic chemotherapy only, mean overall survival was 14.2 and 11.9 months in patients with stage IIIC and IV,

respectively. This study also demonstrated the significant treatment benefit of HIPEC in stage IIIC and IV disease with both platinum sensitivity and platinum resistance.

17.3 Ongoing Clinical Trials

Despite the few RCTs that have been completed, retrospective data has shown a significant impact on the combined use of CRS and HIPEC for CRC, as well as gastric and ovarian malignancies. A number of trials, internationally, are currently enrolling patients to determine the effects of both HIPEC and early postoperative intraperitoneal chemotherapy (EPIC) on PM of various origins. These studies vary in phase, as well as their approach to HIPEC. We seek to highlight some of the more notable RCTs currently ongoing and actively enrolling patients, while a complete list can be found in Table 17.1.

17.3.1 Colorectal/Appendiceal

The ICARuS (Intraperitoneal Chemotherapy After Cytoreductive Surgery) trial (NCT01815459), with principal investigator Garrett M. Nash of Memorial Sloan Kettering Cancer Center (MSKCC), seeks to determine the benefit of HIPEC with MMC versus early postoperative intraperitoneal chemotherapy (EPIC) with floxuridine after optimal CRS in patients with appendiceal and colorectal cancers. Enrollment began in March 2013, with an estimated completion date of March 2018. The primary outcome measure of the study is disease-free survival, within 3 years, though secondary measures will monitor surgical and chemotherapy-related toxicities (grades 3–5) up to 60 days postoperative.

At Wake Forest University Health Sciences, Levine et al., in collaboration with the National Cancer Institute (NCI), are conducting a phase II, non-blinded randomized investigation comparing the hematologic toxicity profiles of CRS and HIPEC with MMC to CRS and HIPEC with oxaliplatin for the management of PM from carcinoma of the appendix or primary peritoneal cavity malignancies (NCT01580410). Because CRS and HIPEC are considered the mainstay of treatment for these types of malignancies, this group is seeking to identify the safer intraperitoneal chemotherapeutic [1, 2]. The primary outcome measure will be the difference in rate of grade 3 or 4 hematologic toxicities between the two groups, with secondary outcome measures of disease-free survival and quality of life assessments (3 years) between MMC and oxaliplatin-treated patients. As of December 2015, this study has completed patient recruitment, with an initial estimated enrollment of 116 patients.

PRODIGE 7 is a randomized, multicenter, phase III trial led by François Quénet, of the Insitut du Cancer de Montpellier Val d'Aurelle (Montpellier, France), in which 270 patients with colorectal cancer and limited peritoneal dissemination were randomized intraoperatively to receive HIPEC or not, if complete cytoreduction was achieved. The study was designed to evaluate the added benefit of HIPEC to a complete cytoreductive surgery. This study finished accrual at the end of 2013 and results are pending. In this study oxaliplatin (460 mg/m^2) in 2 L/m^2 of dextrose 5% over 30 min at a minimal temperature of 42 °C was used. One hour before the HIPEC, 20 mg/m^2 of leucovorin and 400 mg/m^2 of 5-fluorouracil were given intravenously. While this study is promising, it does come with potential issues. The participation of multiple institutions with varying degrees of experience and the fact that the timing of incorporation of systemic therapies and the agents used were not mandated to participate on the trial may cloud the definitive role of HIPEC in the management of these patients. In addition, it is possible that patients randomized to the no-HIPEC arm might receive another surgery with HIPEC after they recur. However, a very important contribution will be that it will show the value of having surgery to remove the peritoneal metastases and receiving systemic chemotherapy. Therefore, this may become a landmark study highlighting the importance of a multidisciplinary management of patients with CRC-PM.

The APEC study, a multicenter, randomized, phase II trial sponsored by Fudan University (Shanghai, China), will investigate the addition of HIPEC with raltitrexed or oxaliplatin to CRS and

Table 17.1 All studies on the ClinicalTrials.gov registry investigating the role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy on peritoneal malignancies

ClinicalTrials.gov ID	Phase	Country	Primary institution/group	Malignancy	Treatment arms
NCT02349958	2	USA	Bay Area Gynecology Oncology	Ovarian, fallopian tube, uterine, mesothelioma, GI, cervical, primary peritoneal	All patients will undergo CRS and HIPEC
NCT02124421	2	USA	Mercy Medical Center	Ovarian, fallopian tube, primary peritoneal	CRS/HIPEC vs. adjuvant chemotherapy vs. CRS and combo adjuvant IV/IP chemotherapy
NCT01970722	2	USA	City of Hope Medical Center	Ovarian, uterine, fallopian tube, primary peritoneal	All patients will undergo CRS and HIPEC, ± adjuvant IP or IV therapy
NCT01539785	3	Italy	Catholic University of the Sacred Heart	Recurrent ovarian	CRS vs. CRS and HIPEC; both arms undergo adjuvant systemic chemotherapy
NCT02672098	1	USA	Loma Linda University Cancer Center	Recurrent ovarian	All patients will undergo CRS and HIPEC
NCT01767675	2	USA	Memorial Sloan Kettering Cancer Center	Recurrent ovarian	CRS vs. CRS and HIPEC; both arms undergo adjuvant systemic chemotherapy
NCT02567253	2	Belgium	University Hospital, Ghent	Ovarian	CRS and HIPEC, varying temperature and dosage
NCT01628380	3	Italy	A.O. Ospedale Papa Giovanni XXIII	Ovarian	CRS vs. CRS and HIPEC
NCT02681432	3	Spain	Hospital General de la Ciudad Real	Ovarian	CRS vs. CRS and HIPEC
NCT01376752	3	Multiple European countries	UNICANCER	Recurrent ovarian	CRS vs. CRS and HIPEC
NCT02356276	3	China	Affiliated Tumor Hospital of Guangzhou Medical University	Gastric	Surgery vs. surgery and surgery; both arms undergo adjuvant systemic chemotherapy
NCT02891447	2	USA	MD Anderson Cancer Center	Gastric	All patients will undergo CRS and HIPEC
NCT02672865	1	USA	Loma Linda University Cancer Center	Gastric	All patients will undergo CRS and HIPEC
NCT02158988	3	Germany	Charité University	Gastric	Neoadjuvant/CRS/adjuvant vs. neoadjuvant/CRS and HIPEC/adjuvant

(continued)

Table 17.1 (continued)

ClinicalTrials.gov ID	Phase	Country	Primary institution/group	Malignancy	Treatment arms
NCT02240524	3	China	Affiliated Tumor Hospital of Guangzhou Medical University	Gastric	Surgery/systemic chemotherapy vs. surgery/HIPEC/systemic chemotherapy
NCT02356276	3	China	Affiliated Tumor Hospital of Guangzhou Medical University	Gastric	Surgery/systemic chemotherapy vs. surgery/HIPEC/systemic chemotherapy
NCT02960061	3	China	Sixth Affiliated Hospital, Sun Yat-sen University	Gastric	Neoadjuvant/surgery/peritoneal lavage/adjuvant vs. neoadjuvant/surgery/HIPEC/adjuvant
NCT02549911	2	China	Zhejiang Cancer Hospital	Gastric	All patients will undergo HIPEC/surgery/adjuvant chemotherapy and secondary CRS if necessary
NCT03023436	3	China	Nanfang Hospital of Southern Medical University	Gastric	CRS, HIPEC, and systemic therapy vs. systemic therapy alone
NCT02396498	3	China	Tangdu Hospital	Gastric	Surgery/systemic therapy plus S-1 vs. surgery/HIPEC/systemic therapy plus S-1
NCT02528110	2	China	Wuhan University	Gastric	Gastrectomy with or without HIPEC
NCT02969122	2	China	Peking University	Gastric	HIPEC during laparoscopic staging followed by systemic therapy and later resection if peritoneal cytology negative vs. resection and HIPEC followed by systemic therapy
NCT02381847	3	China	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School	Gastric	Radical gastrectomy with or without HIPEC
NCT01683864	2/3	Germany	University Hospital Tübingen	Gastric	Gastrectomy with or without HIPEC
NCT01882933	3	France	Hospices Civils de Lyon	Gastric	Resection with or without HIPEC
NCT02995850	1b/2	South Korea	Yonsei University	Gastric	All patients will undergo CRS and HIPEC with EPIC
NCT02420509	2	USA	University of California, San Diego	Appendiceal	All patients will undergo systemic therapy after CRS and HIPEC
NCT01815359	2	USA	Memorial Sloan Kettering Cancer Center	Colorectal and appendiceal	CRS and HIPEC vs. CRS and EPIC

Table 17.1 (continued)

ClinicalTrials.gov ID	Phase	Country	Primary institution/group	Malignancy	Treatment arms
NCT02965248	2	China	Fudan University	Colorectal	Surgery alone, surgery and HIPEC with raltitrexed, or surgery and HIPEC with oxaliplatin
NCT02179489	3	China	Zhejiang University	Colorectal	Surgery vs. surgery and HIPEC for prevention of PM in high-risk patients
NCT02830139	2	China	Wuhan University	Colorectal	Surgery vs. surgery and HIPEC, both groups under systemic therapy
NCT02758951	2/3	Netherlands	Catharina Hospital	Colorectal	CRS/HIPEC with pre/postoperative systemic therapy vs. CRS/HIPEC
NCT02231086	3	Netherlands	Academisch Medisch Centrum, Universiteit van Amsterdam	Colorectal	Adjuvant systemic therapy only vs. adjuvant HIPEC and systemic therapy for prevention of PM in high-risk patients
NCT02399410	2	Belgium	Ghent University Hospital	Colorectal	All patients will undergo CRS and HIPEC with perioperative systemic bevacizumab
NCT01226394	3	France	Gustave Roussy, Cancer Campus, Grand Paris	Colorectal	Surveillance vs. follow-up laparotomy with HIPEC after primary resection
NCT02866903	1/2	France	Hospices Civils de Lyon	Colorectal	All patients will undergo CRS and HIPEC with systemic FOLFIRI and bevacizumab
NCT02974556	3	Italy	University of Roma La Sapienza	Colorectal	Prophylactic CRS/HIPEC and systemic therapy vs. systemic therapy only after primary resection for prevention of PM
NCT02614534	3	Spain	Maimónides Biomedical Research Institute of Córdoba	Colorectal	All patients will undergo CRS and HIPEC
NCT02863471	1/2	Germany	University Hospital Tübingen	Pancreatic	All patients undergo R0/R1 resection and HIPEC
NCT02850874	2	USA	Carolinas Medical Center	Pancreatic	Pancreaticoduodenectomy with HIPEC compared to historic controls
NCT01833832	2	USA	National Cancer Institute	Adrenocortical	All patients will undergo CRS and HIPEC

systemic therapy (NCT02965248). Patients will be randomized to CRS without HIPEC, CRS, and HIPEC with raltitrexed or CRS and HIPEC with oxaliplatin. The primary outcome measure will be "peritoneal metastasis rate," with secondary outcome measures including overall survival, disease-free survival, toxicity, liver metastasis rate, and a questionnaire on the quality of life. Enrollment began in 2016, with an accrual goal of 147 patients and estimated completion date of 2023.

The CAIRO6 study will focus on the role of perioperative systemic therapy in improving survival in patients undergoing CRS and HIPEC for CRC (NCT02758951). This phase II/III study will randomize patients to undergo neoadjuvant systemic therapy with FOLFOX (5-fluorouracil,

leucovorin, oxaliplatin) or CAPOX (capecitabine, oxaliplatin) with bevacizumab followed by CRS and HIPEC and then adjuvant systemic therapy with FOLFOX or CAPOX [24, 25]. The control arm will undergo CRS and HIPEC only. The primary measures will be Clavien-Dindo grade III–V postoperative complications and overall survival, with up to 3 years of follow-up [26].

In Amsterdam, at the Academisch Medisch Centrum, Universiteit van Amsterdam, the COLOPEC study aims to determine the effectiveness of adjuvant HIPEC in preventing PM (NCT02231086). Up to 176 patients with T4 or intra-abdominally perforated colon cancer that have undergone curative resection will be randomized to receive adjuvant HIPEC with oxaliplatin or not. The investigators hypothesize that, because the peritoneum is the second most common site of recurrence in CRC patients, HIPEC may prevent peritoneal spread in this cohort of high-risk patients. Patients will be followed for recurrence-free survival up to 18 months postoperatively, as well as with endpoints related to safety/toxicity, disease-free survival, overall survival, and presence of concomitant liver or lung metastases.

Lastly, the "Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus "in Principle" (Hyperthermic Intraperitoneal Chemotherapy) HIPEC in Colorectal Patients," or ProphyloCHIP, began patient enrollment in 2010, with a goal of 130 patients (NCT01226394). This multicenter, randomized, phase III study aims to compare the effectiveness of exploratory laparotomy and HIPEC as a prophylactic, follow-up procedure, as compared to standard surveillance. After primary resection of disease, patients will undergo 6 months of standard, adjuvant chemotherapy (currently FOLFOX-4 regimen); if work-up is then negative, patients will be randomized and undergo surveillance or laparotomy with HIPEC. The primary outcome measure will be 3-year disease-free survival, with secondary measures of 3-year, 5-year, and peritoneal disease-free survival.

17.3.2 Ovarian

At MSKCC, an initial small, phase I study demonstrated the safety of CRS and HIPEC in patients with recurrent, platinum-sensitive, epithelial ovarian cancers undergoing secondary cytoreduction [27]. With this information, a multicenter, phase II RCT is currently enrolling patients with ovarian, fallopian tube, and primary peritoneal cancers, led by Dennis Chi and Roisin O'Cearbhaill at MSKCC (NCT01767675). The study, entitled "A Phase II Randomized Study: Outcomes After Secondary Cytoreductive Surgery With or Without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer," will randomize patients to secondary CRS with or without carboplatin-based HIPEC, followed by systemic chemotherapy; the HIPEC arm will receive five cycles, and the CRS-only arm six cycles of platinum-based therapy. Despite initiating patient enrollment in January 2013, with a goal of 98 patients, this study has been significantly hampered by a lack of patient accrual.

Similarly, UNICANCER, comprised of HIPEC centers in Belgium, France, and Spain, is recruiting patients for a study entitled "A Phase III Randomized Study of Phase III Evaluating Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in the Treatment of Relapse Ovarian Cancer" (NCT01376752). Much like the MSKCC trial, this group is investigating the effect of CRS with or without HIPEC on overall survival (primary outcome) and relapse-free survival (secondary outcome) of patients with resectable, recurrent, platinum-sensitive ovarian cancer isolated to the peritoneum. With an initial start date of April 2011, this group aims to enroll 444 patients and complete data collection, with up to 4 years of follow-up, by December 2020. This study, however, has met similar challenges with patient accrual.

Mercy Medical Center (Baltimore, MD) is currently investigating the combination of CRS and HIPEC (carboplatin) with adjuvant chemotherapy (carboplatin and paclitaxel) as compared to CRS with adjuvant, combination systemic (paclitaxel) and IP (cisplatin and paclitaxel) chemotherapy in patients with stage III/IV ovarian, fallopian tube, or primary peritoneal cancer (NCT02124421). The planned accrual of 48 patients in this phase II study will be newly diag-

nosed, without prior intervention. The goal of this trial will be to determine the safety of HIPEC in the perioperative period, with a primary outcome measure of 30-day postoperative complication rates. Secondary outcome measures will track progression-free survival (at 24 months), overall survival (up to 5 years), and quality of life. This study is unique in that it acknowledges the effectiveness of IP chemotherapy in the management of PM of ovarian or fallopian tube origin but seeks to identify the safest timing of intraperitoneal delivery.

Recently, Loma Linda University began enrollment in 2015 for a phase I investigation into the efficacy of CRS and HIPEC with carboplatin for recurrent ovarian cancer (NCT02672098). All patients will undergo complete cytoreduction and HIPEC, followed by systemic therapy 4–6 weeks later. This single-arm study will be compared to historical controls and followed for recurrence-free survival at 6, 9, 12, and 18 months after surgery based on RECIST 1.1 guidelines [28].

17.3.3 Gastric

The incidence of gastric cancer in China remains one of the highest in the world, with many diagnosed at an advanced stage, leading to poor survival and frequent recurrence [29]. This has led to a number of studies developed in China to employ HIPEC in managing disease recurrence. Peng et al. from the Sixth Affiliated Hospital of Sun Yat-sen University in China will soon begin a randomized phase III trial to investigate the addition of HIPEC to standard treatment for patients with primary gastric cancer (NCT02960061). All patients will undergo neoadjuvant chemotherapy, followed by gastric resection with D2 lymphadenectomy, and adjuvant chemotherapy. The experimental arm will receive HIPEC, while controls will receive only peritoneal lavage with distilled water. While HIPEC has previously been shown as an effective tool to prolong survival in patients with PM from gastric cancer, and is currently recommended in treatment guidelines from the Health Committee of China, this group seeks to determine the safety and efficacy of HIPEC prophylactic measure to prevent recurrence due to potential peritoneal seeding at initial resection [30]. Their estimated enrollment of 640 patients will be followed for overall survival for up to 5 years and progression-free survival for 1–3 years.

Cui et al. of the Affiliated Tumor Hospital of Guangzhou Medical University in China are currently recruiting patients for a similar study. This randomized phase III trial, which began in July 2014 and estimates enrolling 582 patients, will similarly study the effect of HIPEC after gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer (NCT02240524). Patients will be randomized to surgery with adjuvant therapy or surgery with HIPEC and adjuvant therapy. Primary outcome will be overall survival for up to 5 years, with secondary measures of recurrence-free, locoregional-free, and hepatic metastases-free survival with a planned final completion date in July 2019.

The phase III study from the Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School is unique in that it will be double-blinded (NCT02381847), investigating the role of HIPEC in stage T3–T4 gastric cancer treatment. Patients will undergo D2 radical gastrectomy, subsequently randomized to receiving HIPEC or not, with both groups undergoing adjuvant, systemic therapy. This group hopes to show improved overall survival (at 24 months) while also monitoring complication rates, time to progression, and time to distant metastases.

While the USA has a lower incidence of gastric cancer, it accounts for 1.3% of new cancer diagnoses annually [31]. Senthil et al. at Loma Linda University Cancer Center (Loma Linda, CA) aim to enroll 15 patients for a phase I trial to determine the safety and tolerability of HIPEC with cisplatin and MMC within the 90-day postoperative period (NCT02672865). All patients will be stage T3 or T4 and/or have clinically positive nodes. Enrollment is ongoing with a study completion date of December 2018. MD Anderson Cancer Center is currently recruiting up to 18 patients for a phase II study investigating the efficacy of HIPEC with MMC and cisplatin, in addition to gastrectomy and cytoreduction for patients with PM from gastric cancer (NCT02891447).

Charité University (Berlin, Germany) has taken this further with a phase III trial, the GASTRIPEC study, which began in March 2014. All patients will receive neoadjuvant therapy, followed by CRS, and adjuvant therapy, but patients in the experimental arm will also receive HIPEC. Overall survival will be the primary outcome in this study (2.5 years), as well as secondary measures, which include time to progression, quality of life, time to distant metastases, toxicity, and requirement of second surgery.

17.3.4 Pancreatic

Beckert et al. of University Hospital Tübingen (Tübingen, Baden-Württemberg, Germany) seek to expand the accepted use of CRS and HIPEC to metastatic pancreatic adenocarcinoma (PANHIPEC; EUDRA-CT 2015-002288-41) [32]. Only 15–20% of patients with pancreatic adenocarcinoma are eligible for curative resection, and 66–92% will eventually develop recurrent disease, typically locoregionally [33]. The primary endpoint of this study is 30-day mortality, with secondary endpoints of safety and toxicity based on Common Terminology Criteria for Adverse Events (CTCAE) 4.0. This study seeks to validate this aggressive treatment strategy for pancreatic cancer, as often, due to anatomic location and advanced disease at diagnosis, an R0 resection may not be possible. The investigators seek to weigh the increased risk of morbidity and mortality with the increase in survival benefit that has been previously demonstrated in previous studies [34, 35]. Enrollment for this study is ongoing, with only two patients included thus far.

Carolinas Medical Center plans to similarly investigate the surgical outcomes and clinicopathological results of treating patients with T1–T3, resectable pancreatic ductal adenocarcinoma with pancreaticoduodenectomy and HIPEC with gemcitabine, in conjunction with perioperative systemic therapy (NCT02850874). This phase II, proof-of-concept study is enrolling a small cohort of ten patients and will primarily examine peritoneal disease-free survival, as well as overall survival. Postoperative morbidity and mortality will also be monitored. These patients will be compared to historical controls that have been treated with 6 months of adjuvant gemcitabine per their institution's protocol.

17.3.5 Improving CRS and HIPEC

Further studies are being conducted internationally that seek to improve the delivery of chemotherapeutics during HIPEC, as well as eliminate remaining disease after maximal cytoreduction. These studies investigate the dosage, temperature, pressure, and timing of intraperitoneal chemotherapy in an effort to define the most effective treatment strategies.

The Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) is investigating the ability to improve the uptake of chemotherapy by neoplastic tissue after CRS. This will be achieved by using high intra-abdominal pressure (IAP) (18–22 mmHg). Currently enrolling up to 38 patients, this phase II study will randomize each patient to undergo CRS and HIPEC, with low IAP (8–12 mmHg) in the control arm and high pressure in the experimental arm (NCT02949791). Postoperatively, tumor tissue concentration of cisplatin, collected within 15 min of procedure, will be compared to that of normal tissue. Secondary outcome measures will track pharmacokinetic advantage and patient physiologic parameters, as well as toxicity and postoperative complications.

A phase III study at Hasselt University, in collaboration with Ziekenhuis Oost-Limburg (Belgium), is enrolling up to 60 patients in order to compare the effectiveness of a concentration-based versus body surface area-based protocol for dosing intraperitoneal chemotherapy. Many institutions utilize a body surface area (BSA)-based approach; however, this group postulates that sex, pathophysiologic changes, and presence of ascites can affect the initial homogenous drug concentration delivered to the patient. Others using a concentration-based approach face unpredictability in the levels of plasmatic chemotherapy and the toxicity profile of chosen dosage. These two methods will be compared by randomizing patients to

receiving either a BSA-based or concentration-based regimen of HIPEC after CRS, for a duration of 30 min. Primary outcome measures will be an assessment of pharmacologic advantage via area-under-the-curve ratio of IP fluid oxaliplatin concentration versus time, as well as drug excretion in urine, intraoperative drug concentration within tumor nodules, and 3-month overall morbidity and mortality. Secondary measures will track the quality of life at discrete time points and overall 1-year survival.

Andersson et al. in Norway are currently conducting a phase I/II clinical trial (NCT02219893) investigating the use of a novel immunotoxin, MOC31PE, comprised of a monoclonal antibody that targets EpCAM found in a number of peritoneal malignancies, a tumor-associated cell surface antigen and pseudomonas exotoxin (ImmunoPeCa trial) [36–38]. In 15 patients, the phase I portion of this trial demonstrated no major toxicity in the maximum tested dosage of 10 μg/kg. Interestingly, MOC31PE was not detected in the serum of any treated patients, suggesting a lack of systemic absorption. Additionally, in patients treated at the highest dosage, the toxin was detected in peritoneal fluid samples collected at 6 and 24 h post-HIPEC, still in its fully active form. The lack of systemic absorption is consistent with the lack of major toxicity demonstrated in this study. With this data, the Norwegian group plans to continue recruitment for an expanded phase II trial utilizing MOC31PE for post-CRS and HIPEC treatment [39].

17.4 What is the Ideal Trial?

Ethical and moral dilemmas make designing the perfect surgical trial difficult. Physicians and patients must weigh the safety and efficacy of treatment options when determining the proper strategy for management of PM. CRS and HIPEC have been shown to prolong overall and disease-free survival in a number of retrospective studies and previous clinical trials, yet the ideal study remains unperformed. Oncologists and surgeons desire a study that will clearly define the proper sequence and duration of the currently available strategies. A number of questions have to be answered via clinical trials in order to accomplish this daunting task: What is the role of HIPEC for each diagnosis? Which drugs should be used? At what temperature should they be delivered? How long should they remain in the abdomen? Which technique is more effective, open or closed? Is there a role for repeat CRS and HIPEC in all diagnoses?

Using the example of PM from CRC, one such possibility for a clinical trial would be based on patient stratification using the peritoneal surface disease severity score (PSDSS) to determine resectability of those with an initial diagnosis of PM [40–42]. Upon diagnosis patients would receive 2–3 months of best systemic therapy. Patients would then be restaged and, if still surgical candidates, would be randomized to one of three arms: continued systemic therapy, CRS only followed by systemic therapy, or CRS and HIPEC followed by systemic therapy. Patients would cross over to more aggressive treatment at first signs of progression. This model would allow for direct comparison between traditional chemotherapy and CRS/HIPEC while also clarifying the role of HIPEC in improving survival and delaying progression in these patients.

Conclusion

CRS and HIPEC have become preferred treatments for a number of peritoneal malignancies; however, further studies will be crucial toward validating these strategies before they can become the standard of care and earn the full support of the wider oncologic community.

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Part III

Beyond Cytoreductive Surgery and HIPEC

18 Cytoreductive Surgery and HIPEC in the Elderly

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18.1 Introduction

With an increase in the overall life expectancy worldwide, there has been an increase in the aging/elderly population. The life expectancy of a 65-year-old individual is about 20 years and that of an octogenarian is more than 9 years. As estimated by the UN and some other health authorities, this tendency will prevail from the present 14.5% to above 20% in 2040 [1]. Despite advances in surgical techniques and perioperative management, age has remained an independent predictor of worse short-term outcomes after major oncologic resection [2]. Similar to other major surgeries like hepatic, pancreatic, and gastric resections in the elderly population that are now performed with a controlled morbidity and mortality, the feasibility of CRS and HIPEC has been demonstrated with morbidity and mortality rates between 20–42% and 0–10%, respectively [3–8]. There is no strict definition of what constitutes "elderly," and different investigators use this term for patients aged >65, 70, or 75 years [9–14]. Previously, the age of >65 or >70 or >75 years was used as a cutoff for excluding patients from clinical trials/prospective studies related to CRS and HIPEC due to uncertainty of the benefit in this patient population [15].

18.2 Cancer Incidence in the Elderly

Approximately 60% of all newly diagnosed neoplasms and 70% of cancer-related mortality occur in patients 65 years of age and older [9]. Peritoneal metastases occur in 8% of colorectal cancer (CRC) cases [10]. Colorectal cancer liver metastases (CRLM) are the most common followed by lung metastasis and metastasis to the peritoneum (CPM). In Western countries, CPM is a major health issue especially in elderly patients since most of the CRC patients are diagnosed at an age of 65 and above with a major increase in the patients diagnosed at the age of 75 or older [11]. CRPM may be synchronous, but it is often metachronous, diagnosed months or even years after resection of the primary tumor.

Another common indication of CRS and HIPEC is peritoneal metastases arising from appendiceal primary tumors. The mean age of presentation of appendiceal cancer varies, but in the most common types, i.e., mucinous and colonic, the mean age is above 60 years of age [12].

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been established as one of the most effective therapeutic options for peritoneal metastases (PM)

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originating from the colon and rectum and appendix as well as some other malignancies that are abundant in older ages, such as mesothelioma and gastric cancer [13, 14, 16, 17].

The exact incidence of PSM diagnosed at old age is yet to be defined, but it was shown in different studies that patients at the age of 70 years and above comprise of 8.5% of PSM diagnosed and comprise up to 30% of the patients undergoing CRS and HIPEC [18, 19]. Since, this data mainly comes from studies in which elderly patients have undergone surgery, those that were not offered surgical treatment have been excluded, and the actual incidence of PM in the elderly is likely to be higher.

18.3 Aging Considerations

Although age by itself is not a contraindication for major surgery, still many surgeons are reluctant to operate on elderly patients. More than 75% of patients above the age of 65 years suffer of at least one chronic medical condition [20]. Furthermore, aging is accompanied by physiologic decline in different organ systems, an aspect that may adversely affect the postoperative course of the elderly patient.

18.3.1 Respiratory System

The most frequent postoperative complications in elderly patients are respiratory failure and superimposed infection. The age-dependent decline in respiratory function is attributed to diminished chest wall compliance and the weakening of the respiratory muscles. Loss of elasticity leads to decreased alveolar compliance and to gradual decline in arterial oxygen tension. The risk of pneumonia increases with age mainly due to compromised immune system and less effective mucociliary performance.

18.3.2 Cardiovascular System

The cardiovascular system is also a major concern for perioperative complications. With aging, morphologic changes in the myocardium, conducting pathways, and heart valves develop. Endothelial dysfunction evolves with aging including vasculature of the heart and great vessels. There is also a decreased ability for an adequate stress response and increased dependence on preload and atrial function (atrial kick). These changes lead to increased risk for cardiac ischemia and failure [21]. Almost 50% of elderly individuals are hypertensive and treated by various medications affecting the cardiovascular and other systems [22], and these issues need to be addressed in the postoperative period.

18.3.3 Mental Status

In elderly patients, diseases such as Alzheimer's disease, depression, and dementia are common. Even elderly individuals without mental disorders may respond to major surgery with disorientation and even delirium. Noncompliant patients due to disorientation or delirium are difficult to manage postoperatively.

18.3.4 Nutritional Status

In elderly individuals, especially in nursing homes, caloric intake, as well as daily protein consumed, is reduced leading to poor nutritional status. Mild malnutrition may interfere with wound healing, immune function, and cardiac and pulmonary function.

18.3.5 Immune System

Immunosenescence is characterized by enhanced susceptibility to infections, an increase in autoantibodies and monoclonal immunoglobulins, and an increase in tumorigenesis. The main difference in T cells is the type of lymphocyte (a decrease in the naïve T cells vs. an increase in the memory T cells) rather than the absolute number of T cells. The function of B cells is affected due to a change in the helper T-cell activity. These changes are apparent only during active infec-

tious process and are not seen in regular state and ordered WBC count [23]. It is well known that the risk of developing cancer increases with age [24–27], and older patients may also exhibit larger and more aggressive tumors [28]. The decline in the immune function may be one of the reasons for the increased risk of cancer in the elderly.

Functional decline is present in other organ systems as well such as the renal system, hepatobiliary system, and hormonal homeostasis.

18.4 Preoperative Evaluation

A comprehensive evaluation of elderly patients for fitness for the procedure and functional optimization is necessary before taking up these patients for CRS and HIPEC. Preoperative workup should include a full history and physical examination; imaging of the thorax, abdomen, and pelvis; and preoperative blood work including relevant tumor markers. The cardiac evaluation should comprise of a 12-lead electrocardiogram and 2D echocardiography. Further testing will depend on the associated comorbidities and functional status. In high-risk patients, exercise stress testing may be performed if the functional status is poor or unknown. A specialist's opinion should be sought where required.

Each patient should undergo multidisciplinary evaluation by a team comprising of medical and surgical oncologists, radiologists, anesthesiologists, pathologists, and nutritionists to determine the oncological benefit in terms of survival and improvement in the quality of life as opposed to the risk of morbidity and mortality entailed.

The response to surgical stress is diminished in elderly patients, and this should be kept in mind during the decision-making process.

Several scoring systems are used for evaluation of patients undergoing surgery. One or more of these scores may be used to determine the functional status before the procedure.

American Society of Anesthesiologists (ASA) score is based on the severity of comorbid conditions. Even though it does not include the patient's age, the ASA score has been shown to accurately predict postoperative mortality up to and above 80 years of age.

It is important to emphasize that all patients that are candidates for CRS-HIPEC are at least scored at ASA III due to their underlying disease.

Metabolic Equivalents (METs) It is possible to assess the functional status of a patient from the activities of his/her daily life [29, 30]. Functional capacity is often expressed in terms of metabolic equivalents (METs), where 1 MET is the resting or basal oxygen consumption of a 40-year-old, 70 kg man. In patients undergoing surgery, functional capacity is classified as excellent (>10 METs), good (7 METs to 10 METs), moderate (4 METs to 6 METs), poor (<4 METs), or unknown. Inability to perform 4 METs of work as part of routine daily activities has been associated with an increased perioperative and cardiovascular risk as well as long-term adverse consequences. Examples of activities associated with <4 METs are slow ballroom dancing, golfing with a cart, playing a musical instrument, and walking at approximately 2–3 miles per hour. Examples of activities associated with >4 METs are climbing a flight of stairs or walking up a hill, walking on level ground at 4 mph, and performing heavy work around the house. In patients who have a high surgical risk but a good functional capacity of >4–10 METs, further exercise testing can be omitted.

"*Up and go test*": Testing gait and mobility is also important. In addition, history of falls should also be taken into account.

Eastern Cooperative Oncology Group (ECOG) Test The ECOG performance status has been extensively used for selecting patients for CRS and HIPEC [31, 32].

The performance status is an expression of both the physiological and functional capacities, and though it is of great prognostic significance in younger patients, its importance is less in the elderly. In young patients, loss of functional capacity can be correlated with the extent of disease; in the elderly, aging may be in part responsible for the deterioration. Younger patients with performance status of ECOG 0 or 1 have superior

survival over ECOG 2 patients. In elderly patients, ECOG has less prognostic significance, possibly because it functions as an expression of both physiologic aging and volume of disease. Frailty is a better marker of physiological reserves in the elderly [33].

Frailty Geriatricians define frailty as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes [34–39]. Frailty is not the same as disability [40, 41]. An objective and reproducible measurement of frailty has been developed by Fried and collaborators. Frailty is defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (10 lbs. in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. An operational method of calculating frailty is provided in Table 18.1 [42].

Frailty is known to cause disability, independent of clinical and subclinical diseases. The syndrome of frailty may be a physiologic precursor and etiologic factor in disability, due to its central features of weakness, decreased endurance, and slowed performance. This test could be specifically useful in elderly patients with no overt comorbidities.

Table 18.1 Operational method of calculating frailty [adapted from Ref. 42]

A. Characteristics of frailty	B. Cardiovascular Health Study Measure
Shrinking—weight loss (unintentional) Sarcopenia (loss of muscle mass)	Baseline: >10 pounds lost unintentionally in the previous year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance—exhaustion	Exhaustion (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% Males: <383 Kcals/week Females: <270 Kcals/week
	C. Presence of frailty
	Positive for frailty phenotype: >3 criteria present
	Intermediate or prefrail: 1–2 criteria present

18.4.1 Charlson Comorbidity Index

Charlson comorbidity index (CCI) is a valid and reliable comorbidity score. Each comorbidity (such as cardiovascular disease, diabetes mellitus, renal failure, AIDS, and malignancy) is scored from 1 to 6. The total score is correlated with the risk of death in 1 year, acute disease surgery, and other stressors [43]. It was also validated for acutely hospitalized elderly adults [44].

Of the various methods of functional assessment, one or more may be used to evaluate the functional status. The choice of the method will depend on the individual patient as well as institutional protocols.

18.5 Reported Outcomes of CRS and HIPEC in the Elderly

Elderly patients have been either underrepresented or totally excluded from most prospective randomized clinical trials relating to cancer treatments [15]. In the few randomized trials that were performed studying CRS and HIPEC, age was used as a selection criterion, excluding patients older than 71 or 65 years of age [45, 46]. Moreover, some authors considered age >75 as a contraindication for CRS and HIPEC [47].

However, this exclusion criterion has been challenged by several investigators, and recent studies have shown that similar surgical and oncological outcomes in selected elderly patients with CRS and HIPEC appear outdated, and several recent studies show that age does not influence the oncologic outcome of surgery and that cancer-specific survival in these patients is similar to that of younger patients.

In one of the first multi-institutional studies evaluating risk factors in CRS with HIPEC, age over 65 years appeared to be an unfavorable

prognostic factor in both univariate and multivariate analyses [48].

The first study reporting CRS and HIPEC in the elderly was published in 2011 by Macri et al. [49]. They compared the outcome of 11 patients older than 65 to 19 patients younger than 65. Severe complications and perioperative mortality as well as median overall survival were similar in both groups. Subsequently, several other small and large single and multi-institutional studies have reported outcomes of CRS and HIPEC in the elderly (Table 18.2).

Two studies included patients aged 65 years and older, and two other studies used 75 years old as a cutoff, while the patients older than 70 years were considered elderly in the remaining studies. All except two series included patients with PM arising from various primary sites. 4/8 studies used a control group for comparison. Three studies focused only on the perioperative outcomes while others reported survival outcomes as well.

18.6 Morbidity and Mortality

CRS and HIPEC is a complex surgical procedure. The incidence of morbidity and mortality at 1 month postoperatively may not capture the physiological impact of the procedure completely; hence some investigators have recorded and reported these outcomes at 3 months as well [18, 56].

The reported morbidity rates across age groups range from 27 to 56% and mortality rates from 0 to 4% [32, 59, 60]. The reported morbidity rates for CRS and HIPEC in the elderly range from 14.1 to 56%. One study reported grade I–IV complications together, and hence the incidence of morbidity was higher in this series, whereas others reported major morbidity (grades III–IV) separately. The highest morbidity of 76% was observed in a study of 29 patients aged over 70 years with PM from multiple primary sites [55]. In the largest multi-institutional study, Alyami et al. reported a major morbidity of 45.7% and mortality of 5.4% at 90 days [56]. The 188 patients were matched with a control group of 704 patients, and in the control group, the morbidity and mortality were 44.5 and 2.7%, respectively, which were not statistically different. The incidence of surgical complications was similar in both groups except for a higher rate of wound dehiscence in the elderly. The renal toxicity was higher though it did not reach statistical significance. The hematological toxicity was also significantly higher though it did not have a significant impact on the clinical outcome [56]. The elderly patients had significantly more cardiovascular complications (13.8 vs. 9.2%, $p = 0.044$). A PCI >7 (odds ratio 2.469; 95% CI 1.051–5.798, $p = 0.038$) and the HIPEC duration (odds ratio 2.626; 95% CI 1.106–6.235, $p = 0.028$) were independently associated with increased morbidity, and no factor significantly impacted the mortality. A higher rate of cardiovascular complications was also noted in by Tabrizian et al. in a series of 35 patients aged more than 65 years [51].

In a study of 14 patients aged over 70 years, Kitai et al. reported similar rates of surgical site complications between the older and younger age groups but a higher rate of systemic complications. Grade IV–V respiratory failure occurred in three male patients all of whom had a complete cytoreduction; the median operating time was 10.5 h, and bilateral subphrenic peritonectomy which is known to cause respiratory problems was performed in all the patients. Subphrenic peritonectomy restricts the diaphragmatic movements in the postoperative period and causes varying degrees of pleural effusion which combined with the large volumes of fluid transfused in these patients leads to respiratory complications. Severe respiratory distress can lead to early postoperative death, and this is more likely in elderly patients with a decreased functional reserve [58].

Tabrizian reported that the respiratory failure rate was 5.9% in patients aged ≥65 years and 6.2% in those aged <65 years [51].

Contrary to other reports, Votanopoulos et al. in their 20-year institutional experience observed high mortality rates of 13.6 and 27.4% at 1 and 3 months, respectively, which was significantly higher than that in a matched group of patients younger than 70 years ($p < 0.0001$) [18]. Similarly, the morbidity of 38% in the elderly group was significantly higher than that in the younger age group ($p = 0.002$). The authors attributed this to

Table 18.2 Treatment outcomes in elderly patients undergoing CRS and HIPEC

Ref no. year	Age limit (years)	No.	Primary site	Morbidity (%)		*p* value	Mortality (%)		*p* value	Median DFS (months)	Median OS (months)
				Control	Study		Control	Study			
[49] 2011	>65	11	Multiple primary sites	–	27.3		–	18.2		Not reported	Not reported
[50] 2012	>70	24	Colorectal	–	34		–	0		12	35
[18] 2013	>70	81	Multiple primary sites	23	38	0.002	10.2	27.4**	<0.0001	Not reported	47
[51] 2013	>65	35	Multiple primary sites	21.8	19.4	0.05	5.9	11.4**	0.272	Not reported	21.2
[52] 2014	>75	9	Ovarian	16	56	<0.05	0	0		6	13
[19] 2014	>70	30	Multiple primary sites	0	50		1.4	3.3	NS	Reported	30
[53] 2015	>70	15	Recurrent ovarian	–	20		–	0		15.6	35
[54] 2015	>65	124	Multiple primary sites	44	40	0.64	2	3	0.60	Not reported	43
[55] 2015	>70	29	Multiple primary sites	47	76	0.04	0.9	0		Not reported	Not reported
[56] 2016	>70	188	Multiple primary sites	44.5	45.7	0.17	2.7	5.4**	0.05	Not reported	Not reported
[57] 2016	>75	85	Multiple primary sites	–	14.1		–	5.9**		Not reported	Not reported
[58] 2017	>70	14	Multiple primary sites	7.6	35.7	0.02	0	14.2**	0.06		

their own learning curve and selection of patients. Over the years, the indications of this procedure have become better defined, and certain patients who tend to have a poor prognosis are no longer offered this procedure. In their last 42 patients (50%), there was a drop in the 1- and 3-month mortality from 17.9 and 35.9% to 9.5 and 19.3%, respectively, though the 9.5 and 19.3% 1- and 3-month mortality are still higher than reported by most other series [18].

The authors evaluated the impact of comorbidities on the morbidity and found that one comorbid condition led to a more than doubling of the odds of having a complication with an odds ratio of 2.19 (95% CI 1.06–4.53, $p = 0.035$). The rate of complications was significantly higher in smokers than in nonsmokers ($p = 0.012$).

A multi-institutional study from ten Spanish hospitals that are part of the Spanish Group Peritoneal Cancer Surgery (GECOP) analysis showed an association between grade III and IV morbidity and preoperative albumin levels of less than 3.5 mg/dl ($p < 0.002$), diabetes mellitus ($p < 0.022$), the need for diaphragmatic peritonectomy procedures ($p < 0.003$), perioperative blood transfusion ($p < 0.005$), and the need for more than three peritonectomy procedures per patients ($p < 0.049$) [57]. On multivariate analysis, independent predictors of grade III–IV morbidity were the presence of a preoperative albumin levels <3.5 mg/dl ($p < 0.017$), the need for diaphragmatic peritonectomy procedures ($p < 0.023$), and perioperative blood transfusion ($p < 0.018$).

In addition to morbidity, failure to rescue is an important metric for evaluating the surgical outcomes [61]. In the study by Alyami et al., though there was no increase in the morbidity in older patients, the failure-to-rescue rate was higher (11.6 vs. 6.1%, $p = 0.078$), implying that elderly patients are at a higher risk of death following a complication.

There is a trend toward increase in the overall morbidity and grade III and IV morbidity in elderly patients undergoing CRS and HIPEC. The incidence of surgical complications tends to be similar to that in younger patients, but the incidence of medical complications is higher. Though reported only in one study, there is a higher rate of "failure to rescue" in elderly patients.

18.7 Survival Outcomes

Elderly patients can experience a prolonged survival after CRS and HIPEC. In 124 patients with PM arising from various primary sites, treated by Huang et al., the median overall survival (OS) of patients who were less than 65 years old was 58.0 months (95% CI = 47.0–68.9) with a 5-year OS of 47.7%, whereas the elderly group had a median OS of 43 months (95% CI = 38.1–47.9) with a 5-year OS of 42.9% [54]. However, such a difference did not reach a statistical significance ($p = 0.698$). Cox regression analysis showed that age alone is not a prognostic factor for survival of PM ($p = 0.795$) [54]. Spiliotis et al. reported a 5-year OS of 30% in elderly patients compared to 52% in younger patients. The statistical analysis showed that 3 years after the initial operation, there is a survival benefit in the younger population. A PCI of <10, CC score of 0, and primary tumor histology were the factors influencing overall survival [19]. The impact of PCI was also reported in Delotte et al. In 15 patients aged >70 with advanced ovarian cancer receiving HIPEC in addition to interval CRS, all the patients with a PCI of >13 developed recurrences within 2 years. Similarly, patients who had a complete cytoreduction (CC-0) experienced a prolonged survival as compared to those with CC-1 all of whom recurred within 2 years [52]. Klaver et al. in their study of 24 patients with CRC PM found that none of the factors evaluated which included age >75 years, histologic type of tumor (mucinous adenocarcinoma vs. adenocarcinoma), completeness of cytoreduction score, amount of blood transfused, completeness of cytoreduction as represented by CCR, performance of HIPEC, administration of EPIC, and occurrence of a postoperative complication requiring radiological drainage or return to theater had an influence on survival [50].

In 81 patients aged over 70 with PM arising from various primary sites, Votanopoulos et al. found postoperative morbidity to be the single and

most important factor impacting survival [18]. Patients without complications (n = 27) had 1-year survival of 81% (±8%) and 3-year survival of 59% (±10%), while the median survival was 39 months. Patients with postoperative complications (n = 54) had 1-year survival of 53% (±7%) and 3-year survival of 25% (±7%), while the median survival was 13 months [18]. Stepwise multivariate models were created with and without complications as a variable. The presence of any complication has a significant negative impact on the survival in both univariate and multivariate analyses (p = 0.004). The authors concluded that given the negative impact of morbidity on survival in elderly patients, careful selection for CRS and HIPEC should be performed.

In stepwise multivariate analysis, type of primary tumor (p = 0.03), serum albumin level (p = 0.02), and completeness of cytoreduction R status (p = 0.007) were predictive of survival only in the absence of complications. Patients with pseudomyxoma peritonei, malignant mesothelioma, and ovarian cancer experience a better survival than those with colorectal or gastric PM. Splitting the data at the midpoint of surgical experience, there was a drop in 1- and 3-month mortality over time to 9.5 and 19.3%, respectively, while the median survival increased from 11.2 (N = 39) to 46.9 months (N = 42) [18].

In a study of 9 patients with recurrent ovarian cancer aged over 75 years, undergoing CRS and HIPEC, the median DFS was 6 months, and the median OS was 13 months which was significantly lower than patients younger than 75 years of age. Overall survival at 1 and 3 years was 92 and 67%, respectively, in patients <75 years and 55% and 0% at 1 and 3 years in patients ≥75 years [52].

In a recently published study by Kitai et al. of 14 patients, the survival was significantly inferior in elderly patients, with 5-year survival rates being 41.3 and 74.2%, respectively (p = 0.0166). These poor outcomes were attributed to an increased rate of grade IV–V complications in these patients [58].

CRS and HIPEC can provide a survival benefit to selected patients with PM. Careful selection and management of patients are needed. To optimize the outcomes, it is important to avoid unnecessary resections to prevent potential added morbidity and mortality. Patients with limited disease have less morbidity and experience a longer survival.

The insult of an extensive surgical effort may therefore be potentially fatal in a poorly selected patient with significant comorbidities. Detailed explanation of the risks and benefits of the combined treatment modality and the awareness that major surgery, intensive care stay, and the existence of comorbidities may potentially complicate the recovery and increase the morbidity and mortality is of utmost importance. The increased risk of medical complications can be offset by age-appropriate care, including geriatric consultation, supplemental enteral nutrition, and early rehabilitation placement planning. Pathways for perioperative management of these patients as described by Passot et al. may especially be useful in this setting [62].

Conclusions

The elderly patients with PM pose a therapeutic challenge to peritoneal surface oncologists. They can experience a significant prolongation in survival with CRS and HIPEC which needs to be balanced against the risk of increased morbidity. Preoperative evaluation of functional status using scores like the frailty index helps in selecting patients who have the physical reserve to withstand the procedure irrespective of the chronological age. A multidisciplinary evaluation is also needed to select patients who are most likely to derive a benefit an oncological benefit. Patients with a low PCI and those who undergo complete cytoreduction and have PM from appendiceal and ovarian primary tumors or peritoneal mesothelioma derive the maximum benefit. There is a higher incidence of medical complications in the elderly with a larger proportion of patients succumbing to their complications; hence all efforts should be made to avoid complications in these patients.

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19 Quality of Life Issues in Patients Undergoing Cytoreductive Surgery and HIPEC

Julianna P. Englisch, Andreas Brandl, Ute Goerling, and Beate Rau

19.1 Introduction

Current treatment of peritoneal surface malignancy (PSM) involves cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Primary peritoneal disease is associated with malignant mesothelioma, pseudomyxoma peritonei, and serous adenocarcinoma of the peritoneum, whereas secondary peritoneal malignant disease arises from solid tumor in the history such as gastrointestinal cancer. In these situations, only palliative chemotherapy is delivered to the patients, because distant metastases especially PSM are associated with a poor prognosis. The mean survival time in the presence of PSM is around 6 months. During the last 20 years, a therapeutic approach was developed to surgically treat PSM and reduce the peritoneal dissemination of the disease. Some of the reasons for the surgical approach are, first, the difficulties for chemotherapy to get into the tumor cells, because of bad blood supply of the peritoneum; second, reduction of the tumor mass; and third, topical intraperitoneal chemotherapy for some free tumor cells.

The role of CRS has become a new role in surgical oncology. Usually, PSM are widely spread in the peritoneal cavity and are often combined with malign ascites. There is a broad range of tumor burden; therefore the indication for surgical cytoreductive treatment has to be taken very carefully.

Complete cytoreductive surgery (CRS) can achieve curation or long-term survival in selected patients with peritoneal malignancies. The procedure aims for complete tumor removal. That means in case of synchronous disease, the primary tumor has to be oncologically resected analogous to the existing guidelines for the primary tumor combined with cytoreductive surgery. Complete macroscopic cytoreductive surgery stands for the removal of peritoneal lesions in the abdomen and can be achieved by parietal and visceral peritonectomy. The completeness of cytoreduction depends on the extent and the kind of the peritoneal tumor manifestation.

The *mucinous type of PSM* including pseudomyxoma peritonei, low-grade adenomucinousis neoplasia (LAMN), peritoneal mucinous adenocarcinoma (PMCA), and mesothelioma usually requires a total peritonectomy and infragastric and lesser omentectomy, whereas in *nonmucinous type of PSM* removing of the tumor-bearing piece of the peritoneum and infragastric omentectomy are recommended.

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In the case of *infiltrating tumor lesions* of the visceral peritoneum, surgery may include organ resections, such as splenectomy, cholecystectomy, resection of liver capsule, small bowel resection, subtotal colectomy, extraperitoneal anterior rectal resection (and if female combined with hysterectomy and ovariectomy), (subtotal) gastrectomy, hysterectomy, ovariectomy, and urine bladder resection. The extended resection of the organs should only be considered, if the aim of nearly total tumor resection is achievable.

Usually directly after extended CRS, HIPEC is performed for at least 30–90 min depending on the center experiences. The advantage of HIPEC can be explained with a higher concentration of chemotherapy, which might be more effective against tumor cells. However, the treatment itself, also associated with HIPEC is associated with systemic and local toxicity.

Extensive surgery such as complete cytoreductive surgery in huge tumor mass is combined with a higher morbidity. There are a lot of factors which might be responsible for that. There are *not CRS-related factors*, like preoperative chemotherapy, bad condition of the patient expressed by the ECOG or Karnowsky status, renal dysfunction, extent of tumor burden, and others. Evaluated *CRS-related factors* are operation time, blood loss, extent of organ resection, and others. The morbidity has to be separated into factors which are related with surgical and nonsurgical treatment. The most common surgical-related complications are anastomotic leakage, pancreatic fistula, postoperative bleeding, surgical site infections, compartment syndrome, and pleural effusion.

Nonsurgical-related complications have a wider diversification with neurological, hematological (neutropenia, thrombocytopenia), urinary (infections), cardiovascular (rhythmic disorder, infarction, thrombosis), pulmonary (pneumonia, embolism), and renal complications (dysfunction, dialysis).

Although CRS and HIPEC showed a considerable perioperative morbidity of up to 62% and mortality of up to 10%, selected patients significantly benefit from this treatment regarding patient survival and quality of life [1, 2]. However, CRS followed by HIPEC has resulted in promising survival rates with acceptable treatment-related morbidity and mortality [3]. Many retrospective studies showed median overall survival rates >36 months and 5-year survival rates between 30 and 40%. Therefore, CRS and HIPEC is currently considered to be the standard of care in selected patients with colorectal peritoneal metastases in several countries [4].

These tumor-related endpoints, however, are not necessarily validated surrogates for overall survival nor do they translate into significant improvements in the duration and/or quality of survival.

Because of the very aggressive treatment of disseminated disease and the respect to quality of life (QoL) of the patients for their hopefully extended lifetime, the measuring of QoL parameters is important for both, the surgeons and the patients—for the patients to be informed that the future after CRS and HIPEC might be harmful and for the surgeons to be able to inform the patients adequately. Communication and decision-making are important in order to ensure that invasive surgical treatments are not administered to patients who would prefer less aggressive forms of care at the end-of-life.

19.2 Quality of Life (QoL)

Quality of life is a subjective parameter and seems to be very personal to every individual. Nevertheless, there are many approaches to define quality of life to make it measurable and comparable. Quality of life is multidimensional and can be even more meaningful to an individual than overall survival.

McQuellon et al. defined the quality of life as the ability to participate in normal social and physical activities related to the individual health of a person. These questionnaires focus on physical, social, family, functional, and emotional well-being and additional aspects, such as spirituality, family functioning, financial, support resources, psychological resilience, and sexuality [5]. These items mirror the situation of the patient

on the basis of symptoms or other important features of the patient's life.

A different definition of QoL is health-related quality of life (HRQoL), which exists as a concept since the 1980s. It is a multidimensional concept considering both physical and mental health. There are validated instruments to measure the quality of life such as questionnaires following below, e.g., FACT-C, SF-36, or EORTC-QLC C30 [6].

Additionally, the QoL is impaired to the disease itself in most of the cases [7].

19.3 Ways of Measuring Quality of Life

The most common and useful way of measuring QoL of patients are questionnaires. One of the most commonly used is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire score 3.0 (EORTC QLQ-CR30). It contains five functional scales, three symptom scales, a global health status scale (GHS), and six single items for additional symptoms. The score ranges from 0 to 100. A high score means a higher response level, e.g., high healthy status or a high score for symptoms. This may lead to confusion in assessment of the quality of life in patients because a high score does not automatically mean a high quality of life [2]. This questionnaire should be supplemented by modules specific to a tumor site or treatment modality.

Another commonly used questionnaire is the FACT-C (Functional Assessment of Cancer Therapy-Colorectal). This is a specialized and often used version for peritoneal metastases in colorectal cancer consisting of the FACT-G (general) version of 28 items plus 9 items for the colon subscale. The measured items are the physical, functional, social, emotional, and family well-being and the treatment outcome index (TOI). Each item is rated from 0 to 4. The maximum score is 136. A higher score indicates a better quality of life. This questionnaire has its limitations to a defined group of colorectal cancer patients. It emphasizes especially several aspects of quality of daily life [6].

The SF-36 questionnaire (medical outcomes study health survey, short form) includes 36 items and conducts a score ranging from 0 to 100 points. It contains items of physical and emotional functioning, body pain, general and mental health, and vitality. This score is often used for patients with colorectal cancer but can additionally be used for other origins [6].

19.4 Quality of Life in Patients with CRS and HIPEC

CRS and HIPEC is a possible way to treat peritoneal metastases in a (semi-)curative intent. It can be offered to selected patients with peritoneal metastases originating from the stomach, intestine, appendix, and ovaries or patients with pseudomyxoma peritonei or mesothelioma. Due to the multimodal therapy concept of CRS and HIPEC in combination with preoperative and postoperative intravenous chemotherapy, selected patients have a significantly better overall survival and tumor-free survival compared to chemotherapy only. In the initial postoperative phase, the quality of life is reduced and the perioperative morbidity is high, up to 40%. One should consider that quality of life is already reduced through the advanced disease itself. The disease leads to emotional and social stress in most of the cases [2]. However, the number of patients with peritoneal metastases treated with CRS and HIPEC is growing [8].

19.5 Semicurative Intent of CRS and HIPEC

Depending on the underlying primary cancer, the prognosis of disseminated disease with PSM is poor. Therefore, the indication to perform CRS and HIPEC should take the results of QoL parameters into consideration.

Recent investigations have shown that the baseline QoL, before a surgical intervention of an advanced metastatic disease, has a very important impact on the outcome after the surgery and on the coping and surviving of cancer. Also an early

colorectal cancer series has shown that preoperative emotional well-being and a low postoperative anxiety are independent predictors for a long-term survival. But a high TNM state remained an independent predictor for survival [9].

McQuellon et al. evaluated change in the quality of life following CRS and HIPEC in 2001. They observed a decrease in the physical and functional well-being scored from the baseline which improved gradually at 3, 6, and 12 months [5]. Most patients returned to their baseline within 3 months postsurgery and the remaining at 1 year; 74% of the patients resumed at least 50% of their activities. In an evaluation of QoL in 17 patients who had survived 3 years or more, 94% had no limitation in performing moderate physical activity [5]. Functional and physical well-being scores had all improved compared to their baseline.

The largest prospective single-center study by Dodson et al. included 598 patients undergoing CRS and HIPEC and referring to the QoL. Patients with peritoneal metastases treated between 2000 and 2015 were included. Patients answered to different questionnaires such as SF-36 and FACT-C at the postoperative time of 3, 6, 12, and 24 months after operation. The primary tumors were mostly appendiceal cancer (58%) and colorectal cancer (22%). The mortality was significantly associated with age, complications, diabetes, and peritoneal carcinomatosis index (PCI). Most of the attrition of missing was due to other reasons than death, especially in the first 3 months. After the third month, emotional well-being improved significantly and remained better than preoperatively. Social well-being declined. Initially, functional well-being and FACT-C declined at 3 months but returned to baseline after 6 months (Table 19.1) [10].

Chia et al. elucidated peritoneal metastases for colonic origins in a prospective way after 3, 6, and 12 months postoperatively. In this smaller collective study, only 23 patients were investigated. QLQ-C30 and QLQ-CR29 were used as questionnaires. These scores are very simplistic and do not integrate additional symptoms or function scores. The mean PCI was 8. Seventy-six percent (19 patients) underwent CRS and HIPEC without major complications. The 3-year overall survival was 77%. A higher PCI score, a longer duration of surgery, a CC score of 1, the presence of a stoma, and a recurrence were all associated with a poorer QoL at 3 months. Patients who received adjuvant chemotherapy following CRS and HIPEC had lower QLQ-C30 global health status scores after 12 months compared to patients who did not. Age, longer hospital stay, and the presence of a postoperative complication, including the high-grade ones, did not affect the QoL [11]. QoL after CRS and HIPEC improved or returned to baseline in all categories by 6–12 months after surgery. Patient selection is important not only for improved survival but also for improved QoL [11].

Another prospective study showed similar results concerning the decrease of quality of life up to 6 months and a recovery to baseline within 12 months. They included 216 patients in a single-center study. Furthermore, they pointed out that the origin of the cancer does not play the major role for the recovery after 1 year. More important seems to be the multidimensional postoperative care concept with involving psycho-oncologist and resilience for the patients (Table 19.2) [12].

Table 19.1 QoL questionnaires and outcome

Author	Return of questionnaires	QoL (related in percentage to baseline)			
		After 3 months	After 6 months	After 12 months	After 24 months
Tsilimparis et al.	80%	Unknown	95%	95%	101%
Dodson et al.	71%	Unknown	Unknown	Unknown	Unknown
Hamilton et al.	48%	Unknown	92.00%	Unknown	Unknown
Chia et al.	88%	Unknown	Unknown	Unknown	Unknown
Passot et al.	81%	88%	95%	98%	Unknown
Hill et al.	81%	56%	70%	73%	Unknown

Table 19.2 Prospective studies of QoL in PSM

	Number of patients	Questionnaires	Overall survival rate	Tumor entities	Clinical symptoms	Complications	QoL to baseline
Dodson et al.	598	SF-36, FACT-C	1 year 77%	Various	Anxiety, depression	21.70%	6 months
Chia et al.	23	QLQ-C29/30	5 years 58%	Colorectal	Anxiety, depression	76%	6–12 months
Passot et al.	216	GIQLI	1 year 92%	Various	Unknown	42.00%	12 months
Hill et al.	62	FACT-10, SF36	1 year 71%	Colorectal	Depression, pain	48.00%	3–6 months

In agreement to the studies mentioned above are the results of Hill et al.'s another prospective study from America. They investigated 62 patients with peritoneal metastases of different origins using FACT-C, SF-36, and the depression scale CES-D. The recovery times of QoL were nearly the same as Passot et al. and Dodson et al. with an impairment of QoL for the first postoperative 3 months. A recovery near baseline occurred after 12 months. The emotional function recovered earlier, after 6 months. Additionally, they found out that the presence of a stoma did not influence QoL scales. Patients accepted the new situation very quickly and communicated a better QoL than before [13].

Kirby et al. investigated the quality of life of 63 patients with pseudomyxoma peritonei. They focused in their research on physical, emotional, functional, and social well-being. The mean time of surgery was 9–10 h. Seventy-nine percent of these patients stated that they would repeat CRS and HIPEC, if necessary. Symptoms that occurred most were appetite loss, loss of bowel control, and problems with digestion [14].

The improvement of QoL after CRS and HIPEC may result in a mostly bad initial state of the person's health before surgical treatment. Most of the patients suffer from vomiting, nausea, and pain. Offering CRS and HIPEC should consider the prognosis and surgical consideration, not the sex or preoperative QoL [7].

McQuellon et al. mentioned that 74% of the patients reach more than 50% of their normal activity after 6 and 12 months [15]. These patients mostly suffered from problems such as fatigue, appetite loss, financial problems, and future perspective [2].

One big problem is the depressive status of many patients before CRS and HIPEC. In total, 32% of all patients show depressive symptoms at the baseline. They even decrease within the first months after treatment. That's why a complex treatment with a psycho-oncologist and an interdisciplinary team can achieve a big effort [8].

The prenutritional status is even more important for gastric and colorectal cancer than for pseudomyxoma peritonei. Usually, patients are already starting the therapy with a low bodyweight. The prenutritional assessment and improvement are very important for the outcome and QoL, especially for patients with gastric cancer [5]. Nearly all patients lose weight in the early preoperative phase.

Emotional functioning is mainly getting well with and without major complication, because after an operation there is renewed hope. The recovery of social functioning in patients, who suffer from PSM, needs longer time compared to the other QoL items. This is mainly related to disturbed bowel function, e.g., diarrhea [16].

Most of the studies don't differentiate between the primary cancer of peritoneal metastases. The QoL at the beginning of the studies is reported in most of the studies as very bad and mostly related to the disease itself. An advanced gastric cancer may subjectively cause more problems for the patient than a colorectal cancer. Surprisingly, there was no difference in the recovery time of the quality of life in regard to the different tumor entities in some studies after CRS and HIPEC [7].

While CRS and HIPEC achieved good results in survival of patients with peritoneal metastases of different origins, the benefit has to be counterbalanced with the postoperative QoL and the

morbidity and mortality. The usage of scores predicting the QoL after major operations might be very helpful. It is possible to identify predictors for complications and QoL which can be discussed with the patient upfront [8].

There are different scores validated. Some of them were criticized because of being too simplistic. That's why in many studies further symptom or function scores are additionally used [11]. However, just a few studies focusing on the QoL after CRS and HIPEC are prospective, while the majority contains a retrospective study design [11].

Conclusion

In conclusion, many studies showed a drop of quality of life within the first 3 months and a recovery afterwards, especially in emotional and functional well-being. Limitations of these studies were high attrition rates and the inclusion of different primary cancers. The attrition rate is mainly explained by mortality, because of an end-stage disease and incompliance.

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20 New Treatment Modalities for the Management of Peritoneal Metastases

Aditi Bhatt and Akash Mehta

20.1 Introduction

Over the last three decades, the management of peritoneal metastases secondary to gastrointestinal and ovarian malignancies has seen a radical change in the approach. From the predominantly palliative approach in the 1980s with an expected survival of no more than a few months, selected patients with PM experience long-term survival when treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and can even be cured [1]. This combined modality treatment is considered the standard of care for patients with colorectal peritoneal metastases (PM) with limited disease spread, pseudomyxoma peritonei arising from appendiceal primary tumors, and malignant peritoneal mesothelioma [2]. It is under investigation of PM from ovarian and gastric cancer.

However, this treatment can be used only for a highly selected group of patients. Treatment strategies are needed for effective management of patients who are not candidates for this procedure. For colorectal cancer the peritoneal cancer index (PCI) cutoff beyond which CRS and HIPEC is not of clinical benefit is 17–20 [3]. Of these only patients who have a PCI of less than ten can be cured [4]. Moreover, in certain cases (primarily with widespread small bowel involvement), a complete cytoreduction is not possible, irrespective of PCI. While the focus has shifted on preventive strategies, a substantial portion of patients continue to be diagnosed with PM up front. Similarly, in gastric cancer, CRS and HIPEC is ineffective for a PCI of more than 13, and only patients with a PCI of 6 or less can be cured [5, 6]. Secondly, even after CRS and HIPEC, peritoneal recurrence itself is common [7, 8]. In patients with PMP, ovarian cancer, and mesothelioma where there is no PCI cutoff, recurrence rates are more than 50%. Recurrence after complete CRS and HIPEC or other forms of intraperitoneal chemotherapy (IPC) is considered to be a failure of IPC itself [9]. Broadly, strategies to improve outcomes in patients with PM include

- Improving the efficacy of CRS and IPC
- Locoregional therapies for patients who are not candidates for CRS and HIPEC
- New locoregional therapies for all patients with PM
- More efficacious systemic therapies

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This chapter provides an overview of new modalities of locoregional treatment that are being evaluated in the preclinical or clinical phase and have shown promising results for future use in the management of PM.

20.2 Rationale for Locoregional Therapy for Peritoneal Metastases

It was for long believed that peritoneal cancer spread was similar to other distant metastases and was an incurable consequence of intra-abdominal malignancies amenable only to palliative therapies. Peritoneal cancer dissemination has a propensity to remain confined to the peritoneal cavity for short or long periods depending on the site of origin of the tumor, thus making locoregional therapy a plausible approach in these patients [10]. CRS comprises of complete removal of macroscopic disease. It is coupled with intraperitoneal chemotherapy which is usually performed in the operation theatre immediately after tumor removal and uses hyperthermia-hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC acts only on microscopic disease. The penetration of intraperitoneal chemotherapy is only 2–3 mm [11, 12]. An understanding of the pathophysiology of peritoneal cancer spread forms the basis of treatment for peritoneal metastases.

20.3 The Intraperitoneal Route for Chemotherapy Administration

The peritoneum is now considered an organ with structural and protective functions [10, 13]. The peritoneum consists of a single layer of mesothelial cells resting on multiple layers of connective tissue and encloses between its reflections and folds a large space called the peritoneal cavity that lies around major abdominopelvic viscera [14]. The ultrastructure was described in detail by Baron who observed that a layer of mesothelial cells rests on five layers of connective tissue [15]. The total thickness of this membrane is 90 μm. The connective tissue adjacent to the mesothelial layer has few blood vessels, and most of them are found at a distance of 40 μm or more from the surface. One of the main functions of the peritoneum is regulating the transport of fluid and cells from the peritoneal cavity to the extraperitoneal systemic compartment [16]. The mesothelial cells secrete a lubricant comprising of phospholipids and gylcosaminoglycans that ensures smooth gliding between the visceral and peritoneal surfaces that is essential for normal intestinal peristalsis [17]. The mesothelium also plays a major role in host defense within the peritoneal cavity.

20.4 The Peritoneal Transport Barrier

The peritoneum is considered to be an anatomic barrier between the peritoneal cavity and systemic circulation/plasma. However, this plasma-peritoneal barrier does not comprise solely of the physical “peritoneum” but is a complex, three-dimensional structure made up of the peritoneum (mesothelial layer) and the underlying connective tissue that comprises parenchymal and interstitial cells, endothelial lining of the blood vessels and the pericytes around it, and the interstitial matrix (Fig. 20.1) [14]. In animal experiments it has been shown that the clearance of protein from the peritoneal cavity is not proportional to the rise in its blood levels. Some of the protein leaving the peritoneal cavity reaches the blood stream, while the rest of it gets deposited in the interstitial tissue [18, 19]. The rate of protein transfer was quantitatively the same as the rate of fluid transfer from an isotonic solution placed in the cavity. This means that the protein acts as a marker of fluid transport from the peritoneal cavity into the surrounding tissues and implies that the peritoneum is a very loose barrier to albumin and immunoglobulin.

In a study carried out in rodents, complete removal of the peritoneum did not affect the transfer of fluid or solutes from the peritoneal cavity to the interstitial space [20]. Similar findings

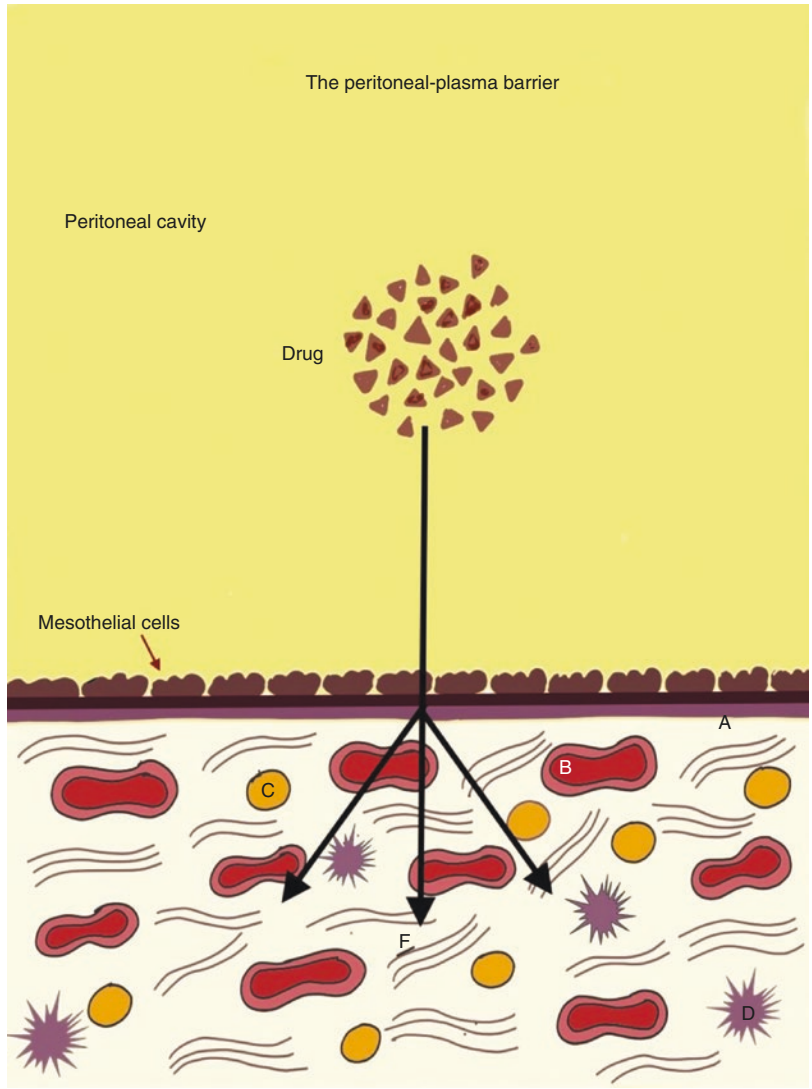

Fig. 20.1 The plasma-peritoneal barrier. The peritoneum comprises of a single layer of mesothelial cells resting on a basement membrane (A) and the underlying interstitial tissue which comprises of blood vessels (B), lymphatic vessels (C), fibroblasts (F), and connective tissue with collagen (F). The peritoneum itself is not a physical barrier to the passage of fluid and solutes. The major resistance to transport is the capillary endothelium and the surrounding cells (Adapted from Ref. [26] with permission)

were noted in patients undergoing total or partial peritonectomy for PM in whom the extent of peritoneal resection did not affect the clearance of mitomycin C from the peritoneal cavity [21]. From these studies, it can be concluded that it is the blood vessels and the surrounding interstitium that are barriers to the transport of solutes and macromolecules and not the anatomic peritoneal lining itself. The volume of intraperitoneal fluid also affects the transport. Hence the term peritoneal fluid-plasma barrier is preferable to "peritoneal-plasma barrier" [21].

20.5 Intraperitoneal Chemotherapy

The peritoneal cavity has been used as a route for drug delivery. Pharmacokinetic studies of the intraperitoneal route of administration of chemotherapeutic agents have demonstrated a protracted local concentration as compared to systemic levels. A distribution model was proposed by Dedrick et al. to explain this phenomenon [22]. The Dedrick model is a two-compartment model of peritoneal transport in which transfer of a drug

from the peritoneal cavity to the blood occurs across a membrane—the peritoneal membrane (now known as the plasma-peritoneal barrier). This transfer is governed by the permeability-area product (PA) which can be calculated by measuring the rate of drug disappearance from the cavity and dividing by the overall concentration difference between the peritoneal cavity and the blood (or plasma).

A simplified mathematical formula describes the transport as follows: rate of mass transfer = PA ($CP-CB$), where PA = permeability area (PA = effective contact area x permeability), CP = concentration in peritoneal cavity, and CB = concentration in the blood [23].

This equation allows calculation of the pharmacokinetic advantage, but it does not predict the penetration of chemotherapeutic drugs into tumor nodules or the surrounding tissues [24]. It does not predict the value of the effective contact area either. It simply describes the transfer between two compartments [23]. However, all these factors are important and have an impact on the efficacy of the intraperitoneal chemotherapy (IPC).

The peritoneal clearance of a drug is inversely proportional to the square root of its molecular weight. This results in a significantly higher concentration in the peritoneal cavity as compared to the plasma after intraperitoneal administration. In the Dedrick model, delayed systemic drug distribution is predictable and dependent on drug diffusivity within the adjacent tissues in the peritoneal cavity and the rate of drug removal from tissue by capillary blood [21]. Low systemic drug concentrations are maintained by a rapid systemic metabolism or excretion by the kidneys and liver. Following the publication by Dedrick in 1978, several studies demonstrated clinical activity in patients including pathologically proven complete responses in patients who had persistent or recurrent disease following systemic chemotherapy [22, 25, 26].

The intraperitoneal route of drug delivery has several pharmacokinetic advantages—it allows the peritoneal tumor deposits to be exposed to significantly higher drug concentrations than those achieved by systemic delivery of the same agents. The drug concentration is important for achieving a therapeutic benefit. Peritoneal tumor deposits are hypoxic and have a poorly developed vasculature which makes targeting these nodules by the systemic route difficult [27]. Any increase in the concentration gradient between the peritoneal compartment and the tumor stroma will theoretically enhance drug delivery. Most chemotherapeutic agents exhibit a steep (near exponential) dose-effect relationship, which is more pronounced in small, rapidly growing tumor deposits [28]. Preclinical data with cisplatin showed an exponential dose-related reduction in survival of human ovarian cancer cells [29]. Also, higher intracellular drug concentrations can partially help to overcome platinum resistance [30]. The activity of cell cycle-independent drugs like alkylating agents and platinum compounds is a function of concentration, while drugs like 5-fluorouracil, gemcitabine, and pemetrexed are time dependent requiring prolonged exposure times [31]. Since approximately 70% of the peritoneum lines the visceral surfaces, the main absorption barrier consists of submesothelial connective and muscle tissue and, ultimately, the endothelial lining of the microvascular network. Transport of drugs from the peritoneal to the vascular compartment occurs mainly via the portal circulation. Moreover, chemotherapeutic drugs administered or absorbed systemically will access the microcirculation of peritoneal nodules and thus act synergistically with the intraperitoneal administered therapy [32].

The two main physical mechanisms of drug transport into tumor tissue are diffusion and convection [33]. For small agents (molecular weight < 6000 daltons), transport occurs mainly by diffusion, which is driven by the concentration gradient. Large solutes, such as proteins diffuse much more slowly, and their transport is typically governed by solvent drag or convection which is driven by the pressure gradient. Conventionally, the pharmacologic efficacy of intraperitoneal chemotherapy regimens is quantified by calculating the area under the curve (AUC) ratio of the intraperitoneal exposure over the AUC of the intravenous exposure. The importance of pharmacodynamic variables was highlighted by Van Der Speeten et al. When the same amount of doxorubicin was administered to patients with

diffuse peritoneal adenomyosis (DPAM) subtype of appendiceal malignancy and those with peritoneal mucinous carcinomatosis (PMCA), the concentration in the DPAM patients was significantly lower than in those with PMCA [21]. The identical pharmacokinetic advantage (expressed as AUC IP/IV ratios) resulted in different drug levels according to the density of the tumor nodules; this highlighted the importance of pharmacodynamic variables like density of tumor nodules, their size, and vascularity. Table 20.1 summarizes the pharmacokinetic and pharmacodynamic variables involved in perioperative intraperitoneal and intravenous chemotherapy.

Several other models have been developed for a better understanding of IP drug delivery [34–36]. Steuperaert et al. developed a three-dimensional computational fluid dynamics (CFD) model for drug penetration in a tumor nodule to study the impact of various factors like vascular normalization therapy, drug diffusivity, the presence of a necrotic core, and tissue permeability on the drug penetration [37]. According to this model, smaller tumors showed better penetration than larger ones, which could be attributed to the lower interstitial fluid pressure in smaller tumors (Fig. 20.2).

Table 20.1 Pharmacokinetic and pharmacodynamic variable in IPC (From Ref. [23] with permission)

Pharmacokinetic variables	Pharmacodynamic variables
Dose	Temperature
Volume	Size of residual tumor nodules
Duration	Density
Carrier solution	Binding
Pressure	Interstitial fluid pressure
Vasoactive agents	Charge
Macromolecular vehicles	Vascularity

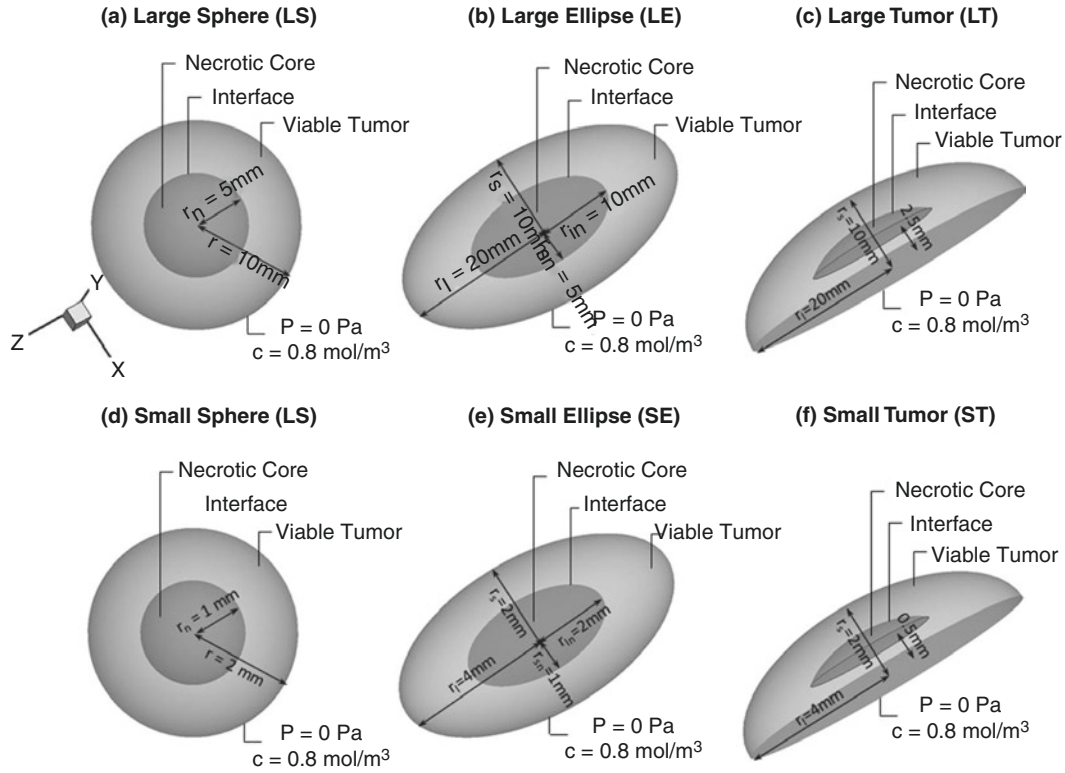

Fig. 20.2 Three-dimensional computational fluid dynamics model. Figure shows the six different geometries used in the model considering that peritoneal tumor nodules have a large variety of shapes and sizes. (**a** and **d**) Geometries of spherical tumor shape comprising two different zones: a necrotic center of radius r_n (darker gray area) and the viable tumor zone. A concentration and pressure boundary condition are applied at the outer edge of the tumor. (**b** and **e**) Geometries of an ellipsoid tumor shape. (**c** and **f**) Geometries of the peritoneal tumor shape (Adapted from Ref. [37] with permission)

Vascular normalization therapy led to large improvements in the depth of penetration of the chemotherapeutic drug into the tumor nodule. This model also demonstrated the importance of selecting the appropriate drug for therapy—not just transport parameters but biological factors like protein binding and depth of penetration also had an impact on the efficacy. During IPC, the diffusive and convective drug transport occurs in different directions: the diffusive transport is directed inward into the tumor, whereas the convective transport is directed outward out of the tumor. The convective force is more in large tumor nodules making the drug penetration in these nodules lower than that in smaller tumors [37]. These experimental studies provide important insights about drug transport and penetration during IPC that are important in selecting drugs and devising protocols for IPC in clinical practice.

Currently there are several methods of administering intraperitoneal chemotherapy in clinical practice. In the perioperative period, hyperthermic intraperitoneal chemotherapy (HIPEC) that is performed immediately after cytoreductive surgery (CRS) in the operation theatre and has the benefit of thermal enhancement is one of the commonly employed methods. Early postoperative intraperitoneal chemotherapy (EPIC) is given for 3–5 days starting from postoperative day 1 and is administered via drainage tubes inserted during surgery. Another method is sequenced intraperitoneal chemotherapy (SIPC) in which an indwelling peritoneal catheter connected to a subcutaneously implanted chamber is used for administering numerous cycles of normothermic chemotherapy over a period of time. Heat itself is cytotoxic to cancer cells and is known to potentiate the action of certain chemotherapeutic agents.

20.6 The Problems with Current Methods of Intraperitoneal Chemotherapy

HIPEC requires dedicated equipment, is expensive, and may not be available at all centers. It is a single time treatment with an exposure time of 30 to 120 min which may not be sufficient to produce the desired therapeutic effect in all cases. The clinical data reporting the benefit of EPIC is lacking, and its current role as the sole method of IPC or in addition to HIPEC remains undefined [38]. It has been associated with higher rates of complications in some studies [39]. SIPC requires an implantable port. There are problems with long-term maintenance of ports and catheter-related problems, such as catheter obstruction, increased risk of infection, and bowel complications [40, 41]. Moreover intraperitoneal adhesions limit the homogenous distribution of the drug.

From the pharmacokinetic perspective, there are two main limitations of IPC—limited penetration of the drugs into tissue and poor exposure of a large proportion of the serosal surface to the drug-containing solution. The solution of these two problems could potentially improve, perhaps dramatically, the efficacy of the procedure [42].

As the basic research to better understand these phenomena continues, new treatment methods have been developed to overcome some of the limitations of IP therapy and for patients who are not candidates for CRS and IPC. These therapies are being evaluated in preclinical or clinical studies. A list of the same is provided in Table 20.2.

Table 20.2 New treatment modalities for PM

Mode of action	Treatment
Enhancing intraperitoneal drug delivery • Increased exposure time • Increasing the IP pressure • Hyperthermia • Reducing the interstitial fluid pressure	• Drug delivery systems • PIPAC, laparoscopic HIPEC • Noninvasive hyperthermia using nanoparticles • Vascular targeting agents and vascular destroying agents
New concepts in intraperitoneal therapy	• Intraperitoneal radioimmunotherapy • Photodynamic therapy
New drugs for intraperitoneal use	• Intraperitoneal immunotherapy • Intraperitoneal monoclonal antibodies • Mucin-lysing agents
New surgical strategies for PM	• PDT for diagnosis of occult disease • Small bowel transplant

20.6.1 Drug Delivery Systems

Pharmacokinetic approaches to increase drug delivery include maximizing the peritoneal/plasma AUC ratio and drug exposure time [43]. HIPEC is performed for 30–120 min depending on the protocol, and this exposure time is considered to be short [43]. With such an exposure time, increasing the concentration gradient does not increase the tissue penetration proportionally. The dose-response curves and their dependency on exposure time have been theoretically modelled by Gardner [44]. These studies as well as in vitro experiments have shown that increasing the drug dose will not always compensate for a shorter exposure time [43]. One of the main challenges of IP therapy is to maintain a high intraperitoneal drug concentration to provide a sufficient concentration gradient between the peritoneal cavity and tumor tissue that will drive the drug into the tissue by diffusion. Small molecules do not remain in the peritoneal cavity long enough to have a therapeutic effect as they are rapidly absorbed by the capillaries into the systemic circulation [45].

Inadequate drug delivery to solid tumors is a major cause of IP treatment failure. Most of the drugs used for IPC are intravenous preparations, and preparations for IP use are not available [43]. A number of drug delivery systems (DDSs) that increase the retention time of chemotherapeutic drugs in the peritoneal cavity have been developed and tested in preclinical studies. The rationale behind the additional effect of a carrier includes an increase in intraperitoneal chemotherapy concentration for a longer duration of time without additional systemic toxicity [46]. In experimental settings, nanoparticles, micelles, microspheres, and hydrogels have been used as carriers in the treatment of peritoneal metastasis [47, 48].

All experimental studies used mice as test animals, most commonly BALB/c mice. Comprehensive reviews on the various DDSs that have been tested in animal peritoneal cancer models have been published by de Hingh et al. and Vervaet et al. [9, 43]. A description of the various DDSs and the results of various experimental studies are described below.

20.6.1.1 Hydrogels

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers [49]. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. They have unique physical properties like a highly porous structure and an affinity for the aqueous environment in which they are swollen. Drugs can be loaded into the gel matrix of the hydrogels because of their porosity; subsequent diffusion into the tissues depends on the diffusion coefficient of the drug molecule itself. Hydrogels have many pharmacokinetic benefits. They function as depot formulations from which the drugs are released slowly and over a prolonged period of time, maintaining a high concentration in the local tissues. Hydrogels are also generally highly biocompatible, as reflected in their successful use in the peritoneum and other sites in vivo [50]. Thermosensitive hydrogels used for intraperitoneal therapy have been widely studied [51]. The ideal thermosensitive hydrogels remain in liquid form at low temperatures turning into a gel at body temperature of 37 degrees Celsius [52]. The delivery of chemotherapeutic agents with thermosensitive hydrogels can prolong the exposure time of the peritoneal surfaces to the drug and reduce systemic toxicity [53]. However, drugs loaded directly into hydrogels are often released rapidly from the hydrogels due to the large size of pores and the high water content. The quantity and homogeneity of hydrophobic drug loading into hydrogels may be limited [49, 54]. Liu et al. used a biodegradable DDS consisting of camptothecin (CPT)-loaded polymeric microspheres in a thermosensitive poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCEC) hydrogel [54]. Combining chemotherapy with microspheres and hydrogel increased survival significantly and showed a dramatically decreased number and weight of tumor nodules indicating that not only growth was inhibited but also the process of metastasizing itself was inhibited. The experimental combination was more effective

Table 20.3 Outcomes of using hydrogels as DDSs in the treatment of PM in animal models

Year (ref)	Species	Tumor line	Treatment	DDS	Days after inoculation	Time to death (days)	Result
2013 [55]	Mouse, BALB/c,	CT26 IP 2 × 105	Camptothecin 4 mg/kg	PCL-PEG-PCL microsphere hydrogel	7	50	Tumor number + weight decrease, hydrogel increased survival
2010 [56]	Mouse, BALB/c,	CT26 IP 2 × 105	5FU 25 mg/kg	PEG-PCL-PEG copolymer hydrogel	5	20	Tumor number + weight decrease, hydrogel increased survival
2007 [57]	Mouse, BALB/c, male	CT26/Luc IP 1 × 105	ED-catalase 0.1 mg/mg	Acidic gelatin hydrogel	0	21	Retardation of tumor growth, increased survival
2013 [58]	Mouse, BALB/ female	MKN45P gastric cancer	Cisplatin 1 mg/m^2	In situ cross-linkable hyaluronic acid gel	7, 14, and 21	28	Decreased tumor weight
2012 [59]	Mouse, BALB/c, male	TMK1 human gastric cancer IP 1 × 107	Docetaxel 10 mg/kg	Linoleic acid-incorporated poloxamer hydrogel	7	28	Reduced tumor cell survival, number decreases, increased survival
2012 [60]	Mouse, BALB/c, male	HSC44Luc human gastric cancer MKN45P	Paclitaxel, 15 mg/kg	Biodegradable thermosensitive hydrogel	3	–	Quantitative photon count decrease
2012 [61]	Mouse, euthymic nu/nu, female	SKOV-3 ovarian cancer	Paclitaxel, 30 mg/kg	Hyaluronic acid-based hydrogel	14	28	IP retention of PTX increased, no difference in reduction of the tumor

than microspheres loaded with camptothecin or free camptothecin [54]. The experimental studies that used hydrogel, the tumor cell lines used to induce carcinomatosis, and their outcomes are listed in Table 20.3.

20.6.1.2 Microspheres

Microspheres (>1 μm) can be designed to release the drug gradually over time using a wide variety of biodegradable and biocompatible polymeric substances. The retention time and peritoneal concentration of MS is higher than that of nanoparticles or micelles [62]. Therefore, microspheres are a suitable DDS for intraperitoneal administration. The problem with microsphere is the short retention time in the peritoneal cavity due their size especially when it is less than 8 μm [63]. The various biodegradable substances used for making microspheres are poly(lactic-*co*-glycolic) acid (PLGA) used for cisplatin- or paclitaxel-containing microspheres, phosphoester polymer matrix for paclitaxel microspheres, and the triblock poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL) copolymer for camptothecin-loaded microspheres [63–65]. Cisplatin is released from the PLGA matrix by diffusion for up to 14 days after IP administration and has a pharmacokinetic advantage over systemic injection in animal models. The paclitaxel-loaded polyphosphoester polymer matrix microspheres (Paclimer) measure 53 μm and release paclitaxel over a period of 8 weeks. Although these formulations are retained in the peritoneal cavity for longer durations, they are

Table 20.4 Outcomes of using microspheres as DDSs in the treatment of PM in animal models

Year (ref)	Species	Tumor line	Treatment	DDS	Days after inoculation	Time to death (days)	Result
2013 [67]	Mouse, BALB/c, male	CT26 IP 1 × 106	Cisplatin 2 mg/ml	Gelatin microspheres	1 or 4	Survival	Decreased nephron and hematotoxicity, decreased tumor weight, and increased survival
1996 [68]	Mouse, BDF1, male	B-16 PC melanoma IP	5FU 100–400 mg/kg	Microspheres	4	150	Increased survival

known to induce inflammatory reactions and adhesions [66]. The outcomes of experimental studies in which microspheres were used as drug delivery systems are detailed in Table 20.4.

20.6.1.3 Nanoparticles

Nanoparticles are smaller than microspheres and hence induce less inflammation and adhesions [69]. However, due to their small size, they also undergo rapid clearance from the peritoneal cavity. To overcome this drawback, nanoparticles that can undergo activation by triggers like pH, temperature, light, and ultrasound are being developed and investigated.

Nanoparticles can bypass drug efflux pumps and thus achieve a higher concentration in multidrug-resistant cells compared to unformulated-free drugs [70, 71]. For IPC, paclitaxel-loaded pH-responsive nanoparticles were developed which were designed to deliver paclitaxel intracellularly after endocytosis. These nanoparticles react to an endosomal pH (pH ≤5) and increase in volume to release their drug load. On intraperitoneal injection in mice with induced peritoneal carcinomatosis, these nanoparticles remain in the peritoneal cavity for 7 days [72].

Epothilone B, a microtubule-stabilizing agent, is many times more effective than paclitaxel, but clinical use is limited by side effects. In an experimental study, this drug was encapsulated into bioadhesive nanoparticles with the goal of releasing the drug only in the proximity of the tumor nodules, thus maintaining its concentration at the site of action and limiting systemic exposure and toxicity [73]. This study showed a higher therapeutic activity and limited toxicity by using epothilone B with bioadhesive nanoparticles in mice with peritoneal carcinomatosis from serous ovarian cancer or uterine serous carcinoma compared to nonadhesive nanoparticles loaded with epothilone B or carrier-free epothilone B [73]. Mesoporous silica nanoparticles (MSNs) containing paclitaxel for intraperitoneal delivery were developed to exploit the tumor-specific accumulation of these nanocarriers after intraperitoneal injection and the slow release of paclitaxel from the MSNs. A 3.5-fold increase in tumor drug uptake was observed for the paclitaxel-loaded MSNs compared with free paclitaxel [74]. Vassileva et al. implanted paclitaxel-loaded nanoparticles in mice inoculated with intraperitoneal ovarian cancer [75]. Mice that were treated with these nanoparticles on day 7 after inoculation had a complete tumor inhibition. This DDS allowed a higher paclitaxel dosage with no observable toxicities.

Reddy et al. used etoposide in a mouse model in which PC was induced using intraperitoneally administered Dalton's lymphoma cells [76]. Incorporation of etoposide, a topoisomerase inhibitor, in a solid lipid nanoparticle had a significant effect on the cell cycle, cytogenetic damage, and survival compared to etoposide or nanoparticles alone. Another study showed prolonged retention of PTX (paclitaxel)-loaded amphiphilic copolymer (PECT, poly (e-caprolactone-co-1,4,8-trioxa [4.6] spiro-9-undecanone)-poly(ethylene glycol)-poly(e-caprolactone-co-1,4,8-trioxa [4.6]spiro-9-undecanone)) nanoparticles and antitumor activity as compared to free paclitaxel (Fig. 20.3) [78].

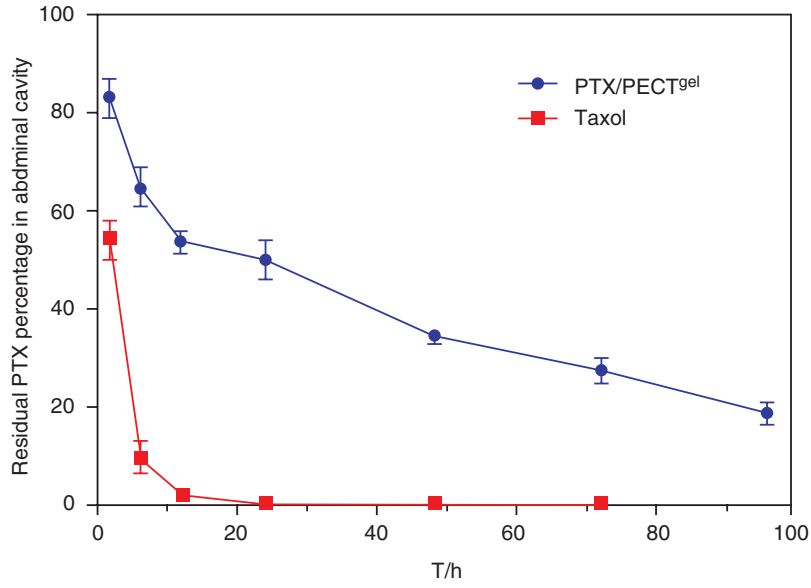

Fig. 20.3 Prolonged retention of PTX/PECT gel as compared to paclitaxel alone in an experimental study (From ref [78] with permission)

Table 20.5 Outcomes of using nanoparticles as DDSs in the treatment of PM in animal models

Year (ref)	Species	Tumor line	Treatment	DDS	Days after inoculation	Time to death (days)	Result
2007 [75]	Mouse, CD-1, female	SKOV-3 ovarian cancer IP 1 × 107	Paclitaxel 280 mg/ kg/ week	Polylactide nanoparticles	7 or 14	28 or end point	Induction of apoptosis, complete tumor inhibition
2005 [76]	Mouse, Balb/C, both genders	Dalton lymphoma IP 5 × 106	Etoposide 30 mg/kg	Solid lipid nanoparticles	6	Survival	Induction of apoptosis increased survival
2012 [77]	Mouse, BALB/c, female	MKN45P gastric cancer IP 2 × 106 + SC 1 × 106	Paclitaxel 40 mg/kg	Micellar nanoparticle	7, 14, and 21	19	Decreased number and weight of tumors, enhanced penetration in nodules, and longer retention in circulation

The outcomes of using nanoparticles as DDSs in the treatment of PM in animal models are described in Table 20.5.

20.6.1.4 Liposomes

Liposomes measure 100–1000 nm leading to a fast clearance from the peritoneal cavity. Their lipid composition, surface charge, and properties can be altered according to the therapeutic requirement. Negatively charged liposomes are more rapidly absorbed than those that are positively charged since the peritoneal surface itself is negatively charged, thus attracting the positively charged liposomes. The uptake by macrophages is also less [79]. Changing the type of phospholipid (the main building block of liposomes) has no effect on the retention time in the abdominal cavity, whereas the incorporation of polyethylene glycol in the phospholipid membrane showed a 30% higher peritoneal retention

which was largely due to a decreased uptake by the macrophages [79]. An experimental study used pegylated liposomes as a carrier for 111In-labelled vinorelbine in a colorectal cancer ascites model [80]. They achieved higher areas under the curve (AUCs) in ascites and tumor in the intraperitoneally administrated group compared to the intravenous group.

20.6.1.5 Micelles

Paclitaxel has been formulated using Cremophor EL (i.e., a polyethoxylated castor oil surfactant), to produce a micellar form of paclitaxel IP treatment of ovarian cancer. This formulation showed a longer residence time in the abdominal cavity compared to free unformulated paclitaxel [81]. Encapsulation of paclitaxel in this way is an effective way of prolonging its retention in the peritoneal cavity and reducing hypersensitivity reactions and neurotoxicity [82]. Another formulation in which nanocrystalline paclitaxel stabilized by Pluronic F127 (i.e., polyethylene oxide-polypropylene oxide (PEO-PPO) block copolymer) has also been tested in animals by intraperitoneal administration [83]. Similarly, docetaxel has also been used with a carrier leading to a prolonged retention time in the peritoneal cavity and AUC values similar to paclitaxel [84, 85].

20.6.1.6 Implantable Systems

Implantable systems were developed for IP treatment of ovarian cancer. One example is an implant that is composed of paclitaxel-loaded poly-D, L-lactide, and poly(lactide)-block-poly (ethylene glycol) (PLA-b-PEG) particles dispersed throughout a chitosan egg-phosphatidylcholine matrix. This formulation provides a sustained and localized release of 1% PTX per day in mice over a period of 3 months [86, 87]. These implants have a higher efficacy and are less toxic and more biocompatible than paclitaxel. Although the implantable systems have promising results, the biggest issue for using those systems is the need for surgical expertise to implant the system.

DDS application does not require any additional machinery and is less time-consuming since no perfusion or heating is required [9]. This makes it possible to use DDSs in the setting of an unexpected finding of PM in nonspecialized centers.

These systems can also be used for the prevention of peritoneal spread after resection of primary gastrointestinal tumors or application of DDSs in the treatment of malignant ascites [88, 89].

There are also several drawbacks in the studies evaluating these DDSs. In most of these studies, the choice and dose of the chemotherapeutic agents was random though it has a significant impact on the treatment outcomes [9]. Most of these experimental studies are performed without the use of hyperthermia which can potentiate the action of chemotherapeutic drugs. In some of these studies, the comparison is made with systemic chemotherapy agents [9]. Moreover, CRS was not performed which is an essential component of curative treatment of PM. In contrast, up to 25% of animal models evaluating standard intraperitoneal chemotherapy involved CRS [9, 90, 91]. This makes a comparison of outcomes impossible.

The advantages and disadvantages of each DDS are described in Table 20.6.

Currently, the use of DDSs is experimental. DDSs are being evaluated in preclinical studies for over a decade now. The formulations have been undergoing constant refinement. There are no studies reporting the use of these therapies in clinical practice, and though the experimental data is promising, further studies are needed before these therapies can be used in clinical practice. Moreover, none of the preclinical studies compared DDSs directly with HIPEC, which is the current standard of care in intraperitoneal chemotherapy.

20.6.2 Increased Intra-Abdominal Pressure

By counterbalancing tumor interstitial and capillary pressure, intra-abdominal pressure increases the depth of penetration of chemotherapeutic drugs in small peritoneal tumor nodules left behind in case of incomplete cytoreduction, thereby potentiating their cytotoxic effect [91, 92].

Table 20.6 Advantages and disadvantages of various drug delivery systems for intraperitoneal chemotherapy (Adapted from Ref. [43] with permission)

Drug delivery system	Advantages	Disadvantages
Hydrogels	Biocompatible, thermosensitive, prolonged retention time	Risk of adhesions
Microspheres	Prolonged retention time	Limited tumor penetration, risk of peritoneal adhesions
Nanoparticles	Small size, passive targeting, avoiding MDR, lower incidence of peritoneal adhesions	Rapid clearance from the peritoneal cavity
Liposomes	Similar to nanoparticles, active targeting by varying parameters	Similar to nanoparticles
Micelles	Prolonged retention time	Increase systemic toxicity
Implantable systems	Prolonged retention time Localized and sustained drug delivery Lower systemic toxicity Prevention of peritoneal adhesions	Invasive Surgical expertise

Dedrick et al. postulated that the penetration distance is equal to the square root of the ratio of the tissue diffusivity and the rate constant for drug removal from the tissue [42]. The tissue diffusivity is a property of the interstitium and can be altered. In animal experiments it has been shown that when intra-abdominal pressure is raised, there is increased accumulation and antitumor effect of intraperitoneal cisplatin, oxaliplatin, and doxorubicin [21, 93, 94]. Based on the above findings, it has been suggested that the closed technique of HIPEC may have a benefit over the open method in a study carried out in pigs. Facy et al. reported no benefit of the closed technique of HIPEC though it was easier

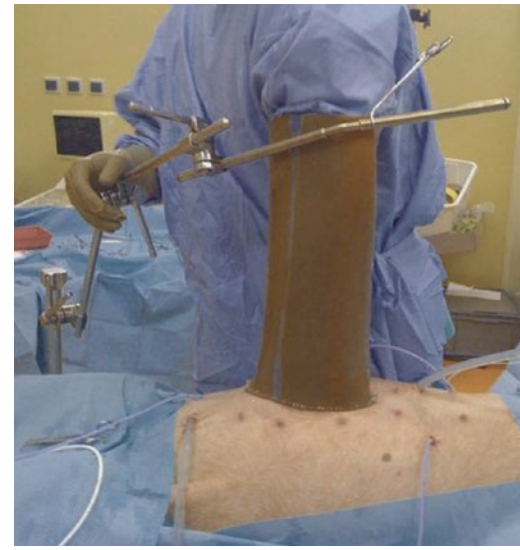

Fig. 20.4 Open high-pressure HIPEC (25 cm H_2O) in a pig model. After insertion of the thermal probes (T) and the inflow (IF) and outflow (OF) catheters, a 40 cm latex expander (LE) is stapled to the edge of the incision. The abdomen and the expander are filled in with perfusate to 25 cm above the laparotomy. According to the principle of Pascal, the pressure in the abdominal cavity is at least equal to the level of the liquid (25 cm) (From reference [96] with permission)

to achieve a high intra-abdominal pressure [95]. In another study, they created an intra-abdominal pressure of 25 cm H_2O using a water column in the open technique as well (Fig. 20.4) [96]. A raised IAP led to an increase in the tissue concentration of oxaliplatin, but there was no increase in the depth of penetration. There was no benefit of increasing the IAP to 40 cm H_2O which had hemodynamic consequences. The clinical benefit of this strategy remains to be proven.

Two new treatments/strategies that employ a raised intra-abdominal pressure for increasing the efficacy of IPC are described here.

20.6.2.1 PIPAC

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel approach to deliver IP chemotherapy to patients with PM.

Background, Rationale, and Preclinical Data

The concept of a therapeutic pneumoperitoneum was introduced in 2000 by Marc Reymond and colleagues who developed a micropump suitable for minimally invasive surgical procedures in which microdroplets of the drug could be distributed in the carbon dioxide pneumoperitoneum, creating a "therapeutic capnoperitoneum" [97]. In vitro, the pump created aerosols from various aqueous solutions including those of chemotherapeutic agents. The size of the microdroplets was optimized to prevent visual artifacts. In an animal model, this therapeutic capnoperitoneum was created during a sigmoid resection and showed drug distribution over the entire peritoneal surface. The aerosol was produced by piezoelectric crystals stimulating three microperforated silicon chips. A feedback system regulated the amount of drug delivery depending on the effective gas flow. In vitro, the micropump was shown to be able to aerosolize various aqueous and ethanol solutions, including cytostatic and bacteriostatic drugs and adhesion-modulating agents. However, the function of the micropump was limited in vivo because of water condensation on the surface of the chips, so that further development was abandoned. Subsequently, the same investigators developed a spraying device, similar to a nebulizer that consisted of an injector, a line, and a nozzle and used mechanical pressure [98]. It could be introduced through a trocar. In an experimental study, it showed a more even distribution of methylene blue and better tissue uptake as compared to simple lavage. The distribution to areas like the unexposed part of the stomach and the cecum, surfaces of the small and large intestines, and undersurfaces of the diaphragm which often remained untouched by simple peritoneal lavage was superior and uniform in this study. The use of a nebulizer laparoscopically has been described by other investigators for different purposes like postoperative pain control and intraperitoneal tumor control [99, 100].

In a review on the therapeutic used of capnoperitoneum, Canis et al. stated that this strategy was promising for development of future therapies and could be considered a "revolution in laparoscopic surgery" [98, 101].

In a proof of principle study, a nontoxic therapeutic agent (Dbait) was aerosolized into a box containing diseased human peritoneum under a pressure of 12 mmHg CO_2 [102]. Dbait (noncoding DNA fragments) acts through jamming DNA damage sensing and signalling, ultimately inhibiting DNA repair system of cancer cells. Dbait was coupled to cholesterol molecules to facilitate intracellular uptake and to cyanine (Cy5) to allow detection by fluorescence. When compared to conventional lavage, uptake by tumor tissue up to a depth of 1 mm was seen in the therapeutic capnoperitoneum group and was not seen in the lavage group. Intranuclear phosphorylation of H2AX was seen in the nebulized sample and no activity in the lavage sample. Detection of histone gamma-H2AX (phosphorylated H2AX) indicated activation of DNA-dependent protein kinase (DNA-PK) by Dbait, which has been shown to be the key step for sensitization to genotoxic therapy [102].

Nebulization of the molecule was significantly more effective than conventional lavage.

The authors concluded that proof of principle supported the need for clinical studies applying therapeutic capnoperitoneum together with Dbait for treating peritoneal metastases [102].

Pharmacokinetic Advantages of PIPAC

The term pressurized intraperitoneal aerosol chemotherapy (PIPAC) was coined for this therapy which combined the principles of a "therapeutic capnoperitoneum" with that of aerosolized chemotherapy [103]. Instead of distributing the chemotherapeutic substance in the form of a liquid solution into the abdomen, the drug is nebulized with carbon dioxide to create an aerosol. Aerosols consist of two phases: a liquid phase (droplets) and a gaseous phase; if the droplet size is small, the aerosol behaves like a gas which has a more homogenous distributions and can lead to a more even drug concentration in different areas of the abdominal cavity. Parameters, such as composition, temperature, pressure, and humidity, of the gas are well defined [98].

The second advantage of PIPAC is the elevated intra-abdominal pressure during the procedure which creates an artificial gradient between the

intraperitoneal and extraperitoneal spaces, thus enhancing the diffusion of liquids, solutes, and macromolecules across the peritoneum. It also reduces the interstitial fluid pressure that forms a major barrier to drug uptake by solid tumors and leads to drug resistance [104].

Thus, PIPAC overcomes several limitations of the commonly used methods of intraperitoneal chemotherapy.

Technique of PIPAC

The technique of PIPAC first described by Marc Raymond and collaborators is as follows: a capnoperitoneum of 12 mmHg at 37 degrees Celsius is created, and two balloon trocars are applied [105]. A laparoscopic evaluation is performed and the PCI is determined. Representative areas are biopsied and ascites is drained. A biopsy of specific areas can be done for response evaluation in the subsequent procedures, and areas of suspicion can also be biopsied. A nebulizer is connected to a high-pressure injector and inserted into the abdomen through a trocar (Fig. 20.4). A pressurized aerosol containing cisplatin at a dose of 7.5 mg/m^2 body surface in 150 ml NaCl 0.9% is administered immediately followed by doxorubicin 1.5 mg/m^2 in 50 ml NaCl 0.9% for gastric PM, ovarian PM, and peritoneal mesothelioma (Fig. 20.5). For colorectal PM and appendiceal tumor, oxaliplatin (92 mg/m^2) is used. The system is kept in this steady-state for 30 min (application time). The toxic aerosol is then removed through a closed system. The trocars are removed and the wounds repaired.

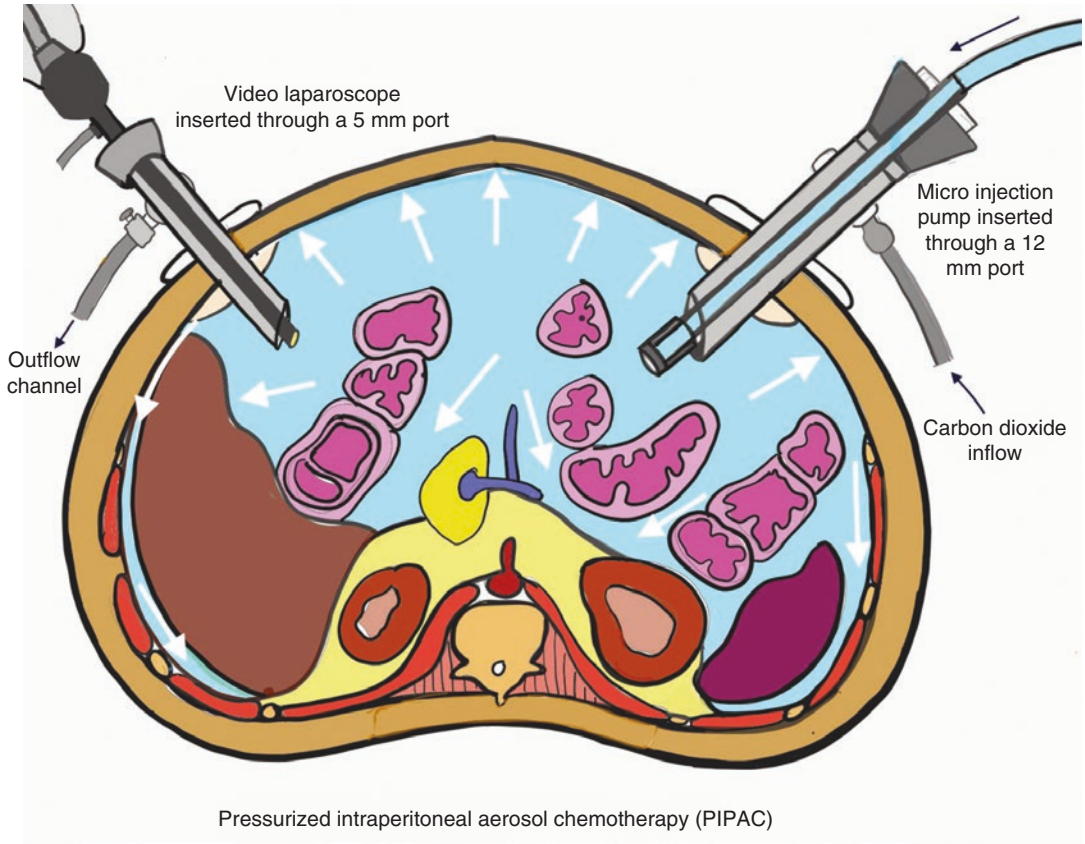

Fig. 20.5 Pressurized intraperitoneal aerosol chemotherapy. A microinjection pump is used to aerosolize the chemotherapy solution that is administered intraperitoneally in the setting of a carbon dioxide pneumoperitoneum maintaining an intra-abdominal pressure of 12 mm of Hg for 30 min (Adapted from reference [105] with permission)

Electrostatic PIPAC

Kakchekeeva et al. have introduced electrostatic PIPAC (ePIPAC), proposing that electrostatic charging the aerosol particles may further enhance the pharmacologic properties of PIPAC [106]. The system used for electrostatic precipitation integrates the following components: a generator unit (voltage 7500–9500 V, current ≤10 μA), an active cable that charges the aerosol, and a return electrode with a patient return plate. A stream of electrons is emitted by the generator, creates negative gas ions which collide with particulate matter and pass on the negative charge. The return electrode confers a weak positive charge on the subject, which results in the electrostatic attraction of the negatively charged aerosol particles to the tissue surfaces of the contained space—that is, the peritoneum [106].

The performance and safety of this equipment has been demonstrated in bench studies, preclinical testing, and clinical testing, including a clinical study on 30 patients undergoing laparoscopic cholecystectomy [107].

They performed a comparative study of PIPAC and ePIPAC assessing the pharmacologic properties using an in vivo porcine model which showed that ePIPAC allowed a more efficient drug uptake as a result of which a lowering of the drug dose and a shorter application time was possible with ePIPAC. The tumor drug concentration with ePIPAC was ten times the concentration obtained with PIPAC.

Current Clinical Evidence

In the first report of safety and efficacy, in which ten PIPAC procedures were performed in three patients, the plasma concentration-time profile analysis of PIPAC was favorable [105]. The nuclear presence of doxorubicin was documented throughout the peritoneum, reaching a high local concentration (≤4.1 μmol/g) while maintaining a low plasma concentration (4.0–6.2 ng/ml). PIPAC required only 1/10 of the doxorubicin dose to achieve a higher tumor concentration (0.03–4.1 μmol/g) than HIPEC (0.02 μmol/g). In contrast, systemic availability of doxorubicin after PIPAC and HIPEC was equal as indicated by the approximately ten times lower maximal plasma concentration after PIPAC.

Two patients showed a complete and one a partial histological remission. Mean survival after the first PIPAC was 288 days. Moreover, in contrast to HIPEC, PIPAC was very well tolerated, and the only severe adverse effect observed was a bowel perforation after CRS.

Most of the published reports are case reports, prospective and retrospective case series, and a II trial. Tempfer et al. reported outcomes in a series of 18 women with PM from recurrent ovarian cancer treated with multiple sessions of PIPAC performed at 4–6-week intervals using doxorubicin 1.5 mg/m^2 and cisplatin 7.5 mg/m^2 [108]. Thirty-four PIPAC procedures were performed in 18 women, of which 8 underwent CRS before PIPAC. Eight women who had more than one PIPAC were eligible for response evaluation. In eight women who had more than one procedure, response evaluation was possible of which one had complete remission, two had partial remission, and three others had stable disease. Median follow-up was 192 days (range 13–639 days). Cumulative survival after 400 days was 62% and mean actuarial survival time was 442 days. On multivariate analysis, patient age (<75 vs. >75 years), serum CA-125 (<1000 vs. >1000 U/mL), and the presence of ascites (yes vs. no) did not have an impact on response to therapy. 12/18 patients had mild abdominal pain, fever, and/or elevated acute phase proteins such as C-reactive protein (CRP). Of importance was that five women had CTCAE grade 3–4 events with four of them potentially related to the PIPAC procedure and three of these occurred in women who had CRS with PIPAC. The results of this series indicate that PIPAC has activity in women with recurrent, platinum-resistant ovarian cancer and should not be combined with CRS.

There are case reports of an objective response in a patient with recurrent pseudomyxoma peritonei of appendiceal origin and in an octogenarian with advanced ovarian cancer treated with PIPAC alone [109, 110].

De Simone et al. reported their experience with 40 procedures performed in 14 patients [111]. Most of the patients received systemic

chemotherapy in addition to PIPAC, and there was no significant hepatic or renal toxicity of this combined therapy. They reported good symptom control in patients who had symptomatic ascites and subacute intestinal obstruction. The use of systemic therapy permitted the application of PIPAC in patients with retroperitoneal lymphadenopathy and/or extra-abdominal metastases who were symptomatic from PM. They suggested that dose-finding studies were needed to determine ideal dose, and this strategy could have a role in standard frontline therapy for PM [111].

In a phase II trial evaluating the role of PIPAC in patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer, of the 64 patients enrolled, 17% could not undergo PIPAC due to laparoscopic nonaccess. Sixty-two percent of the patients had an objective tumor response—3 had a partial response and 30 patients had stable disease. Thirty-four patients could undergo all three PIPAC sessions in accordance with the study protocol. Tumor regression on histology and peritoneal cancer index (PCI) improvement were observed in 26/34 (76%) and in 26/34 (76%) patients who underwent all 3 PIPACs. There were no treatment-related deaths [112]. In addition, EORTC QLQ-30 global physical health scores, nausea/vomiting, appetite loss, diarrhea, and constipation improved during therapy. The mean time to progression was 144 days. The authors concluded that further evaluation as an alternative to or in addition to systemic therapy as a palliative option is needed in clinical trials.

Reymond et al. evaluated the role of PIPAC in gastric PM retrospectively [113]. Sixty PIPAC were applied in 24 consecutive patients with PM from gastric cancer. Sixty-seven percent of patients had previous surgery and 79% previous platinum-based systemic chemotherapy. Mean PCI was 16 ± 10 and 18/24 patients had tumors with signet-ring cells. Cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2 were given for 30 min at 37 °C and 12 mmHg at 6-week intervals. Median follow-up was 248 days (range 105–748), and median survival time was 15.4 months. Seventeen patients had >one PIPAC. Objective tumor response was documented in half of the patients after PIPAC, including complete histological regression in six patients. This study showed that there was a benefit of PIPAC in patients with recurrent platinum-resistant gastric PM, and it needed further prospective evaluation. Though the selection criteria for PIPAC could not be defined based on this study, the authors suggested using PIPAC soon after development of recurrence would be most beneficial [113].

In a retrospective study of 48 PIPAC procedures performed in 17 patients with colorectal PM, all patients had previously undergone surgery, and 16 had undergone previous lines of systemic chemotherapy; objective tumor responses were observed in 12/17 patients (71%) [114]. The mean PCI was 16 ± 10. PIPAC was performed using oxaliplatin (92 mg/m^2) repeated every 6 weeks at 37 °C and 12 mmHg for 30 min. There were no intraoperative complications. The mean number of PIPAC administrations per patient was 2.8 (minimum 1, maximum 6). Postoperative adverse events (CTCAE level 3) were observed in four patients (23%), no CTCAE level 4 adverse events were reported. The hospital mortality was zero, and the overall responses were as follows: complete pathological response (n = 7), major response (n = 4), partial response (n = 1), no response (n = 2), and not eligible (n = 3). The mean survival after first PIPAC was 15.7 months. This study showed that PIPAC with oxaliplatin could induce regression of pretreated colorectal PM and needed further evaluation in prospective studies [114].

In some patients who are not candidates for CRS and HIPEC up front, PIPAC could be used as neoadjuvant therapy to reduce the tumor burden. Reymond et al. reported their institutional experience of 406 patients who had undergone 961 PIPAC procedures. Twenty-one patients underwent a subsequent CRS and HIPEC [115]. Twelve of these patients were candidates for the procedure even without the use of PIPAC; nine patients who were initially not candidates for complete CRS experienced significant down staging making them candidates for CRS and HIPEC. Most of these patients had extensive small bowel involvement precluding a complete cytoreduction up front. In these nine patients,

an objective tumor regression was observed after repeated PIPAC (mean number of cycles 3.5 ± 0.9). Notably, these patients required at least 4 and even up to 6 months for the tumor to become resectable. Six out of these nine patients had colorectal primaries. This early data indicates that the use of PIPAC as neoadjuvant strategy is promising and should be further evaluated prospectively. The advantages in this setting are that it can be combined with systemic therapy, and the 6-week interval between two therapeutic sessions allows effects of both local and systemic therapies to be evaluated.

Toxicity

Toxicity data related to PIPAC have also been published. During PIPAC, only about 10% of a usual systemic drug dose is applied into the abdomen. This dose was in proportion to that used for HIPEC and, considering the pharmacokinetic differences, one tenth of the dose used for HIPEC [116]. The systemic drug concentration is minimal, about 1% of a systemic dose or 5% of a HIPEC dose. Apart from the dose used, the potential for complications is due to the hemodynamic changes, use of intra-abdominal pressure application directly on the surface of organs having the potential for local toxicity. Patients may have chemical peritonitis leading to abdominal discomfort and a rise in C-reactive protein.

In the first report of 3 patients who had undergone 8 PIPAC procedures, Reymond et al. observed no cumulative toxicity after repeated PIPAC application at 4-week intervals. The preoperative mean serum creatinine level was not increased, as compared with the reference value before the first PIPAC which excluded cumulative nephrotoxicity. A similar pattern was observed for liver toxicity: levels of transaminases and bilirubin did not increase significantly and returned to normal within a few days after each PIPAC. There was no cumulative toxicity [116].

In another report of 158 procedures performed in 91 patients, Reymond et al. reported a mortality rate of 3.3% ($n = 3$) in 91 end-stage patients or 1.9% in 158 PIPAC procedures. Two deaths were in relationship with PIPAC (two iatrogenic bowel injuries during laparoscopic access) and one because of disease progression (small bowel obstruction, refractory ascites). One (1%) CTCAE 4 adverse event (anaphylactic shock after intraoperative metamizol injection) and 8 (8.8%) CTCAE 3 adverse events were observed [117].

Robella et al. reported no major morbidity in 40 PIPAC procedures performed in 14 patients. CTCAE grades 1 and 2 were observed after 6 and 8 procedures, respectively, for abdominal pain and nausea. Renal and hepatic functions were not impaired; no cumulative renal toxicity was observed after repeated PIPAC procedures in association with systemic chemotherapy [111].

Some complications that can arise are trocar site hernias, bowel access lesions, subcutaneous toxic emphysema, small bowel obstruction, port site metastasis, and therapy-resistant ascites. At least some of these, like bowel access lesions, subcutaneous toxic emphysema, and trocar site hernias, can be avoided by the use of proper surgical technique.

Quality of Life

Worldwide the experience with PIPAC is preliminary. PIPAC has been used for patients who are heavily pretreated and symptomatic from their PM. There is a subgroup of patients that have a good performance status despite their extensive disease and numerous lines of therapy who have been treated with PIPAC [117]. Reymond et al. evaluated the quality of life (QoL) in 91 patients who had undergone 158 PIPAC procedures as salvage therapy [117].

QoL was assessed before starting PIPAC and 3 months after the procedure when the treatment was still continuing. Quality of life stabilized in patients undergoing PIPAC with stable functional scores. Gastrointestinal symptoms remained the same, and only pain scores deteriorated though the effect was short lived. PIPAC leads to chemical peritonitis which causes abdominal pain. Common side effects of chemotherapy like mucositis, nausea/vomiting, diarrhea, paresthesia, cutaneous symptoms, and alopecia were not reported by the patients. However, accord-

ing to the authors, these results should be interpreted with caution since it was a retrospective study; patients who could not tolerate the therapy were excluded, and the stabilization of symptoms could be in part due to discontinuation of systemic therapy. Similar results were reported by Robella et al. for 40 PIPAC procedures performed in 14 patients [111].

Safety Considerations

The use of chemotherapy as an aerosol has the potential to put the exposed healthcare workers at an increased risk of exposure as compared to other routes of administration. Phase 1 studies have demonstrated the feasibility and safety of aerosol delivery of doxorubicin and gemcitabine in lung cancer patients [118, 119]. Solass et al. tested the occupational safety aspects of PIPAC under standardized conditions, using PIPAC in simulation experiments as well as in two human patients using chemotherapeutic drugs (doxorubicin and cisplatin). The air samples were tested for the presence of chemotherapeutic agents [120]. In these tests, no cisplatin was detected in the air (detection limit <0.000009 mg/m^3) at the working positions of the surgeon and the anesthesiologist under real PIPAC conditions. To further reduce the risk, all workers stayed out of the operating room throughout the procedure which was remote controlled. It was concluded that PIPAC fulfils the requirements of the European Community working safely law and regulations provided it was performed according to the conditions specified by the authors [120]. However, this test was performed only for cisplatin and may need to be performed separately for other drugs. Because PIPAC is applied within a closed system, the risk of skin contamination with chemotherapy is also minimal. Some of the other measures that can reduce the risk include following standard safely protocols while handling the drug in the drug preparation room and during transport, using one-block systems (nebulizer and infusion tubing), repeated training and drills in order to minimize human errors, and using personal protective equipment like double gloves (or special gloves for handling chemotherapy spills if such are available) and protective glasses. Like in other cases of intraoperative chemotherapy use, the operating room should be cleaned after every case to reduce the risk of other sources of contamination like blood spills. Other waste generated during the procedure like tubes, drapes, and sponges should be disposed in sealed and appropriately labelled containers.

A recent report of 127 procedures in 58 patients showed that with standardized surgical approach and dedicated safety checklist, PIPAC can be safely introduced in routine clinical practice with a minimal learning curve [121].

Clinical Trials

Following the favorable reports of preclinical and clinical studies, several trials are currently underway to further evaluate the role of PIPAC (Table 20.7).

An open-label, single center, single arm, phase II study, PI-CaP (ClinicalTrials.gov Identifier: NCT02604784), evaluating the role of PIPAC in patients with colorectal, ovarian, gastric, and primary peritoneal cancer is currently recruiting patients in Italy. Patients with gastric PM and primary peritoneal cancer should have received at least one line of systemic chemotherapy and patients with colorectal PM and ovarian cancer, at least two lines of chemotherapy. These patients should not be candidates for CRS and HIPEC and should have a tumor mass on CT scan that allows tumor response evaluation by RECIST criteria. The primary end point is tumor response after two–three PIPAC procedures, and other end points include overall survival, histological regression, and time to progression.

Another phase II study (Clinicaltrials.gov identifier NCT02320448) from Denmark evaluating the adverse events and occupational safety has closed for accrual in March 2017, and the results are being evaluated.

For gastric PM, PIPAC-GAO1 (ClinicalTrials.gov Identifier: NCT01854255) a phase II study has completed accrual. This study will evaluate the role of PIPAC in patients with recurrent gastric cancer in terms of clinical benefit rate and objective response at 3 months after treatment completion and overall survival at 1 year after treatment completion. PIPAC is performed using

Table 20.7 Ongoing clinical trials evaluating the role of PIPAC

Trial	Country	Design	Status	Clinical end points	Primary tumor site
NCT02604784 (PI-CaP)	Italy	Single-arm phase II	Recruiting	Feasibility, efficacy, and safety of PIPAC	Colorectal, ovarian, and gastric cancer, PM of unknown origin
NCT02735928 (PARROT)	Italy	Single-arm phase II	Recruiting	Feasibility, efficacy, and safety of PIPAC	Recurrent platinum-resistant ovarian cancer
NCT0230448	Denmark	Single-arm phase II	Active, not recruiting	Feasibility and safety of PIPAC	Various primary sites
NCT01854255 (PIPAC GA-01)	Germany	Single-arm phase II	Completed	Feasibility, efficacy, and safety of PIPAC	Gastric cancer
NCT-2475772	Germany	Single-arm phase 1 Dose escalation	Recruiting	Safety and tolerability of doxorubicin and cisplatin every 4 weeks using a three-group, dose-escalation protocol	Ovarian cancer
PIPAC EstoK-01	France	Parallel-arm phase II, randomized controlled trial	Recruiting	Efficacy, safety, and tolerability of PIPAC with oxaliplatin in patients with PCI > 8	Gastric cancer
PIPOX-01	France	Single-arm phase I/II Dose escalation	Recruiting	Dose-limiting toxicity Efficacy of PIPAC with oxaliplatin	Gastric, colorectal, and small bowel cancer

cisplatin and doxorubicin, and three procedures should be performed for each patient.

PIPAC applied to platinum-resistant recurrence of ovarian tumor (PARROT-ClinicalTrials.gov Identifier: NCT02735928) is a phase II study currently recruiting patients that aims to evaluate the clinical benefit rate (CBR) according to the RECIST/GCOG criteria after three PIPAC procedures using cisplatin and doxorubicin in patients with first or second platinum-sensitive recurrence from epithelial ovarian cancer. The secondary end points include median time to progression, histological response rate, and quality of life assessment.

A phase I dose-escalation study (NCT02475772) for patients with recurrent ovarian cancer who have received at least one line of platinum-based chemotherapy is currently recruiting patients in Italy. The first 5 patients will receive doxorubicin 1.5 mg/m^2 body surface in 50 ml sodium chloride (NaCl) 0.9% and cisplatin 7.5 mg/m^2 in 50 ml NaCl 0.9% every 4 weeks for three courses. The next 5 patients will receive doxorubicin 2.25 mg/m^2 body surface in 50 ml NaCl 0.9% and cisplatin 11.25 mg/m^2 in 50 ml NaCl 0.9% every 4 weeks for three courses. The next 5 patients will receive doxorubicin 3 mg/m^2 body surface in 50 ml NaCl 0.9% and cisplatin 15 mg/m^2 in 50 ml NaCl 0.9% every 4 weeks for three courses. This schedule represents a three-step, 50% dose-escalation. Dose density will not be changed. The primary end point is adverse events occurring within 12 weeks, and the secondary end point is response at 12 weeks according to RECIST criteria.

The PIPAC EstoK 01 is a prospective, multicenter, randomized, open-label, controlled, parallel-group, phase II trial designed to evaluate the effect of PIPAC with oxaliplatin combined with systemic chemotherapy in patients with gastric PM with a PCI >8. The primary end point of this trial is the progression-free survival at 24 months. The secondary end points are the 24-month OS, safety, tolerability, and quality of life. It will also evaluate the feasibility of three successive PIPAC procedures and secondary resectability rate in these patients. Six specialized centers target to recruit 2×47 patients over 36 months.

Table 20.8 Advantages, disadvantages, and contraindications of PIPAC

Advantages	Disadvantages	Contraindications
• High tumor drug concentration using 1/10 of systemic dose • Easy to perform—no learning curve • Limited grade 3–5 morbidity • Possibility of multiple applications • Can be combined with systemic chemotherapy • Evaluation of response to therapy possible • No risk of port site metastases • Minimal adhesion formation • Subsequent CRS and HIPEC is possible	• Cannot be combined with CRS • Prior adhesions limit its application and efficacy • Certain areas like the lesser sac remain untreated	• Laparoscopic nonaccess • Malignant bowel obstruction • Debilitating ascites with malnutrition

PIPOX-01 is a phase I/II multicentric study in which a dose-escalation study for oxaliplatin will be performed to treat patients with unresectable gastric, colorectal, and small bowel peritoneal metastases. The primary end point of the phase I study is the dose-limiting toxicity and that of the phase II study is the secondary resectability rate. Four centers in France will recruit 6 and 50 patients for the 2 studies.

Advantages and Limitations of PIPAC

PIPAC has pharmacokinetic benefits like increased tumor drug penetration using 1/10 the dose used in HIPEC with limited systemic absorption [116]. There is more homogenous drug distribution over the peritoneal surfaces [108]. Overall incidence of complications is low and the average hospital stay is 2–5 days. It can be combined with systemic chemotherapy without significant toxicity. Repeated applications are possible and the time interval of 6 weeks allows evaluation of response to therapy [105].

PIPAC has limitations as well. The current protocol does not allow it to be performed with CRS. Reported toxicity is more when is it performed immediately after CRS [116]. The technical feasibility and the efficacy of PIPAC are largely dependent on the degree of enteroenteral and entero-parietal adhesions. Reported rates of nonaccess are 5–17%. Moreover, only exposed peritoneal surfaces that can be reached by the aerosol can be treated with PIPAC. At present, there is no method of stratifying patients according to adhesions; however, it may be difficult or impossible to perform PIPAC in patients who have had CRS and/or HIPEC before [115].

The advantages, disadvantages, and contraindications are summarized in Table 20.8.

Based on the current evidence, PIPAC can be used for symptom palliation in selected patients with PM and in patients who have failed on one or more lines of systemic chemotherapy. Further clinical evidence is needed before it is used for other indications. Standardization and improvement of certain technical aspects of the procedure like the drug dosage and possibility of use in conjunction with CRS will be important for increasing its future use and efficacy.

Laparoscopic HIPEC

Lotti et al. have described the technique of laparoscopic HIPEC which combines the theoretical advantages of the open and closed techniques. In their technique, stirring of the abdominal contents is performed from time to time during a closed HIPEC procedure [122]. Laparoscopic CRS is performed for patients with limited disease followed by HIPEC by the closed method [123]. In a pig model, a hand-assisted laparoscopic device has been used, but it may not perfuse the anterior abdominal wall completely [94].

In the technique described by Lotti et al., at the end of CRS, four Jackson-Pratt drains, which are the outflow channels, are inserted in the abdominal cavity: the right superior in the right subphrenic space, the right inferior in the hepatorenal recess, the left superior below the left hemidiaphragm, and the left inferior in the

pelvis. The length of the wound, between the xiphoid and the pubis, is divided into 4 parts, the skin sutured, and 3 12 mm balloon trocars are placed at the junction between sutures. The upper trocar is connected to the HIPEC inflow tube, the middle trocar to the heated CO_2 insufflator, and the lower trocar to the smoke evacuator device. Balloon trocars with locking gel cones are used which reduced the risk of drug leakage through the wound. After 5 min of stirring, CO_2 insufflation is stopped, the patient is placed in Trendelenburg position, and pneumoperitoneum is evacuated under vision through the lowest trocar. Perfusion continues in a closed-technique fashion for 10 min, so as to perfuse the anterior abdominal wall with the perfusate. During this phase of perfusion, the abdomen is shaken manually and the inclination of the operating bed frequently changed, to further promote the distribution of the perfusate into the abdomen.

After 10 min, pneumoperitoneum is again established, and the cycle restarts. During a 90 min HIPEC, alternating cycles of laparoscopic stirring (5 min) and closed perfusion (10 min) are performed.

The pneumoperitoneum-laparoscopic stirring interspersed with evacuation of the pneumoperitoneum—closed perfusion allows perfusion of the anterior abdominal wall for an adequate time period. An experimental study carried out in pigs showed that the absorption of oxaliplatin in tumor tissue was more in the closed HIPEC procedure as compared to the open procedure [94]. Although the resulting increase in IAP could have a positive effect on penetration of cytotoxic drugs in tissues, this effect is still under study [94, 124]. The authors concluded that further evaluation of this technique is needed, to demonstrate a clinical benefit, and the effect of pneumoperitoneum on the absorption of chemotherapeutic drugs needs to be determined as well.

20.6.3 Noninvasive Hyperthermia

In IPC the use of heat can potentiate the action of chemotherapeutic agents and hyperthermia itself if cytotoxic. HIPEC requires a dedicated machine and set up to perform and, being invasive, repeated applications are difficult [125]. Wu et al. developed a method of applying hyperthermia by a noninvasive method in mouse ovarian cancer models using nanoshells [126]. Nanoshells have a core of a different material coated by a thin layer of gold. The core material is dielectric, with silica being the most common material used [127]. Gold nanoshells (GNSs) are usually close to 50–150 nm in diameter and are generally moderately stable in solution, especially if stored at low temperatures.

They conjugated pegylated silica-core gold nanoshells (pSGNs) with antihuman CD47 monoclonal antibody and combined this with near-infrared laser (NIR) irradiation [126]. Silica-GNSs that get activated by NIR light are 150 nm in diameter, with a 120 nm diameter silica core [127]. They showed that the NIR laser penetrated the abdominal wall, exerted a photothermal effect (intraperitoneal hyperthermia), and caused tumor cell death without harming normal intraperitoneal tissues. Repeated applications of this therapy were possible. Conjugated pSGNs specifically target and bind to cancer cells inside the peritoneal cavity. This is a new strategy for producing hyperthermia and could have future use in clinical practice. Nanoparticle-mediated hyperthermia has shown benefit in preclinical studies in treating other tumors at other anatomical sites as well [128, 129].

20.6.4 Reducing the Interstitial Fluid Pressure

The penetration of drug into tumor tissue is dependent on the intra-tissue diffusivity and the rate constant for drug removal which is fixed [130]. The tissue diffusivity is a function of the tissue structure and the drug properties; it is equal to the diffusivity in the interstitial space of the tissue (which incorporates the tortuous path that a molecule must traverse) and the volume fraction of tissue interstitial space. Reducing the interstitial fluid pressure could be one mechanism that could increase the penetration of drugs into the tissues [130].

High tumor interstitial pressure (TIP) is known to reduce efficacy of cancer therapy via several mechanisms.

1. The high TIP is due to increased tumor vessel permeability which impairs convection by reducing the pressure gradient. This leads to a reduced uptake and heterogenous distribution of drugs (chemotherapy, targeted therapy), other macromolecules in the tumor tissue. In this situation, diffusion is the main transport mechanism for the macromolecules which is slow due to the dense extracellular matrix [131].
2. Rapidly proliferating cells lead to high pressure within the tumor which compresses the blood vessels and increases the vascular resistance. As a result, the blood flow and drug delivery to the tumor tissue is reduced [132].
3. Abnormal and tortuous tumor vasculature causes blood stasis, which leads to the reduction of oxygen and blood flow in tumors and thus hypoxia [133]. There is lactic acidosis which degrades or deactivates some therapeutic drugs and renders them ineffective.

In preclinical models, intraperitoneal drug penetration could be enhanced by lowering the IFP, by using hypotonic carrier fluids, or by increasing the intraperitoneal pressure [97, 134, 135].

Several strategies have been devised to reduce TIP in preclinical studies. Targeting factors like abnormal tumor vasculature, high intratumoral vascular resistance, abnormal lymphatic drainage, and abnormal extracellular matrix components pharmacologically and physically have shown to reduce TIP and improve intratumoral drugs distribution and uptake.

Vascular targeting agents (VTA)—VTAs aim to normalize tumor vasculature making them less permeable [136]. These drugs inhibit the proangiogenic factors like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). This "normalization" of tumor vasculature leads to reduced vessel diameter, increased pericyte coverage, and a normal basement membrane and its function, thus making it less permeable and tortuous with suppression of the erratic sprouting of tumor vessels. This in turn reduces the fluid and protein extravasation into the interstitium leading to a reduction in the TIP [137]. Gremonprez et al. investigated whether tumor VTAs enhance the effectiveness of intraperitoneal chemotherapy. A mouse xenograft model with two large peritoneal implants of colorectal cancer cells was developed to study drug distribution and tumor physiology during intraperitoneal oxaliplatin perfusion. Mice were treated for 6 days with either placebo, imatinib (anti-PDGFR, daily), bevacizumab (anti-VEGF, twice), or pazopanib (anti-PDGFR, anti-VEGFR, daily) followed by intraperitoneal oxaliplatin. Bevacizumab and pazopanib significantly lowered interstitial fluid pressure, increased oxaliplatin penetration (assessed by laser ablation inductively coupled plasma mass spectrometry), and delayed tumor growth of peritoneal implants (assessed by MRI) [138]. These findings suggest that neoadjuvant therapy with VEGF(R)-inhibitors may improve the efficacy of IPC, especially for patients for whom a complete cytoreduction might not be feasible. However, there are several caveats to applying such a strategy in clinical practice. Bevacizumab is not effective alone and is used with cytotoxic agents to have any impact on the tumor burden. The antiangiogenic effect is known to last not more than a month after discontinuation of therapy, and normalization of oxygenation, perfusion, or pressure is not necessarily concurrent [139, 140]. Clinical trials are needed to determine the optimal dosage and the treatment window to achieve the desired effect.

Vascular disrupting agents—VDAs target the existing tumor vasculature by binding to microtubules and destroying the endothelial cells leading to increase vascular permeability and thereby the TIP. At the same time, there is a reduction in the tumor blood flow due to the occlusion of the vessels feeding the tumor that eventually lead to tumor necrosis. Development of necrosis increases the interstitial hydraulic conductivity which decreases the TIP [130]. VDAs that have been shown to reduce TIP include ZD6126, combretastatin A-4, and patupilone [141–143].

Taxanes (paclitaxel and docetaxel) are known to reduce the TIP by both vascular targeting and disrupting properties. Other pharmacological and physical therapies for reducing TIP include TGF-b inhibitors, vasodilators, proteases, irradiation, hypo- and hyperthermia, hyperbaric oxygen therapy, ultrasound therapy, and PDT [130]. However, none of these has been used for potentiating the effect of IPC.

20.6.5 New Concepts in Intraperitoneal Therapy

20.6.5.1 Radioimmunotherapy

Radioimmunotherapy using radiolabeled monoclonal antibodies directed against tumor-associated antigens conjugated with radioactive material has been investigated as an adjuvant therapy for advanced ovarian cancer with PM and colorectal PM in several clinical and preclinical studies for almost three decades [144, 145]. In a prospective study of patients with ovarian cancer who had complete remission after first-line therapy, treatment with one intraperitoneal administration of 25 mg of monoclonal antibody HMFG1 labelled with 18 mCi/m^2 of 90Y led to a prolonged disease-free and overall survival (78% at 10 years) [146]. In a randomized controlled phase III study, a single IP administration of 90Y-muHMFG1 to patients with epithelial ovarian cancer who had a negative second look laparotomy after primary therapy did not extend survival or time to relapse [147]. However, these and other studies evaluating intraperitoneal radionuclide therapies have used beta emitter antibody conjugates which have dose-limiting marrow suppression [148–151]. Less toxicity can be expected when radionuclides with shorter half-lives are used, as less radioactivity would distribute systemically [152]. Additionally, application of the more radiobiologically potent alpha emitters such as the ^{212}Pb/^{212}Bi parent-daughter pair (^{212}Pb half-life = 10.6 h) or ^{211}At (half-life = 7.2 h) can improve efficacy over prior beta emitter radioimmunotherapy while limiting irradiation of neighboring healthy cells [153]. Aarts et al. compared CRS alone with CRS and HIPEC or CRS and radioimmunotherapy which consisted of intraperitoneal administration of 74 MBq Lutetium-177-labelled MG1. Survival after CRS was significantly increased by the use of radioimmunotherapy with Lutetium-177-MG1 in rats with PM of colorectal origin [154]. In another experimental study, a "brief intraperitoneal radioimmunotherapy (bip)" mimicking HIPEC was performed in mice. The mice received intraperitoneal injection of 185 MBq of ^{125}I-35A7 (anti-CEA mAb) (740 MBq/mg), and, after 1 h, the peritoneal cavity was abundantly washed with saline solution to remove unbound radioactivity. Bip-^{125}I-35A7-RIT resulted in threefold higher tumor-to-blood uptake ratio than intravenous-^{125}I-35A7-RIT, and the mean absorbed irradiation doses by tumors were 11.6 Gy (Bip-RIT) and 16.7 Gy (intravenous-RIT), respectively. This therapy had a low toxicity and a high tumor to healthy tissue uptake ratio indicating that it might be of clinical benefit especially when used with radiosensitizing agents [155]. A phase 1 study carried out in women in complete clinical remission after second-line chemotherapy for recurrent ovarian cancer showed intraperitoneal administration of ^{211}At-MX35 F(ab′)$_2$ can achieve therapeutic doses in microscopic tumor clusters without significant toxicity [156]. Patients were infused with ^{211}At-MX35 F(ab′)$_2$ (22.4–101 MBq/L) in peritoneal dialysis solution via the peritoneal catheter. In another study, ^{212}Pb-TCMC-trastuzumab was delivered IP less than 4 h after giving 4 mg/kg IV trastuzumab to patients with peritoneal carcinomatosis who had failed standard therapies and had HER-2 + 1 or more in a phase I design for dose escalation [157]. ^{212}Pb-TCMC-trastuzumab was expected to provide more potent radiation to targeted malignant cells, while limiting radiation exposure to normal tissues as compared to beta emitter conjugates, due to the shorter half-life and path length of ^{212}Pb alpha radiation. All the planned dose escalations were performed with low toxicity. A follow-up study showed IP Pb-TCMC-trastuzumab up to 27 MBq/m to be safe for patients with PM who have failed standard therapies with no long-term toxicity.

Radioimmunotherapy needs further evaluation in terms of ideal dose and indications for clinical use. Survival data in clinical studies are not available, and the timing of therapy/integration with other therapies needs to be defined.

20.6.5.2 Photodynamic Therapy

Photodynamic therapy (PDT) is a therapy that uses photosensitizers (or their precursors) with an affinity for tumor cells and visible light to trigger a photochemical reaction. Reactive oxygen species are generated in cancer cells, leading to cell death. Photodynamic therapy has been used for treatment of surface lesions like precancerous lesions and early invasive carcinomas of the cervix, esophagus, stomach, and lung [158–160]. Given the high propensity of PM to recur, this therapy has been evaluated as an adjunct to CRS in animal models of colorectal and ovarian cancer. Development of intraperitoneal PDT has been limited by its poor tolerance related to the lack of specificity of photosensitizers and the location of the metastases in proximity to adjacent intraperitoneal organs [161]. Five-aminolevulinic acid methyl ester hydrochloride (methyl-ALA) is a photosensitizer precursor with an affinity for tumor cells has been used in some experimental studies. PDT with hexaminolevulinate (HAL), a second-generation photosensitizer, had a high toxicity but provided the opportunity to diagnose and treat PM at the same time [162]. Azais et al. developed a folate-conjugated photosensitizer (Porph-s-FA) that has an affinity for folate receptor α (FRα) [163]. This receptor is overexpressed in 72–100% of ovarian cancers (81% of the serous carcinomas and only 39.9% of the mucinous carcinomas) [164–167]. This expression is retained in recurrent tumors and is not affected by chemotherapy. They proposed that this new generation folate-targeted photosensitizer is specific to epithelial ovarian peritoneal metastasis in the experimental setting and may allow the development of efficient and safe intraperitoneal PDT procedures.

The other problem is the light source and the type of light. The light source should be able to cover broad surfaces and at the same time deal with difficult areas like the undersurfaces of the intestines, provide a homogenous distribution, should be portable, easy to maneuver, and occupy less space. Green light is more suitable for intestinal surfaces as the depth of penetration is less as compared to red light that has a deeper penetration [161]. Yokoyama et al. in an experimental study demonstrated that concurrent therapy consisting of PDT with 5-aminolevulinic acid methyl ester hydrochloride (methyl-ALA) and clofibric acid is effective at treating PM from ovarian cancer without damaging the adjacent organs [168]. Mroz et al. used functionalized fullerenes, a new class of functionalized photosensitizer (PS) for PDT to treat colorectal PM in mice. Intraperitoneal injection of a preparation of N-methylpyrrolidinium-fullerene formulated in Cremophor EL micelles, followed by white-light illumination delivered through the peritoneal wall (after creation of a skin flap), produced a statistically significant reduction in bioluminescence and a survival advantage in mice [169]. PDT is conceptually suited to treat PM, but the technical aspects of the procedure and the photosensitizer used need optimization before it can be used in the clinical setting.

20.6.6 New Drugs for Intraperitoneal Use

20.6.6.1 Intraperitoneal Immunotherapy

Just as systemic chemotherapeutic agents have been used for intraperitoneal therapy, various immunotherapies have been evaluated for intraperitoneal use.

20.6.6.2 Immune Checkpoint Inhibitors

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a protein expressed on the surface of T cells. Its activation dampens the adaptive immune response to malignancy [170]. The programmed death-1 receptors (PD-1) are also present on cytotoxic T cells and block their activity by inducing apoptosis when activated via ligand

binding on the tumor cell surface [171, 172]. In an experimental model of PM, the effect of checkpoint inhibiting antibodies αPD-L1 and/or αCTLA-4, with or without IL-18, on peritoneal metastases via IP injection or tail vein injection was compared [173]. Intraperitoneal use of immune checkpoint inhibitors had a survival advantage over the control group receiving immunoglobulins, and this effect was augmented by the use of IL-18 [173].

20.6.6.3 Chimeric Antigen Receptor-T Cells (CAR-T Cells)

T cells engineered with chimeric antigen receptors (CAR-T cells) have the ability to bind to tumor cells, causing cell lysis, independent of the action of the major histocompatibility complex (MHC) [174–176]. These cells have been applied to the treatment of hematologic malignancies, such as acute lymphoid leukemia and chronic lymphoid leukemia, but more recently as treatment of hepatic metastases from colorectal cancer. In an experimental study, mice with colorectal PM were treated with CAR-T via IP or tail vein injection, in combination with antibodies for inhibition of immunosuppressive cells, over a 2-week period. They reported a 37-fold reduction in PM tumor burden in IP-treated mice as compared with the tail vein injection group [177]. CAR-T cells targeting specific antigens like the MUC-16ecto antigen overexpressed on most ovarian cancer cells and L1-CAM, a cell adhesion molecule, have shown improved survival after intraperitoneal use in ovarian cancer animal models as compared to controls who received no treatment [178, 179]. CAR-T cells have been used in the clinical setting as well. In a study of four patients with recurrent ovarian cancer, autologous T cells stimulated against a hypo-glycosylated MUC1 antigen were instilled intraperitoneally at monthly intervals to complete three sessions each [180, 181]. Treated patients demonstrated elevated levels of MUC1-specific cytolytic activity and generation of both effector and memory T cells leading to diminished CA125 levels, elevated IFNγ, and improved survival, ranging from 3 to 16 months [181].

20.6.6.4 Dendritic Cell Vaccine

IP use of dendritic cell vaccine and cytokine-induced killer cells has been investigated in the clinical setting. Ai et al. used this therapy prepared from patient's peripheral blood mononuclear cells in 22 patients. 77.3% of the patients with PM from different primary sites experienced control or reduction in the ascites [182].

20.6.6.5 Catumaxomab

Epithelial cell adhesion molecule (EpCAM, CD326) is a surface antigen that is expressed on normal epithelial cells as well as tumor cells [183]. Catumaxomab is a non-humanized chimeric antibody, consisting in a mouse-derived anti-EpCAM Fab (fragment antigen-binding) region and a rat anti-CD3 Fab. Thus, catumaxomab can bind to three different types of cells: tumor cells expressing the epithelial cell adhesion molecule (EpCAM-positive), T lymphocytes (CD3 positive), and also accessory cells that are Fcγ receptor positive, such as macrophages, natural killer cells, and dendritic cells [184, 185].

Catumaxomab binds to human EpCAM-positive tumor cells, thereby activating a complex antitumor immune reaction through various mechanisms like antibody-dependent cellular cytotoxicity, phagocytosis, and T cell-mediated cytotoxicity [186–189]. Catumaxomab after intraperitoneal administration has shown to reduce ascites and delay the requirement for paracentesis in patients with refractory malignant ascites from ovarian and other non-gynecologic malignancies [190, 191]. In a phase II/III trial (EudraCT 2004-000723-15; NCT00836654), patients (n = 258) with recurrent symptomatic malignant ascites refractory to conventional chemotherapy were randomized to paracentesis plus catumaxomab (catumaxomab) or paracentesis alone (control) and stratified by cancer type (129 ovarian and 129 nonovarian) [192]. Catumaxomab was administered as an intraperitoneal infusion on days 0, 3, 7, and 10 at doses of 10, 20, 50, and 150 μg, respectively. The puncture-free survival was significantly longer in the catumaxomab group (median 46 days) than the control group (median 11 days) (haz-

ard ratio = 0.254: $p < 0.0001$) as was median time to next paracentesis (77 versus 13 days; $p < 0.0001$). Patients were less symptomatic from their ascites in the catumaxomab group. A prospective analysis showed a benefit in OS in the catumaxomab group, and this was more significant in patients with gastric cancer ($n = 66$; 71 versus 44 days; $p = 0.0313$). The most commonly reported catumaxomab-related adverse events were cytokine release-related symptoms (pyrexia, nausea, and vomiting) and abdominal pain which were generally mild to moderate in intensity and reversible. There were no cases of catheter-related infections. Fifteen percent of the patients had serious adverse events [193].

Following intraperitoneal injection with catumaxomab, antitumor immunity develops which can be long lasting in some patients [194].

In another randomized study published in 2008, of the 55 patients undergoing surgery for gastric adenocarcinoma (T2b/T3/T4, N±, M0) with a curative intent, 28 received an intraperitoneal catumaxomab infusion in the immediate postoperative period and were compared to 27 patients who underwent resection alone [193]. Catumaxomab was administered during surgery and then postoperatively on days 7, 10, 13, and 16 at increasing doses. The EpCAM antigen was present in 100% of patients. Seventy-eight percent (22/28) of the patients treated with catumaxomab received all 5 infusions. Treatment-related adverse events occurred in 40% of the patients most of which resolved. The most frequent adverse events in the catumaxomab group were anemia, pyrexia, inflammatory syndrome, and abdominal pain. This study demonstrated that adjuvant intraperitoneal catumaxomab, after gastrectomy, is feasible, safe, and well tolerated. The same finding was reported in another study [195].

A multicenter, randomized, phase II study is ongoing comparing dosages of catumaxomab in patients with limited PM (PCI < 12) from gastric cancer, after complete cytoreduction of disease. The goal of this study will be to assess 2-year overall survival, as well as, monitor toxicity and morbidity. Besides this analysis, translational research will be conducted to determine immunological markers of catumaxomab efficacy and to correlate these markers with clinical efficacy [196].

20.6.6.6 Bevacizumab

Vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis, is secreted by tumor cells in a paracrine manner and leads to formation of ascites. In addition, peritoneal mesothelial cells and monocytes/macrophages infiltrating malignant effusions and even tumor-infiltrating T cells are known to produce VEGF [197–199]. Bevacizumab is a humanized monoclonal antibody that acts against the vascular endothelial growth factor (VEGF). Animal studies have shown that its intraperitoneal administration is safe and can lead to ascites control [200–203]. It has been used in the clinical setting for palliative treatment of refractory malignant ascites with varying results. A few case reports and small case series have shown good control of ascites with IP bevacizumab [204–207]. The dose used varied from 5–15 mg/kg administered every 3–4 weeks. Some studies showed the control of ascites with a single dose [207].

In a study of 29 patients, the median paracentesis-free survival was 17 days and 11 days for patients with ovarian and gastric cancer, respectively, using IP bevacizumab [208].

A multicenter, double-blind, placebo-controlled phase II study—AIO SUP-0108—showed no benefit of intraperitoneal bevacizumab as compared to placebo in patients with chemotherapy refractory malignant ascites of gastrointestinal origin though there was a reduction in the ascites in patients receiving bevacizumab [209]. However, 17 of the 33 patients in the study group had ascites secondary to pancreatic adenocarcinomas which may be responsible for the poor results overall. The complication rate was similar in the experimental and control groups.

20.6.6.7 Mucin-Lysing Therapy

Peritoneal cancer spread from mucinous tumors of gastrointestinal origin is common. Some of these tumors like pseudomyxoma peritonei which usually arise from a mucinous appendi-

ceal primary tumor are associated with debilitating mucinous ascites. Though CRS and HIPEC have resulted in long-term survival in these patients, 25% of the patients with PMP present with advanced disease that is unresectable, and in those undergoing CRS and HIPEC, recurrence is common [210, 211]. The characteristics of the mucin produced by these tumors have been described [212]. The mucinous deposits are hypoxic, acidic, and impenetrable to chemotherapy [213]. MUC2, the prototype of secreted mucins, is expressed in the small intestine and colon and contributes significantly to the peritoneal spread in gastric and colorectal tumors. It is the PMP-specific mucin that is responsible for the high degree of gel formation. The copious secretion of MUC2 gives rise to an "appendiceal mucocele" also leading to its rupture and release of tumor cells. The presence of mucin allows the cells to float freely and redistribute in the peritoneal cavity [214]. MUC5AC is expressed only by a minority of goblet cells, in the normal colon. However, it is frequently expressed in colorectal adenomas and carcinomas and ovarian mucinous tumors and has been associated with adverse clinic-pathological factors [215, 216]. These mucins can lead to resistance to chemotherapy by formation of a physical barrier and resistance to apoptosis and drug metabolism [217].

There is a theoretical possibility to using a mucolytic agent in addition to CRS and HIPEC to reduce the risk of recurrence. Similarly, it can be used dissolve mucinous masses and aid surgery or be used as a palliative option.

Dextrose has been proposed as mucolytic agent, but its clinical benefit is unproven [218–221]. There are case reports showing benefit of other agents like sodium bicarbonate [222]. Other in vitro studies showed a benefit of agents like ascorbic acid and hydrogen peroxide used in combination [223]. N-acetyl cysteine (NAC) is a mucoactive agent with both mucolytic and mucoregulatory functions. Mucolytic activity of NAC has been evaluated in a variety of respiratory and gastrointestinal tract diseases associated with mucus hypersecretion [224, 225]. As a mucoregulatory agent, NAC controls mucin production and secretion in a content-dependent manner [226, 227]. Morris et al. have demonstrated the mucin-lysing effects of N-acetyl cysteine and bromelain, enhanced in combination therapy, in in vitro studies as well as in in vivo studies in animal models without significant adverse effects [228, 229]. Subsequently, the same investigators reported that bromelain and NAC decrease production and/or secretion of mucins, in particular when the cells are exposed to combined regimens [230]. In addition, they reported that the mucin-depletion resulting from this therapy led to increased chemosensitivity of the tumors in in vitro and in vivo models. This combined therapy appears to be promising in preclinical studies [229, 231].

20.6.6.8 Personalized Intraperitoneal Therapy

Another problem with the current method of IP drug delivery is the lack of consideration for tumor drug sensitivity. For example, it is known that mitomycin C in its native form is inactive and needs to undergo a process of bioreductive activation for it to be oncologically effective [232–234]. This process is mediated by enzymes in the target tissue, i.e., the tumor, so tumors which do not express these enzymes will have an advantage in that MMC will not be activated [235, 236]. Some retrospective studies have even shown that polymorphisms in the genes encoding some of these enzymes have an effect on the outcomes of CRS and MMC-based HIPEC for colorectal peritoneal metastases [237, 238]. So in future, it would be ideal to use tumor biopsies to devise a "sensitivity profile" for individual patients.

20.6.7 New Surgical Strategies for the Treatment of PM

20.6.7.1 Detection of Occult Peritoneal Metastases

Aminolevulinic acid-mediated (ALA) photodynamic diagnosis (ALA-PDD) has been used for detecting occult peritoneal metastases. ALA is a

prodrug of heme biosynthesis that has an affinity for cancer cells. After oral administration, it accumulates in the cancer cells and is converted to protoporphyrin IX (PpIX). When tissue is illuminated with light of a specific wavelength (blue light 440 nm), the tumor tissue emits fluorescence of a specific color (red) leading to its easy identification [238]. This process also leads to the generation of cytotoxic free radicals. ALA-PDT has been used in detecting and treating a variety of precancerous and cancerous lesions like dysplasias arising in Barrett's esophagus, ulcerative colitis and precancerous and cancerous lesions arising from the skin cancers [238–240].

This strategy can be used to detect occult tumors which are missed by white light. Areas of inflammation could produce false positive results [241]. In a study by Kishi et al., staging laparoscopy (SL) using ALA-PDD was performed in 13 advanced gastric cancer patients with serosa-invading tumors, and the detection sensitivity of ALA-PDD was compared to the observations using WL [242]. The tumor detection rate using ALA-F was significantly higher than the detection rate using WL (72% vs. 39%, respectively, $P < 0.0001$). Peritoneal metastases were detected in five patients using SL with ALA-PDD, and liver metastases were detected in one patient. These metastases were confirmed using histological examination. Three metastatic lesions that were invisible under WL were detected under ALA-F.

In a study of 20 patients with primary peritoneal and ovarian cancer, ALA-PDD showed a high sensitivity (95%) and specificity (100%) in detecting peritoneal metastasis. ALA-PDD did not add to the morbidity of CRS and HIPEC [236].

ALA-PDD can be used with staging laparoscopy also and has shown a higher rate of detection of occult metastases compared to white light [243]. The same authors reported outcomes of the same strategy in 38 patients in 2016. Twelve of the 38 patients (32%) were diagnosed with peritoneal metastases by conventional laparoscopy. However, laparoscopy with ALA-PDD detected peritoneal metastases in 4 (11%) of the 26 remaining patients. Three of these four patients had negative cytological results from the evaluation of the peritoneal fluid [244].

20.6.7.2 Small Bowel Transplant

For patients with advanced and recurrent PMP, multi-visceral transplant has been attempted. The peritoneal surface malignancy team from Basingstoke in conjunction with an organ transplant team from Oxford has performed small bowel and multi-visceral transplant for seven patients of PMP with end-stage disease combined with intestinal and abdominal wall failure over a period of 4 years (unpublished data) [245]. Two patients died of postoperative complications. Of the remaining five patients, four have remained disease-free. All patients are independent of TPN and experience a good quality of life and, in some patients, successful return to employment (unpublished data) [245]. The long-term outcomes of such procedures need to be looked into to determine their role in the treatment of PMP.

Conclusion

New therapies have been developed for treatment of PM in addition to CRS and HIPEC. Some of these therapies are designed to overcome the existing drawbacks of various forms of IPC. Preclinical and clinical studies show promising results for future use in clinical practice. New forms of intraperitoneal therapy have been developed, and new drugs that have shown a benefit when used systemically are being evaluated for intraperitoneal use. While most of these therapies are in the preclinical phase, others like PIPAC and PDT are already in clinical use and being evaluated in clinical trials. Ongoing research continues to provide further insight and an improved understanding of the pathophysiology of peritoneal cancer spread and pharmacological aspects of intraperitoneal drug therapy which forms the basis of developing new therapies for treating peritoneal metastases.

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21 Registries and Collaborative Groups in Peritoneal Surface Oncology

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21.1 Background

21.1.1 The Need for Registries in Peritoneal Surface Oncology

Peritoneal cancer spread can be primary or secondary. Whereas the peritoneum is considered to be a common site of secondary tumor spread, tumors arising from the peritoneum itself are rare. Patients with peritoneal metastases (PM) suffer from significant and disabling symptoms as compared to other cancer patients, and hence the development in this field has largely focused on disease site rather than histology [1]. Surgical oncologists who are often faced with the challenge of managing these symptoms looked "beyond" systemic chemotherapy and other palliative procedures as the sole treatment for patients with peritoneal metastases (PM). This coupled with an improvement in the understanding of the disease biology and has led to the use of an aggressive locoregional therapy comprising of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [2, 3]. With this treatment, there is a significant prolongation in survival and improvement in the quality of life of a selected group of patients with PM. Surgeons offering this treatment have collaborated and pooled their data and published their results that clearly showed a benefit of such treatment as compared to the standard of care which was systemic chemotherapy [4–6]. Indeed, most of the evidence to support the use of CRS and HIPEC comes from multicentric retrospective data; few clinical trials have been completed pertaining to this treatment till date [7–11]. A new aspect of treatment of PM is preventing of PM using HIPEC in patients at high risk of developing PM. As more and more centers adopt this treatment worldwide, there are numerous questions pertaining to this treatment that need to be answered like the timing and indications for CRS and HIPEC, the role of HIPEC in addition to CRS, the role of HIPEC in prevention of PM, and the standardization of the methodology and drug regimens. Though randomized controlled trials could provide answers to some of these questions, there are several problems in conducting clinical trials related to CRS and HIPEC [1].

Phase I dose escalation studies may need to be terminated because of surgical complications/morbidity rather than the toxicity of the drug itself which could make interpretation difficult [1]. In phase II trials, as there is no residual tumor/dis-

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ease, the clinical endpoints have to be disease-free and overall survival [1]. Again these need to be compared to systemic chemotherapy which represents a moving target due to the constant introduction of new drugs and regimens. Moreover, the chemotherapy data is not available for patients with PM alone but is mixed with other sites of metastatic cancer spread which makes a comparison even more difficult. Phase III trials are difficult to conduct for similar reasons. Most of these trials have to be multi-institutional to recruit an adequate number of patients, and variability in the surgical skill, perioperative care, and HIPEC methodology may influence outcomes. Trials evaluating surgical therapies are difficult to perform because of the high cost as well. It is not possible to conduct trial for all aspects of HIPEC like drug type, dose, duration of treatment, temperature, perfusion fluid, and open/closed method, and these questions may remain unanswered even if the trial results are positive [1]. Despite all these limitations, numerous clinical trials are currently underway, and their outcomes will provide answers to some questions pertaining to this treatment [12, 13]. Patient accrual has been a problem for some of these trials and one of the reasons being patients not wanting to undergo randomization and opting for CRS and HIPEC [13]. And though detractors of this therapy have raised the issue whether it is appropriate to compare CRS and HIPEC with CRS alone instead of systemic chemotherapy which is still the standard of care, it is not possible for randomized patients to receive no surgical therapy when there is significant level II evidence supporting its benefit. In the largest multi-institutional study reporting the outcomes in patients with pseudomyxoma peritonei (PMP) of appendiceal origin, 2298 patients from 16 specialized institutions around the world treated with CRS and HIPEC experienced a median survival rate of 196 months (16.3 years) and a median progression-free survival rate of 98 months (8.2 years), with 10- and 15-year survival rates of 63% and 59%, respectively [14]. CRS and HIPEC are now accepted as the standard of care treatment of patients with PMP of appendiceal origin. Similarly, in a multicentric study of 523 patients from 23 French-speaking centers, Elias et al. reported a median overall survival of 30.1 months, a 5-year overall survival of 27%, and a 5-year disease-free survival of 10% with CRS and HIPEC in colorectal PM [15]. Patients of colorectal PM treated with chemotherapy alone experience a median survival of 10–15 months [16–18]. These results established the role of CRS and HIPEC in the management of colorectal PM, though the role of HIPEC in addition to CRS is still under evaluation. These multi-institutional studies used common data forms to collect relevant information and analyze it. A registry could be considered a more organized way to meeting this end, and in the last decade, several national and international registries have been established to serve this purpose [19–21].

21.2 What Is a Registry: Features of a Registry

A registry is defined as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects" [22].

The term registry is defined both as the act of recording or registering and as the record or entry itself. Therefore, "registries" can refer to both programs that collect and store data and the records that are so created.

The use of registries can allow investigators to study the natural history of disease and the clinical effectiveness of therapies such as CRS and HIPEC and to measure or monitor safety and quality. Not all aspects of treatment can be studied in clinical trials, and data from registries provides a useful alternative. Primary peritoneal tumors are rarer and have distinct natural histories despite having a common site of origin. Conducting clinical trials in these patients is even more difficult. Population-based registries have provided insights into the natural history of secondary peritoneal metastases [23, 24]. Multi-institutional registries can be useful for

understanding the natural history of these rare primary peritoneal tumors as well.

Reports from registries are not a replacement for randomized controlled trials (RCTs) but play a complementary role [25]. They are representative of the real-world scenario since the treatment is not predetermined or protocol based. Registry data captures events as they occur, and since only few patients are excluded when evaluating the outcomes, the results could be applied to the population at large. Studies from patient registries and randomized controlled trials (RCTs) have important and complementary roles in evaluating patient outcomes [25].

21.2.1 Goals of Setting Up a Registry for Peritoneal Surface Malignancies

- To study the natural history of the disease
- To determine the effectiveness of therapy
- To compare variables affecting outcomes
- To monitor quality
- To assess the safety of a therapeutic intervention

21.2.1.1 Setting Up a Registry

The Agency for Healthcare Research and Quality (AHRQ) in collaboration with the Centers for Medicare & Medicaid Services (CMS) through the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network of AHRQ's Effective Health Care (EHC) Program has published a "User's Guide" as a reference for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes. A synopsis of this exhaustive guide is provided in this section [26].

21.2.1.2 Design of a Registry

Every registry must have a carefully considered design that can answer specific scientific questions. The key elements that should be taken into account when developing a registry are identifying the point of study or research question; developing a study design, translating questions of clinical interest into measurable exposures and outcomes; choosing the number and characteristic of patients to be included in the study, including deciding whether a comparison group is needed; and determining the duration of the study [26].

It is most important to clearly define the included cohort of patients. While this can introduce a systematic error or bias, clear definition of cohorts of patients included adds to strength of inference from a registry.

The number of study subjects to be recruited and the length of observation (follow up) should be planned in accordance with the overall purpose of the registry. The registry can be time bound or "open ended."

21.2.1.3 Data Elements

Specific data elements relevant to the goals of the registry should be captured keeping in mind the established clinical data standards, common data definitions, and whether patient identifiers will be used. The mandatory elements should be distinguished from the desirable but not essential elements [26]. Clinical outcomes should be reported using tool and scales that have been appropriately validated, e.g., Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 adverse events scale [27]. It is also important in designing a registry to include clear data elements with specified alphanumeric structures. Including logic checks of variables is a must to allow for structured entry of data. Once data elements are selected, a data map must be created and data collection tools must be linked. Such data collection tools can be web or mobile based or based on host computers with software supporting data entry. Understanding the data's purpose allows for the best definition of the data elements and tools [26].

21.2.1.4 Ethics, Data Ownership, and Privacy

Critical ethical and legal considerations should guide the development and use of patient registries. The purpose of the registry, the body that maintains it and individuals/organizations that contribute to it, and the extent to which individuals are identified in the registry all affect the regulations that apply to the registry. The activ-

ities should be transparent and closely monitored and data ownership predefined [26]. All collection of human data must be in concordance with the ethical conduct of human subjects based on the Belmont Principles (Ethical Principles and Guidelines for the Protection of Human of Research). Adherence to the Health Insurance Portability and Accountability Act (HIPAA) is preferable and mandatory in the United States. The oversight of an institutional review board and/or an ethics committee is a must for both retrospective and prospective registries. Sharing of data must occur by secure means and risk of exposure of data must be minimized. It is important to define data ownership especially when the purpose of the registry is for scientific research. Models such as the "confederate" model provide ownership of data which facilitates publications in a harmonious way [26].

21.2.1.5 Informed Consent for Registries

Informed oral and/or written consent is mandatory in most registries. The format of consent (physical or electronic), indications for re-consent and revisions, rules for withdrawal from the study, and handling of biological specimens should all be considered while planning informed consent procedures [26].

21.2.1.6 Confidentiality and Legal Concerns

The concerns about privacy and confidentiality can arise in registries especially at the time of legal proceedings or when dealing with administrative problems [26].

21.2.1.7 Patient and Provider Recruitment and Management

Patients can be recruited in a registry by medical practitioners, hospitals, or pharmacies. The benefits of participating in a registry need to be highlighted to the recruiting bodies/authorities to recruit and retain an adequate number of patients. The risks and benefits of participation should be properly explained. The plan for recruitment, retention, and follow-up should be laid out before starting the registry. The risk of bias should be evaluated and minimized.

21.2.2 Interfacing of Registries with Electronic Health Records

Interlinking electronic health records (EHRs) simplifies the process of data collection and entry. Interoperability depends on similarity in the data variables and customization may be required if the elements do not match.

21.2.3 Data Collection and Quality Assurance

The use of an organized system is only valid when rigorous methods for data collection and quality assurance are undertaken. Often data is lost or misinterpreted when the data collection tools or data entry is ambiguous. Quality assurance allows that the data is in accordance with the established policies and the intended use of the data. Requirements for quality assurance must be established at the time of the registry deployment.

21.2.3.1 Analysis, Interpretation, and Reporting of Registry Data

Before analyzing the data, analysis of the recruitment and retention, completeness of data, and its quality needs to be performed. How missing data was handled, accounting for losses to follow up, and completeness of key elements are important factors that affect the analysis. Analysis of a registry should provide information on the characteristics of the patient population, the exposures of interest, and the endpoints. Descriptive registry studies focus on describing frequency and patterns of various elements in a patient population, whereas analytical studies concentrate on associations between patients or treatment characteristics and health outcomes of interest.

21.3 Registries for Peritoneal Surface Malignancies

In the last decade, numerous national and international registries have been set up to capture information related to peritoneal surface malignancies (Table 21.1). All of these have been set up by surgeons primarily those performing CRS and HIPEC or surgical societies in order to standardize indications, intraperitoneal chemotherapy, and peritonectomy techniques and to evaluate outcomes of these procedures [28]. Hence most of the registries include only those patients undergoing CRS and HIPEC [28].

Table 21.1 Select multi-institutional registries collecting information on peritoneal surface malignancies

Registry	Quality assurance purposes	Research purposes
PSOGI registry	–	+
Indian registry	–	+
German registry (CAO-V)	+	+
RENAPE observational registry (French)	–	+
Dutch registry (Netherlands Cancer Registry)	–	+
International Registry on Peritoneal Mesothelioma	–	+
HYPER-O (Ovarian Cancer Registry US)	–	+
DANISH Gynecological Cancer Database	–	+
SweGCG (Swedish Quality Registry for cancer ovary, peritoneum)	–	+
National French Registry	–	+
Japanese Society for Cancer of the Colon and Rectum (JSCCR)	–	+
Australian Mesothelioma Registry (AMR)	–	+
Brazilian Registry of Peritoneal Diseases	–	+

21.3.1 Population-Based Registries

Cancer is not a notifiable disease in some countries [29]. Many national cancer registries exist; however, these are epidemiological registries, and their primary function is to primarily examine the rates of occurrence of various cancers and their frequencies in a defined region. Most of these registries do not provide information specific to peritoneal surface malignancies and more specifically outcomes of CRS and HIPEC. However, some population-based registries and single/multi-institutional registries that are not exclusive for peritoneal metastases have helped understand the natural history of PM secondary to gastrointestinal and gynecological primary tumors as well as the outcome of various therapies in these patients [30–32]. An example is the Netherlands Cancer Registry (NCR) that collects data on all newly diagnosed cancer patients in the Netherlands, covering a population of approximately 16 million inhabitants. Histopathological and cytopathological reports of the diagnosed tumors are entered in the nationwide Dutch Pathology Network (PALGA) by pathologists and are then submitted to the NCR.

In a report from this registry published in 2015 reporting outcomes of various treatments in 4430 patients with synchronous colorectal PM, the median overall survival was more than 32 months and was significantly better than other palliative treatments (Fig. 21.1). Denmark has a similar population-based registry.

21.3.2 Disease-Specific Registries for PM

Some registries/collaborative groups are site specific, e.g., SweGCG (Swedish Quality Registry for cancer ovary, peritoneum), Japanese Society for Cancer of the Colon and Rectum (JSCCR), BIG-RENAPE (Base clinico-biologique des carcinoses péritonéales d'origine dIGestive), the French Oncologic and Gynecologic HIPEC (FROGHI) Group, and the HYPER-O registry for ovarian cancer that recruit patients with secondary peritoneal metastases [33–37]. The goals and scope of each of these are different.

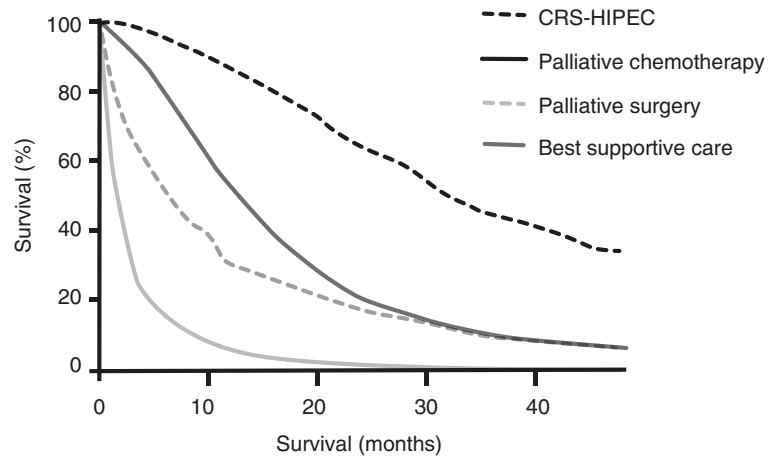

Fig. 21.1 Overall survival of patients with synchronous PC of colorectal origin treated with CRS–HIPEC, systemic chemotherapy, palliative surgery, or best supportive care (n = 4430) (From ref [74] with permission)

21.3.3 Registries for Rare Peritoneal Tumors

In contrast to secondary PM, tumors arising de novo from the peritoneum are rare, and though they have a common origin from the peritoneum, the biological behavior is quite variable. Because of their rarity, lack of awareness and knowledge about these tumors often leads to diagnostic delays and misdiagnosis leading to a delay in definitive treatment that is offered at centers specializing in peritoneal surface oncology. Clinicians and researchers also face unique challenges with these rare cancers, because it is hard to conduct adequately powered, controlled trials in such small patient population [38]. The RENAPE (Réseau National de prise en charge des Tumeurs Rares du Péritoine) is an observational multi-institutional registry that was launched in 2010 in France [39]. RENAPE is a registry for patients with histologically confirmed rare peritoneal tumors that include pseudomyxoma peritonei (secondary to appendiceal and other primary tumors), peritoneal mesothelioma, diffuse peritoneal leiomyomatosis, desmoplastic small round cell tumors, and primary peritoneal serous carcinomas. The goals of this registry are to monitor the incidence and prevalence of rare peritoneal tumors in France, to establish the natural history of these tumors, to assess the clinical effectiveness of new interventions, to measure the quality of care, and to provide an inventory of patients to recontact for participation in epidemiological studies and clinical trials or for health technology assessment to monitor real access to treatments [39]. There are other registries that are specific to a single rare peritoneal tumor like the International Mesothelioma Registry and the Australian Mesothelioma Registry.

21.3.4 Registries for Patients with Primary and Secondary PM

Some registries recruit patients with both primary and secondary peritoneal tumors like the Peritoneal Surface Oncology Group International (PSOGI) registry, the German HIPEC registry, the Indian HIPEC registry, and the Brazilian Registry of Peritoneal Diseases [21, 40].

Thus, based on the disease site, registries including patients with PM can be categorized as:

- Population-based registries
- Site-specific registries for secondary peritoneal tumors
- Registries for rare peritoneal tumors
- Registries for patients with primary and secondary peritoneal tumors

Over the years the management of PM has evolved—locoregional therapies other than CRS and HIPEC have been introduced, and new systemic therapies are available that may have

an impact on the outcomes of these patients. New registries will have to consider these aspects while defining the scope and inclusion criteria.

Some of the questions that specifically need to be addressed in setting up a registry for peritoneal surface malignancies are:

- Site(s) of primary tumor included in the registry
- Treatment modalities evaluated
- Inclusion of patients not eligible for a curative approach/locoregional therapies

21.4 Key Aspects for Registries for Peritoneal Malignancies

21.4.1 Selection Bias in Registries

One of the significant challenges in the current peritoneal registries is the "denominator" problem. It is generally believed that surgeons are highly selective and introduce "selection bias" when they report their outcomes. It is important to consider a registry that captures all patients with a specific diagnosis regardless of their therapeutic modality although majority of current registries include all patients undergoing surgical intervention.

Their kind of selection bias varies according to the coverage of the registry. In the international registries which are open to every center in the world, the entry is based on the selection criteria in the centers which contribute to the registration. In case that the contributing centers have similar selection and criteria and are covering all patients within their catchment area, this registration system can be useful for analyzing outcome of less frequent diseases. However, both similar selection criteria and catchment of all patients in the area are unlikely. Selection criteria depend for an import part on local customs and local healthcare systems, and catchment of all patients is depending on referral mechanisms which are also not similar throughout the world. For this reason these registrations can best be seen as large collections of cases [41].

The national registries may have a more uniform selection on entry and may include biobank data which is fundamental for the evaluation of rare peritoneal disease but also for the evaluation of tumor response and for translational research [39]. The institutional systems have probably the most homogenous entry. However, besides this there is difference in entry over time. If a center starts establishing itself, it will have a smaller number of referrals compared to when it is established for a longer time; therefore, it will by definition have a smaller coverage. There will also be a difference in disease load between the starting centers and the well-established centers [42–44]. This will not only have an influence on the numbers of patients in the registry but also in the severity of the disease. All these factors need consideration when evaluating data from registries.

The registries for PSM are usually not time bound, i.e., "open ended."

21.4.2 Important Data Elements Pertaining to PM

One of the problems in reporting outcomes in PSM is the heterogeneity in the terminology used. At the consensus meeting, the various terms pertaining to PSM were standardized by a group of international experts. The same must be adhered to while reporting outcomes and be incorporated in registries [45]. Data elements in such registries include patient information, preoperative work-up, per-operative data, a 90-day postoperative follow-up, neoadjuvant and adjuvant therapies used, and long-term follow-up. Common prognostic scores for PSM like the peritoneal cancer index (PCI), completeness of cytoreduction score (CC score), and other validated classifications like CTCAE should be used for capturing data [46]. Figure 21.2 shows the details of HIPEC that are captured in the Indian registry.

In the RENAPE Registry, pathological review by an expert pathologist is sought where deemed necessary before accepting the case to the registry. The various data elements pertaining to

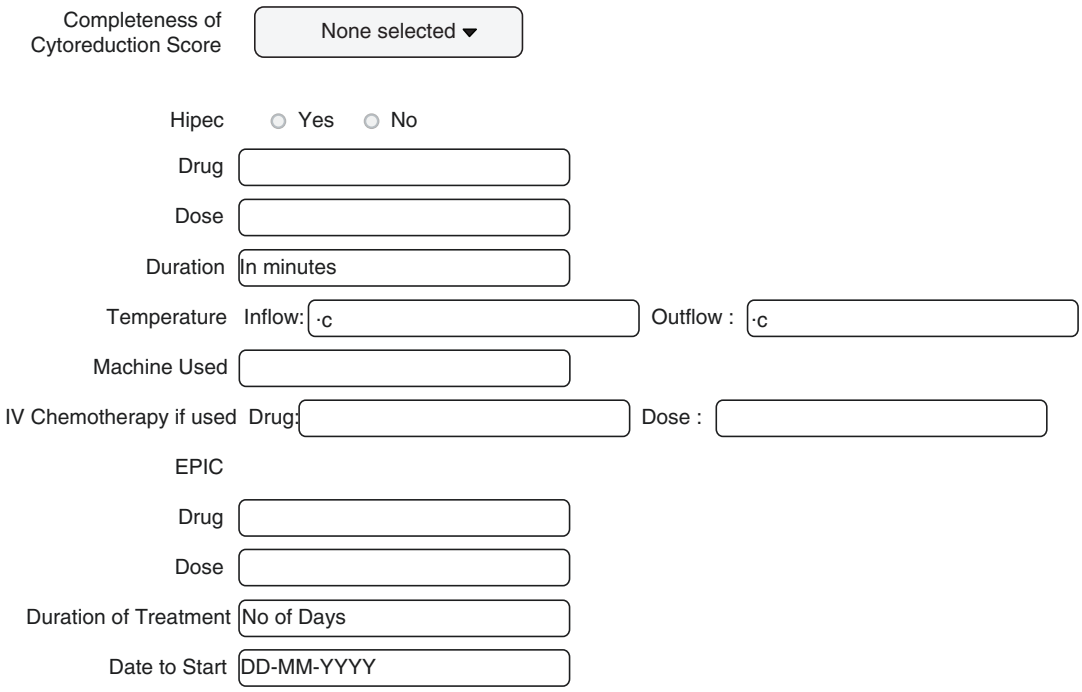

Fig. 21.2 Details of the HIPEC procedure that are captured in the Indian HIPEC registry

pathology captured by the RENAPE Registry are listed in Table 21.2.

Other useful tools can aid more uniform capturing of data like the calculation of the CT-PCI. A useful Internet-based tool that is freely available is the PROMISE® Internet application [47]. It has been developed by the RENAPE working group to allow for a standardized assessment of the peritoneal disease extent intended of multidisciplinary teams and centers that treat patients with RPM.

21.4.3 Data Entry

The functioning of a registry through a web-based application/online database eases out the processes of data entry and facilitates participation of multiple centers [21, 37, 39]. Linking hospital information systems/electronic health records (EHRs) to the database can facilitate this process further though data elements need to be matched appropriately. Depending on the resources, data entry is done by participating surgeons or specially trained personnel for the same. The completeness and accuracy of data entered needs to be monitored from time to time. This can be done manually by designated personnel or inbuilt monitoring systems in the application. Regular monitoring is important to maintain the quality of the data entered. The rules for updating or changing data on file, follow-up, and data exchange also need to be formulated. Measures should be taken to avoid duplication.

21.4.4 Follow-Up of Patients

Patient follow-up is essential. The participating centers/surgeons need to take up the responsibility of updating the status of each patient from time to time. Patients who do not turn up for timely follow-up need to be contacted through phone calls, mails, etc. The information can be obtained from referring physicians or primary care physicians as well.

Table 21.2 Data elements pertaining to the pathology of the tumor captured in the RENAPE Registry [39]

General information signet ring cell	
Receive date	Ronnett classification: DPAM, PMCA-I/D, PMCA
Procedure: biopsy, resection	WHO 2010 classification: LAMN, high-grade mucinous adenocarcinoma
Peritoneal cytology	• Involved organs (list)
No. blocks	• Lymph node involvement: pNtot, Pn+
Referring pathologist, surgeon	**Peritoneal mesothelioma**
Biobanking	• No. blocks
Patient consent form	• Histologic forms—Epitheloid, biphasic, sarcomatoid, multicystic, well-differentiated papillary mesothelioma
Conditions: frozen/formalin-fixed paraffin-embedded	
Pseudomyxoma peritonei	• Lymph node involvement: pNtot, Pn+
• Appendix diagnostic	**Primary peritoneal serious carcinoma/peritoneal desmoplastic small round cell tumors/diffuse peritoneal leiomyomatosis**
No. blocks	
LAMN/adenocarcinoma	• Diagnosis
• Peritoneum diagnostic	• No. blocks
No. blocks	• Lymph node involvement: pNtot, Pn+

21.4.5 Data Security for Online Databases

Security measures are needed for the application itself to prevent third-party manipulation during transfer from one server to another. One of the systems used to ensure secure transfer of data is SSL certified (Secure Sockets Layer) which is the standard security technology for establishing an encrypted link between a server and a browser and is commonly used for online transactions.

The RENAPE Registry benefits of a safe and secure hosting in France based on Information Technology Infrastructure Library (ITIL) security management [39].

The degree of access given to individuals needs to be determined. Most systems have a unique username and ID for each individual entering data, and this may further be validated with an electronic signature [39]. In the RENAPE Registry, an audit trail module allows tracking of all accesses, modifications, and deletions of data. All exported files are archived with history within the system.

Individuals usually have limited access confined to their own institutional data/patient data.

21.4.6 Privacy

A highly sophisticated registry like the RENAPE has a systematic process of de-identification of individual patients. Each patient is identified by a unique alphanumeric code. In other registries as well, patients are not identified during data analysis or reporting of outcomes. The regulatory body maintaining the registry and governing the functioning should be made known beforehand, and rules for data ownership and publication need to be laid down as well [39]. Critical ethical and legal considerations should guide the development and use of patient registries. It is important to define data ownership especially when the purpose of the registry is for scientific research. The "confederate" model for ownership of data facilitates publications in a harmonious way. In the Indian registry, e.g., where the registry itself is not under the governance of any regulatory body and has been initiated and is run by surgeons, a list of regulations including those governing data publication and authorship is agreed to and signed by each surgeon joining the registry [21]. This agreement is also countersigned by the service provider maintaining the online database to ensure there is not misuse of information from any side [21]. In most cases, users have access only to their own data.

21.4.7 Funding

Some national registries are funded by government/national organization. Others are maintained by surgeons/stakeholders responsible for creating

and running the registry. Country-specific rules and priorities for allocating resources determine whether such registries are funded by regulatory bodies and the extent of such funding.

21.4.8 Recruitment of Centers/Surgeons

Recruitment of centers/surgeons is usually voluntary. Mandatory participation is there in some countries like Germany where centers are accredited by the surgical society and participation in the national registry is one of the requirements for accreditation. In other scenarios, a degree of dedication and collaboration between centers and surgeons is required for the smooth and effective functioning of such registries. This may be a problem where manpower and resources for such programs are limited or rather not channelized in the right direction.

21.5 Guidelines for Rare Disease Registries

The European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD), and the Canadian Organization for Rare Disorders (CORD) have jointly published a declaration on common principles regarding Rare Disease Patient Registries [48].

These common reflections and principles may serve as a reference to all other stakeholders when shaping policies and taking actions in the field of Rare Disease Patient Registries. The principles are listed in Table 21.3.

Table 21.3 The European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD), and the Canadian Organization for Rare Disorders (CORD) declaration on common principles regarding Rare Disease Patient Registries [adapted from reference [48] with permission]

1. Patient registries should be recognized as a global priority in the field of rare diseases
2. Rare Disease Patient Registries should encompass the widest geographic scope possible
3. Rare Disease Patient Registries should be centered on a disease or group of diseases rather than a therapeutic intervention
4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued
5. A minimum set of common data elements should be consistently used in all Rare Disease Patient Registries
6. Rare Disease Patient Registries data should be linked with corresponding biobank data
7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals
8. Public-private partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries
9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries
10. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities

21.6 Adjuncts to Peritoneal Surface Malignancy Registries

21.6.1 RENA-PATH

Within the RENAPE network, the RENA-PATH is a group of pathologists from the participating centers of RENAPE actively involved in the management of rare peritoneal malignancies. This group gathers the pathologists actively involved in the management of rare peritoneal malignancies [49]. The actions of RENA-PATH are focused primarily on the harmonization of pathological diagnostic criteria, reporting of new cases in the RENAPE Registry, and histology reviewing. Any pathologist may request a diagnostic opinion by directly soliciting one of the group's pathologists RENA-PATH. The group meets twice a year to discuss cases in the presence of referring pathologists and also to reach a consensus on the diagnostic criteria.

21.6.2 Biobanks

Biobanks collect human biomaterial and are important tools for basic and translational research. It is ideal to link rare disease registries

with corresponding biobanks [50]. The high value of biological samples needs to be complemented with well-documented data from a registry.

The RENA-PATH Group also leads collaborative translational research projects based on the virtual biobank linked to the Registry clinical database [51, 52]. The collected specimens are stored locally at biological resource centers (BSR). In translational collaborative studies, corresponding clinical information is obtained from the RENAPE Registry, and only those specimens for which patients have given their consent are used.

21.6.3 RENE-RAD

The RENA-RAD, a nationwide French radiological network for management of rare peritoneal malignancies, has been formed recently with expert radiologists in peritoneal carcinomatosis imaging [39]. They share experiences and develop common tools in order to standardize radiological assessment of patients who are suitable for CRS with HIPEC [47].

21.7 Contribution of Various Registries and Collaborative Studies to PSM: What Registries Have Told Us So Far

The information and evidence derived about the natural history of PM and outcomes with CRS and HIPEC from reports of various registries and collaborative studies are outlined in Table 21.4.

21.7.1 Natural History of Primary and Secondary Peritoneal Tumors

Numerous population-based studies have provided information about the natural history of PM from various primaries and the risk factors and prognostic factors. Some of these are described here.

The natural history of appendiceal tumors and their association with PMP were described in a population-based study from the Netherlands. In the 10-year period, 167,744 appendectomies were performed, in which an appendiceal lesion was found in 1482 appendiceal specimens (0.9%), and 9% of these developed PMP. Thirteen percent of the patients had coexisting epithelial lesions in the colon and the appendix. A mucinous epithelial neoplasm was identified in 0.3% (73% benign, 27% malignant) of appendiceal specimens, and 20% of these patients developed PMP. PMP developed in 2 and 3% of the patients with a mucocele and non-mucinous tumors, respectively. The conclusions drawn from this study were:

- Primary epithelial lesions of the appendix are rare.
- One third of these lesions are mucinous and can progress to PMP.
- The incidence of PMP seems to be higher than presumed.
- There is a substantial risk of an additional colonic epithelial neoplasm in patients with an epithelial neoplasm at appendectomy [53].

A report from the Eindhoven Cancer Registry, a subsidiary of the Netherlands Cancer Registry, analyzed 5220 patients diagnosed with gastric cancer between 1995 and 2011of whom 2029 (39%) presented with metastatic disease. PM were present in 706 patients (14%); in 491 patients (9%), the peritoneum was the only site of metastatic disease. Younger age (<60 years), female gender, advanced T- and N-stage, primary tumor of signet ring cells or linitis plastica, and primary tumors covering multiple anatomical locations of the stomach were all associated with higher odds ratios of developing PM. Median survival of patients without metastases was 14 months, but only 4 months for patients with PM. This study showed that PM was common in patients with gastric cancer and had a detrimental influence on the survival [54].

Another study from the Netherlands Cancer Registry comprising of 4277 patients with colorectal PM aimed to provide information about the timing, anatomical location, and predictors of metachronous disease in patients with colorectal cancer [23]. In a study from the same

Table 21.4 Information derived from various registries about peritoneal metastases

Ref.	Country	Registry	Type	Tumor	No of patients	Reported outcomes
Natural history of PM						
[54]	Netherlands	NCR	Population based	Appendiceal tumors and PMP	1482	Natural history
[55]	Netherlands	Eindhoven	Population based	Gastric cancer	5220	Incidence and risk factors for PM
[56]	Netherlands	NCR	Population based	Colorectal cancer	4227	Predictive factors for metachronous PM
[57]	Netherlands	NCR	Population based	Colorectal cancer	4227	Impact of the histologic subtype
[58]	Netherlands	Eindhoven	Population based	Colorectal cancer	5638	Outcomes of liver metastases and PM
[59]	Netherlands	NCR	Population based	PM of unknown origin	1051	Prognosis of PM of unknown origin
[60]	Netherlands	NCT	Population based	Non-endocrine pancreatic tumors	2924	Survival outcomes
[63]	Sweden	National registry	Population based	CRC		Risk factors for PM
[64]	Denmark	National registry	Population based	Borderline ovarian tumors	45	Origin of peritoneal implants
Efficacy/outcomes of CRS and HIPEC						
[14]	Multiple	PSOGI	Multi-institutional	PMP arising from appendiceal tumors	2298	Outcomes of CRS and HIPEC
[63]	Multiple	PSOGI	Multi-institutional	Malignant peritoneal mesothelioma	405	Outcomes of CRS and HIPEC
[64]	France	Collaborative multi-institutional study		Gastric cancer	159	Outcomes of CRS and HIPEC
[65]	France	BIG-RENAPE	Multi-institutional	Gastric cancer	81	Rate of cure of PM using CRS and HIPEC
[15]	France	Collaborative multi-institutional study		Colorectal cancer	523	Survival benefit of CRS and HIPEC
[67]	Multiple	PSOGI	Multi-institutional	Multicystic peritoneal mesothelioma	26	Outcomes of CRS and HIPEC
[68]	Multiple	Collaborative multi-institutional study		Primary peritoneal serous carcinoma	36	Outcomes of CRS and HIPEC
[69]	France	Collaborative multi-institutional study—FROGHI		Recurrent epithelial ovarian cancer	314	Outcomes in platinum-sensitive and platinum-resistant tumors
Role of chemotherapy in the treatment of PM						
[70]	Multiple	Collaborative multi-institutional study		Malignant peritoneal mesothelioma	126	Role of neoadjuvant and adjuvant chemotherapy in patients undergoing CRS and HIPEC
[71]	Multiple	Collaborative multi-institutional study		Malignant peritoneal mesothelioma	294	Staging of peritoneal mesothelioma

Table 21.4 (continued)

Ref.	Country	Registry	Type	Tumor	No of patients	Reported outcomes
[72]	Netherlands	National cancer registry	Population based	CRC	1235	Addition of bevacizumab in addition to systemic chemotherapy
Other aspects of treatment of PM						
[73]	Multiple	Collaborative multi-institutional study		Various primary sites	52	Role of CT in determining the extent of PM
[74]	Netherlands	Netherlands Cancer Registry	Population based	Colorectal cancer	4623	Increased diagnosis of synchronous PM
[75]	France	BIG-RENAPE and RENAPE	Multi-institutional	Various primary sites	189	Increased medical morbidity of CRS and HIPEC in the elderly
[76]	France	BIG-RENAPE and RENAPE	Multi-institutional	Various primary sites	771	Increase incidence of hemorrhagic complications with oxaliplatin HIPEC
[77]	Multiple	Collaborative multi-institutional study		Colorectal cancer	539	Comparison of HIPEC with oxaliplatin and mitomycin C

registry evaluating the impact of the histological subtype of colorectal cancer, mucinous cancer (MC) was associated with a significantly lower risk of death compared with adenocarcinoma (AC) (hazard ratio, 0.9; 95% confidence interval, 0.79–0.95). In rectal cancer, no such effect was observed. AC was associated with a significantly poorer survival rate in the case of primary colonic tumor localization (7.4 months in colon vs. 10.9 months in rectal cancer). This study showed that the histological subtype is an important prognostic factor in patients with synchronous PM of colorectal origin and this should be considered while counseling patients and making treatment-related decisions [55]. Another study from the same registry reported outcomes in patients with liver metastases, PM or both from colorectal cancer. In all, 27,632 patients diagnosed with colorectal cancer from 1995 to 2010 were included in the study, of whom 5638 patients (20%) presented with metastatic disease. Synchronous liver metastasis and PM were present in 440 patients, of which 11% had liver metastases alone, 34% had PM, and 8% had both; altogether these patients summed up to 2% of all patients diagnosed with colorectal cancer. Median survival for patients with liver metastasis and PM was 5 months, in comparison with 95 months for patients with non-metastatic disease. No improvement in survival was noted with passage of time, and patients were not treated with a curative intent during this period [56].

In another report from the Eindhoven Cancer Registry, of 1051 patients with PM of unknown origin, in 606 patients (58%) the peritoneum was the only site of metastasis, and 445 patients also had other metastases. This study reported that the prognosis of PM of unknown origin is extremely poor and did not improve over time and effective treatment strategies needed to be developed for patients in whom the organ of origin remains unknown [57].

In a study on patients with non-endocrine pancreatic cancer from the same registry from 1995 to 2009, 265 (9%) out of 2924 had synchronous PM. Median survival in patients presenting with PM was only 6 weeks (95% confidence interval, 5–7 weeks) and did not improve over time, contrasting improvements among patients with non-metastasized disease (19–30 weeks) and patients with metastasized disease confined to the liver (8–12 weeks) [58].

The Stockholm County Council Registry in Sweden caters to a population of 2.1 million and

every resident has a unique identification number. The surgeons and pathologists classify every case of cancer diagnosed in the region according to the International Classification of Diseases and type of surgery performed and enter the information into the registry. In addition, since 1995 (rectal cancer) and 1996 (colonic cancer), information on all patients with colorectal cancer in Stockholm County has been reported prospectively to a Regional Quality Registry by the surgeon, pathologist, and oncologist [59, 60]. According to a report from this registry, independent predictors for metachronous PM were colonic cancer, advanced tumor (T) status, advanced node (N) status, and non-radical resection of the primary tumor. Patients aged >70 years had a decreased risk of metachronous PM(HR 0.69, 0.55–0.87; $P = 0.003$) [61].

There is lack of clarity about the origin of peritoneal implants secondary to serous borderline tumors/atypical proliferative serous tumors (SBT/APSTs) of the ovary. It is uncertain whether they are derived from the primary ovarian tumor or arise independently in the peritoneum. SBT/APSTs from 45 patients with advanced-stage disease identified from a nationwide tumor registry in Denmark were analyzed. This study provided evidence that the vast majority of peritoneal implants, noninvasive and invasive, harbor the identical *KRAS* or *BRAF* mutations that are present in the associated SBT/APST, supporting the view that peritoneal implants are derived from the primary ovarian tumor [62].

21.7.2 The Efficacy of CRS and HIPEC

Similarly multi-institutional registries have provided evidence to support the use of CRS and HIPEC for treating PM from various primary sites. In the largest multi-institutional study of patients with PMP of appendiceal origin, nearly 2300 patients were treated with CRS and HIPEC at 16 specialized centers. Treatment-related mortality was 2% and major morbidity was 24%. The median survival rate was 196 months (16.3 years), and the median progression-free survival rate was 98 months (8.2 years), with 10- and 15-year survival rates of 63% and 59%, respectively, which were significantly higher than the rates reported by any other treatment modality for these patients. The authors concluded that minimizing non-definitive operative and systemic chemotherapy treatments before definitive cytoreduction could facilitate the feasibility and improve the outcome of this therapy to achieve long-term survival and optimal cytoreduction resulting in the best outcomes [14]. For malignant peritoneal mesothelioma, multi-institutional data registry that included 405 patients with diffuse malignant peritoneal mesothelioma (DMPM) treated by CRS and HIPEC reported an overall median survival was 53 months (1–235 months), and 3- and 5-year survival rates were 60% and 47%, respectively. On multivariate analysis, independent predictors of OS were an epithelial subtype ($P < 0.001$), absence of lymph node metastasis ($P < 0.001$), completeness of cytoreduction scores of CC-0 or CC-1 ($P < 0.001$), and HIPEC ($P = 0.002$). The data suggest that CRS combined with HIPEC achieved prolonged survival in selected patients with DMPM [63].

For gastric PM, a multi-institutional study that included 159 patients from 15 institutions between February 1989 and August 2007 showed that CRS and HIPEC could achieve long-term survival in a selected subgroup of patients [64]. In a report from the BIG-RENAPE group of 81 patients with gastric PM who had a complete cytoreduction, 11% were disease-free at 5 years and were considered to be cured. This was possible in highly selected patients (low disease extent and complete CRS) [65].

As mentioned above, in a multicentric study of 523 patients from 23 French-speaking centers, Elias et al. reported a median overall survival of 30.1 months, a 5-year overall survival of 27%, and a 5-year disease-free survival of 10% with CRS and HIPEC in colorectal PM. These results are far superior to those produced by systemic chemotherapy alone. Though the role of HIPEC is being evaluated, the role of CRS in the treatment of PM is established [15].

In a multi-institutional study of 405 patients with peritoneal mesothelioma, 26 (6.4%) had multicystic tumors. Multicystic peritoneal

mesothelioma was shown to be a distinct subtype of peritoneal mesothelioma, where long-term survival may be achieved through cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [66].

Primary peritoneal serous carcinoma (PPSC) is a rare condition, histologically identical to ovarian serous carcinoma and often diagnosed at late stage. There is no standardized treatment for PPSC. A multi-institutional study showed that CRS and HIPEC may achieve long-term survival in patients with PPSC. Between September 1997 and July 2007, 36 patients with PPSC from 9 institutions underwent 39 procedures. The overall survival at 1, 3, and 5 years was 93.6, 71.5, and 57.4%, respectively. The median overall survival was not reached. By univariate analysis, the only factor that had prognostic value was PCI ($P = 0.03$) [67].

In a study carried out by the FROGHI, 314 patients with first recurrence in epithelial ovarian cancer were treated with CRS and HIPEC following systemic chemotherapy from 2001 to 2010. Mortality and morbidity rates were, respectively, 1% and 30.9%. Median follow-up was 50 months; 5-year overall survival was 38.0%, with no difference between platinum-sensitive and platinum-resistant patients; and 5-year disease-free survival was 14%. This study showed that HIPEC led to an encouraging survival in the treatment of first recurrence from ovarian cancer, better in case of complete surgery, with acceptable mortality and morbidity rates [68].

21.7.3 Studies That Evaluate the Role of Chemotherapy in the Treatment of PM

In a multi-institutional study from 1991 to 2014, 126 DMPM patients underwent CRS-HIPEC at 20 tertiary centers. This retrospective study suggests that adjuvant chemotherapy may delay recurrence and improve survival and that neoadjuvant chemotherapy may impact negatively the survival for patients with DMPM who undergo CRS-HIPEC with curative intent and such a strategy should be avoided in favor of CRS and HIPEC upfront [69].

A report from an international mesothelioma registry developed a staging system for malignant peritoneal mesothelioma. Eight institutions contributed to the registry. Data was prospectively collected for patients undergoing CRS and HIPEC. Two hundred ninety-four patients had complete clinicopathological data and formed the basis of this staging project. The proposed TNM staging system resulted in significant stratification of survival by stage when applied to the current multi-institutional registry data [70].

A study from the Netherlands Cancer Registry included a total of 1235 patients who received palliative chemotherapy, of whom 436 also received bevacizumab (35%). The results of this nationwide population-based study supported the rationale for bevacizumab in addition to palliative chemotherapy for patients with PM from colorectal cancer [71].

A French study aimed to define the role of adjuvant CT in addition to CRS and HIPEC for colorectal PM. Early postoperative CT does not improve OS after CRS and HIPEC for colorectal PM though a small benefit in progression-free survival was observed [72].

21.7.4 Other Aspects of Treatment of PM

In a multi-institutional study that included 52 patients from 16 institutions, the role of CT in determining the extent of PM was evaluated using the CT-PCI. The clinical impact of inaccuracies of CT-PCI was modest, and it was concluded that despite its drawbacks, CT-PCI remained an important tool for preoperative patient evaluation for CRS and HIPEC and should be supplemented with a PET-CT and diagnostic laparoscopy where required [73].

In a Dutch study, data pertaining to all patients diagnosed with synchronous PM from colorectal cancer between 2005 and 2012 was extracted from the Netherlands Cancer Registry ($n = 4623$). The proportion of patients diagnosed with synchronous PM from CRC treated with CRS-HIPEC has increased significantly over time, and at the time of publication, 10% of

patients with PM were being treated with CRS-HIPEC. Median survival in this population-based group is 32.3 months [74].

A study by the BIG-RENAPE and RENAPE groups showed that CRS and HIPEC is feasible for selected patients older than aged 70 years, albeit with a higher risk of medical complications associated with increased mortality [75].

Another study by the BIG-RENAPE group reported on hemorrhagic complications (HC) with oxaliplatin-based HIPEC. The overall incidence of HCs was 9.8%. When used with HIPEC, oxaliplatin significantly and independently increased the rate of HCs (15.7 vs. 2.6% for other drugs; $P = 0.004$, odds ratio 32.4). The authors concluded that the potential oncologic benefit of oxaliplatin and the risk of HCs should be considered in patients with PM who have a high PCI, as well as in at-risk patients [76].

A French multi-institutional study showed that signet ring cell gastric adenocarcinoma has a worse prognosis and different prognostic factors and is only poorly sensitive to perioperative chemotherapy as compared to non-signet ring cell adenocarcinoma and should be considered a different entity [77].

A study by the American Society of Peritoneal Surface Malignancies showed that mitomycin C (MMC) could be of greater clinical benefit than oxaliplatin in patients with colorectal PM undergoing complete cytoreduction. This benefit was observed in patients with favorable histologies and a low burden of disease with peritoneal surface disease severity score (PSDSS) of I OR II (PSDSS I/II). Median OS of 539 patients with complete cytoreduction was 32.6 months, 32.7 months for the MMC group, and 31.4 months for the oxaliplatin group ($P = 0.925$). However, when stratified by PSDSS, the median OS in patients having PSDSS I/II was 54.3 months in patients receiving MMC vs. 28.2 months in those receiving oxaliplatin ($P = 0.012$), whereas in patients with PSDSS III/IV, the median OS was 19.4 months in those undergoing HIPEC with MMC vs. 30.4 months in those undergoing HIPEC with oxaliplatin ($P = 0.427$) [78].

Studies on bio-specimens have allowed identification of diagnostic and prognostic biomarkers that could be useful adjuncts for therapeutic decision-making [79].

Another multi-institutional study explored the possibility of pregnancy after CRS and HIPEC.

Seven pregnancies were reported after CRS and HIPEC in women treated for peritoneal malignancies with or without the use of assisted reproductive technologies [80].

A study by the BIG-RENAPE group showed that protocols regarding cytoreductive surgery/HIPEC and the associated professional risks in France lack standardization and should be established [81].

Conclusions

This review highlights the importance of collaborative groups and registries in peritoneal surface oncology. Registries have helped in understanding the natural history of PM, risk factors, and prognostic factors and studying the effect of various therapies. They provide real-time evidence about what is actually happening in clinical practice. They provide level II evidence supporting the use of CRS and HIPEC in the treatment of PM, and this evidence/information can be used for designing clinical trials and treating patients when the results of clinical trials are awaited. The aspects of therapy that cannot be evaluated in clinical trials can be studied from the data provided by registries. Despite certain limitations like bias in recruiting patients, registries have been and will continue to be an important source of clinical evidence. Biobanks linked to registries are important for research and should be developed further. The RENAPE Registry and the Netherlands Cancer Registry could be considered two model registries of different kinds, and newer registries could be modelled on these. Effective collaboration between clinicians of various specialities is required to successfully run such programs especially in countries where there are no regulatory norms. The information derived from clinical practice is as important for research as the information derived from preclinical and clinical studies, and resources should be invested in capturing this information adequately for which registries seem to be ideal tool.

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22 Locoregional and Palliative Therapies for Patients with Unresectable Peritoneal Metastases

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22.1 Introduction

Nearly 30% of intra-abdominal malignancies present with peritoneal metastases (PM). Historically peritoneal metastases were considered a death knell with an average median survival of 6 months. For nonovarian malignancies, with peritoneal metastases, the median survival, if not treated, is 6 months for colorectal peritoneal metastases (CPM), 0.7 months for pancreatic cancers, and 3 months for gastric peritoneal metastases (PM) [1].

The combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can lead to prolonged survival with a significant improvement in the quality of life in certain selected patients with peritoneal metastases. It is the standard of care for patients with pseudomyxoma peritonei (PMP), peritoneal mesothelioma, and colorectal PM with limited peritoneal spread. Its role in ovarian cancer and gastric PM is currently being evaluated in clinical trials [2].

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However, a large proportion of patients with PM metastases are not candidates for this aggressive locoregional therapy and are treated with systemic chemotherapy alone. These patients may be symptomatic due to the peritoneal disease and may require medical surgical or endoscopic management. A peritoneal surface oncologist should treat these patients with equal vigor as those in whom the intent is curative especially in regions where palliative care services are deficient. This chapter will aim to define this subset of patients, the problems faced in managing such patients and how to manage such patients; the paucity of data for making evidence-based guidelines for managing such patients and the reasons for paucity of the data.

22.2 Defining Unresectable PM

Virtually any primary tumor can metastasize to the peritoneum. Of these, peritoneal spread is most common in patients with gastric, colorectal, and ovarian cancer. In most cases, PM are a part of widespread metastatic disease. The incidence of isolated peritoneal metastases (PM) varies from 60% in ovarian cancers to 50–75% in gastric cancer and in 40–50% of the patients with colorectal cancer (CRC) [2–4].

Patients with PM represent a poor prognostic subgroup. The survival in these patients is inferior compared to other sites of metastases [5].

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Systemic chemotherapy is less effective in these patients. Patients with PM become symptomatic more often as compared to other sites of metastases. In addition to systemic therapy, these patients often require management of symptoms related to peritoneal disease [6].

A curative approach is possible only in selected patients with PM. The remaining patients are excluded from radical surgery due to one of the following reasons:

- Extensive disease which precludes a complete cytoreduction (extensive small bowel involvement, involvement of the porta hepatis, bladder trigone or massive involvement of the pleural space for patients with PMP, ovarian cancer, malignant mesothelioma).
- Disease distribution and extent precludes a therapeutic benefit though the disease is technically resectable (patients with a PCI of >17–20 in colorectal cancer and >13 in gastric cancer).
- In patients with uncommon primary and secondary peritoneal tumors, CRS and HIPEC are performed for patients with limited disease and good general condition though the evidence is less robust in most cases. Patients who are excluded from CRS and HIPEC are treated with other locoregional and systemic therapies and require symptomatic treatment like other patients with PM.
- Patient's general condition and comorbidities make them unfit for a radical surgical procedure.

22.3 Natural History of Patients with Unresectable PM

The exact incidence of patients, who are unresectable and/or in an advanced stage to begin with, is difficult to define. The term peritoneal carcinomatosis was initially used in 1931 in a patient with ovarian cancer [7]. In the 1980s, PM was diagnosed when patients presented with bowel obstruction [8]. PM was the underlying cause in 15% of the patients requiring surgical intervention for intestinal obstruction [9–11].

In 1989, Chu et al. described the outcomes in 100 patients with PM arising from non-gynecological primary sites. The most common primary tumors were colorectal ($N = 45$) and pancreatic ($N = 20$) carcinoma. Of the patients with pancreatic cancer, 65% had liver metastases and 60% had ascites. Ascites was a poor prognostic factor in both pancreatic and colorectal cancer with no patient with PM of pancreatic origin with ascites surviving for more than 30 days. In patients with CRC, the disease-free interval after treatment of the primary, the presence of lung metastases, and ascites significantly influenced survival. The presence of liver metastases and extent of PM did not have an impact on survival. PM in sarcoma ($N = 7$) and breast cancer ($N = 6$) patients had median survival of 12 and 7 months, respectively [12].

The EVOCAPE 1 study was a prospective study carried out at nine centers in France from 1995 to 1997 to study the natural history of patients with PM arising from non-gynecologic primary sites [1]. All 370 patients underwent exploratory laparotomy to confirm the diagnosis and determine the extent of PM. The three commonest primary sites were the stomach, colon and rectum, and pancreas. The number of patients with metachronous and synchronous PM was similar. 34.3% has ascites and 16% had bowel obstruction. Majority of the patients had diffuse carcinomatosis and a poor median OS (3.1 months for gastric cancer, 6 months for colorectal cancer, and 2 months for pancreatic cancer).

In another study of 43 patients from Denmark, 70% of the patients had diffuse PM, 58.1% had extensive involvement of the small bowel mesentery, and 32% had ascites. Median OS was 6.3 months (range 0.4–33.1). Thirty-one patients (72.1%) received palliative chemotherapy. Median OS was 9.3 months (range 0.9–33.1) with versus 3.1 months (range 0.4–6.5) without chemotherapy (p ¼ 0.000). This difference was attributed to the less favorable patient characteristics in the latter group [13].

In a retrospective study of 3019 patients with colorectal cancer diagnosed over a 10-year period at Singapore General Hospital, the incidence of PM was 13% (349 patients) [14]. Of these patients only 3% (80%) had localized disease which could be treated with CRS and HIPEC.

Given the strong prognostic impact of disease extent in patient with colorectal cancer and gastric cancer, the focus is now of strategies for prevention and early detection of PM [15].

However, majority of the patients continue to be diagnosed with advanced disease, and recurrence in patients treated with CRS and HIPEC is common.

In a Dutch study, all patients diagnosed with synchronous PM secondary to colorectal cancer between 2005 and 2012 were extracted from the Netherlands Cancer Registry (n = 4623). The proportion of patients diagnosed with synchronous PM from CRC treated with CRS-HIPEC has increased significantly over time, and almost 10% of PM patients were treated with CRS-HIPEC. Median survival in this population-based group is 32.3 months [16].

Though CRS and HIPEC are performed with the intent of cure, around 70–80% of the patients will develop recurrent disease, and about half of these recurrences are confined to the peritoneal cavity [17–20].

In ovarian cancer, majority of the patients are diagnosed in an advanced stage in which PM is a common finding. Of these patients 75% develop recurrent disease within a few years, and the peritoneum is a common site for recurrence [21, 22]. Most of the patients who recur die within 5 years since recurrent disease is usually incurable [23].

The patients who are not treated with a curative intent may or may not have symptoms related to their disease. The symptoms need to be managed with surgical or nonsurgical treatment, and management of these symptoms which can severely impair the quality of life takes precedence over other treatment goals.

Thus, the goals and indication of treatment in patients with unresectable PM are as follows:

1. Symptomatic patients
To relieve symptoms—surgery, endoscopic procedures, medical management
To control the disease and prolong life—chemotherapy and other regional therapies
2. Asymptomatic patients
To control disease, to prolong life, and to prevent the development of complications/symptoms—chemotherapy and other regional therapies

22.4 Management of Symptomatic Patients

22.4.1 Clinical Presentation of Unresectable PM

Patients with PM are more likely to become symptomatic because of their disease than those with PM at other sites [24]. Many of the patients with unresectable PM maybe asymptomatic to start with but eventually develop symptoms due to disease. With chemotherapy there may be some reduction in the symptoms temporarily.

- General symptoms

Most of the advanced and metastatic cancers have a somewhat similar constellation of symptoms which adversely affects the quality of life. These are as follows:

- Nausea and vomiting

These symptoms are common in patients with metastatic disease with or without PM. It is one of the most common symptoms in advanced cancer. It is usually multifactorial. In peritoneal metastatic disease, it could be related to the disease itself, secondary to bowel involvement and/or gastritis, or it could also be due to various factors like anxiety, ongoing chemotherapy, gastritis, metabolic disturbances, and so on.

- Fatigue, drowsiness, lethargy, and weakness

Generalized weakness and cachexia are common in these patients. These are due to catabolic state which is seen in patients with metastatic disease. Loss of appetite, lethargy, and easy fatiguability are common. Drowsiness and delirium are usually preterminal.

- Nutrition and hydration problems

These could be specific because of any bowel obstruction secondary to the abdominal disease or due to poor intake secondary to general debility. A study had shown that almost 85% of the

patients will have some level of malnutrition which will preclude the use of chemotherapy which may improve the survival or control of the disease [25]. Further this small yet elegant study also showed that survival in patients who started chemotherapy during or after parenteral nutrition was higher than those who did not. A higher number of patients could also withstand the chemotherapy better.

- Constipation

Though this is often a general symptom in many extra-abdominal cancer, it is almost always seen in abdominal cancers with peritoneal disease. It is a very common complaint which is often ignored or undertreated. It is caused by a combination of factors like immobility, reduced fluid and food intake, and/or drugs. It can also be the presenting symptom of malignant bowel obstruction (MBO) if the obstruction is more distal.

- Edema and lymphedema

These are commonly present in abdominopelvic cancers presenting with peritoneal metastasis. Thromboembolic phenomenon, nutritional deficiency, and occasionally abdominal wall metastases can lead to edema and lymphedema of the abdominal wall and lower extremities [26]. Along with the general debility, this worsens the patients' quality of life [26].

22.4.2 Specific Symptoms

The two commonest and specific symptoms related to PM are bowel obstruction and ascites.

- Ascites

Malignant ascites forms due to increased vascular permeability and impaired lymphatic drainage [27]. The increase production of fluid outreaches the capacity of the lymphatic system to drain it, and this is aggravated by lymphatic blockade caused by cancer cells. As it has a high protein content, secondary alterations in vascular permeability also add to the fluid accumulation. Due to decreased venous return, the blood volume also reduces activating the renin-angiotensin system, leading to sodium retention and worsening of the situation [25]. Steadily increasing ascites leads to increase in the abdominal pressure leading to symptoms of pain, nausea and vomiting, dyspnea, loss of appetite, and reduced mobility.

VEGF plays a role in the pathophysiology of malignant ascites. Malignant cells that overexpress VEGF cause increased ascites production that is seen in ovarian, colorectal, and breast cancer patients [28]. In preclinical models, the administration of malignant ascitic fluid to animals without malignant ascites can cause malignant ascites [29]. In a study of CRS and HIPEC performed in patients with mucinous adenocarcinoma of colonic or appendiceal origin, the overall survival was longer in patients whose tumors did not express VEGF compared to those that did [30].

The VEGF family constitutes five structurally related proteins, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor. VEGF-C and VEGF-D are important in the process of lymphangiogenesis, while VEGF-A, VEGF-B, and placental growth factor are important in neovascularization of which VEGF-A is the most potent [31–33]. It acts through receptors VEGFR-1 and VEGFR-2 resulting in increased endothelial cell survival, proliferation, migration, and differentiation [34].

Malignant ascites may be complicated by hemorrhage, leading to chronic anemia. This could be due to vascularization of the PM or bleeding from the primary tumor and carries a poorer prognosis. No treatment has shown its effectiveness on peritoneal bleeding associated to malignant ascites. As malignant ascites is a poor prognostic factor, the aim of therapy is palliation and improvement of quality of life [35].

- Malignant bowel obstruction

At a consensus conference in 2008, malignant bowel obstruction was defined using the following criteria: clinical evidence of bowel obstruction (history/physical/radiological examination),

bowel obstruction beyond the ligament of Treitz, the presence of disseminated intra-abdominal cancer that is incurable, or a non-intra-abdominal primary tumor with clinical evidence of peritoneal metastases [36].

Retrospective reviews show that 10–28% of patients with colorectal cancer and 20–50% of the patients with ovarian cancer will develop MBO in the course of their disease [37]. Most commonly, involvement of the bowel is a diffuse process with disseminated intraperitoneal disease, and in only 10% of the patients, the metastases are isolated [38]. Breast cancer or melanoma is the most common non-gastrointestinal cause and can occur many years from primary presentation [39].

MBO can be mechanical or functional (Table 22.1) [40]. Mechanical obstruction can arise due to extrinsic tumor compression, intraluminal obstruction, or intramural occlusion. A adynamic obstruction is due to loss of peristaltic activity of the bowel which results from tumor involvement of the mesentery, wall, or nerves or malignant involvement of the celiac plexus or due to paraneoplastic syndromes.

Patients may have complete or partial obstruction. Generally, an intraluminal growth will produce complete obstruction at one site. Extrinsic compression can occur at multiple or a single site. Patients present with colicky pain, nausea and vomiting, and loss of appetite which gradually worsens. Abdominal distension develops which resolves with the passage of flatus or loose stool. The pain can be a dull continuous ache due to the tumor mass itself or colicky pain due to luminal bowel obstruction.

Table 22.1 Pathophysiology of bowel obstruction [40]

Pathophysiology of malignant bowel obstruction
Mechanical obstruction
Extrinsic occlusion of the lumen—enlargement of the primary tumor or recurrence, mesenteric and omental masses, abdominal or pelvic adhesions, postirradiation fibrosis that cause bowel compression
Intraluminal occlusion of the lumen results from tumor growth within the bowel
Intramural occlusion of the lumen—intestinal linitis plastica, tumor within the wall of bowel resulting in poor motility
Adynamic or functional obstruction
Intestinal motility disorders—tumor infiltration of the mesentery or bowel wall muscle and nerves or malignant involvement of the celiac plexus
Intestinal motility disorders—paraneoplastic neuropathy particularly in patients with lung cancer, chronic intestinal pseudo-obstruction (CIP), paraneoplastic pseudo-obstruction

22.4.3 Management

- Investigations

Basic blood investigations are performed to determine the organ function and general health of the patient.

- Imaging

An X-ray of the abdomen and ultrasound is performed as a screening modality to initially determine the presence of or absence of obstruction and ascites and see the status of the liver. A baseline CT scan with contrast is essential for evaluating the extent of disease, accurate staging, and deciding the choice of therapy for the patient. CT has a sensitivity of 93%, a specificity of 100%, and an accuracy of 94% in finding the cause and site of obstruction which is superior to an ultrasound and plain X-ray. A delineation of the cause of obstruction whether neoplastic or nonneoplastic needs to be done. A study by Woolfson et al. showed that almost 30% of patients with documented carcinomatosis can have obstruction from nonneoplastic causes like adhesions, hernia, mesenteric ischemia, and radiation enteritis [41]. Oral contrast is often not possible and is unnecessary as the fluid-filled bowel along with IV contrast actually enhances any mural abnormalities better than a contrast-filled bowel [42]. However, this limits the ability to evaluate the extent of disease distal to the obstruction which may be important in the decisionmaking.

Even in patients with no bowel obstruction, a CT scan has a limited ability to accurately predict the extent of the disease. In colorectal and ovarian cancer, the diagnostic accuracy of CT for deposits less than 0.5 cm or deposits located in

the pelvis, on the mesentery, or on small bowel is poor (<20%). The use of CT scans alters management plans in 21% of cases [40]. Alternatively, where the expertise is available, a MRI can be performed.

Endoscopy: After identifying the site of obstruction, an endoscopy helps to determine the cause and select patients for procedures like stent placement.

- Treatment

The management of peritoneal metastases has seen a radical change in the approach from essential palliative treatment for all patients to a potentially curative approach in at least some of the patients. As a result the level of expectation of both physicians and patients is high. Because of the lack of guidelines, it is difficult to define which patients may derive some benefit. Some poor prognostic factors are known and these should be kept in mind while making treatment decisions. The surgeons are specifically faced with moral and ethical dilemmas as a surgical intervention carries the risk of morbidity without providing any benefit.

22.5 Malignant Bowel Obstruction

The treatment of malignant bowel obstruction depends on the age and general health status of the patient, the site and type of obstruction, the extent of peritoneal and other disease, and the possibility of further therapy.

There is a lack of objective criteria for selecting patients, and no randomized controlled trials are available. The end points are not clearly defined. Various parameters have been used to assess the effectiveness of therapy which include survival (30 or 60 days) after intervention, the rate of hospital discharge, and the ability to tolerate oral supplementation for a given length of time (30 or 60 days) [43, 44]. In addition, patient-centric outcomes also need to be considered like symptom relief, improvement in the quality of life, and eventually the quality of death.

Table 22.2 Moral dilemmas according to frequency [45]

Providing honest information without destroying hope
Preserving the patients choice
Using advance directives
Withholding or withdrawing life support
Discontinuing life support
Patient and family with differing goals
Uncertainty about the patient's prognosis
Fear of causing death by giving pain medication

The treatment options for these patients are drug therapy, endoscopic stenting, and surgical intervention.

The patients and relatives' wishes, their understanding of the magnitude of the problem, the desire of the family that the maximum is done, and reluctance of the surgeon to give up all influence the decision. The surgeon may feel obliged to offer some treatment to keep hopes alive, and in most situations patients accept it. Any intervention should have a reasonable possibility of providing physiological benefit though this assessment itself may vary among clinicians. No intervention should be performed to meet the emotional, existential, and/or psychological needs of patients [45].

Some of the moral dilemmas faced by surgeons were outlined by Hoffman et al. (Table 22.2).

22.6 Surgical Interventions

22.6.1 Definition of Palliative Surgery

Palliative care is derived from Latin "palliare": to cloak. Its main focus is to provide relief of symptoms and provide an acceptable quality of life for a patient with a terminal illness. It incorporates not only medical care to alleviate pain and other sign and symptoms but also to ameliorate physical and mental trauma of the terminal diagnosis.

Palliative surgery can be defined in terms of preoperative intent, individual patient prognosis, and postoperative status [46]. Relief of pain and symptoms were regarded the two most important goals, whereas increased patient survival was the

least important goal. If the initial intent itself is not to remove all the tumor and just provide symptomatic relief, the surgical procedure becomes palliative to start with.

However, many times, the intent is to obtain complete tumor removal, and during the surgical process, the same is not possible. In such cases, the procedure is considered palliative based on the postoperative outcome [47]. There are some patients with malignant bowel obstruction where it is possible to completely remove the tumor surgically. The commonest example is a left colonic tumor causing large bowel obstruction. In patients with PMP with one or two levels of obstruction, a broad and commonly accepted definition is "an operative or invasive procedure employed to alleviate symptoms and to improve quality of life, but with minimal anticipated impact on overall survival of the patient" [48].

22.7 Indications and Contraindications

If the patient is unlikely to derive benefit from the procedure, it should not be performed. There are some known poor prognostic factors like gross ascites, prior use of chemotherapy leading to malnourishment and frailty, patients with proximal small bowel obstruction, and diffuse carcinomatosis leading to obstruction which has been associated with poor surgical outcomes [37]. Patients with carcinomatosis usually present with partial and intermittent bowel obstruction that is more commonly multilevel, and the risk of perforation or strangulation is minimal in these patients. In addition, these patients have motility disorders as well as secondary to extensive bowel wall infiltration by tumor deposits and/or involvement of the sympathetic and parasympathetic nerves that regulate peristalsis. Symptoms may resolve temporarily with nasogastric decompression but almost always recur. When such patients are taken to the operating room, the results are generally poor, with a high 30-day mortality (21–40%) and a high complication rate (20–40%), and there is a high likelihood that most will reobstruct within a short period of time [37].

Patients who have progressive disease with a short time to progression, those who have received multiple lines of therapy, are unlikely to have a favorable outcome. The surgical intervention may fail to relieve the obstruction, or the effect may be short-lived. There is a high risk of damage to the bowel and fistula formation which should be borne in mind.

22.8 Surgical Procedures for MBO

A careful evaluation of the prior treatments should be made before carrying out surgical exploration. Previous surgical details should be looked into in detail. Prior peritonectomy procedures with or without intraperitoneal chemotherapy result in dense adhesions between the bowel loops and parities which are more difficult to deal with as compared to patients who have had other major gastrointestinal procedures. The preoperative imaging is usually limited by the inability to administer contrast. Proximal obstruction is more easily evaluated on imaging but is seldom an isolated event. For example, in a patient with recurrent colorectal or ovarian cancer presenting with high jejunal obstruction, there is likely to be disease distal to the site of obstruction which may not be accurately evaluated preoperatively and a bypass procedure in such a patient in seldom possible. Peritoneal metastases involve the distal ileum first and then spread to the more proximal parts of the small bowel. Involvement of the proximal jejunum is usually associated with disease affecting the remaining small bowel as well.

The commonest surgical procedure comprises of a diverting stoma performed proximal to the site of obstruction. Proximal stomas are usually high output stomas that can lead to fluid electrolyte disturbances which needs to be kept in mind before creating such a stoma [40].

Legendre et al. reported outcomes in 98 patients undergoing surgery for malignant bowel obstruction from various primary sites of which colorectal and ovarian cancer were the commonest primaries. The median survival was 64 days and the perioperative mortality was 21%. The

quality of life of patients has been improved in 65% of cases. The survival and success of the procedure was influenced by the cause of the obstruction (local recurrence better than carcinomatosis) and the type of procedure performed (resection better than bypass) [49].

Abbas et al. reported outcomes in 79 patients who had laparotomy for small bowel obstruction due to recurrent cancer [50]. The primary cancer was colorectal in 31 patients, gynecologic cancer in 19, melanoma in 16, and other sites in 13. Patients underwent resection of PM with or without bowel resection. The rate of complications was 35% and mortality was 10%. Median survival was 5 months and was significantly better in patients with colorectal primary sites (median survival 7 months vs. 4 months; $p = 0.02$). Multivariate analysis showed that the extent of PM was the only factor that affected overall survival. Few series have reported mixed outcomes in patients with malignant melanoma presenting with bowel obstruction [51]. Surgery was effective in symptom palliation only and provided no survival benefit.

Patients with limited PM uncommonly present with obstruction, and in these patients, if other factors are favorable, an aggressive approach comprising of complete resection of all the tumors is beneficial. In patients with PM that are unresectable, a diverting stoma and/or a bypass procedure may provide meaningful benefit. Resection of peritoneal deposits or segmental bowel resection may not be successful. If it is successful, the results are short-lived, with a high morbidity and mortality related to the procedure, and are not advisable.

22.9 Endoscopic Procedures for Malignant Bowel Obstruction

Endoscopic procedures are feasible for gastroduodenal obstruction and colonic obstruction. Stents can be tried if the obstruction is at an accessible location, viz., up to duodenum, proximal jejunum in upper gastrointestinal tract, and colon up to 10 cm from anal verge in the lower gastrointestinal tract [52].

Gastric outlet obstruction (GOO) and proximal small bowel obstruction can arise due to direct infiltration of the primary tumor but also due to peritoneal metastases. The technical success rates for placement of a stent have been reported to be >90%, and clinical success with resolution of nausea and vomiting and improved ability to consume food orally is reported over 75% [53–56]. These stents can get obstructed due to tumor ingrowth or food impaction. The two main problems are stent migration which can occur if the tumor shrinks after chemotherapy and stent blockage due to tumor ingrowth which is dealt with by placing another stent of tumor ablation by Nd:YAG LASER or argon plasma coagulator [57].

Once again, such obstruction occurring in the setting of PM as an isolated event is rare and is usually associated with distal obstruction which may or may not be demonstrated on the imaging. The life expectancy of such patients is usually very short, and in the setting of a more distal obstruction, the stenting may fail to provide symptomatic relief.

The technical success rates for insertion of metallic stents range from 80% to 100%, and clinical improvement in symptoms reportedly occurs in more than 75% of patients [58, 59]. Many patients treated with stents have a durable relief of symptoms until death from progression of disease [60, 61]. Tumors located in the proximal transverse colon may be difficult to stent as is obstruction caused by extrinsic compression by tumor.

22.10 Drug Therapy for Malignant Bowel Obstruction

Patients who cannot undergo a surgical intervention have a shortened life span ranging 1–3 months. During this period they experience profound symptoms mainly due to accumulation of secretions leading to nausea and vomiting, colicky pain, and dehydration and due to the tumor itself leading

to pain, generalized weakness, and loss of appetite. A nasogastric tube is required to drain the secretions which produces a lot of discomfort.

The goals of pharmacological therapy are:

- To provide relief of continuous abdominal pain and intestinal colic
- To reduce the frequency of vomiting to a level that can be managed without a nasogastric tube (e.g., 1–2 times in 24 h)
- To provide relief of nausea
- To enable the patients to get discharged and be managed with home/hospice care [40]

Clinical practice recommendations for the management of MBO in patients with end-stage cancer published by the Working Group of the European Association for Palliative Care are elaborated in Table 22.3 [40].

Table 22.3 Clinical practice recommendation for palliative care in patients with MBO

Pain management
Continuous pain
Use of analgesic according to the WHO guidelines (CIV, CSI, TD)
Use of strong opioids
Colicky pain
Anticholinergics—scopolamine butylbromide and scopolamine hydrobromide
Reducing the gastrointestinal secretions
Anticholinergics • Scopolamine butylbromide (40–120 mg/day) • Glycopyrrolate (0.1–0.2 mg TID SC OR IV) • Scopolamine hydrobromide (0.8–2.0 mg/day)
Somatostatin analogue • Octreotide 0.2–0.9 mg/day CIV or CSI
Antiemetics
Metoclopramide (only patients with partial obstruction and no colicky pain)
Neuroleptics
Butyrophenones • Haloperidol (5–15 mg/day CRS)
Phenothiazines • Methotrimeprazine (50–150 mg/day CSI) • Prochlorperazine (25–75 mg/day rectal) • Chlorpromazine (50–150 mg/8 h rectal/SC)
Antihistaminic drugs—cyclizine (100–150 mg/day SC or rectally)

Abbreviations: *CSI* continuous subcutaneous infusion, *CIV* continuous intravenous infusion

22.10.1 Pain Relief

Analgesics are administered according to the WHO guidelines to provide pain relief. The most commonly used agents are opioids [62, 63]. The dose should be titrated according to the requirement and most usually be administered parenterally [64–68].

If colic persists despite the use of an opioid, hyoscine butylbromide or hyoscine hydrobromide should also be administered in association [69–71].

22.10.2 Anti-secretory Agents

The mechanism of action of anti-secretory drugs is complex. Inhibition of intestinal smooth musculature and decrease of the intestinal secretions result in a reduction of intestinal distension. The vicious circle distension-secretion-distension is thus interrupted, and both edema and wall ischemia are decreased thereby reducing the risk of necrosis and perforation. This therapy may lead to recovery of intestinal motility as the functional component is reduced [72, 73].

The two most commonly used anti-secretory agents are octreotide and hyoscine butylbromide.

Octreotide is a synthetic analogue of somatostatin with greater specificity and a longer duration of action (12 h) that inhibits the release and activity of GI hormones; reduces gastric secretion, secretion of bile, and splanchnic blood flow; slows the intestinal motility; and increases the mucous production. It also increases the absorption of water and electrolytes which is probably mediated through the inhibition of vasoactive intestinal polypeptide (VIP) [74–78].

Octreotide has shown to be more effective in reducing nausea and vomiting, producing an improvement in the appetite and reduction in fatigue compared to hyoscine butylbromide [79–81]. Octreotide produces its effect more rapidly as well. In a systematic review, this benefit was confirmed [82]. One study showed that the benefit was short-lived, and after a week the effect of both drugs was similar, whereas others showed that the effect was more long lasting

[79]. The main drawback is the need for subcutaneous injection three times a day or intravenous injections and the cost. Octreotide LAR has already been tested in the case of intestinal obstruction. It appears to be safe and well tolerated, albeit perhaps less effective than the standard formulation against obstructive symptoms [83–85].

The presence of somatostatin receptors (SST 1–5) has been found in tumors such as breast, ovary, prostate, kidney, colon, and pancreas and in lymphomas. Hence, it has been hypothesized that octreotide administration may lead to a prolongation of life, though this remains to be demonstrated in clinical practice [86–88].

Corticosteroids reduce peritumoral inflammatory edema and increase water and salt absorption [89]. As corticosteroids are relatively inexpensive and well tolerated, this class of drugs has been largely used in the palliative care setting for relieving gastrointestinal symptoms or resolving obstruction [90]. However, a clear benefit of these drugs has not been demonstrated [37].

Among the antiemetics, parenteral metoclopramide is the drug of choice for functional obstruction as it increases the GI motility and is contraindicated in complete obstruction [37].

Other antiemetics that can be used are butyrophenones, antihistaminics, or phenothiazines [91]. In patients with complete obstruction, the dopamine antagonist haloperidol is the drug of choice. It can be administered subcutaneously as a bolus or as a continuous infusion and may be combined with scopolamine butylbromide and opioid analgesic. Phenothiazines like methotrimeprazine (levomepromazine), chlorpromazine and prochlorperazine can be used as well [91].

22.10.2.1 Hydration

Maintaining adequate hydration leads to a reduction in nausea and vomiting [92]. Administration of 1–1.5 l/day of fluid containing glucose and electrolytes prevents metabolic complications. Hypodermoclysis is a valid alternative to intravenous administration of fluids for patients in whom venous access is a problem [92]. Providing sips of fluids orally, having frequent mouth care, and sucking ice cubes help in relieving dry mouth, commonly associated with the use of anticholinergics [93].

22.10.2.2 Parenteral Nutrition

The use of total parenteral nutrition (TPN) in patients with advanced incurable cancer is debatable. The role of TPN in the management of patients with inoperable bowel obstruction should be used cautiously and only in patients whom some benefit is anticipated [94, 95].

22.10.2.3 Ascites

This is the most common finding in patients with peritoneal cancer, primary or metastatic. In patients with peritoneal surface disease (PSD), malignant ascites is associated with a short life expectancy, ranging from weeks to a few months [12, 96].

Large amounts of ascites can cause increased abdominal pressure with troublesome symptoms like pain, dyspnea, loss of appetite, nausea, reduced mobility, and problems with the body image.

The best way to control the ascites is to remove the cause, that is, the PM. Systemic chemotherapy is the mainstay of treatment in most of these patients. A modest increase in life expectancy of up to 4–5 months has been observed, depending on the primary disease [97, 98]. There may be a good response initially but it generally recurs. Some patients may have no response.

In addition, supportive measures like paracentesis, fluid and salt restriction, and diuretics are used to provide symptomatic relief but have no effect on the disease process itself. Direct administration of chemotherapy to the peritoneal cavity by various methods and using different agents has been attempted yielding favorable results in selected patients. Most of the times, multiple therapeutic strategies are used for the same patient.

Strategies for managing malignant ascites thus include:

- Supportive therapy for symptomatic relief
- Systemic chemotherapy and targeted therapies
- Locoregional therapies

22.10.3 Supportive Therapies for Symptom Control

22.10.3.1 Paracentesis

Studies show that almost 90% get temporary relief from symptoms caused by ascites [35]. However, repeated large-volume paracentesis is fraught with complications such as hypoalbuminemia, hypotension, renal impairment, and infections. A systematic review done by Becker et al. summarized the following points which should be kept in mind while doing paracentesis [35]:

- Up to 5 liters of ascitic fluid can be removed at one session.
- No fluid resuscitation is required till removal of 5 liters of fluid, if there is no hemodynamic or renal impairment.
- If patient is hypotensive or dehydrated, then fluid resuscitation is necessary before attempting paracentesis. There is no consensus over the choice of fluids, and colloids and albumin have not shown to be better as compared to crystalloids.
- However, face-to-face studies comparing fluid restriction versus fluid replacement during paracentesis have not been done; hence the interpretation of these guidelines is advised with caution [99].

22.10.3.2 Diuretics

Diuretics are inconsistently used for reduction in ascites. However, the evidence available is also weak and as such their use is still controversial.

22.10.3.3 Peritoneovenous Shunts

This is an invasive procedure with its own set of complications and is needed to be used judiciously. Contraindications include ascites protein content >4.5 g/dl and hemorrhagic ascites, coagulation disturbances, liver failure, mutinous ascites, and loculated ascites [100]. There is no increase in the risk of hematogenous metastases to the peritoneo-hematogenous communications [100]. Due to reasons unknown, however, the response rates are better in ascites secondary to peritoneal disease from ovary or breast cancer as compared to gastrointestinal cancer [100, 101]. This is an invasive procedure with almost 6% risk of complications like pulmonary edema, pulmonary emboli, disseminated intravascular coagulation, and infection and hence is advised as a last resort when other techniques have failed and patient has a limited life span [35].

22.10.4 Locoregional Therapies

Palliative HIPEC/laparoscopic HIPEC
Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
New drugs for intraperitoneal administration
Laparoscopic aspiration of mucinous ascites

22.10.5 Palliative HIPEC

Use of palliative laparoscopic HIPEC has been proposed to treat debilitating malignant ascites [102]. By destroying the peritoneal carcinomatosis, HIPEC may induce hemostasis and progressive fibrosis of the peritoneum, preventing ascites and bleeding [102].

The main drawback of CRS and HIPEC is the risk of morbidity and mortality. In laparoscopic HIPEC, since the goal is control of ascites, CRS is not performed which reduces the morbidity significantly. It is further reduced by performing HIPEC laparoscopically leading to fewer perioperative complications [102]. Several studies have reported outcomes of laparoscopic HIPEC for control of ascites (Table 22.4).

The efficacy of HIPEC in all these studies was evaluated by the resolution of ascites, and it persisted in most patients till death due to progressive disease or at the last follow-up. There was minimal morbidity and no mortality and the median survival ranged from 3 to 9 months. None of these studies included validated QOL surveys as part of their assessment. Though the overall impact on QoL cannot be determined, control of ascites leads to an improvement in the performance status of patients. One report describes an ultrasound-guided approach using heated chemotherapy solution.

Table 22.4 Outcomes for palliative HIPEC for control of malignant ascites

Ref/year	No. of patients	Primary site	HIPEC	Drugs used	Response rate (%)	Median survival (range)
[103] 2006	14	Multiple sites	Cisplatin and doxorubicin or mitomycin	Laparoscopic	100	203 days [21–267]
[104] 2008	5	Gastric	Mitomycin and cisplatin	Laparoscopic	100	89 days [33–144]
[105] 2008	1	Mesothelioma	Cisplatin and doxorubicin	Laparoscopic	100	6 months
[106] 2009	52	Multiple sites	Cisplatin and doxorubicin or mitomycin	Laparoscopic	98	98 days [21–796]
[107] 2010	16	Gastric	5-FU and oxaliplatin	Laparoscopic	88	5 months [2–9]
[108] 2013	62	Ovarian Gastrointestinal	Cisplatin and doxorubicin Mitomycin	Laparoscopic B-ultrasound guided	93 94	8 months [2–20] 9 months [2–30]
[109] 2014	299	Multiple sites	Mitomycin Carboplatin Oxaliplatin Cisplatin	Open	93	5.3 months

De Mestier performed HIPEC at 43 °C with mitomycin C and cisplatin in two patients with hemorrhagic ascites causing severe anemia. Both patients had cessation of peritoneal bleeding; there was no postoperative complication or relapse of ascites in either of the patients [108].

In a study of five patients with malignant ascites of gastric origin requiring repeated paracentesis, treated with HIPEC with mitomycin C and cisplatin at an inflow temperature of 45 °C, there was complete resolution of ascites in all five patients. The mean operative time was 181 min, and there was no perioperative morbidity except for delayed gastric emptying in one patient or mortality [104].

In another study of 14 patients with malignant ascites from various primary sites, HIPEC was performed with cisplatin and doxorubicin or mitomycin C leading to control of ascites in all the 14 patients. There was a small clinically insignificant fluid collection in one patient [103].

At a Chinese center, the possibility of placing HIPEC perfusion catheters using B-mode ultrasound was explored and the cost and perioperative outcomes compared to laparoscopic HIPEC [108, 110]. Sixty-two patients with malignant ascites secondary to ovarian or gastrointestinal primary tumors were randomly treated with B-ultrasound-guided HIPEC (therapeutic group) or laparoscopy-assisted HIPEC (control group). A monthly follow-up with ultrasound or CT scan was done for 21 months for all patients. The patient characteristics were matched in the two groups. The duration of procedure was shorter in the ultrasound group (35 vs. 85 min), and mean hospitalization cost was also lower ($p < 0.01$) with no significant difference in ascites remission rates, median survival times, and port site metastases (or drain site metastases) between the two groups. The authors concluded that B-mode ultrasound-guided HIPEC had a similar efficacy to laparoscopic HIPEC but shortened the operating time and reduced the hospitalization costs [108].

Randle et al. performed a retrospective analysis of 1000 patients undergoing CRS and HIPEC at their center of which 299 had malignant ascites due to PM from various primary sites. The efficacy of HIPEC in controlling ascites was evaluated in these patients. There was a complete resolution of ascites in 288 (93%) patients at a follow-up of three months. In

patients with ascites, complete cytoreduction was obtained in 15 versus 59% when ascites was not present ($p < 0.001$). In patients who had resolution of ascites, 84% had gross residual disease, and in patients who had persistent ascites at 3 months, 86% had gross residual disease. Univariate analysis revealed that the type of primary disease, resection status, duration or agent of chemoperfusion, and performance status did not predict failure to control ascites. They concluded that HIPEC in patients with incomplete cytoreduction could provide a benefit by controlling ascites in selected patients [109]. These patients as a whole represent a better prognostic group as they were considered for a curative resection as opposed to patients in other studies where HIPEC was performed for palliation alone, and thus, the benefit of HIPEC as a purely palliative procedure cannot be determined from this study though the number of patients is relatively large.

The authors attributed the control of ascites to HIPEC rather than CRS as indicated by the resolution of ascites in patients with gross residual disease.

They also developed a scoring system for ascites based on the findings of the preoperative CT scan.

The abdominal cavity was divided into nine regions similar to those used in calculating the PCI except that the small bowel regions were excluded. When ascites was present within a particular region, 1 point was assigned, without ascites a score of 0 was assigned. Thus, preoperative ascites was graded on a scale from 0 to 9 using this point system. For those cases where a preoperative CT was not available but the operative note indicated volume >3.5 l of ascites, a score of 9 was applied.

Valle et al. reported complete resolution of ascites in 51/52 patients treated with laparoscopic HIPEC for malignant ascites. There was no perioperative mortality [106].

The raised intra-abdominal pressure during laparoscopic HIPEC may increase the drug penetration into tissues. Though this has been demonstrated in experimental studies, clinical evidence to support this benefit is lacking [111, 112]. It has been hypothesized that the heated chemotherapy may eradicate viable cancer, several cell layers deep on all the peritoneal surfaces. Then, a thin layer of fibrosis may develop on the exposed surfaces. The fibrous layer may direct the cancerous fluid into the capillary bed and thereby into the systemic circulation, causing a resolution of the problematic re-accumulation of ascites [103]. Abdominal sclerosis and induction of dense adhesions are probably the major factor of efficacy of this technique.

These results seem promising but the selection criteria and prognostic factors have not been defined. A comparison with systemic chemotherapy is lacking; however, the morbidity is minimal and systemic chemotherapy itself is not without side effects. It may be concluded that patients with ascites from unresectable PM may experience control of ascites with laparoscopic HIPEC with minimal morbidity. The efficacy in patients who have chemotherapy refractory ascites is not known.

22.10.6 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel approach to deliver IP chemotherapy to patients with PM. It has shown efficacy in the palliative setting in patients with PM who have progressed on one or more lines of chemotherapy. It has also been used to control chemotherapy refractory ascites though the results in these patients have not been reported separately. PIPAC is a feasible option in patients with malignant ascites who have failed to respond to one or more lines of chemotherapy and in patients who do not want chemotherapy. The dose of chemotherapeutic drugs is one-tenth of their systemic dose leading to fewer side effects, multiple applications are possible at 6–8 week intervals, and systemic chemotherapy can be used concurrently.

22.10.7 New Agents for Intraperitoneal Use

Two new drugs that have shown benefit in this situation are catumaxomab and bevacizumab. Apart from these, researchers have tried various methods like intraperitoneal instillations of tumor necrosis factor, interferons, *C. parvum*, or radioisotopes like gold. However, none has shown to have great benefits [113–116].

22.10.8 Catumaxomab

Epithelial cell adhesion molecule (EpCAM, CD326) is a surface antigen that is expressed on normal epithelial cells as well as tumor cells [117]. Catumaxomab is a non-humanized chimeric antibody, consisting in a mouse-derived anti-EpCAM Fab (fragment antigen-binding) region and a rat anti-CD3 Fab. Thus, it can bind to three different types of cells: tumor cells expressing the epithelial cell adhesion molecule (EpCAM positive), T lymphocytes (CD3 positive), and also accessory cells (Fcγ receptor positive), such as macrophages, natural killer cells, and dendritic cells [118, 119].

Catumaxomab binds to human EpCAM-positive tumor cells, thereby activating a complex antitumor immune reaction through various mechanisms like antibody-dependent cellular cytotoxicity, phagocytosis, and T cell-mediated cytotoxicity [120–123]. Catumaxomab after intraperitoneal administration has shown to reduce ascites and delay the requirement for paracentesis in patients with refractory malignant ascites from ovarian and other non-gynecologic malignancies [124, 125]. In a phase II/III trial (EudraCT 2004-000723-15; NCT00836654), patients (n = 258) with recurrent symptomatic malignant ascites refractory to systemic chemotherapy were randomized to paracentesis plus catumaxomab (catumaxomab) or paracentesis alone (control) and stratified by cancer type (129 ovarian and 129 nonovarian) [126]. Intraperitoneal catumaxomab infusion was given on days 0, 3, 7, and 10 at doses of 10, 20, 50, and 150 μg, respectively. The puncture-free survival was significantly longer in the catumaxomab group (median 46 days) than the control group (median 11 days) ($p < 0.0001$) as was median time to next paracentesis (77 versus 13 days; $p < 0.0001$). Patients receiving catumaxomab were less symptomatic from their ascites and showed an increase in OS with the most significant benefit seen in patients with gastric cancer (n = 66; 71 versus 44 days; p = 0.0313). Most of the side effects were mild and there were catheter-related infections. Of the patients 15% had serious adverse events [127].

Following intraperitoneal injection with catumaxomab, antitumor immunity develops which can be long lasting in some patients [128].

In another randomized study published in 2008, of the 55 patients undergoing surgery for gastric adenocarcinoma (T2b/T3/T4, N±, M0) with a curative intent, 28 received an intraperitoneal catumaxomab infusion in the immediate postoperative period and were compared to 27 patients who underwent resection alone [127]. Catumaxomab was administered during surgery and then postoperatively on days 7, 10, 13, and 16 at increasing doses, and 78% of the patients were able to receive all five infusions. The EpCAM antigen was present in 100% of patients. Treatment related side effects were seen in 40% of the patients and resolved in most of the cases. This study demonstrated that adjuvant intraperitoneal catumaxomab, after gastrectomy, is feasible, safe, and well tolerated. The same findings were reported in another study [129].

A multicenter, randomized, phase II study is ongoing comparing dosages of catumaxomab in patients with limited PM (PCI < 12) from gastric cancer, after complete cytoreduction of disease. The goal of this study will be to assess 2-year overall survival, as well as monitor toxicity and morbidity. Besides this analysis, translational research will be conducted to determine immunological markers of catumaxomab efficacy and to correlate these markers with clinical efficacy [130].

22.10.9 Bevacizumab

Vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis, is secreted by tumor cells in a paracrine manner and leads to formation of ascites. In addition, peritoneal mesothelial cells, monocytes/macrophages infiltrating malignant effusions, and even tumor-infiltrating T cells are known to produce VEGF [131–133]. Bevacizumab is a humanized monoclonal antibody that acts against the vascular endothelial growth factor (VEGF). Animal studies have shown that its intraperitoneal administration is safe and can lead to ascites control [134–137]. It has been used in the clinical setting for palliative treatment of refractory malignant ascites with varying results. A few case reports and small case series have shown good control of ascites with IP bevacizumab [138–141]. The dose used varied from 5 to 15 mg/kg administered every 3–4 weeks. Some studies showed the control of ascites with a single dose [141].

In a study of 29 patients, the median paracentesis-free survival was 17 days and 11 days for patients with ovarian and gastric cancer, respectively, using IP bevacizumab.

A multicenter double-blind, placebo-controlled phase II study – AIO SUP-0108 – showed no benefit of intraperitoneal bevacizumab as compared to placebo in patients with chemotherapy refractory malignant ascites of gastrointestinal origin though there was a reduction in the ascites in patients receiving bevacizumab. However, 17 of the 33 patients in the study group had ascites secondary to pancreatic adenocarcinomas which may be responsible for the poor results overall. The complication rate was similar in the experimental and control groups.

22.10.10 Laparoscopic Aspiration of Mucinous Ascites in Patients with PMP

In PMP, where the PCI is too high and/or with extensive involvement of the bowel, curative CRS with HIPEC is not feasible. In such patients, laparoscopic aspiration of the mutinous material provides excellent symptom relief with minimal morbidity [142].

22.11 Management of Other Symptoms

Nausea and Vomiting: This can be multifactorial. Often it is impossible to define the cause. The treatment should be multifactorial and should follow the following principles [143]:

- Prescription of multiple drugs if required.
- Liberal dosing patterns including doses as per need.
- If there is significant vomiting, consider subcutaneous patches.
- Commonly used drugs included domperidone, metoclopramide, and dexamethasone. Cyclizine and haloperidol are used with caution in view of their side effect profile.
- Consider longer-acting antiemetics to reduce tablet burden.

22.11.1 Fatigue, Drowsiness, Lethargy, and Weakness

These are secondary to generalized debility and cancer cachexia, the management of which explained in detail in the following section.

22.11.2 Nutrition and Hydration

- It has been seen that almost 85% patients suffer from malnutrition. Correction of this malnutrition can improve the general condition and make the patient fit for further treatment options [25]. Most of the advanced cancers present with cancer cachexia which if not corrected gradually worsens the performance status of the patient. Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully

reversed by conventional nutritional support and leads to progressive functional impairment. Patients have a reduced intake of food and alteration of the normal metabolic processes which leads to a negative protein and energy balance [144]. The treatment goal in these patients is to reverse the loss of body weight and muscle mass. If weight gain is not possible, at least further weight loss should be prevented. The salient features for management of cancer cachexia and improving nutrition and hydration are as follows.

- Mutimodal therapy should be offered.
- Enteral nutrition is the preferred route with daily calorific requirement aimed at maintaining body weight or in the least preventing further loss.
- Steroids and progestins have found to stimulate appetite and have been tried with some success [144].
- Prokinetics may be helpful in cases of gastroparesis and dyspeptic patients.
- Thalidomide, cannabinoids, and omega 3 fatty acids have been tried with mixed results and are thus not recommended.
- Nondrug treatments like counseling and relaxation therapies have found to benefit some patients.

22.11.3 Edema and Lymphedema

Generalized edema or anasarca is usually a result of profound hypoalbuminemia. Correction of cancer cachexia and malnutrition helps in ameliorating it. However, in view of the severe catabolic state of the terminal patient, it is often not possible to reverse the edema. Localized edema with or without cellulitis may happen on the abdominal wall secondary to repeated paracentesis and abdominal wall metastases. Use of antibiotics and local skin care may help in reducing the infection. Occasionally an isolated abdominal wall deposit can be excised. Salt restriction, pressure garments for extremities, and physical therapy are some measures attempted along with nutritional support.

Lymphedema is often seen if previous pelvic surgery or radiation has been done. It is one of the most poorly understood, relatively underestimated, and least researched complications of cancer or its treatment. In advanced peritoneal metastases, it may be seen on the lower extremities and torso. It is an independent predictor of debility and loss of quality of life in the terminal stages [145]. The usual symptoms include edema, skin changes, and heaviness and aching of the limbs. This makes the person less mobile leading to worsening performance status and gradually making the patient bedridden. General treatment principles include skin care, compression and support, movement and exercise, and treatment of superadded infections if any.

22.11.4 Constipation

It is one of the commonest symptoms caused by a combination of factors like debility, decreased mobility, concomitant medications, reduced food and fluid intake, and bowel pathology. Patients can also present with paradoxical overflow diarrhea. This symptom is often undertreated and as such the research on management of constipation is very limited. The following can be used as guiding principles [144]:

- Of utmost importance is patient education and information about the causes of constipation, increasing fluid intake and making appropriate dietary changes to help improve symptoms.
- Patient preference should be followed for greater compliance of laxatives.
- Palatability and drug tolerability should be considered before prescribing.
- Examine lower rectum or stoma should be examined for fecal impaction.
- Most patients on opioids need regular laxatives.
- A combination of still softeners and stimulant laxatives is often required for good control of symptoms.
- Requirements should be reviewed and titrated every 2 days.

- If bowels have not opened in 3 days, further evaluation is necessary.
- If colic is present, the patient should be evaluated to rule out impending MBO.

22.12 Management of Asymptomatic Patients

There are patients with PM who are excluded pre- or intraoperatively from a curative approach and are asymptomatic. The goals of therapy in these patients are to prolong survival and maintain the quality of life. Systemic chemotherapy is the cornerstone of therapy for these patients. Simultaneously, intraperitoneal therapies are being developed to treat these patients who are not eligible for CRS and HIPEC. Some of new and old therapies are being used as neoadjuvant therapy to reduce the burden of peritoneal disease making subsequent CRS and HIPEC feasible.

As such, these patients represent a gray zone as far as treatment is concerned; the management protocols fall in a continuum between curative and palliative. This has been exemplified by Von Grueningen et al. in their integrated model of palliative care algorithm for ovarian cancers. This can be applied to all advanced peritoneal malignancies and inoperable peritoneal metastases as well (Fig. 22.1) [146].

Based on this model, the care is provided from the point of diagnosis, and as curative options diminish, the palliative options become progressively important (Fig. 22.1). Emerging paradigms in palliative care suggest early intervention and use of general care and specialists to provide multidisciplinary care as per the needs.

As the intent of therapy in palliative care is solely for symptom control with no definable end point, palliative care research has its unique set of challenges. Certain points have been suggested for better accrual for patients in clinical trials on palliative care such as keeping the eligibility criteria as broad as possible and at the same time maintaining as much patient homogeneity as possible [147]. With palliative care being recognized as a separate branch of oncology and as speciality

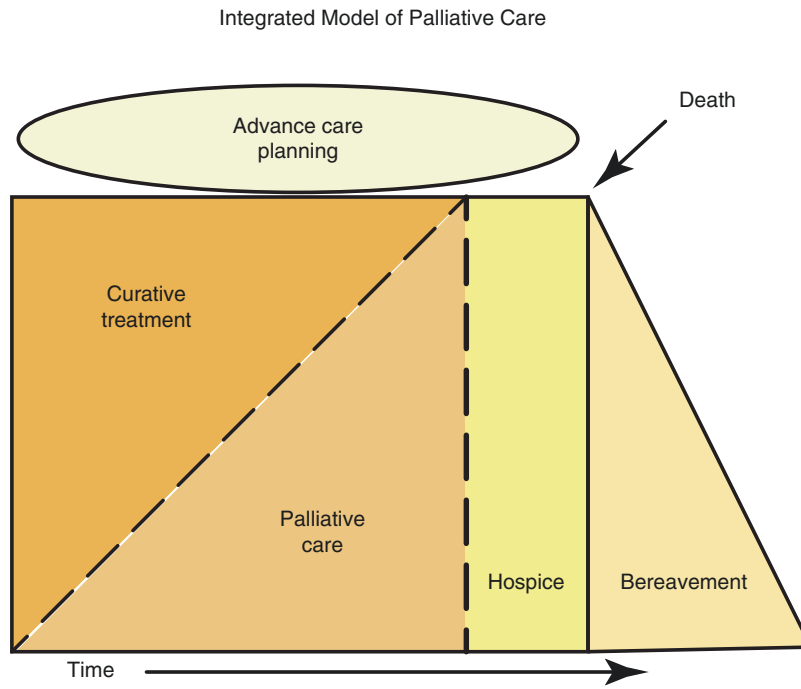

Fig. 22.1 Integrated model of palliative care—care is provided from the time of diagnosis, and as the curative options diminish, the palliative options become progressively more important (adapted from Ref. [146])

in itself, the volume of research has expanded slowly but surely. Many of the therapeutic interventions can marginally improve survival and radically improve the quality of life.

22.12.1 Debulking Surgery

Patients with extensive disease may be declared inoperable before the procedure. Without treatment, these patients experience worsening of symptoms, bowel obstruction, and death. They might obtain some symptom relief and prolongation of life by a debulking surgery. The likelihood of benefit from surgical treatment in such cases has to be balanced against the risk of postoperative complication and the ensuing deterioration in the quality of life. Some patients planned for a complete cytoreduction are found to have unresectable disease during surgery and end up with a CC-2/3 resection.

There is no consensus on what is the most appropriate treatment for such patients.

The questions that need to be addressed in this situation are:

- Should a debulking surgery be performed in patients that seem inoperable?
- Which are the patients that benefit from debulking surgery?
- What should be the extent of surgery?
- Should such procedures be combined with perioperative chemotherapy?

22.12.2 Pseudomyxoma Peritonei Arising from Appendiceal Tumors

There is evidence showing a benefit of debulking surgery in patients with pseudomyxoma peritonei. Moran et al. in their study of 1000 patients reported a 5- and 10-year overall survival of 39.2% and 8.1%, respectively, in 242 patients who had a major tumor debulking [148]. Major debulking in their series comprised of an extended right hemicolectomy, greater omentectomy and splenectomy with an ileocolic anastomosis, or a total colectomy with an end ileostomy [148].

Another strategy as proposed by Delhorme et al. is to perform maximal tumor debulking, leaving less than 20% of the disease in areas where it is not likely to cause symptoms, with the goal of obtaining prolonged OS and long-lasting relief of the symptoms, thus ensuring a good quality of life [150]. The visceral resections mostly performed comprise the distal portion of the stomach, a total or subtotal colectomy, and a part of the small bowel preserving at least 2.5 m. The areas on which tumor may be left behind are the undersurfaces of the diaphragms, the Glisson's capsule, the whole rectum (if there is no stenosis), and the non-obstructive nodules measuring less than 10 mm on the small bowel. The authors recommend that all efforts should be made to avoid creating a stoma as stomas created in such situations have a greater likelihood of being permanent. Use of any form of intraperitoneal chemotherapy is not recommended by them in view of the higher risk of major morbidity. The 5-year overall survival was 46% in this series compared to 15% and 30% in other series [149, 150].

Glehen et al. reported 3-year and 5-year survival rates of 34% and 15%, respectively, in 174 patients who had incomplete cytoreductive surgery with or without perioperative intraperitoneal chemotherapy [151]. Thirty-seven patients who did not receive any form of intraperitoneal chemotherapy due to inter bowel adhesions had an inferior survival to those who received either HIPEC or EPIC or both ($p < 0.001$). Sixty-one patients had HIPEC, and these patients had a better survival than those who did not ($p < 0.001$). The authors also mentioned that there was a selection bias in favor of patients who had perioperative chemotherapy (POC). No patients with lymph node involvement were alive at 2 years, and the 2-year survival of patients with signet ring cells was less than 30%. The authors did not recommend an incomplete CRS and POC for these patients [151].

Thus, there is enough evidence to suggest that such procedures may provide a prolongation of life and symptomatic relief in selected patients. However, such decisions should be made by multidisciplinary teams and the treatment executed in experienced centers, to ensure that no patient

is deprived of a complete cytoreduction where it is possible. Whereas the use of HIPEC is recommended by some, others do not advocate it.

22.12.3 Debulking Surgery for Other Tumors

Patients who have an incomplete cytoreduction do not have a benefit over systemic chemotherapy alone in other primary and secondary tumors. The current literature suggests that HIPEC in the setting of an incomplete cytoreduction does not offer any advantage in terms of overall survival except for selected cases of malignant mesothelioma [152–154].

22.12.4 Neoadjuvant Therapies of Advanced PM

A new bidirectional chemotherapy (neoadjuvant intraperitoneal-systemic chemotherapy protocol (NIPS)) was developed by Yonemura and his collaborators from Japan to induce a reduction of the peritoneal cancer index of patients with gastric PM [155]. NIPS can attack PM from both sides of peritoneum, not only from the peritoneal cavity but also from the subperitoneal blood vessels, and is considered a bidirectional chemotherapy [155]. Following a response to NIPS, selected patients become candidates for CRS and HIPEC. This treatment which has produced response rates of over 70% in patients with gastric PM is being investigated by Francois Quenet from Montpellier for CPM in the NIPOX trial [156]. In a pilot study, six patients with unresectable peritoneal disease of colorectal origin were included in the study. An intraperitoneal implantable chamber catheter was inserted during the laparotomy that evaluated the extent of the peritoneal disease (peritoneal carcinomatosis index 25–39). Patients then underwent intraperitoneal chemotherapy with oxaliplatin 85 mg/m^2 in combination with systemic chemotherapy (FOLFIRI or simplified LV5FU) and a targeted therapy every 2 weeks. Two patients completed the four intraperitoneal (IP) chemotherapy cycles without major toxicity. Two catheter perfusion incidents were reported due to the abdominal wall thickness. For one patient with aggressive disease, best supportive care was initiated after the first course of chemotherapy. The tolerance was acceptable for 85 mg/m^2 IP oxaliplatin combined with systemic therapy in these patients. This study formed the basis for the NIPOX trial [157].

Patients with a PCI of >17 are given a combination of systemic chemotherapy and intraperitoneal chemotherapy through two intraperitoneal catheters with implantable chambers. Responders are subsequently evaluated for CRS and HIPEC. Simultaneously, a dose escalation study for intraperitoneal oxaliplatin is being performed. Along similar lines is the IPOXA trial (NCT02866903), which is a phase 1/2 trial studying the administration of IP oxaliplatin (normothermic port-directed) with systemic FOLFIRI and bevacizumab in CPM of uncertain respectability. Currently, this trial is looking at morbidity, dose-limiting toxicity, and overall response rates of this treatment strategy.

22.12.5 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

PIPAC is a new method of intraperitoneal drug delivery that is currently being used for patients who have unresectable peritoneal metastases and have progressive disease on systemic chemotherapy or do not want systemic chemotherapy.

22.12.5.1 Background, Rationale, and Preclinical Data

The concept of a therapeutic pneumoperitoneum was introduced in 2000 by Marc Reymond and colleagues who developed a micro pump suitable for minimally invasive surgical procedures in which micro droplets of the drug could be distributed in the carbon dioxide pneumoperitoneum, creating a "therapeutic capnoperitoneum" [158]. The current device is a spraying device, similar to a nebulizer that consisted of an injector, a line, and a nozzle, and used mechanical pressure [159]. It could be introduced through a trocar and produces a more even distribution of methylene blue and

better tissue uptake as compared to simple lavage. The distribution to areas like the unexposed part of the stomach and the cecum, surfaces of the small and large intestines, and undersurfaces of the diaphragm which often remained untouched by simple peritoneal lavage was superior and uniform in this study. The use of a nebulizer laparoscopically has been described by other investigators for different purposes like postoperative pain control and intraperitoneal tumor control [160–162].

A proof of principle study confirmed the efficacy of this technique [163].

22.12.5.2 Pharmacokinetic Advantages of PIPAC

The term pressurized intraperitoneal aerosol chemotherapy (PIPAC) was coined for this therapy which combined the principles of a "therapeutic capnoperitoneum" with that of aerosolized chemotherapy [164]. There is more homogenous distribution of the drug and better tissue uptake [165]. PIPAC overcomes several limitations of the commonly used methods of intraperitoneal chemotherapy.

22.12.5.3 Technique of PIPAC

The technique of PIPAC first described by Marc Reymond and collaborators is as follows. A capnoperitoneum of 12 mmHg at 37 °C is created, and two balloon trocars are applied [166]. A laparoscopic evaluation is performed and the PCI is determined. Representative areas are biopsied and ascites is drained. A biopsy of specific areas can be done for response evaluation in the subsequent procedures, and areas of suspicion can also be biopsied. A nebulizer is connected to a high-pressure injector and inserted into the abdomen through a trocar. A pressurized aerosol containing cisplatin at a dose of 7.5 mg/m^2 body surface in 150 ml NaCl 0.9% is administered immediately followed by doxorubicin 1.5 mg/m^2 in 50 ml NaCl 0.9% for gastric PM, ovarian PM, and peritoneal mesothelioma. For colorectal PM and appendiceal tumor, oxaliplatin (92 mg/m^2) is used. The system is kept in this steady state for 30 min (application time). The toxic aerosol is then removed through a closed system. The trocars are removed and the wounds repaired.

22.12.5.4 Electrostatic PIPAC

Kakchekeeva et al. have introduced electrostatic PIPAC (ePIPAC), proposing that electrostatic charging the aerosol particles may further enhance the pharmacologic properties of PIPAC [167].

The performance and safety of this equipment has been demonstrated in bench studies, preclinical testing, and clinical testing, including a clinical study on 30 patients undergoing laparoscopic cholecystectomy [168].

22.12.5.5 Current Clinical Evidence

In the first report of safety and efficacy, in which ten PIPAC procedures were performed in three patients, the plasma concentration-time profile analysis of PIPAC was favorable [168]. The nuclear presence of doxorubicin was documented throughout the peritoneum, reaching a high local concentration (≤4.1 μmol/g) while maintaining a low plasma concentration (4.0–6.2 ng/ml). PIPAC required only 1/10 of the doxorubicin dose and resulted higher tumor drug concentration (0.03–4.1 μmol/g) as compared to HIPEC (0.02 μmol/g). This difference was maintained in the drug concentration in the systemic circulation as well indicating that the proportion of the drug reaching the systemic circulation is similar after both procedures.

Complete tumor remission was seen in two patients and a partial response in 1. Mean survival after the first PIPAC was 288 days. Moreover, PIPAC had a significantly lower morbidity, and only one patient who had a concurrent CRS experienced grade 3–5 morbidity.

Most of the published reports are case reports, prospective and retrospective case series, and a phase II trial. Tempfer et al. reported outcomes in a series of 18 women with PM from recurrent ovarian cancer treated with multiple sessions of PIPAC performed at 4–6 week intervals using doxorubicin 1.5 mg/m^2 and cisplatin 7.5 mg/m^2 [169]. Thirty-four PIPAC procedures were performed in 18 women, and 8 of these underwent a concurrent CRS. In eight women who had more than one PIPAC and a response evaluation was performed, complete remission was seen in one patient, partial remission in two, and stable disease in three women. Median follow-up was 192

days (range 13–639). Cumulative survival after 400 days was 62% and mean actuarial survival time was 442 days. On multivariate analysis, patient age (<75 vs. >75 years), serum CA-125 (<1000 vs. >1000 U/ml), and the presence of ascites (yes vs. no) were not independent predictors of objective tumor response. Five women had CTCAE grade 3–4 events of which four could be potentially related to the PIPAC procedure and three of these four were patients who had PIPAC after CRS. The results of this series indicate that PIPAC has activity in women with recurrent, platinum-resistant ovarian cancer and should not be combined with CRS.

There are case reports of an objective response in a patient with recurrent pseudomyxoma peritonei of appendiceal origin and in an octogenarian with advanced ovarian cancer treated with PIPAC alone [170, 171].

De Simone et al. reported their experience with 40 procedures performed in 14 patients [172]. Most of the patients received systemic chemotherapy in addition to PIPAC, and there was no significant hepatic or renal toxicity of this combined therapy. They reported good symptom control in patients who had symptomatic ascites and subacute intestinal obstruction. The use of systemic therapy permitted the application of PIPAC in patients with retroperitoneal lymphadenopathy and/or extra-abdominal metastases who were symptomatic from PM. They suggested that dose-finding studies were needed to determine ideal dose and this strategy could have a role in standard frontline therapy for PM [172].

In a phase II trial evaluating the role of PIPAC in patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer, of the 64 patients enrolled, 17% could not undergo PIPAC due to laparoscopic nonaccess. Of the patients 62% had an objective tumor response; three had a partial response and 30 patients had stable disease. Thirty-four patients could undergo all three PIPAC sessions in accordance with the study protocol. Tumor regression on histology and peritoneal cancer index (PCI) improvement were observed in 26/34 (76%) and in 26/34 (76%) patients who underwent all three PIPACs. There were no treatment-related deaths [173]. In addition, EORTC QLQ-30 global physical health scores, nausea/vomiting, appetite loss, diarrhea, and constipation improved during therapy. The mean time to progression was 144 days. The authors concluded that further evaluation as an alternative to or in addition to systemic therapy as a palliative option is needed in clinical trials.

Reymond et al. evaluated the role of PIPAC in gastric PM retrospectively [174]. Sixty PIPACs were applied in 24 consecutive patients with PM from gastric cancer. Of the patients 67% had previous surgery, and 79% had previous platinum-based systemic chemotherapy. Mean PCI was 16 ± 10 and 18/24 patients had tumors with signet ring cells. Cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2 were given for 30 min at 37 °C and 12 mmHg at 6-week intervals. Median follow-up was 248 days (range 105–748), and median survival time was 15.4 months. Seventeen patients had >1 PIPAC. Objective tumor response was documented in half of the patients after PIPAC, including complete histological regression in six patients. This study showed that there was a benefit of PIPAC in patients with recurrent platinum-resistant gastric PM and it needed further prospective evaluation. Though the selection criteria for PIPAC could not be defined based on this study, the authors suggested using PIPAC soon after development of recurrence would be most beneficial [174].

In a retrospective study of 48 PIPAC procedures performed in 17 pretreated patients with colorectal PM, all patients had previously undergone surgery, and 16 had undergone previous lines of systemic chemotherapy (median, two lines); objective tumor responses were observed in 12/17 patients (71%) [175]. The mean PCI was 16 ± 10. PIPAC was performed using oxaliplatin (92 mg/m^2) repeated every 6 weeks at 37 °C and 12 mmHg for 30 min. There were no intraoperative complications. The mean number of PIPAC administrations per patient was 2.8 (minimum one, maximum six). Postoperative adverse events (CTCAE level 3) were observed in four patients (23%); no CTCAE level 4 adverse events were reported. The hospital mortality was zero and the overall responses were as follows: complete pathological response (n = 7), major response (n = 4),

partial response ($n = 1$), no response ($n = 2$), and not eligible ($n = 3$). The mean survival after first PIPAC was 15.7 months. This study showed that PIPAC with oxaliplatin could induce regression of pretreated colorectal PM and needed further evaluation in prospective studies [175].

22.12.5.6 Toxicity

Toxicity data related to PIPAC have also been published. During PIPAC, only about 10% of a usual systemic drug dose is applied into the abdomen. This dose was in proportion to that used for HIPEC and, considering the pharmacokinetic differences, one tenth of the dose used for HIPEC [176]. The systemic drug concentration is minimal, about 1% of a systemic dose or 5% of a HIPEC dose. Apart from the dose used, the potential for complications is due to the hemodynamic changes and use of intra-abdominal pressure application directly on the surface of organs having the potential for local toxicity. Patients may have chemical peritonitis leading to abdominal discomfort and a rise in C-reactive protein. There is no cumulative toxicity with multiple applications, and the incidence of grade 3 and 4 adverse events is <10% [176, 177].

Some complications that can arise are trocar site hernias, bowel access lesions, subcutaneous toxic emphysema, small bowel obstruction, port site metastasis, therapy-resistant ascites, and postoperative tumor growth and metastases. At least some like bowel access lesions, subcutaneous toxic emphysema, and trocar site hernias can be avoided by the use of proper surgical technique.

22.12.5.7 Quality of Life

Worldwide, PIPAC has been used for patients who are heavily pretreated and symptomatic from their PM. There is a subgroup of patients that have a good performance status despite their extensive disease and numerous lines of therapy who have been treated with PIPAC [177]. Reymond et al. evaluated the quality of life (QoL) in 91 patients who had undergone 158 PIPAC procedures as salvage therapy [177].

QoL was assessed before starting PIPAC and at 3-month posttreatment. Patients undergoing PIPAC had stabilization of QoL. Functional scores remained stable, and gastrointestinal symptoms did not deteriorate during treatment. Only pain scores increased slightly for a short period of time. Transient abdominal pain was attributed the chemical peritonitis induced by PIPAC. The common side effects of systemic chemotherapy such as mucositis, nausea/vomiting, diarrhea, paresthesia, cutaneous symptoms, and alopecia were not reported by the patients. However, according to the authors, these results should be interpreted with caution; since it was a retrospective study, patients who could not tolerate the therapy were excluded, and the stabilization of symptoms could be in part due to discontinuation of systemic therapy. Similar results were reported by Robella et al. for 40 PIPAC procedures performed in 14 patients [172].

22.12.5.8 Advantages and Limitations of PIPAC

PIPAC has pharmacokinetic benefits like increased tumor drug penetration using 1/10, the dose used in HIPEC with limited systemic absorption [176]. There is more homogenous drug distribution over the peritoneal surfaces [159]. Overall incidence of complications is low and the average hospital stay is 2–5 days. It can be combined with systemic chemotherapy without significant toxicity. Repeated applications are possible, and the time interval of 6 weeks allows evaluation of response to therapy [166].

PIPAC has limitations as well. The current protocol does not allow it to be performed with CRS. Reported toxicity is more when PIPAC is performed immediately after CRS [176]. The technical feasibility and the efficacy of PIPAC are largely dependent on the degree of enteroenteral and entero-parietal adhesions. Reported rates of nonaccess are 5–17%. Moreover, only exposed peritoneal surfaces that can be reached by the aerosol can be treated with PIPAC. At present, there is no method of stratifying patients according to adhesions; however, it may be difficult or impossible to perform PIPAC in patients who have had CRS and/or HIPEC before [178].

The advantages, disadvantages, and contraindications are summarized in Table 22.5.

Table 22.5 Advantages, disadvantages, and contraindications of PIPAC

Advantages	Disadvantages	Contraindications
High-tumor drug concentration using 1/10 of systemic dose	Cannot be combined with CRS	Laparoscopic nonaccess
Easy to perform—no learning curve	Prior adhesions limit its application and efficacy	Malignant bowel obstruction
Limited grade 3–5 morbidity	Certain areas like the lesser sac remain untreated	Debilitating ascites with malnutrition
Possibility of multiple applications		
Can be combined with systemic chemotherapy		
Evaluation of response to therapy possible		
No risk of port site metastases		
Minimal adhesion formation		
Subsequent CRS and HIPEC are possible		

Based on the current evidence, PIPAC can be used for symptom palliation in selected patients with PM and in patients who have failed on one or more lines of systemic chemotherapy. Further clinical evidence is needed before it is used for other indications. Standardization and improvement of certain technical aspects of the procedure like the drug dosage and possibility of use in conjunction with CRS will be important for increasing its future use and efficacy.

In some patients who are not candidates for CRS and HIPEC upfront, PIPAC could be used in as neoadjuvant therapy to reduce the tumor burden. Reymond et al. reported their institutional experience of 406 patients who had undergone 961 PIPAC procedures. Twenty-one patients underwent a subsequent CRS and HIPEC [178]. Twelve of these patients were candidates for the procedure even without the use of PIPAC; however, nine patients experienced significant downstaging making them candidates for CRS and HIPEC. Most of these patients had extensive small bowel involvement precluding a complete cytoreduction upfront. In these nine patients, an objective tumor regression was observed after repeated PIPAC (mean number of cycles 3.5 ± 0.9). Notably, these patients required at least 4 and even up to 6 months for the tumor to become resectable. Six out of these nine patients had colorectal primaries. This early data indicates that the use of PIPAC as neoadjuvant strategy is promising and should be further evaluated prospectively. The advantages in this setting are that it can be combined with systemic therapy and the 6-week interval between two therapeutic sessions allows effects of both local and systemic therapies to be evaluated.

22.13 Other Experimental Therapies

22.13.1 Radio Immunotherapy

Radioimmunotherapy using radiolabeled monoclonal antibodies directed against tumor-associated antigens conjugated with radioactive material has been investigated as an adjuvant therapy for advanced ovarian cancer with PM and colorectal PM in several clinical and preclinical studies for almost three decades [179, 180]. This had been used as adjuvant therapy in advance ovarian cancer with the goal of reducing the recurrence rates [181, 182]. However, these and other studies evaluating intraperitoneal radionuclide therapies have used beta-emitter antibody conjugates which have dose-limiting marrow suppression [183–186]. Less toxicity can be expected when radionuclides with shorter half-lives are used, as less radioactivity would distribute systemically [187, 188]. Aarts et al. compared CRS alone with CRS and HIPEC or CRS and radioimmunotherapy which consisted of intraperitoneal administration of 74 MBq Lutetium-

177-labeled MG1. Survival after CRS was significantly increased by the use of radioimmunotherapy with Lutetium-177-MG1 in rats with PM of colorectal origin [189]. In another study, ^{212}Pb-TCMC-trastuzumab was delivered IP less than 4 h after giving 4 mg/kg IV trastuzumab to patients with peritoneal carcinomatosis who had failed standard therapies and had HER-2 +1 or more in a phase I design for dose escalation [190]. ^{212}Pb-TCMC-trastuzumab was expected to provide more potent radiation to targeted malignant cells while limiting radiation exposure to normal tissues as compared to beta-emitter conjugates, due to the shorter half-life and path length of ^{212}Pb alpha radiation. All the planned dose escalations were performed with low toxicity. A follow-up study showed IP Pb-TCMC-trastuzumab up to 27 MBq/m to be safe for patients with PM who have failed standard therapies with no long-term toxicity.

Radioimmunotherapy needs further evaluation in terms of ideal dose and indications for clinical use. Survival data in clinical studies are not available, and the timing of therapy/integration with other therapies needs to be defined.

22.13.2 Photodynamic Therapy

Photodynamic therapy (PDT) is a therapy that uses photosensitizers (or their precursors) with an affinity for tumor cells and visible light to trigger a photochemical reaction. Reactive oxygen species are generated in cancer cells, leading to cell death. Photodynamic therapy has been used for treatment of surface lesions like precancerous lesions and early invasive carcinomas of the cervix, esophagus, stomach, and lung [191–193]. Given the high propensity of PM to recur, this therapy has been evaluated as an adjunct to CRS in animal models of colorectal and ovarian cancer. Development of intraperitoneal PDT has been limited by its poor tolerance related to the lack of specificity of photosensitizers and the location of the metastases in proximity to adjacent intraperitoneal organs [194]. 5-Aminolevulinic acid methyl ester hydrochloride (methyl-ALA) is a photosensitizer precursor with an affinity for tumor cells which has been used in some experimental studies. PDT with hexaminolevulinate (HAL), a second-generation photosensitizer, had a high toxicity but provided the opportunity to diagnose and treat PM at the same time [195]. Azais et al. developed a folate-conjugated photosensitizer (Porph-s-FA) that has an affinity for folate receptor-α (FR-α) [196]. This receptor is overexpressed in 72–100% of ovarian cancers (81% of the serous carcinomas and only 39.9% of the mucinous carcinomas) [197–200]. This expression is retained in recurrent tumors and is not affected by chemotherapy.

Comparing different wavelengths of light, green light is more suitable for intestinal surfaces as the depth of penetration is less as compared to red light that has a deeper penetration [194]. Yokoyoma et al. in an experimental study demonstrated that concurrent therapy consisting of PDT with 5-aminolevulinic acid methyl ester hydrochloride (methyl-ALA) and clofibric acid is effective at treating PM from ovarian cancer without damaging the adjacent organs [201]. Mroz et al. used functionalized fullerenes, a new class of functionalized photosensitizer (PS) for PDT to treat colorectal PM in mice. Intraperitoneal injection of a preparation of *N*-methylpyrrolidinium fullerene formulated in Cremophor EL micelles, followed by white-light illumination delivered through the peritoneal wall (after creation of a skin flap), produced a statistically significant reduction in bioluminescence and a survival advantage in mice [202]. PDT is conceptually suited to treat PM, but the technical aspects of the procedure and the PS used need optimization before it can be used in the clinical setting.

22.13.3 Intraperitoneal Immunotherapy

Just as systemic chemotherapeutic agents have been used for intraperitoneal therapy, various immunotherapies have been evaluated for intraperitoneal use.

22.13.3.1 Immune Checkpoint Inhibitors

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a protein expressed on the surface of T cells. Its activation dampens the adaptive immune response to malignancy [203]. The programmed death-1 receptors (PD-1) are also present on cytotoxic T cells and block their activity by inducing apoptosis when activated via ligand binding on the tumor cell surface [204, 205]. In an experimental model of PM, the effect of checkpoint-inhibiting antibodies α-PD-L1 and/or α-CTLA-4, with or without IL-18, on peritoneal metastases via IP injection or tail-vein injection was compared [206]. Intraperitoneal use of immune checkpoint inhibitors had a survival advantage over the control group receiving immunoglobulins, and this effect was augmented by the use of IL-18 [206].

22.13.3.2 Chimeric Antigen Receptor-T Cells (CAR-T Cells)

T cells engineered with chimeric antigen receptors (CAR-T cells) have the ability to bind to tumor cells, causing cell lysis, independent of the action of the major histocompatibility complex (MHC) [207–209]. These cells have been applied to the treatment of hematologic malignancies, such as acute lymphoid leukemia and chronic lymphoid leukemia, but more recently as treatment of hepatic metastases from colorectal cancer. In an experimental study, mice with colorectal PM were treated with CAR-T via IP or tail vein injection, in combination with antibodies for inhibition of immunosuppressive cells, over a 2-week period. They reported a 37-fold reduction in PM tumor burden in IP-treated mice as compared with the tail-vein injection group [210]. CAR-T cells targeting specific antigens like the MUC-16ecto antigen overexpressed on most ovarian cancer cells and L1-CAM, a cell adhesion molecule have shown improved survival after intraperitoneal use in ovarian cancer animal models as compared to controls who received no treatment [211, 212]. CAR-T cells have been used in the clinical setting as well. In a study of four patients with recurrent ovarian cancer, autologous T cells stimulated against a hypoglycosylated MUC1 antigen were instilled intraperitoneally at monthly intervals to complete three sessions each [213, 214]. Treated patients demonstrated elevated levels of MUC1-specific cytolytic activity and generation of both effector and memory T cells leading to diminished CA125 levels, elevated IFNγ, and improved survival, ranging from 3 to 16 months [214].

22.13.3.3 Dendritic Cell Vaccine

IP use of dendritic cell vaccine and cytokine-induced killer cells has been investigated in the clinical setting. Ai et al. used this therapy prepared in 22 patients with peripheral blood mononuclear cells. 77.3% of the patients with PM from different primary sites experience control or reduction in the ascites [215].

Conclusion

Despite the awareness about risk factors and better technology for early detection, PM continue to be detected in an advanced stage in a large majority of the patients who get excluded from a curative approach due to the disease site, extent and distribution, or poor general health. Some of the symptoms like bowel obstruction and ascites can severely affect the quality of life and need to be addressed even though the life expectancy is short. Locoregional therapies in addition to systemic therapies are being used to treat asymptomatic patients with unresectable PM with the goal of prolonging and maintaining the quality of life.

Patients with unresectable PM fall in between palliation and cure from the treatment point of view. PIPAC has shown good results in the palliative setting and may have a future role as neoadjuvant therapy for unresectable disease. Several other therapies are in the preclinical phase and may find a place in clinical practice. A multidisciplinary approach keeping in mind the goals of therapy which are based on the disease status and the expectations or the patients and their caregivers should be used to treat these patients.

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23 Training Programs for Cytoreductive Surgery and HIPEC

Beate Rau, Maria Clara Arroyave, and Dusan Klos

23.1 Introduction

Peritoneal surface malignancy (PSM) is associated with poor prognosis. Mean overall survival is 6 months. Historically, patients diagnosed with peritoneal metastasis derived from a solid tumour such as colorectal cancer, appendiceal cancer, ovarian cancer, gastric cancer, gynaecological malignancies or peritoneal mesothelioma receive only chemotherapy with palliative intention, because distant metastases especially PSM are associated with poor prognosis.

Over the last 20 years, a surgical approach has been developed for the treatment of PSM. This procedure was described by Sugarbaker and consists of cytoreductive surgery (CRS) and complete peritonectomy in selected patients associated with hyperthermic intraperitoneal chemotherapy (HIPEC) [1, 2]. The rationale for the surgical approach includes the difficulty of systemic chemotherapy to get into tumour cells due to the limited blood supply of the peritoneum, reduction of the tumour mass and topical intraperitoneal chemotherapy to treat microscopic neoplastic residue. However, surgery is not a treatment option for all patients with peritoneal disseminated disease. Patients have to be carefully selected, because surgical-induced morbidity is high and additional treatment with chemotherapy adds toxicity.

23.1.1 Role of Cytoreduction

Cytoreductive surgery has gain a major role in surgical oncology. It is widely accepted that incomplete tumour resection in primary cancer has a negative impact on long-term survival. Surgery indicated for distant metastases applies the same rules. This is easily possible, if the metastases are diagnosed as a solitary tumour nodule and the localization is peripherally located. However, in peritoneal surface malignancy, this is not the case. Usually PSM is spread all over the peritoneum and is often combined with malign ascites. The tumour burden variable and indication to surgical cytoreductive treatment have to be indicated very carefully.

Complete cytoreductive surgery (CRS) has the potential to achieve curation or long-term survival in selected patients with peritoneal malignancy.

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The procedure aims for complete tumour removal. That means in the case of synchronous disease, the primary tumour has to be oncologically resected following the existing guidelines for the primary tumour combined with cytoreductive surgery. Complete macroscopic cytoreductive surgery stands for removal of peritoneal lesions in the abdomen and can be achieved by parietal and visceral peritonectomy. The completeness of the procedure depends on the extent and the type of the peritoneal tumour manifestation.

Usually following a midline laparotomy, the amount of disease located within the peritoneal cavity is quantified using the peritoneal cancer index (PCI) which provides a numerical approximation of abdominal tumour burden according to the distribution and size of metastatic deposits [1, 3].

The *mucinous type of PSM* including pseudomyxoma peritonei, low-grade adeno-mucinosis neoplasia (LAMN), peritoneal mucinous adenocarcinoma (PMCA) and mesothelioma usually needs a total peritonectomy and infragastric omentectomy and lesser omentectomy, whereas in *non-mucinous type of PSM* partial peritonectomy and infragastric omentectomy, removing the tumour baring peace of peritoneum is recommended.

Standard surgical procedures for CRS integrate complete abdominal exploration, infragastric omentectomy and peritonectomy including the diaphragm bilaterally, the subhepatic space, the Glisson capsule, the paracolic gutter and the cul-de-sac. Small and scattered localizations on the visceral surface are resected by local excision or electrocoagulation. In the case of massive and infiltrating disease, visceral resections might be necessary, including cholecystectomy, gastrectomy, splenectomy, sigmoid, right or total colectomy, extraperitoneal anterior resection and, in women, hysterectomy with bilateral salpingo-oophorectomy. Resection of the ovary or gallbladder per principle is not described. The extended resection of the organs should only be considered, if the aim of nearly total tumour resection is achievable. It is recommended to remove clinically suspicious regional lymph nodes [4].

The extended resection of the organs should only be considered, if the aim of nearly total tumour resection is achievable.

In *extraperitoneal disseminated disease*, the indication for CRS is debatable. Anyhow, if distant metastases in the liver or in the lung are easily removable, the results are acceptable in selected patients [5].

The operation should be performed in a standardized manner. Due to possible tumour manifestation in all four quadrants of the abdomen and extensive intraperitoneal dissection, sound surgical and oncological expertise is prerequisite. Treatment in specialized surgical oncology centres is recommended to minimize morbidity and mortality [6].

Despite CRS and HIPEC being a complex treatment regimen and associated with a high rate of morbidity (up to 60%) and mortality (up to 10%), it is of major interest to bring this kind of treatment to our patients with less complications. Therefore, a platform to learn these complex procedures should be implemented.

23.1.2 Indication

Currently, it is widely proven that CRS should achieve a maximal tumour reduction. But even after optimal surgical procedures, long-term results are not impressive. The peritoneal carcinomatosis index (PCI) has been developed to categorize the tumour burden of PSM. The lowest number is 0 and the highest 39 [7]. PCI influences the prognosis of the patient. A high PCI implies a worse outcome [7]. Another important aspect is the location of the primary tumour. Upper gastrointestinal tumours such as oesophageal, gastric, pancreatic or hepatobiliary cancer have bad outcomes when peritoneal dissemination has developed. Usually the tumour spread is not of mucinous, and mostly the PCI is over 10. These patients do not benefit from multivisceral resection and CRS except in the emergency setting. In lower gastrointestinal tumours including appendix, colon and rectal cancer, CRS can be beneficial, if the PCI is low and the morphology of the PSM is mucinous. Especially in mucinous PSM, even high PCI is accepted for CRS. These patients usually have a higher morbidity after the procedure, but this is widely accepted, because of

the increased rate on long-term survival in these patients. Therefore, preoperative selection is of major importance for the success of CRS in order to achieve acceptable postoperative and oncologic outcomes. Preoperative diagnostics should include physical examination, laboratory parameters (including renal function, liver function, nutritional status and tumour markers as well as echocardiography and others) and computed tomography of the chest, abdomen and pelvis.

23.2 Length of the Learning Curve of a Surgeon in CRS and HIPEC

Kusamura et al. compared the length of the learning curve in two Italian centres—the National Cancer Institute in Milan and Bentivoglio Hospital in Bologna—and demonstrated that extensive surgical tutoring could abbreviate the learning process in the beginning of the CRS and HIPEC program in a starting centre. The first centre began the program after the fellowship of the principal surgeon in the Washington Cancer Centre and Gustave Roussy but without direct supervision of experts. The program included three steps in the second centre (Bentivoglio Hospital). The first step of the tutorial consisted of visits in Milan by members of Bentivoglio centre. The second step was the development of study protocols, the definition of the multidisciplinary team and logistic troubleshooting. The third step was the selection of initial cases and performance of CRS and HIPEC at Bentivoglio Hospital with assistance of the tutor. The expert supervised Bentivoglio's operations, participating actively in every procedure as second surgeon. Rates of incomplete cytoreduction, G3-5 morbidity and procedure-related mortality were 8.4%, 30.1% and 3.9%, respectively, in the entire series [8].

Incomplete cytoreduction, the percentage of severe complications grades 3–5 and procedure-related mortality will be markedly reduced after surgeons experience extensions of more than 140 cytoreduction procedures [8]. The results of this study demonstrate that professional supervision at the beginning of the program significantly reduces the number of cases that must be performed in a centre in order to reduce morbidity and mortality. Nevertheless, the surgical learning curve of 150 cases makes this surgical technique very demanding to master in order to achieve completeness of cytoreduction and low rates of morbidity and mortality.

23.3 Start of a New Centre

Therefore, the number of centres in the countries should be limited to assure good quality in CRS and HIPEC. For example, in the USA, about 149,000 new patients per year develop colorectal cancer—of them 40% will develop peritoneal metastasis [9, 10]. Only on third is possibly available for CRS and HIPEC. Therefore, the numbers of centres which delivers CRS and HIPEC in peritoneal surface malignancy should be limited.

Starting a new centre for CRS and HIPEC is a difficult and complex task. The basic prerequisites include:

1. Participation in workshops and surgical training programs
2. Collaboration and hospitalization with a high-volume reference centre
3. Necessities of a starting centre
4. Creation of a multidisciplinary team
5. Multidisciplinary team training
6. National health system financial support
7. Writing a standard operative procedures (SOP) as a team

23.3.1 Participation in Workshops and Surgical Skilled Training Programs

European School of Peritoneal Surface Oncology (ESPSO) Training Program is the result of the work of pioneers in this method in its systematic and professionally guided implementation in various centres in different countries. The ESPSO provides the opportunity of a high-quality, well-structured training program, comprising both

basic and advanced knowledge that will lead the candidate to the European Certification on peritoneal surface oncology. This program includes a mandatory component comprising a theoretical module that includes attendance to International Congress of Peritoneal Surface Malignancies, as well as local or national events and two advanced courses on Peritoneal Surface Oncology and workshops organized by the European Society of Surgical Oncology. The practical module consists of direct involvement in cytoreductive surgery and HIPEC procedures (mandatory number is 20), participation in multidisciplinary tumour boards, patient selection and therapeutic decision-making meetings (mandatory is also 20 cases). Observation of in-hospital postoperative follow-up is also required. The third—scientific—module includes presentation of the results of their own academic work, as lectures at congress and publications in scientific literature. The meaning of the theoretical module is based on acquiring basic knowledge of peritoneal surface oncology, including a definition of individual pathological conditions epidemiology, incidence, clinical manifestations, diagnosis and therapeutic management possibilities. Another integral part is the acquisition of theoretical skills in cytoreductive surgery techniques, peritonectomy methods, types of HIPEC and use of cytostatic and their combinations and concentrations. The information on the safety and handling of cytotoxic agents and addressing adverse events during their leak at the operating room is essential. Furthermore, recognition of complications secondary to this treatment and their management is crucial for the success of the training. Mutual meetings, cooperation and exchange of the latest knowledge among surgeons dealing with this technique are also important. Clinical practical model allows the participants to obtain direct information about indication and preparation of patients for surgery. Furthermore, direct hands-on participation in the execution of CRS and HIPEC procedures from anaesthesia induction to patient leaving the operation room, participation and attendance to ad hoc tumour board for presentation, discussion patient selection and therapeutic decision-making and presence in in-hospital postoperative follow-up at a training centre. The importance of the scientific module lies in the motivation for systematic scientific management of one's own work in the field of CRS and HIPEC with the necessary presentation of the results at professional forums.

The basic conditions for entry into the training process are:

1. Expert tutor
2. An adequate PSM centre that could harbour the training program
3. Adequacy of the candidate

Both the expert tutor and the centre are recognized by PSOGI regarding aspects to historical contribution to PSO, actual annual case load and proficiency. The tutor is expected to supervise all the activities during the entire duration of the program to ensure a direct transmission of knowledge to the trainee from a PSM expert source. Each participant in the program should be an active surgical oncologist with an inclination to PSO and a focus on structured and professional training; he/she should complete the entire surgical education in accordance with national requirements and have at least basic surgical oncology training and show a continued dedication to surgical oncology in clinical practice and to be involved or have solid plans to get involved in an established or new peritoneal surface malignancies program.

The tutor should be an experienced surgical oncologist and head of the PSM program at the workplace, which should be a reference centre in the country. Overall, there are 29 centres worldwide classified under the ESSO heading.

After the conditions are met, the program participant receives a certificate of its fulfilment. It is awarded once every 2 years at the International Congress on peritoneal surface malignancies.

23.3.2 Collaboration and Hospitalization with a Reference Centre's

Supervision and mentoring from an experienced centre are highly advisable, for surgical training, staff education and design of treatment protocols.

Head surgeon and other team members should visit a training centre to obtain enough experience, knowledge and skills to start a program in their own facilities. Their training should not only include their presence and assistance in operating theatres but also preoperative preparation of patients, tumour board discussion, elaboration of indicating summary, monitoring of postoperative care and subsequent follow-up of the patients. It is also appropriate to visit several international centres, as they may vary in procedural approach, indication criteria and HIPEC procedure (open method, or closed lavage, type of cytostatic, its concentration and duration of hyperthermic intraperitoneal chemotherapy according to the tumour type), due to the fact that each of these centres uses its own standard operating procedure (SOP) list. Further multidisciplinary visits to the training centres have to be planned, including all staff members involved in the project, both nurses and doctors.

23.3.3 Necessities of a Starting Centre

A preliminary step is to identify the optimal location of the centre for CRS and HIPEC. The basic premise requires a surgical ward that routinely runs all major abdominal surgery procedures with a sufficient number of experienced surgeons. It must also have access to suitably equipped operating rooms, intensive care units, central cytostatic preparation and appropriate laboratory facilities for basic and advanced haematological, biochemical, microbiological and histopathological diagnostics. The standard includes access to emergency CT scans, interventional radiology and endoscopy and transfusion services for 24 h. Technical facilities and equipment for HIPEC are essential as well. On the market, there is a wide range of devices registered for commercial use for HIPEC. The choice of a specific HIPEC device should be based upon certain characteristics, such as its ability to achieve adequate hyperthermia in a short period, adjustable flow rate, user-friendliness, ease of assembly, ease of reading and continuous registration of temperatures, availability of technical support and affordability of the machine itself and the disposable circuit tubing kits [11].

23.3.4 Creation of a Multidisciplinary Team

The leader of the team must be an experienced surgeon. The surgical team should be limited in number at the beginning, mainly due to the length of the learning curve. It is not advisable to involve many surgeons at the beginning of a new centre; the ideal number is two. The surgeon must be fully versed in the whole complexity of colorectal and major oncological abdominal surgery. The basic premise is that he/she handles all major resections of the small and large intestine, including procedures in the stomach, liver, gallbladder and biliary tract. He/she should be able to perform basic resections of the pancreas and uro-gynaecology (mainly hysterectomy, salpingo-oophorectomy, pelvic exenterating). He/she should also be experienced in the management treatment of surgical complications during abdominal surgery, especially management of intestinal fistulae, anastomotic leakage, intra-abdominal bleeding, abscesses and surgical wound infections. Surgeons must also participate in international meetings, both theoretical and practical courses, and attend expert centres to gain new experience and information.

Another important partner of the team is a medical oncologist. It is very important from the very beginning of the new program to integrate him/her into the team and discuss various activities with him/her. Conversely, the surgeon must be very careful to respect the opinions of the oncologist. A very close, intense and friendly cooperation of the surgeon-clinical oncologist pair within a multidisciplinary tumour board (MDTB) for peritoneal carcinomatosis is often a key factor in further successful development of the centre. It is extremely useful to discuss every patient with complete oncological history, all chemotherapy cycles and dosages as well as the direct observation of CT scans, which should not be older than 3–4 weeks to exclude patients

with distant metastasis. If preoperative staging laparoscopic videos are available, they should be presented at the MDTB meeting, in order to integrate the team in learning about PCI and outcome.

Integral parts of the team are also experienced specialists—anaesthesiologists, intensivists, radiologists, pathologists, pharmacists, dietetics, physiotherapists, perfusion specialists and oncology psychologists. A very important part of the team are then the theatre and ward nurses. Therefore, it is helpful to invite everybody to a morbidity conference on a regular basis, to learn from pitfalls at the centre.

23.3.5 Training of the Multidisciplinary Team

If the 'CRS and HIPEC team' is founded, the next step is education of the team members. It includes meetings, workshop conferences and regular tumour board meetings once a week. Tumour board meeting is crucial in the indication of patients for this type of treatment. The joint decision of the surgeon, oncologist, radiologist and eventually a pathologist has a decisive influence on the further success of the program, which is reflected in the quality of achieved cytoreduction, satisfactory morbidity and mortality and positive effect on overall survival time and quality of life. At the construction of the new centre, it is necessary to meet certain fundamental conditions of national authorities and legislation. It is a necessary precondition to ensure safe administration of cytostatic in the operating room, which must comply with strict rules; therefore, staff and environmental services must be properly instructed. This includes an adequate response to leaks during the administration of cytotoxic chemotherapy in order to minimize the risk of contamination of the nursing staff. This also applies to staff at intensive care units, where patients are transferred postoperatively. They must also be instructed in the use of technical equipment and devices for HIPEC and responses to complications that may occur during hyperthermic circulation.

23.3.6 National Health System Financial Support

CRS and HIPEC is characterized by a relatively high morbidity, relatively large costs and long learning curve of the surgeon [12]. CRS and HIPEC treatment is recommended in centres worldwide. Nevertheless, the number of CRS and HIPEC centres differs in European and non-European countries for several reasons:

1. Healthcare system
2. Cost of treatment
3. Possibility of payment
4. Experience of the surgical oncology team

The implementation of a new centre requires the support of the National Oncological Program, as well as a hospital with adequate financial and personnel resources. Because this treatment and its complications, particularly at the start of a new centre, represent a significant financial burden for the centre, at least a partial reimbursement via public insurance, private insurance or private patients must also be guaranteed in advance. For example, Bagnoli et al. [13] describe the overall cost per case in the Italian National Health System at € 21,744, while reimbursement per case amounts to just € 8375. Sufficient financial resources are essential.

Personnel resources, both experienced and proactive surgeons, but also oncologists, anaesthesiologists, intensivists, radiologists and nursing personnel are a prerequisite for success. Further development of the centre also requires a direct connection to science centres, whose cooperation can help further develop the technique and present the centre both at professional forums and in the literature. Most often, such centres are created at the level of tertiary reference centres.

23.3.7 Writing an SOP as a Team

It is very helpful to create a standard operative procedure (SOP) in your workplace, which is a basic guiding parameter for all involved personnel. Its contents are the different steps of tumour

board decision regarding the indications for surgery, informed consent forms, preoperative examination and procedures of the day before surgery, the day of surgery and postoperative days (e.g. antiemetic treatment, start of feeding, etc.), including the subsequent follow-up after the discharge from hospital. There must also be a common surgical oncology protocol of indication criteria, which allows for a uniform processing within individual diagnoses. At the beginning of the program, all cases should be discussed prospectively at multidisciplinary meetings with members of expert centres. It is recommended to start with simpler cases in relatively otherwise healthy patients with less advanced disease. It is very frustrating for the team when there are major complications and mortality at the beginning of the program. The enthusiasm of the team can thus be reduced, and these negative results can also negatively influence the opinion of other personnel and unnecessarily discredit the method. At the beginning, the team needs to see good results of their work. All cases should be collected in a meticulous database as it allows to work with the results. Negative experience and adverse events should be referenced in the literature as a prevention of recurrence of these complications in other centres.

23.4 Summary

Cytoreductive surgery and HIPEC conform an increasingly and interesting area of oncological surgery, which, in indicated rigorously selected cases, leads to a significant extension of overall survival and quality of life of patients for diseases that were previously considered unmanageable. Some groups consider it to be the current standard of treatment. Striving for systematic management of new surgeons and centres to further develop this oncosurgery area is an innovative proactive way of training. It will significantly reduce the time of the surgeon's learning curve, and it helps prevent a number of negative experiences and avoid practices that may adversely affect morbidity and mortality after the surgery. These training programs also represent a unique opportunity for mutual cooperation and exchange of experience between centres, both at national and international levels. Nevertheless, it is necessary to remember that this approach has only palliative importance in many cases. Therefore, indication criteria and multidisciplinary oncoboards have to strictly choose this treatment only in patients who will benefit from it. Success and progress of individual centres would be the best motivation to develop this method in the field of peritoneal surface oncology and would encourage other centres to implement this procedure.

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