Peritoneal carcinomatosis —cytoreductive surgery and HIPEC - overview and basics

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ABSTRACT

Tumor involvement of the peritoneum — peritoneal carcinomatosis — is a heterogeneous form of cancer that had been generally regarded as a sign of systemic tumor disease and as a terminal condition. The multimodal treatment approach for patients with peritoneal carcinomatosis, which had been conceived and developed consists of what is known as cytoreductive surgery, followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Depending on the tumor mass as assessed intraoperatively and the histopathological differentiation, patients who undergo cytoreductive surgery and HIPEC have a significant survival benefit. Mean increases in the survival period ranging from 6 months to up to 4 years have now been reported. In view of the substantial logistic effort and the extent of the surgery involved, this treatment approach represents a major challenge both for patients and for surgical oncologists, as well as for the members of the overall interdisciplinary structure required, which includes oncology, anesthesiology and intensive care, psycho-oncology, and patient management. The surgical procedures alone may take 8–14 hours. The present article provides an overview of the basis for the approach and the use of specialized classifications and quantitative prognostic indicators.

KEY WORDS: peritoneal carcinomatosis; HIPEC; colon cancer; pseudomyxoma; gastric cancer
INTRODUCTION

This review includes a systematic overview and discussion of peritoneal carcinomatosis (PC) and all of the essential aspects involved in it, presenting the most important basic information about the procedure under the following headings: General considerations, anatomy and embryology, classification and types of growth in PC, paradigm change in PC, peritoneal carcinomatosis index (PCI), residual tumor classification (completeness of cytoreduction score = CC score), multimodal strategy in PC, hyperthermic intraperitoneal chemotherapy (HIPEC) technique, foundations and rationale for hyperthermic intraperitoneal chemotherapy (HIPEC), value of laparoscopy in PC, selection criteria, contraindications for cytoreductive surgery, morbidity and mortality with peritonectomy and HIPEC, quantitative prognostic indicators (QPIs) for each tumor type, summary and prospects.

GENERAL CONSIDERATIONS

Tumor involvement of the peritoneum — peritoneal carcinomatosis — is a heterogeneous form of cancer that is generally regarded as a terminal stage. It may be characterized by involvement of the abdomen, pelvis, and peritoneum, and/or it may appear in the terminal stage of cancer. Up to the turn of the century, the prognosis for patients with peritoneal carcinomatosis was considered to be hopeless. Many authors developed a multimodal approach for patients with peritoneal carcinomatosis involving what is known as cytoreductive surgery, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) [1]. As these procedures, which are described in detail below, make very heavy demands on surgeons/visceral surgeons working in the field of oncology, as well as on the patient, Sugarbaker described peritoneal carcinomatosis patients as “mother of surgery (MOS) patients.” Many initial results with this
multimodal form of treatment in the late 1990s were reported [2 - 4]. They showed, that depending on the tumor mass assessed intraoperatively—patients with primary colorectal tumors and secondary peritoneal carcinomatosis experienced a significant survival benefit with the treatment [5, 6]. The usual median survival achieved by patients with non-ovarian peritoneal malignancies (6 months) [7] was capable of being increased to a median of 4 years, depending on the intraoperative tumor burden. Specific tumor entities and the current results with the procedure are discussed in detail below. The anatomy of the peritoneum is discussed here briefly to begin with, as familiarity with it is extremely important for a general understanding of the approach and also for the intraoperative strategy.

**ANATOMY AND EMBRYOLOGY**

The peritoneum should be regarded as an organ. With a surface area of approximately 7500 cm², it is in contact with all of the intra-abdominal organs. At the end of the third week of gestation, intraembryonic mesoderm divides bilaterally into the mesoderm, intermediate mesoderm, and lateral plate. In the lateral plate, a mesothelial cell layer divides into the parietal and visceral mesoderm. The parietal mesoderm, which lines the intraembryonic celomic cavity, becomes the parietal mesoderm, the parietal pleura, and the pericardium. From the visceral mesodermal layer, the visceral peritoneum, visceral pleura, and epicardium develop. The dorsal mesentery, to which the intestinal tube is attached, represents the junction between the parietal and visceral peritoneum.

When a peritonectomy is being planned, it is essential to be aware of these embryological facts (which also provide the basis for the lymphadenectomy approaches used in gastric and/or colonic carcinoma, for example), as they are associated with specific sites of predilection for tumor involvement. Interestingly, there
is almost never any tumor penetration into the underlying structures in cases of peritoneal carcinomatosis. This is probably due to the peritoneum’s embryologically established barrier function. A detailed description of the ultrastructure of the peritoneum was published by Baron in 1941 [8]. The peritoneum has a special histological structure, a special type of vascularization, and also a specific function. It consists of a single-cell layer of mesothelial cells, with a basal membrane lying underneath it and five layers of connective tissue (interstitial cells and a matrix of collagen, hyaline, and proteoglycans), with a total thickness of 90 µm. As it also contains other cellular components such as pericytes, parenchymal cells, and blood capillary vessels, the peritoneum is often referred to as the “peritoneal membrane.” The functions of the peritoneum include maintenance of the intra-abdominal mobility of the organs relative to the abdominal wall (through a lubricant consisting of glycosaminoglycans and phospholipids) and also defense against intra-abdominal infections (along with lymphoid aggregates). It is also assumed that the peritoneum represents the primary barrier and initial line of defense against peritoneal carcinomatosis [9]. This view is supported by research, which has shown that intraperitoneal injection of aggressive tumor cell lines leads to a corresponding increase in tumor cell involvement in the peritoneum, depending on whether there is slight, moderate, or severe damage [10]. However, the interaction between the single layer of mesothelial cells together with blood capillaries and the surrounding interstitial matrix, as the theoretical barrier to the clearance of molecules from the abdomen, also appears to be relevant [11].
CLASSIFICATION AND TYPES OF GROWTH IN PC

Peritoneal carcinomatosis can be divided into primary and secondary PC. Primary PC consists of invasion by a mesothelioma or pseudomyxoma peritonei — both extremely rare tumor entities. Secondary PC occurs as a sequela of gastrointestinal tumors [12-14] or urogenital tumors [15]. Other forms of secondary PC involve further types of primary tumor such as malignant melanoma or breast carcinoma. There are important differences between growth types in peritoneal carcinomatosis, which on the one hand may allow a fairly simple subsequent resection or on the other hand may limit a radical surgical procedure a priori, particularly when there is substantial involvement of the mesenteric pedicle (Fig. 1A–E).

PARADIGM CHANGE IN PC

The paradigm change — involving a move away from a fatalistic approach, in which only palliative and/or best supportive therapy could be offered, toward a curative treatment approach using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) — is justified by the current state of the international data. Patients with colorectal tumors and PC who underwent cytoreductive surgery and HIPEC had survival periods of 21–40 months [16, 17], while patients with pseudomyxoma peritonei may even have a 20-year survival rate of 70% [18]. However, these results depend on the intraoperative tumor burden [19]. The curative treatment approach in peritoneal carcinomatosis is a demanding and elaborate interdisciplinary procedure in which surgeons, anesthetists, oncologists, gastroenterologists, dieticians, and psycho-oncologists should be equally involved. Surgeons and visceral surgeons working in the field of oncology have a range of experience that includes not only familiarity with surgical dissection and strategy
planning, but also with anatomy, embryology, carcinogenesis, complication management, and also the use of chemotherapeutic agents and their possible effects.

**PERITONEAL CARCINOMATOSIS INDEX (PCI)**

Pretherapeutic diagnosis should provide reliable information about the tumor location, the extent of the tumor burden, and the distribution and extent of the disease, so that targeted patient selection can be carried out. Studies on the preoperative clinical staging of peritoneal carcinomatosis have shown that the reliability of computed tomography (CT) for predicting the stage is limited. At present, intraoperative staging is the most reliable method of defining the criteria mentioned. Various scoring systems are used for the purpose:

- Sugarbaker peritoneal carcinomatosis index (PCI) [20] (**Fig. 2**)
- Verwaal N score [21]
- Gilly classification [22]
- P score [23]

The Sugarbaker PCI score [20], with or without modifications, is now the established one at centers where there is a major focus on peritoneal carcinomatosis (**Fig. 2**). This was confirmed at a consensus conference held in Milan in 2006 [24]. Sugarbaker divides the abdominal compartment into nine regions, and the small bowel separately into a further four regions. The greatest possible extent of tumor involvement in each region is assessed using the lesion size score (from 0 to 3). The maximum possible number of points is thus 39, and the lowest 0. Sugarbaker’s analyses show that patients with a PCI score of less than 20 have a good and improvable prognosis (in comparison with the previous approach of palliative chemotherapy alone and/or best supportive
care). The main problem so far is achieving reliable pretherapeutic prediction of tumor involvement in the small bowel and/or mesentery, as this represents one of the major limiting factors for radical cytoreductive therapy. The Society of Surgical Oncology recently published selection criteria for patients with peritoneal carcinomatosis that were agreed in the consensus statement in Milan in 2006 [24].

MULTIMODAL STRATEGY IN PERITONEAL CARCINOMATOSIS

PROPERTIES

Most multimodal therapy for peritoneal carcinomatosis basically consists procedures concerned involve elaborate multivisceral operations that take several hours and may even require between 8 and 14 hours [25]. This was the reason why Sugarbaker coined the term “MOS patients.” Particular attention needs to be given to preoperative positioning in order to avoid position-induced postoperative complications, as the patients sometimes have to be placed for 8–14 h in the lithotomy position (including extension of the upper extremities bilaterally), in order to allow rectal resection without problems should it become necessary [26]. Depending on the extent of tumor seeding, primary histology, and also retroperitoneal tumor seeding, preoperative ureter splinting may be necessary.

The cytoreduction operation consists of peritonectomy (parietal and visceral) of areas affected by tumor, omentectomy (greater and lesser omentum), and interventions/resections in the stomach, spleen, small bowel, colorectum, liver, gallbladder, and urogenital tract (Table I). After a median incision on the linea alba, initial dissection as far as the peritoneum is carried out (Fig. 3) [27]. When the patient has undergone several previous operations, this alone may already be challenging. If
there has been no previous surgery, it is best to begin by dissecting free a peritoneal layer of this type laterally (Fig. 4) [27] so that the peritoneum can be demonstrated and resected there later on without problems. Particularly in patients who have previously undergone surgery (as is usually the case), the laparotomy can be followed by careful exploration to check the preoperative findings intraoperatively along with the selection criteria. If another primary operation has been conducted previously, the current laparotomy must include complete scar excision, including excision of the umbilicus. Some authors reported the use of limited laparotomy or laparoscopy at first to avoid extensive laparotomy in case of non resectable disease and contra-indication of the procedure.

If there are no contraindications, cytoreductive surgical therapy is then carried out. Each individual resection specimen removed during the operation must be separately declared and submitted for histopathological examination. This is because, particularly in cases of pseudomyxoma peritonei, postoperative correction of the intraoperatively established PCI score (mainly with histopathological downgrading) may be needed once the histopathological results have been received. The surgeon then has to establish the intraoperative CC score for the completeness of tumor removal (Table II) [26]. The anastomoses may be created either at this point, before HIPEC, or later, after HIPEC; there no established standard for this (as yet). The inflow and outflow peritoneal tubes are then inserted for the subsequent hyperthermic intraperitoneal chemotherapy (HIPEC) and the procedure is handed over to the person responsible for managing the HIPEC machine, who attaches the connections.
**HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) Technique**

HIPEC can be carried out as an open or closed procedure. In our view, HIPEC in particular is an extremely important part of the multimodal treatment procedure in peritoneal carcinomatosis. Open procedures allow manual distribution during HIPEC that is extremely important for certain anatomical regions. The principle is that the abdomen is initially filled with a carrier solution (Dialysis or Ringer’s solution). The carrier solution is then passed through the HIPEC machine to heat it. Once a steady-state temperature of 42 °C has been reached, the chemotherapeutic agent is added and HIPEC starts. The intra-abdominal temperature is measured every minute, and patient-specific temperatures (bladder and head, assessed by the anesthetist) are also recorded and documented. After 30 to 90 min of HIPEC, regarding the protocol used, the carrier solution is drained along with the chemotherapeutic agent, and the abdomen may be lavaged with approximately 8–10 L Ringer’s solution (both solutions have to be disposed of as hazardous waste).

**FOUNDATIONS AND RATIONALE FOR HIPEC**

Locoregional administration of chemotherapy increases the local concentration of the chemotherapeutic agent at the site of action. This reduces the systemic toxicity of the treatment, but at the expense of increased postoperative morbidity resulting from the surgical procedure [6]. In some institution as in Tübingen, Germany, the required anastomoses are created before the administration of HIPEC, although some other peritoneal carcinosis centers use a different method. Interestingly, a recent study in Turkey showed that anastomotic insufficiency is more likely to occur when systemic 5-fluorouracil (5-FU) treatment is carried out than when local chemotherapy is used [28]. Additionally HIPEC investigated in a rat model revealed a delay in healing of the
colon anastomosis [29], raising the question, whether performed gastrointestinal anastomosis after HIPEC should be performed differently and/or monitored in a different way compared to regular anastomosis in GI surgery. In HIPEC, the carrier solution (Dialysis or Ringer’s solution) is initially heated to a temperature of 43 °C, with instillation of the chemotherapeutic agent only being carried out afterward. The agent is administered for 30–90 min, depending on preference at the peritoneal carcinomatosis center concerned. When HIPEC has been completed at approximately 43 °C, the abdomen may be lavaged out. Postoperatively, the patient has to be monitored in the intensive-care unit. It is important to note that cisplatin-containing substances in particular can also have direct cardiotoxic effects. As a result of the large wound surface, it is possible for cis-diaminedichloroplatinum (CDDP) to be washed into the bloodstream, leading to cardiotoxicity as a feared complication. The basic approach in cytoreductive surgery involves regarding the peritoneum as a distinct compartment. At present, the agents used in HIPEC are mainly cisplatin (CDDP), oxaliplatin, and mitomycin C. Intraperitoneal administration of chemotherapeutic agents achieves high response rates in patients with peritoneal carcinomatosis, as the peritoneum–plasma barrier makes it possible to administer high doses [30]. On the basis of analyses conducted during peritoneal dialysis, Dedrick et al. showed in 1978 that the peritoneal permeability of hydrophilic cancer drugs is lower than the known plasma clearance of the same agents [31]. The chemotherapeutic agents mitomycin C, cisplatin and/or oxaliplatin are generally used as HIPEC drugs. Drugs such as mitomycin C and cisplatin, as well as oxaliplatin, have a relatively high molecular weight (mitomycin C, 334; cisplatin, 300; oxaliplatin, 397). Due to reduced permeability into the plasma, they consequently have lower systemic concentrations and thus show lower toxicity [32, 33]. For the sake of completeness, it must be noted
that there are also international centers in which systemic chemotherapy is administered simultaneously.

There are several important aspects of the hyperthermia that is administered. Hyperthermia above 41 °C alone produces a direct antitumor effect. However, tumor cells react through up-regulation of heat shock proteins, which may be able to produce some thermal tolerance [34]. An increase in the cytotoxic effect of chemotherapeutic agents has been demonstrated for drugs containing platinum [35], mitomycin C [36], and others. Thirdly, the use of hyperthermia during intraperitoneal administration produces deeper effects [37]. In summary, the rationale for administering HIPEC immediately postoperatively is based on the following arguments:

• Increased penetration of the chemotherapeutic agent into tissue
• Increased cytotoxic effect
• Cytotoxic effect of HIPEC itself
• Reduced systemic toxicity at higher concentrations
• Direct treatment of free intraperitoneal tumor cells
• Homogeneous distribution of chemotherapeutic agents as a result of intraperitoneal administration of HIPEC

**RESIDUAL TUMOR CLASSIFICATION (CC SCORE)**

Cytoreductive surgery is based on the target criteria used in surgical oncology — achieving complete macroscopic and microscopic freedom from tumor (R0 resection). As it is difficult to speak of an R0 resection after multivisceral resection, the CC classification [26] was developed and was also confirmed at the 2006 consensus conference [24] (Table II). CC stands for “completeness of cytoreduction” [26]. In
patients with mucinous pseudomyxoma peritonei who undergo cytoreductive surgery with HIPEC, the R0 resection referred to elsewhere in the gastrointestinal tract is equivalent to CC 0 and CC 1 status, whereas in invasive gastrointestinal tumors such as colorectal tumors and/or gastric carcinomas, R0 resection is only equivalent to CC 0 status. It has also been clearly shown that this is of significance for the patient. Patients with CC 0/CC 1 resections have a significantly better survival period than those who do not [5, 26, 38, 39]. The classification is now regarded as well established and also has been shown of prognostic value within patients suffering from colorectal cancer with peritoneal spread [40, 41].

VALUE OF LAPAROSCOPY IN PC

Explorative laparoscopy has been used predicting feasibility of complete cytoreduction in patients with peritoneal carcinomatosis [42 – 45]. Within the multimodal therapy concept of peritoneal carcinomatosis, explorative laparoscopy can serve a selection criterium, detecting malignant ascites [46], as well as an evaluation tool of optimal candidates for cytoreductive surgery and HIPEC. Future large prospective studies are necessary, for determination of laparoscopy as a potential standard of a diagnostic algorithm in patients with peritoneal carcinomatosis.
CONTRAINDICATIONS FOR CYTOREDUCTIVE SURGERY

These can be divided into absolute and relative contraindications.

Absolute contraindications:

- Massive involvement of the retroperitoneum
- Invasion of the mesenteric pedicle
- Massive small-bowel involvement (that would result in a short bowel after radical resection)
- Unresectable intra-abdominal and/or extra-abdominal metastases
- Incurable second malignancy
- Karnofsky index < 70

Relative contraindications:

- High body mass index
- Cardiac contraindication
- Hepatic contraindication
- Renal contraindication
- Florid infection
- Acute ileus

MORBIDITY AND MORTALITY WITH PERITONECTOMY AND HIPEC

The postoperative morbidity rates reported in the literature range from 14% to 70% [47 - 52]. This is substantially different from the familiar morbidity/mortality associated with other traditional surgical procedures, since pain as one of the major signs that a complication is developing is hardly ever observed after peritoneectomy.
Patients with complications are usually identified clinically due to fatigue and raised inflammatory parameters. Especially in upper GI surgery, postoperative complication rates are feared, but it had been shown, that also cytoreductive surgery with HIPEC can be performed safely in patients suffering from gastric cancer [53 - 56]. Simultaneous pancytopenia occurring after HIPEC may aggravate the situation. The complications that appear depend on [55, 56 – 58]:

- Metachronous peritoneal carcinomatosis ($P = 0.009$)
- Sugarbaker peritoneal carcinomatosis index $\geq 13$ ($P = 0.012$)
- Five or more affected regions ($P = 0.04$)
- Incomplete initial cytoreductive surgery ($P = 0.035$)
- Blood transfusion requirements due to intraoperative blood loss ($P = 0.28$)
- Three or more anastomoses ($P = 0.018$)

An aggressive approach can be taken when establishing the indication for postoperative CT to exclude a complication, so that adequate action can be taken in a timely manner. This general procedure is very important, because the central “Pain” is eliminated after a performed peritonectomy. Reported mortality rates are in the range of 0–20% in the world literature and 0–8% for active peritoneal carcinomatosis centers. One major impact in reducing morbidity and mortality seems to be the learning curve of cytoreductive surgery with HIPEC, suggesting, that surgeons should first visit established PC cancer centers, before performing these operative procedures [59]. It seems, that the morbidity rate of patients with PC is high, but in centers of expertise (so-called high volume centers) the mortality rates can be lowered nearly zero [60]. A retrospective-cohort, multicentric study from France investigating
cytoreductive surgery and HIPEC revealed also low postoperative morbidity and mortality with prolonged survival [61].

In conclusion, patients, who underwent peritonectomy with HIPEC seem to have a higher risk of postoperative infections and especially candidosis has to be taken into account [62] but morbidity and mortality rates of cytoreductive surgery with HIPEC are similar to major gastrointestinal surgery (high-end-surgery), such as transhiatal extended gastrectomy and/or Kausch-Whipple-procedures [40].

**QUANTITATIVE PROGNOSTIC INDICATORS (QPIs)**

**FOR EACH TUMOR TYPE**

Quantitative prognostic indicators (QPIs) are extremely important clinically, although the quality of the evidence supporting them varies from one tumor entity to another and evidence is sometimes even lacking. They are therefore discussed here separately for each type of tumor and depending on the available data.

**QPIs — Pseudomyxoma Peritonei**

These include tumor markers, as well as histopathological subtypes classified according to the Ronett criteria [63], preoperative imaging findings, and also the Sugarbaker peritoneal carcinomatosis index (PCI) [20]. Levels of tumor markers such as carcinoembryonic antigen (CEA) and CA-19-9 are not a prognostic indicator (Figs. 5a, 5b) [64]. However, pathologically elevated tumor markers do have prognostic relevance (Figs. 6a, 6b) [64]. Histopathological subtypes are classified using the system proposed by Ronett et al. [63, 65] into disseminated adenomucinous
peritoneal (DAP) carcinomas, intermediate and discordant types (hybrid), and peritoneal mucinous adenocarcinoma (PMCA). These classes are further subdivided by grading (good, moderate, or poorly differentiated). Using the Ronett classification and including the CC score and lymph-node status, it is possible to identify four different groups of patients with pseudomyxoma peritonei and correspondingly different survival data [63] (Table III). Additionally molecular biological investigation revealed univariately, that CK20-, CDX-2 and MUC-2 expression correlated to prognosis in patients who underwent cytoreductive surgery and HIPEC [66]. The PCI score, described above, can be used as a preoperative surgical score (PSS; Table IV) [20] that provides prognostic information depending on the proportion of tumor mass and/or regions present (Fig. 7) [38]. Using the PCI score on its own has no prognostic relevance in pseudomyxoma peritonei [67]. The score appears to be helpful only when the histopathological subtype is used. The completeness of cytoreduction (assessed using the CC score) has very high prognostic significance [68] (Fig. 8).

QPIs — Malignant Peritoneal Mesothelioma

The Washington Cancer Institute has published a classification here that allows differentiation into four subtypes (Table V) [69]. A histopathological subdifferentiation due to the size of the nucleus and nucleoli (Table V) was shown to be of significant relevance by of multivariate testing (Fig. 9). It is interesting that sex per se appears to be a prognostic indicator, as it was shown that male patients have a much poorer prognosis (Fig. 10) [26]. Cytoreductive surgery with HIPEC can be determined nationally and internationally as standard treatment of care in peritoneal mesothelioma. An Italian multicenter study in 61 patients showed clearly, that completeness of cytoreduction is one of the major important factors predicting
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The recently published multi-institutional registry study investigating 405 patients with diffuse malignant peritoneal mesothelioma revealed a significant prolonged survival using cytoreductive surgery and HIPEC [71].

**QPIs — Ovarian Carcinoma**

The data for the cumulative 5-year survival rates must be generally evaluated as poor (Fig. 11) [72]. In Germany, patients suffering from primary ovarian carcinoma are treated primarily by Gynecologists so far. The PCI score (Fig. 12) [72], preoperative surgical score (Fig. 13) [73], and also the CC score (Fig. 14) [73] have prognostic significance here. The 5-year survival rates can be increased in patients with recurrent ovarian cancer by cytoreductive surgery adding HIPEC to that multimodal treatment from 17 up to 58% [74]. Additionally cytoreductive surgery plus HIPEC as a salvage multimodal therapy concept in primary chemoresistant and recurrent advanced epithelial ovarian cancer patients might achieve long-term survival in selected patients [75]. The significant prognostic factor is the residual tumor status. However, HIPEC plus cytoreductive surgery also increases the recurrence free interval from 24 up to 48 months.

**QPIs — Gastric Carcinoma**

There are no data either for the use of tumor markers or for different histopathological types. It is also unclear whether preoperative imaging findings have any prognostic significance. The PCI score has significant prognostic value and using the CC score is helpful [13]. The determination of peritoneal carcinomatosis can be performed by diagnostic laparoscopy during the primary staging. The percentage rate of patients with gastric cancer and diagnosed peritoneal carcinomatosis is between 10 to 50%, especially if the serosa is tumor involved [76, 77]. The median survival time in case of
peritoneal carcinomatosis is between 1 to 9 months without a 5-year survival time in patients with gastric cancer [7, 16, 78, 79]. Until now, 3 studies from institutions in Japan (n=42, retrospective study) [80], France (n=49, prospective study) [81] and USA (n=34, comparing study) [82] are available. Major prognostic factors had been completeness of cytoreduction and missing ascites. In up to 50% of the reported patients, a CC-0 / CC-1 resection was achievable with survival rates between 19 and 21 months [83]. Additionally, it had been shown in a prospective randomized multicenter study from Japan, that extensive intraoperative peritoneal lavage with followed intraperitoneal chemotherapy significantly improved the 5-year survival time in 88 investigated patients with gastric cancer [84]. Therefore adding Hyperthermia into this therapy schedule seems to be a logical consequence.

**QPIs — Colorectal Carcinoma**

No data are available on tumor markers as qualitative prognostic markers. With regard to histopathology, the only available data show that patients with poorer differentiation have a poorer prognosis. The value of a preoperative CT appears to be limited in mucinous carcinomas. Our own research on the use of preoperative $^{18}$F fluorodeoxyglucose positron-emission tomography and computed tomography (FDG-PET/CT) scanning in comparison with the intraoperative PCI score shows that it has prognostic value [85]. The Sugarbaker PCI score ($P < 0.0001$) and CC score ($P < 0.001$) are both prognostically very helpful in colorectal carcinoma [26]. The results of the randomized phase 3 study conducted in the Netherlands by Verwaal et al. are relevant [86, 87]. In treatment arms each including 105 patients with confirmed peritoneal carcinomatosis with colorectal tumors, either systemic therapy with 5-FU/leucovorin or multimodal therapy with cytoreductive surgery and HIPEC and
Subsequent chemotherapy (5-FU/leucovorin) was carried out. The latter treatment increased the 2-year survival rate from 22% to 44%. The completeness of cytoreduction was also within this study collective of major prognostic relevance (Fig.15) [86, 87].

**SUMMARY AND PROSPECTS**

In view of the convincing national and also international data that are available, the fatalistic view that only palliative therapy is possible in patients with peritoneal carcinomatosis now needs to be abandoned. From a critical point of view, of course, most of the studies currently available are only phase 2 ones, and phase 3 studies are still lacking. Even now, however, it must be noted that the available phase 3 study on colorectal carcinoma by Verwaal et al. [86, 87] shows a clear survival benefit after a procedure combining cytoreductive surgery with HIPEC—so that negative assertions and hollow statements of the type regularly heard in conference discussions (“There are no data on this”) are now no longer acceptable.

Frequently heard arguments of this type cannot be based merely on the fear of losing a specific group of patients. It is quite clear that a procedure as elaborate as this in the treatment of peritoneal carcinomatosis can only be carried out jointly, on an interdisciplinary basis. It has also been pointed out that there are still many open questions with regard to the pharmacokinetics and on the way in which HIPEC should be carried out (with a closed or open procedure), which also still require intensive research. Additional possible treatment strategies that could be used in the future include targeted therapy and the use of hydroxycamptothecin, a topoisomerase I inhibitor [88]. However, it should also be mentioned that the very latest results on targeted therapy alarmingly show that although vascular endothelial growth factor
(VEGF) inhibitors reduce primary tumor growth, they can also simultaneously lead to promotion of tumor growth and metastatic spread [89 - 91].

Although there is still much to be done in the field of multimodal therapy for peritoneal carcinomatosis, it is already clear that it will become a new standard in the treatment of patients with PC. In peritoneal mesothelioma, as well as pseudomyxoma peritonei, cytoreductive surgery with HIPEC can already be regarded as the standard form of treatment in centers for treating PC.

In general the principle discussion of an Evidence-based-Medicine (EBM) which has to be applied in cytoreductive surgery with HIPEC is for sure justified. Otherwise, any colleague of any discipline knows also for sure, that there are many historical examples of treatments, which are meanwhile standard treatments without any kind of controlled clinical study and which are day by day in use in our patients: antibiotics in sepsis, tracheostomy in tracheal obstruction, Jodide$^{131}$ in thyroid carcinoma, GLIVEC therapy in GIST, combined chemotherapy in patients suffering from carcinoma of the testis, surgical resection of 1 up to 3 liver metastasis, as well as cytoreductive surgery and HIPEC in appendiceal carcinoma and peritoneal mesothelioma [92]. However with the exception of a single institution Phase-III-trial in colorectal cancer and some retrospective and small prospective phase-II-trials, more evidence has to be worked out by the community of surgical and medical oncologists, who treat patients with peritoneal carcinomatosis [93].

In Germany as well as in Europe internal medical and health care interests still lead to a delay in acceptance of the multimodal and elaborative therapy: multiple DRG-codes after multivisceral resection with a strong insecurity of appropriate gratuity.
Other reasons are the general financial insecurity of an appropriate payment after those complex and expensive surgical treatment plus HIPEC, the application of HIPEC by a surgeon, a general perception of a high postoperative morbidity and mortality. But of course there are also other well known reasons: lack of integration between specialized tumor programs (by institutions as well as in regard to different societies), lack of representation of cytoreductive surgery and HIPEC within guidelines, lack of representation of oncological surgeons as experts in those committees and lack of networking between some societies. Another contraproducive argument is, that the complex surgical treatment (cytoreductive surgery plus HIPEC) will increase medical costs significantly. On the other hand, an evaluation in Australia clearly showed, that the multimodal treatment parallel increases in survival [94].

Certain properties of tumor cells themselves may become important for future treatment strategies — characteristics such as thigmotaxis, contact spread, spread of tumor cells along specific anatomic structures such as neural sheaths, mediated by laminin receptors or fibronectin receptors, for example), contact inhibition, and cell adhesion and segregation. Molecular-biological research on the way in which metastatic spread takes place in gastrointestinal tumors can be expected to have a direct influence on the development of future treatment strategies for patients with peritoneal carcinomatosis.
REFERENCES


Legends to Tables

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