Cytoreductive Surgery and "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)"

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12.1 Introduction

For a long time malignant tumor manifestation of the peritoneum, peritoneal carcinomatosis (PC) was regarded as terminal. This meant that both medical and surgical palliation treatments came into question which aimed to keep quality of life as long as possible. These methods are known as "best supportive care."

We must differentiate between tumors with primary peritoneal manifestation such as peritoneal mesothelioma and peritoneal carcinomas and secondary tumors of the peritoneum from gynecological and gastrointestinal primaries.

The French EVOCAPE 1 study [1] examined the median survival rate of tumors originating in the gut that were treated with best supportive care. Gastric cancer was found to have a median survival rate of 3 months and colorectal carcinomas of 6 months. By comparison, ovarian cancer can have a median survival time as long as 2 years [2–4]. Assuming that the peritoneal manifestation of a tumor was not a systemic disease but, as the first author Sampson described in 1931 [5], was rather a local progression of tumor mass into the peritoneal cavity, the first aggressive intraperitoneal treatments were developed in the 1980s [6, 7]. The effectivity of aggressive surgery for the treatment of PC was first shown for ovarian cancer in a multimodal therapeutic approach [8]. The proof that aggressive surgical treatment of colorectal metastases of the liver [9] led to a longer survival rate caused a change of perspective in the oncological treatment of this disease and following it the treatment of PC. At the end of the 1980s, the concept of treatment by the combination of the radical reduction of peritoneal tumor mass – cytoreductive surgery – and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) was developed [10],

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mainly through the work of Paul Sugarbaker and team. He was able to show that a considerable improvement of the prognosis could be achieved for a selected group of patients [11–13]. In the 1990s, several phase II studies were published [14–19] showing improved survival rates and in some cases even curative results, in patients treated with cytoreduction and HIPEC. These results were confirmed in the first meta-analysis by Glehen in 2004 [20] with 28 phase II studies including 506 patients with mainly colorectal carcinomas. The median survival rate was 19.2 months. Patients with a macroscopic complete cytoreduction showed a higher survival rate of 32.4 months compared to patients where a total resection was not possible. The latter had a median survival rate of 8.4 months, comparable to patients just receiving best supportive care. The morbidity of 23 % and mortality of 4 % are acceptable considering the very limited treatment alternatives. However, it is shown that this high risk can only be tolerated in patients who undergo total cytoreduction because it is only then that there is a prospect of improved prognosis or even total recovery [13, 20–22]. This means that the operating surgeon's decision carries a huge responsibility but also that the interaction of the perioperative anesthetists and the subsequent ICU treatment plays a major part in the success of the procedure [23, 24].

12.2 Epidemiology and Pathophysiology

The peritoneal manifestation rate of tumors is varied. Whereas primary peritoneal tumors are rare, secondary manifestation of the peritoneum by gynecological or gastrointestinal tumors is common. For example, PC is manifest in 10–15 % of cases with first diagnosis of colon cancer [20, 25, 26]. Of these 10 %, 25 % have isolated PC. With 70,000 first diagnosis of colon cancer annually in Germany [27], this means about 1800 patients. In patients with tumor recurrence, even 10–35 % shows an isolated PC [25, 28].

Further risk factors for PC are mucinous carcinoma, perforated tumors, or iatrogenic tumor perforation. Secondary adhesion of free tumor cells then causes tumor progression. Systemic therapy fails because the limited peritoneal vascularization does not permit adequate therapeutic levels of pharmaceuticals in the peritoneum [28].

12.3 Patient Selection and Preoperative Diagnostics

Selection of suitable patients is extremely important in cytoreductive surgery, and HIPEC as a genuine improvement in prognosis can only be achieved in patients with optimal cytoreduction [29]. The operation is often very prolonged and invasive; therefore, patients should be in a good preoperative condition (ECOG performance status <2). The entity of the tumor and the spread of the tumor both play an important role. Tumor spread is diagnosed by all modern scanning methods. However, it has been shown that the tumor spread found intraoperatively is often not identical to that diagnosed preoperatively [30]. CT diagnostic often underestimates

the degree of tumor spread. This is mainly on the small intestine where disseminated spread of small tumor lesions can lead to incomplete cytoreduction. In individual cases, diagnostic laparoscopy can be helpful [29]. However, CT scans are a firm part of preoperative diagnostics because they are needed for excluding further metastases despite their limited use in determining local peritoneal tumor spread. The Peritoneal Surface Malignancy Group has laid down eight clinical and radiological criteria that may increase the probability of total cytoreduction for colorectal tumors and which may be valid for other tumors too [31, 32]:

1. ECOG performance status <2
2. No extraabdominal tumor manifestation
3. No more than three small liver metastases easily resectable
4. No cholestasis
5. No stricture of the ureters
6. No more than one intestinal stenosis
7. No small intestine mesenterium involved
8. No involvement of the hepatic duodenal ligament

12.3.1 Cytoreduction

After successful scanning and decision-making to operate, intraoperative assessment is of greatest importance. First the spread of the PC both in size of the lesions and distribution over the peritoneal surface must be determined. Several indices are available to do this. Paul Sugarbaker's "peritoneal cancer index" (PCI) [13] is the most commonly used internationally (Fig. 12.1). The abdomen is divided in 13 regions. The small intestine alone into four regions shows its considerable importance in the index. The size of the lesions is determined for each region (lesion size = LS). LS-0 signifies that there is no macroscopically identifiable tumor. LS-3 means that the tumor is >5 cm in that region. This way, a maximum score of 39 can be achieved. Different PCI levels for different tumor entities are seen as the limit for viable resection. In the case of colon cancer, it has been shown that resection is possible with a PCI <20, whereas with gastric cancer, the PCI should lie between 10 and 15 [31, 33]. A PCI >20 is no exclusion for viable resection with pseudomyxoma peritonei (PMP). Yet the PCI is only an aid for determining the tumor spread and does not permit a definite assessment about total tumor resectability. Advanced involvement of the small intestine or of anatomically "critical" regions, such as the hepatic duodenal ligament, may make total tumor reduction impossible and lead to a bad prognosis even with a low PCI.

To be able to evaluate the prognosis, it is important to determine the degree of tumor removal. This is measured in the "completeness of cytoreduction score" (CC) ([13], Table 12.1). A CC score of 0 means there is no macroscopic residual tumor at the end of the operation. A CC score of 1 means residual tumor <2.5 mm. Whereas with a score of two, residuals between 2.5 mm and 2.5 cm remain. Finally, a CC score of 3 means residuals >2.5 cm. Several studies [34–37] have confirmed the prognostic relevance of the CC index.

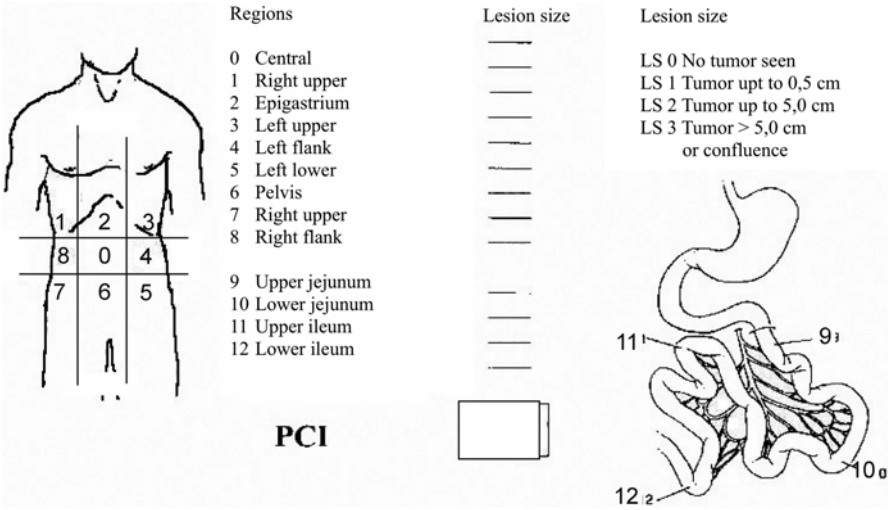


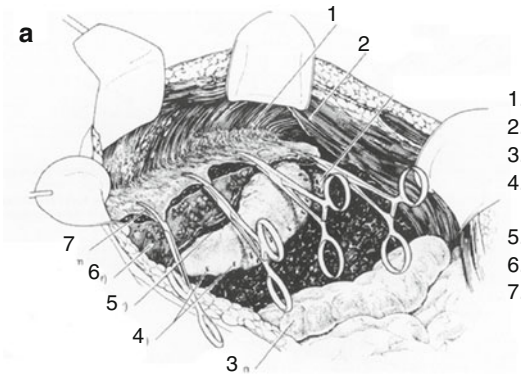
Fig. 12.1 "Peritoneal cancer index" (PCI) defined by Sugarbaker for intraoperative determination of the extense of peritoneal carcinomatosis spread

Table 12.1 Completeness of cytoreduction (CC)

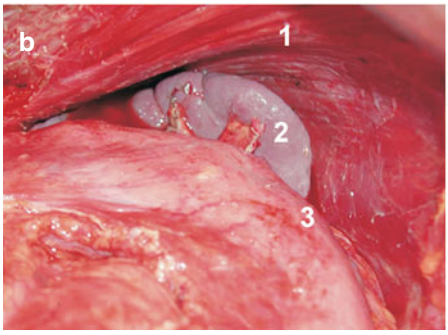
Score	Size of remnant tumor
CC-0	No tumor remnants macroscopically
CC-1	Tumor remnants <0.25 cm
CC-2	Tumor remnants 0.25–2.5 cm
CC-3	Tumor remnants >2.5 cm

To achieve total cytoreduction, the complete affected visceral and parietal peritoneum must be resected. This is relatively easy in the case of the parietal peritoneum of the lateral abdominal wall. It is more difficult in the pelvis and diaphragm as well as the visceral peritoneum of the small intestine stomach and hepatic arch. This often necessitates multivisceral resections and several visceral anastomoses. Sugarbaker described the techniques for the most common visceral and parietal peritoneal resections [11, 38] and grouped these in six operative sections.

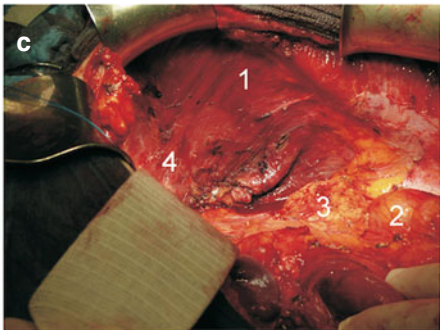
He starts with a median laparotomy from the xiphoid to the pubic symphysis to allow complete exploration of both diaphragm and the pelvis. If the greater omentum is affected or an omental cake has formed, the omentum is resected. This is carried out removing the gastroepiploic arch and the gastrica brevis vessels along the greater curvature. Then the peritoneal resection is continued in the left upper abdomen (Fig. 12.2). The peritoneal coating of the diaphragm, the rear wall of the rectus abdominis, the adrenal gland, the fascia of Gerota, parts of the pancreas, and the transverse colon are removed. If there is tumor occurrence in the splenic hilum or the pancreas tail, splenectomy and/or left pancreatic resection may be necessary [39]. In the right abdomen, the procedure is similar (Fig. 12.3), and the dissection is removed "en bloc" along the lateral abdominal wall, the diaphragm, and the Morrison pouch right over to the inferior vena cava. Should the tumor be adherent to the tendinous part of the diaphragm a partial diaphragm resection will be necessary. The resection



1. left hemidiaphragm muscle
2. Peritoneum
3. Transverse colon
4. Stomach with ligated branches of the gastroepiploic arterie
5. Lesser omentum with tumor
6. Liver with surface tumor
7. Tumor beneath left hemidiaphragm



1. left hemidiaphragm muscle
2. Splen
3. Stomach with ligated branches of the gastroepiploic arterie



1. left hemidiaphragm muscle
2. Transverse colon
3. Pancreas
4. sutured hemidiaphragm after partial resection

Fig. 12.2 (**a**) Peritoneal resection in the upper left abdomen (Sugarbaker), (**b**) intraoperative site after peritoneal resection in the upper left abdomen retaining the spleen, (**c**) intraoperative site after peritoneal resection involving splenectomy and partial resection of the tendinous diaphragm

in the upper abdomen finishes with peritoneal resection of the greater omental pouch along the hepatic duodenal ligament and the superior surface of the pancreas to the celiac trunk and finally the affected parts of the lesser omental pouch.

For the pelvic peritoneal resection (Fig. 12.4), the peritoneum is mobilized along the laparotomy. Caudally, the rectus muscles are identified and the peritoneum swept off the bladder. Laterally, the ureters are identified and followed down to the bladder. In female patients, both round ligaments and ovarian veins are divided. Following this, the mesorectal layer is opened; the rectum is mobilized below the peritoneum and then separated so the complete peritoneal funnel can be removed from the lower pelvis. In female patients, the uterine artery is divided at the crossing point with the ureters, and the uterus and adnexes are removed en bloc with the rest of the lower pelvis.

The effectiveness of the resection is considerably determined by the involvement of the visceral peritoneum despite the systematic method described. An extended cytoreductive resection may often lead to a multivisceral resection with parietal and

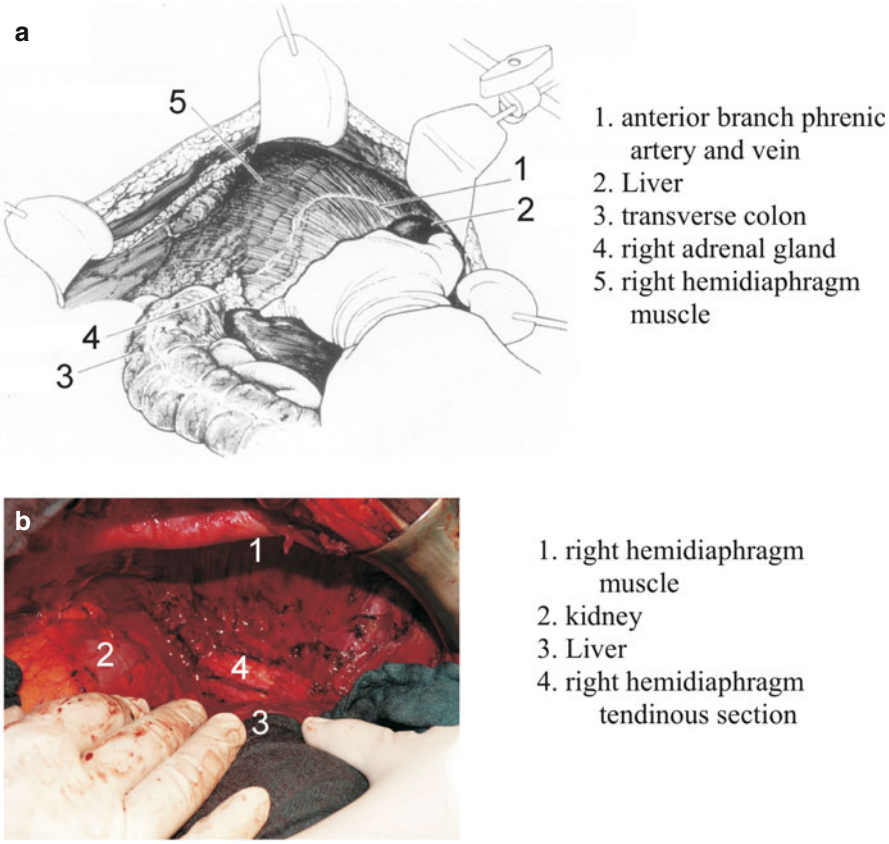


Fig. 12.3 (**a**) Peritoneal resection in the upper right abdomen (Sugarbaker), (**b**) intraoperative site after peritoneal resection

visceral peritoneal resections; resection of the omentum, spleen, parts of the pancreas, lesser sac, and liver capsule; atypical liver resection; cholecystectomy (partial); gastric resection (multiple); small intestine resections; colonic and rectum resection; ovariectomy; hysterectomy; and occasional partial bladder resection. This means that severe reflection about the postoperative quality of life is necessary when determining the extent of the resection.

12.3.2 The Rationale and Technique of Hyperthermic Intraperitoneal Chemotherapy: HIPEC

After termination of the cytoreductive surgery, the hyperthermic intraperitoneal chemotherapy follows. HIPEC is the most commonly applied form of local perioperative chemotherapy. The rationale of intraperitoneal chemotherapy is that this form of application allows high concentrations of chemotherapy locally while the

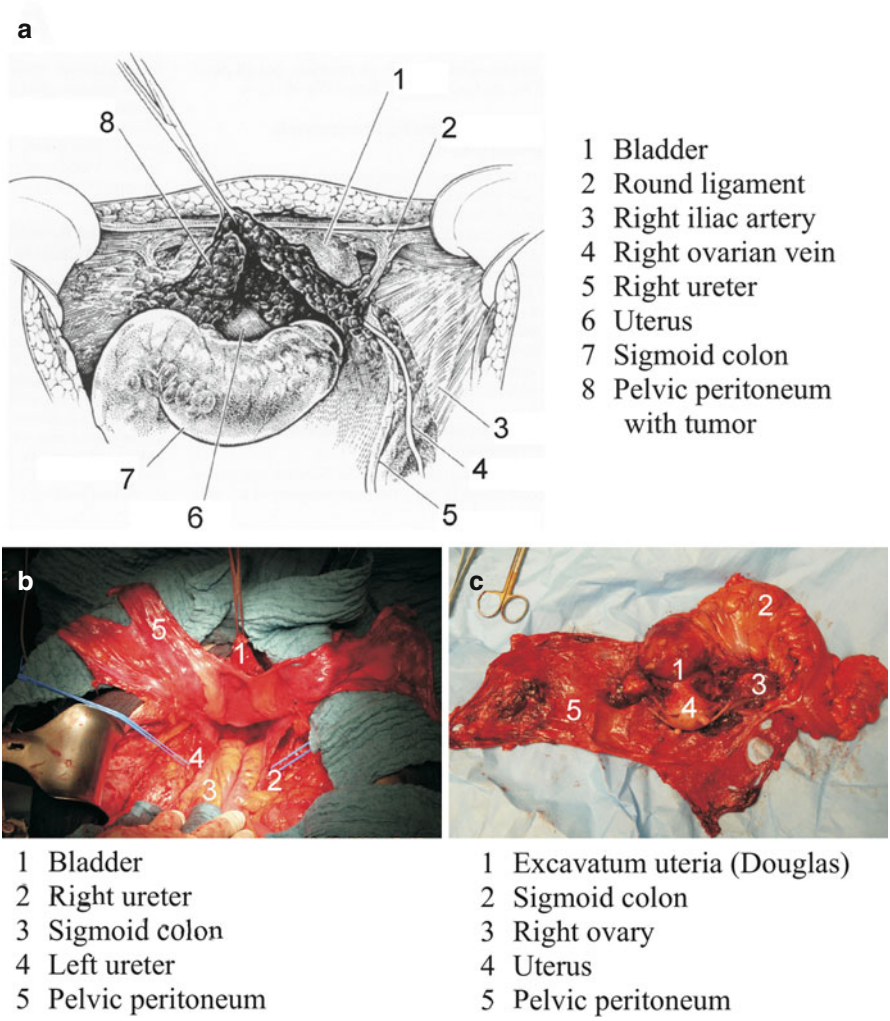


Fig. 12.4 (**a**) Peritoneal resection in the lower pelvis (Sugarbaker), (**b**) intraoperative site with both ureters looped, (**c**) the resection of the lower pelvis with rectum, uterus, both ovaries and parietal peritoneum

systemic concentration levels remain low [40]. This concentration gradient is sustained by the peritoneal plasma barrier (ppb) [41, 42]. Surprisingly even extended peritoneal resection does not change the pharmacokinetics of chemotherapeutics applied intraperitoneally [43]. However, the ppb does lead to diminished chemotherapeutic tissue penetration which limits the effect of intraperitoneal chemotherapy. Estimates of the depth of tissue penetration range from a few cell layers to a depth of 5 mm [44–48]. This is the reason that cytoreductive surgery precedes chemotherapy and the resection is rated as optimal when at most tumor lesions of

<2.5 mm remain (CC 0–1). The hyperthermia has varied effects. First hyperthermia between 41° and 43 °C has a cytotoxic effect, especially on malignant cells [49–51]. Hyperthermia leads to an increase in lysosomes and lysosomal enzymatic activity in malignant cells. Further, hyperthermia in malignant tumors causes a decrease in cell perfusion [52] with resulting acidosis which again increases lysosomal activity and thus accelerates death of malignant cells [50]. Increased membrane permeability and transport mechanisms of malignant cells allow increased intake of pharmaceuticals and so an increase of pharmaceutical activity [47, 51, 53]. However, the synergistic effect of different chemotherapeutics under hyperthermia differs.

12.3.3 HIPEC Procedure

HIPEC is carried out – as mentioned – after the cytoreductive surgery has been completed. However, opinions differ as to whether the reconstruction of the gut should be carried out before or after HIPEC. Theoretically, the concern about recurrence of the carcinoma in the anastomoses is an argument for reconstruction after HIPEC; however, no increased rate of anastomosal recurrences has been found after preceded reconstruction [40]. The drug is given in a standard dose related to body surface area and the volume of carrier solution [54, 55]. Basically, HIPEC may be carried out as an open procedure or with a closed abdomen. The open technique is often referred to as the "coliseum technique" by Sugarbaker [13]. Here, the laparotomy remains open; the skin is fixed continuously on a frame and elevated so that a crater-like opening is formed. Inlet and outlet catheters are brought in through the abdominal wall and get fixed. The optimal temperature is regulated by temperature gauges in inlet and outlet sluices during perfusion. The system is covered with a foil to ensure that theater contamination is at a minimum and below the foil a drainage system is installed. The foil may be opened by the surgeon permitting intra-abdominal manipulation to ensure even perfusion of each region by the chemotherapeutics (Fig. 12.5). The perfusion solution is introduced via a heat exchange and perfusion pump at a rate of about 1 l/min (Fig. 12.5). When a temperature between 41 and 43 °C is reached on the inlet and outlet catheters, the chemotherapeutic is added, and perfusion is performed for 30–90 min according to the therapeutic regime. The advantage of the open technique lies in the homogenic distribution, yet there is a greater heat loss, and the theater staff is potentially endangered. In the closed technique, perfusion is commenced after the catheters have been placed and the wound has watertight closure. The advantages of the closed technique are that the target temperature is achieved rapidly and remains stable [56]. Furthermore, the theater staff is less exposed to contamination. The disadvantages lie in a proven inhomogeneous distribution of the chemotherapeutic as well as the risk of local overheating and overloading with chemotherapeutic with the risk of postoperative complications [40].

Over the last years, so-called bidirectional HIPEC methods have become established. Here the intravenous (iv) chemotherapy is applied simultaneously with HIPEC. Elias performed this with 5-FU and folic acid i.v. and oxaliplatin

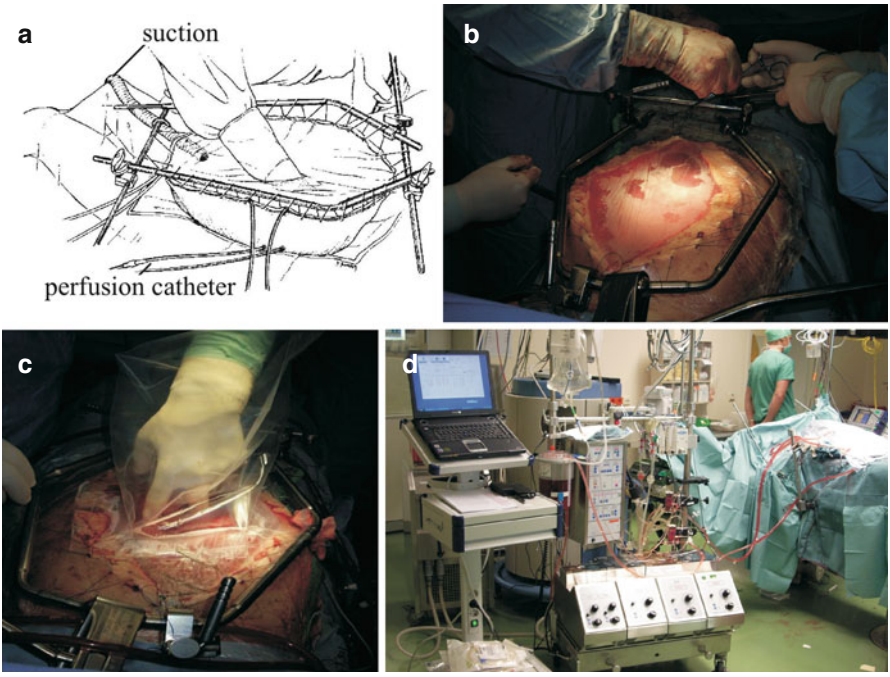


Fig. 12.5 (**a**) Coliseum technique by Sugarbaker. (**b**) Variation of the Coliseum technique as carried out in Giessen. (**c**) Intestinal manipulation during perfusion. (**d**) Heart lung machine for generating the hyperthermia

intraperitoneally [54]. Van der Speeten showed that under these circumstances, it came to an increase in the concentration of 5-FU in the peritoneal cavity [57].

Up till now, there are no standards for the chemotherapeutics used or the time of perfusion. This has led to worldwide different standards of which chemotherapeutic is perfused for how long on which tumor. From all used drugs, mitomycin C is the most commonly used one. The standard drugs of systemic chemotherapy cisplatin, doxorubicin, oxaliplatin, and irinotecan are being applied increasingly especially in cases of bidirectional treatment of colorectal cancer.

For example, in bidirectional HIPEC, leucovorin (20 mg/m^2) and 5-FU (400–450 mg/m^2) are given intravenously over 30 min, 30–60 min before HIPEC with oxaliplatin being carried out.

12.3.4 Aspects of Risks and Safety for Theater Staff

Intraoperative administration of chemotherapeutics does potentially endanger theater staff. Above all, the open coliseum technique involves risks of contamination of the staff and the operating table. When using mitomycin in the coliseum technique, Stuart took urine samples of the theater staff and air samples above and below the

foil and checked the theater gloves for permeability for this chemotherapeutic. All the tests for contamination were negative [58]. Similar test with platin-based chemotherapeutics showed low contamination, but significantly higher levels were measured at the HIPEC pump and around the theater table especially when the pump reservoir was filled with the chemotherapeutic with a syringe [59, 60]. Contamination may however be kept at lower levels if certain safety measures are adhered to [40, 61]. Reusable drapes must not be used. Theater staff must be kept to a minimum during and after perfusion. Theater doors must be closed with warnings about HIPEC to keep staff translocation and so air disturbance at a minimum. The theater floor around the table should be covered with absorbent nonreusable cloths. All the staff involved in the process must wear water repellant protective clothing. All potentially contaminated material must be removed in specially labeled stabile containers after HIPEC so that cleaning staff is not endangered. Within the first 48 h after HIPEC, all the patients' body liquids must be regarded as contaminated and treated as such. Low-permeability double gloving is compulsory for every contact with the chemotherapeutic [58]. In cases of continual contact with the chemotherapeutic, the gloves must be changed every 30 min. Air evacuation above the theater table is compulsory. Should contamination still occur, it must be removed with every possible regard to personal safety but without causing an aerosol effect. Theater instruments must be washed several times before clearance. Contamination of theater staff can be kept to a minimum if these methods are adhered to.

12.4 Perioperative Management

The perioperative management during cytoreduction and HIPEC involves different phases, each needing specific individual care [24]. During resection, the large laparotomy, the long operation time, and the enormous wound surface result in considerable fluid loss [62]. Further, hypothermia threatens with negative effects on coagulation, patient neurology, immunology, as well as the metabolic situation [63–65]. Fluid control remains important during perfusion. Patient's hyperthermia during perfusion of up to 40.5 °C increases the metabolic rate requiring more 0_2 [66]. Further, a higher pulse rate, lactate levels, and metabolic acidosis [62, 66–69] require adjustments in pulmonary ventilation. This means that one of the aims of the anesthesia is to achieve normothermia but be able to react correctly to changes in body temperature [24]. Next to temperature control, fluid management is as important during intraoperative care of the patient. Maintaining normovolemia has a very important effect on both systemic and regional perfusion, something extremely important especially when performing HIPEC. Hyperthermia causes a drop in the peripheral resistance and so leads to further unwanted fluid distribution. If it comes to a relevant fluid deficit, decreased perfusion of internal organs leading to kidney failure may occur [68]. On the other side, hypervolemia has severe side effects in the future course [70]. Several factors have to be considered to estimate the necessary volume substitution. Fluid need is higher than normal and may reach 12 ml/kg/h, the extensive resection causes severe protein loss through the large wound

surface [71], and the blood loss may be high. All factors and also the coagulation situation mean that a balanced substitution with crystalline and colloid solutions as well as fresh plasma and red blood cell concentrates is necessary [24]. Under HIPEC conditions, the perfusion solution and the type of chemotherapeutic must be taken into account. Using oxaliplatin, a 5 % glucose solution is normally used as a carrier causing hyperglycemia and hyponatremia [72, 73]. When cisplatin is administered, its cardiotoxic side effects must be considered [74].

In the first postoperative phase, fluid control is still at the center of our efforts as the enormous wound surface causes considerable fluid and protein loss leading to late volume redistribution [23, 69, 75]. So it can be clearly followed that postoperative respiratory training with continuous positive airway pressure (CPAP) improves the pulmonary situation and convalescence [23]. In the postoperative phase, the peridural thoracic catheter has many advantages. Postoperative ventilation time is reduced as well as the i.v. opioid therapy regime causing bowel movement to commence earlier. A recent publication [76] has shown that there may even be an oncological advantage in using supplementary peridural anesthesia. On the other hand, there are several publications describing higher complication rates of peridural anesthesia under HIPEC [77–79]. A possible alternative pain therapy could be continuous local wound infiltration as carried out in our center in cases of suspected coagulation disorders using a "PainBuster system®" [80].

12.5 Morbidity, Mortality, and Quality of Life (QoL)

Up till now, there is no unitary scheme to document complications after cytoreduction and HIPEC. Postoperative complications may occur through extended resections or through toxic effects caused by HIPEC. These may interact additively. In the joint paper of Milan [81], an expert committee agreed to use the "common terminology criteria for adverse events (CTCAE)" by the National Institutes of Health (NIH) for the documentation of postoperative complications following cytoreduction and HIPEC as the general classification. Here minor complications (grade 0–2) and major complications (grade 3–5) are differentiated by a detailed classification of 28 categories to clearly define morbidity. Increased fluid transfer, bowel atony, anastomosis failure, bleeding, thrombosis, pulmonary embolism, and wound infections are common postoperative complications. Direct complications of the chemotherapeutic are cardio- and hematotoxicity as well as liver and kidney damage. Major complications grade 3 and 4 are described in 30–40 % of the cases with a mortality between 0 % and 8 % [29].

In large centers performing cytoreduction and HIPEC, the morbidity and mortality rate is comparable to that of other multivisceral resections [82].

After cytoreduction and HIPEC, the QoL of the patient is severely limited in the postoperative phase due to the extended operation and the high rate of complications.

However, studies by McQuellon showed that after an initial worsening, patients showed a better QoL 3.6 and 12 months after the operation compared with the

preoperative status. Seventy-four percent of the patients had renewed more than half their activities of daily life 1 year postoperatively. An acceptable QoL with little pain can be achieved after 3–6 months. At the time of operation, one third of the patients show signs of depression, and these persist in 24 % of the cases after 1 year of follow-up [83, 84].

An actual meta-analysis by Shan et al. including McQuellon's data shows similar results. If individual aspects of the QoL score are analyzed, patients show a significant improvement in emotional health 3 months after cytoreductive surgery and HIPEC, most easily explained by a newly resolved hope for a new lease of life [85].

The present state of the studies shows that cytoreduction and HIPEC have acceptable results in patients who appreciate the prognostic outcome of their disease and that despite the enormity of the treatment, the postoperative QoL is improved as well as the emotional situation because of the new hope of a longer lease of life.

12.6 Results of Different Tumor Entities

12.6.1 Primary Peritoneal Malignomas

12.6.1.1 Malignant Peritoneal Mesothelioma (MPM)

The malignant mesothelioma is a rare tumor which can develop from the pleura, peritoneum, pericard, or the tunica vaginalis testis [86]. Its rate of occurrence has increased in the past decades due to the widespread exposure to asbestos and will probably reach its maximum in the next 20 years [87]. The diffuse malignant peritoneal mesothelioma (DMPM) represents about 10–30 % of all mesothelioma diseases [88]. The causality of asbestos exposure and DMPM is far less conclusive than in pleura mesothelioma [89, 90]. Histologically, there are three subtypes: epithelial, sarcomatous, and mixed type. The diagnostic classification is not easy as the tumor morphology is very variable, and it is often difficult to differentiate between mesothelioma and benign reactive changes or metastases of an adenocarcinoma [91]. Immunohistology is helpful although there is no typical mesothelioma marker. The tumor can often be defined by its constellation of positive or negative immunoreactivity.

Generally, the disease remains in the abdomen. Autopsies have shown that in 78 % of the cases, patients died of complications of the locoregional tumor growth [92]. It is because of this locoregional tumor progression that treatment with cytoreduction and HIPEC seems a good policy. Without aggressive therapy, the median survival rate lies between 6 and 12 months due to the rapid tumor growth [93]. Under the treatment with cytoreduction and HIPEC, it can be extended and presently lies between 30 and 92 months [94]. An actual meta-analysis showed the 1-, 3-, and 5-year survival rates to be 84 %, 59 %, and 42 %, respectively [95]. Patients with an epithelial mesothelioma have a longer median survival rate [96]. As the disease progresses, the small intestine is involved to a high degree [94]. In a controlled trial, Baratti et al. examined the outcome of patients in whom only affected peritoneum was resected compared with a group in which, regardless of the tumor

spread, the entire peritoneum was removed. The median survival time in the subtotally resected group was 29.6 months; in the second, the median survival time had not been reached after a follow-up of 50.3 months. The 5-year survival rate was 40 % in the first group and 63.9 % in the second group. This difference is significant so that the total peritoneal resection is associated with a higher survival rate [97].

Special forms of peritoneal mesothelioma are multicystic peritoneal mesothelioma (MPM) and well-differentiated papillary peritoneal mesothelioma (WDPPM). Both subtypes are rare and show questionable malignant growth behavior. Recurrence is common, and the transformation to malignant mesothelioma is possible. Both forms appear mainly abdominally in fertile females with no case history of asbestos exposure. Different therapeutic approaches have been developed because of the recurrence and transformation rate to malignant tumors, but because of the low number of cases documented, no standards can be advised. Baratti [98] describes cytoreduction and HIPEC in 12 patients with a 5-year survival rate of 90 %. One of the patients suffered transformation to malignant mesothelioma. Considering these results, cytoreduction and HIPEC seem to be a justifiable strategy.

12.6.2 Secondary Peritoneal Malignomas

12.6.2.1 Colorectal Cancer and Appendiceal Cancer

The most common indication for cytoreductive surgery and HIPEC is colorectal cancer with PC. As the appendiceal cancer is included in many studies, it will be included here too. Glehen's meta-analysis [20] from 2004 on 506 patients showed that the median survival time was 32.4 months for patients with macroscopic total tumor removal and HIPEC. In comparison, the median survival time of patients with best supportive care (EVOCAPE 1) was 6 months [1]. Patients without total resection had no benefit. The colorectal cancer was the first tumor entity examined in a randomized controlled trial. This was carried out by Verwaal et al. in the Netherlands examining the effectivity of the combination therapy [21]. The median survival time of the control cohort was 12.6 months compared with 21.6 months in the trial cohort with cytoreductive surgery and HIPEC. Patients with macroscopic total resection showed even better results. The follow-up data on this study after 8 years showed a 5-year survival rate of 45 % on patients with total resection [21]. Several phase II studies showed 5-year survival rates up to 50 % [99, 100]. The results of these studies have made cytoreductive surgery and HIPEC the therapy of choice for the treatment of colorectal cancer with PC in many countries.

In the group of colorectal cancer, it seems that rectal cancer is less respondent to therapy than colon cancer in other regions. Da Silva [101] has shown that the median survival time of patients with rectal cancer was 17 months, whereas that for other colonic regions was 33 months. Furthermore, the histology of the cancer seems to play an important part in the effect of the therapy. The long-term prognosis for signet-ring cell carcinoma is bad despite cytoreductive surgery and HIPEC, and so the indication for this treatment in such cases must be carefully considered [102, 103].

Elias [104] carried out second look operations after 1 year on patients thought to have a high risk of developing PC. These were patients with local PC on the primary operation, ovarian metastases, or a perforated cancer. This collective of 29 patients showed 16 patients (55 %) having PC which was not visible in the CT scan in most cases. Even if there are no long-term results available for this collective as yet, the strategy does seem reasonable for patients at a high risk of developing PC.

12.6.2.2 Pseudomyxoma Peritonei (PMP)

PMP is a rare disease identified by mucinous ascites and peritoneal spreading [105, 106]. During disease progress, large volumes of mucinous ascites are formed causing obstruction and occlusion of the intestine. The disease was first described by Rokitansky in 1842 in a patient with a mucocele of the appendix [107]. For a long time, there was no consensus as to the origin and the pathological classification of PMP. According to pathological examinations, the majority of PMP evolves from low-grade tumors of the appendix [108–110], in rare cases from other organs. These are mainly the ovaries but also the stomach, colon, pancreas, and other intra-abdominal organs [111, 112]. PMPs do not just differ in their origin but also in their growth rate. Ronnett [108] suggested a now popular classification on the results of a retrospective tumor analysis. Three subtypes were described. Low-grade tumors were defined as disseminated peritoneal adenomucinosis (DPAM), high-grade tumors as peritoneal mucinous carcinomatosis (PMCA), and the intermediate type (IG) whose long-term behavior is not different to that of PMCA. Further classifications have been put forward, all of which differentiate between aggressive and less aggressive forms of PMP.

Symptomatic PMP patients often underwent repeated tumor reductive surgery. This led to a short-term improvement in the symptoms but had little influence on the long-term survival rate [105, 106]. Almost all patients had recurrences, and as the number of reoperations increased, the therapy became less effective and the complication rate increased. Histopathologically, it was shown that in some cases, the low aggressive forms transformed to high aggressive forms. Under these conditions, 10-year survival rates between 10 % and 30 % [113, 114] were achieved even though in some cases extremely aggressive treatment with intraperitoneal radiation and chemotherapy was applied.

Many studies showed that therapy with cytoreduction and HIPEC shows improved survival rates when compared to past control groups [116]. With a cohort of 501 patients, Sugarbaker et al. showed that a median survival time of 156 months and a 5- and 10-year survival rate of 72 and 55 % can be achieved [115]. Based on these studies and despite the fact that there were no large randomized studies, the leading HIPEC centers working on the treatment of PMP published a consensus paper in 2008 stating that the combination of cytoreductive surgery and HIPEC is the only scientifically based, promising treatment available [116].

In a study by Chua et al. [117], the data of a multicentric retrospective data bank involving 2298 patients from 16 centers were analyzed. A mortality of 2 % and a complication rate of 24 % were shown for cytoreductive surgery and HIPEC. The median survival time was 196 months with a 10- and 15-year survival rate of 63 and

59 %. Independent factors for a low survival rate were old age, severe postoperative complications, preoperative chemotherapy, and aggressive histological subtype (PMCA).

12.6.2.3 Gastric Cancer

PC is found in 5–20 % of patients with a planned curative gastrectomy [118, 119]. This has a terrible prognosis and a mean survival time of 3 months [1]. Sixty percent of gastric cancer patients die because of PC [120]. Polychemotherapy is the preferred therapy in advanced gastric cancer and is superior to best supportive care [121]. However, several studies have shown that as with other tumor forms, PC does not respond as well as organ metastases to systemic chemotherapy because of the blood peritoneal barrier [122, 125]. The results shown for cytoreductive surgery and HIPEC were not convincing for a long time. The PCI level for gastric cancer which makes a resection an option is lower than for colon cancer [126–128], and a total cytoreduction (CC-0) is a must to improve the prognosis. A meta-analysis and systematic reviews have shown that if these conditions are fulfilled then, an improvement of the prognosis can be achieved by cytoreductive surgery and HIPEC [118, 129, 130]. The median survival time in these studies lays between 7.9 and 15 months and the 5-year survival rate between 6 % and 16 %. Glehen and Yonemura published better results for patients with total cytoreduction (CC-0) with a median survival time between 15.4 and 21.3 months and a 5-year survival rate between 15 % and 29.4 % [131, 132].

The preoperative staging is very important in cases of gastric cancer because of the high incidence of PC. Unfortunately, CT scan is unsuitable to detect the typical tiny PC lesions. It has been shown that spreads of less than 5 mm were only detected with a sensitivity of 11 % [133] and that the PCI determined by CT scan often underestimated the spread [128].

In comparison, laparoscopic staging shows good results with 90 % accuracy. Valle could show in a cohort of 97 patients that the laparoscopic score only varied from the intraoperative score in 2 out of 97 patients [134]. As new neoadjuvant treatments have become available, the initial staging is of tremendous importance, and the staging laparoscopy is therefore the method of choice.

12.6.2.4 Neoadjuvant Strategy for Advanced Gastric Cancer with PC

Various neoadjuvant concepts have been developed to transform an initially nonresectable gastric cancer into a resectable one. Classical neoadjuvant systemic chemotherapy with various drug combinations is able to increase the share of patients in whom a total cytoreduction is possible and thus increase the life expectancy [123, 124, 135]. Realizing that the advantages of local chemotherapy were counterbalanced by the low penetration depth, Yonemura developed a bidirectional neoadjuvant intraperitoneal and systemic chemotherapeutic strategy (NIPS). The results of this method appear favorable. In a group of 79 patients, 65 had positive ascites cytology at first diagnosis. After NIPS, 41 (63 %) of these 65 patients had negative ascites cytology. In half of the patients with PC, it came to a complete remission, and in the rest the rate of total cytoreduction was very high [132, 136, 137]. As a

whole, few studies have been performed with favorable results; therefore, the treatment should only be carried out under controlled study conditions.

12.6.2.5 Ovarian Cancer

Ovarian cancer is one of the most common gynecological malignant diseases [138]. Epithelial ovarian cancer represents the most common form with over 70 %. When diagnosed, the disease is usually in an advanced stage with peritoneal involvement [139]. As ovarian cancer is generally chemosensitive, standard therapy is cytoreductive surgery followed by adjuvant systemic chemotherapy with paclitaxel and a platin-based therapeutic [140]. Recurrence is common and chemoresistance develops. The 5-year survival rate for advanced tumor is under 25 % [141]. The degree in which cytoreduction can be carried out in ovarian cancer is highly relevant. A meta-analysis on almost 7000 patients showed that maximal cytoreduction is the most relevant factor for survival [8]. Adjuvant intraperitoneal chemotherapy was tried with success as the initial high chemosensitivity was well known [142]. The logical deduction seems that cytoreductive surgery and HIPEC could be used successfully in the treatment of this tumor form. However, the evidence is unclear and this has several reasons. In many studies, the cohorts of patients are not standardized. In a systematic review [143], Chua et al. show that in the examined cohorts, patients with first diagnosis of ovarian cancer, patients with recurrent cancer, patients who have undergone chemotherapy, patients with chemoresistant tumors, and patients with chemosensitive tumors are grouped together, so making the conclusions of the examinations very questionable. Furthermore, there are different interpretations of the definition of "optimal" cytoreduction [144]. On one hand, extensive multivisceral resection to achieve total cytoreduction (CC-0) leads to high morbidity in the treatment of a chemosensitive tumor, whereas on the other hand, the radicality of the resection is diminished to reduce the morbidity. There are enough arguments to defend either position. Winter et al. [145] showed that in a study with 360 patients, radically resected patients had significantly higher survival rate in an otherwise identical therapeutic regime.

Different points of time can be used to evaluate the effectivity of cytoreductive surgery and HIPEC in ovarian cancer. Primary therapy at first diagnosis of ovarian cancer or secondary therapy at persisting, progressing, or recurrent disease [146]. A French multicenter study [147] has recently been published involving 92 patients who underwent primary therapy with cytoreduction and HIPEC. The median survival time was 35.4 months. Those who had total cytoreduction had a median survival time of 41.5 months.

In the first randomized trial of patients with recurrent ovarian cancer published by Spiliotis, treatment with cytoreductive surgery and systemic chemotherapy was compared to cytoreductive surgery and HIPEC with the same adjuvant systemic chemotherapy. The HIPEC group was found to have a significantly longer survival time of 26.7 months compared to 13.4 months. The 3-year survival rate was 75 % in the HIPEC group but only 18 % in the non-HIPEC group [148]. At the moment, several randomized controlled trials are being carried out to position the value of cytoreductive surgery and HIPEC. The Netherlands Cancer Institute is comparing

cytoreductive surgery with HIPEC to cytoreductive surgery alone [149]. The second study from Sidney is comparing the effect of cytoreductive surgery and HIPEC on primary ovarian cancer and on recurrent disease [150]. In a French study [151] (CHIPOR), patients with recurrent ovarian cancer are treated with systemic chemotherapy followed by maximal cytoreductive surgery with and without HIPEC.

After these studies have been completed, we can expect a new evaluation of the combination of cytoreductive surgery and HIPEC in ovarian cancer.

12.7 Summary

The combination of cytoreductive surgery and HIPEC has left the experimental stage for some tumor entities. In large-scale meta-analysis, good results could be achieved for PMP, colorectal cancer, and appendiceal cancer, even in randomized trials. This has lead France and the Netherlands to include this treatment in their guidelines for the treatment of colorectal cancer. Similar results for gastric and ovarian cancer have not yet been achieved although there are signs that under certain conditions, cytoreductive surgery and HIPEC are of use. Still there are many unanswered questions. There are no standardized therapeutic regimes, neither for the choice of chemotherapeutic or for the time of perfusion. The extense of peritoneal resection is not standardized, so in some centers only macroscopically affected peritoneum is resected; in others, a total peritoneal resection is carried out with proven long-term success [95].

The most important factor overall is patient selection because it is only by maximal cytoreduction (CC-0, CC-1) that an improvement of the prognosis may be achieved.

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