

Carcinose péritonéale, peritonectomie et chimiohyperthermie intrapéritonéale : une lueur d'espoir ?

Peritoneal Carcinomatosis, Peritonectomy and HIPEC: A Glimmer of Hope

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Mots clés

- ◆ Carcinose péritonéale
- ◆ Péritonectomie
- ◆ Chimiohyperthermie intrapéritonéale
- ◆ Indications
- ◆ Pronostic

Résumé

Peritonectomie et chimiohyperthermie intrapéritonéale (HIPEC) ont gagné un intérêt croissant dans le traitement multimodal des patients avec carcinoses péritonéales d'origine gastrointestinale. Le pseudomyxome péritonéal, le carcinome colorectal et gastrique sont considérés actuellement comme indication à cette procédure. Pour le staging et la classification, le score PCI et la classification CCS sont proposés. Bien que les deux systèmes ne soient pas validés, ils sont utiles pour déterminer la résecabilité mais aussi le pronostic. À la suite d'une conférence de consensus, un score PCI >20 est considéré comme contre-indication sélective à la péritonectomie. Des données récentes du Japon, cependant, indiquent que cette limite doit être réévaluée. Il a été possible de montrer qu'un PCI ≤ 10 dans le cancer colorectal et ≤ 6 dans le cancer gastrique ont un meilleur pronostic de survie à distance. Peritonectomie et HIPEC entraînent une morbidité substantielle en partie corrélée avec l'agressivité tumorale. La morbidité peut atteindre 60 % alors que la mortalité est habituellement autour de 3 %, cependant pas plus haute que d'autres résections importantes pour cancers gastro-intestinales. Ces données cependant ne sont acquises actuellement seulement à la suite d'une courbe d'apprentissage. En ce qui concerne le pronostic, la survie à cinq ans chez des patients sélectionnés avec tumeur colorectale peut atteindre 30 % dans certaines séries, mais la plupart des données montrent un plateau de survie de 20 % après la troisième année postopératoire. En dépit de ces résultats prometteurs pour une infection considérée habituellement comme fatale, de nombreuses questions controversées restent posées. Cela concerne l'indication elle-même, le système de staging pour la classification de l'étendue de l'affection, la description de l'importance de la cytoréduction, la durée, les drogues, la température et la méthode de l'HIPEC aussi bien que le taux de morbidité et de mortalité de la procédure. Des données définitives à toutes ces questions manquent encore, car la plupart des études sont uni-centriques et rétrospectives ne permettant donc pas une conclusion définitive. De plus, la péritonectomie et l'HIPEC doivent être évaluées dans des conditions de recherches d'efficacité comparatives par rapport aux résultats de la chimiothérapie systémique qui montre au moins une survie médiane comparable grâce aux modalités améliorées de la chimiothérapie avec ajout d'anticorps monoclonaux. Ces considérations éclairent les défis de la péritonectomie et de l'HIPEC. Elles montrent aussi que de prochaines études sont nécessaires pour déterminer précisément la valeur de cette procédure dans le but de rechercher les patients avec carcinose péritonéale qui pourraient le plus en bénéficier. Malgré cela, péritonectomie et HIPEC représentent une lueur d'espoir pour des patients sélectionnés ayant une carcinose péritonéale d'origine colorectale ou gastrique.

Keywords

- ◆ Peritoneal Carcinomatosis
- ◆ Peritonectomy
- ◆ Hyperthermic intraperitoneal Chemotherapy
- ◆ Indication
- ◆ Prognosis

Abstract

Peritonectomy and HIPEC have gained increasing interest in the multimodal treatment of patients with peritoneal carcinomatosis of gastrointestinal origin. Pseudomyxoma peritonei, colorectal and gastric carcinoma are currently considered to represent an indication for this procedure. For staging and classification purposes the PCI-score and the CCS classification are applied. Although both staging systems are not validated they are useful for determining resectability as well as prognosis. According to a consensus conference, a PCI score > 20 is considered as a selective contraindication for peritonectomy. Recent data from Japan, however, indicate that this cut-off needs to be reevaluated. It could be shown, that a PCI of ≤ 10 in colorectal and ≤ 6 in gastric cancer patients result in improved long term survival. Peritonectomy and HIPEC are associated with a substantial morbidity, which is in part correlated to tumor burden. Morbidity may be as high as 60%, whereas mortality usually is around 3%, therefore not higher than after other major gastrointestinal oncological resections. These data, however, are only achieved following a learning curve. Regarding prognosis, 5-year survival rates in selected colorectal patients may be as high as 30% in some studies, but most data show a plateau of around 20% survival after the 3rd postinterventional year. Despite these promising results for a disease usually considered to be fatal, many controversial issues need to be addressed. This refers to the indication itself, the staging systems for the classification of the extent of disease, the description of the completeness of cytoreduction, the length, drugs, temperature and method of HIPEC as well as the morbidity and mortality rates of the procedure. Definite

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data for these questions are still missing, because most of the studies are unicentric and retrospective and do therefore not allow a definite conclusion. Additionally, peritonectomy and HIPEC need to be evaluated under the condition of comparative effectiveness research by exploring the results of systemic chemotherapy which show at least a comparable median survival due to improved chemotherapeutic regimens by adding monoclonal antibodies. These considerations elucidate the challenges of peritonectomy and HIPEC. They also demonstrate that further studies are necessary to precisely determine the value of this procedure in order to define those patients with peritoneal carcinomatosis who may benefit most. Nevertheless, peritonectomy and HIPEC represent a glimmer of hope for selected patients with peritoneal carcinomatosis of colorectal or gastric origin.

Peritonectomy and HIPEC for the treatment of peritoneal carcinomatosis have gained increasing interest in the last years. At least in Germany, there exists a real surgical hype around this multimodal treatment, and it can be assumed that around 30-40 hospitals have started this therapy within the last 5-10 years. This is even more surprising since hard and reliable data of randomized trials are still missing. Since peritonectomy and HIPEC are procedures with a substantial morbidity and mortality a number of questions arise, for example: Is it justified? Do patients benefit? What are the indications? The following article will give an overview and addresses the issues of indication, scoring-systems, operative technique, morbidity and mortality as well as prognosis.

A brief history of peritonectomy and HIPEC

As early as 1987 the pioneer of peritonectomy, Paul Sugarbaker, published an article about a curative approach to malignant pseudomyxoma peritonei (1). With an incidence of just 1-2 out of a million, pseudomyxoma peritonei belongs to the rare diseases (orphan disease), usually originating from neoplastic transformation of appendiceal goblet cells (2). Histologically, pseudomyxoma peritonei can be divided into disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis, the latter one with a much poorer prognosis (3). A number of publications demonstrated the excellent survival benefits of peritonectomy and HIPEC in patients with pseudomyxoma peritonei with an overall disease-free survival of 40% at eight years (4). Although these data are promising, they neglect an important factor: Pseudomyxoma peritonei is a slow-growing disease - even without any treatment, long-term survival may be possible. Therefore, the treatment of pseudomyxoma peritonei raises more questions than answers (5).

Despite these facts, however, the multimodal treatment of pseudomyxoma peritonei was subsequently applied to peritoneal carcinomatosis of solid gastrointestinal malignancies. Peritoneal carcinomatosis in these tumors is a common problem. In colorectal, gastric and ovarian cancer, the incidence of peritoneal carcinomatosis varies between 15-20%, 10-20% and 60-80% resp. It is therefore not surprising that peritonectomy and HIPEC are considered as a valuable therapeutic option, offering a curative approach to peritoneal carcinomatosis for the first time. The high incidence of peritoneal carcinomatosis may explain the surgical hype around peritonectomy and HIPEC among surgeons, because - up till now - peritoneal carcinomatosis is usually treated by medical oncologists with palliative intent.

ECOG performance status: ≤ 2
No extraabdominal metastases
Up to three resectable liver metastases
No stenosis at the common bile duct and/or ureter
Only one lumen-narrowing stenosis at the bowel
No extensive involvement of small bowel
Low tumor burden at the hepatoduodenal ligament

Table 1: Selection criteria for patients with peritoneal carcinomatosis, peritonectomy and HIPEC (7).

Current indications

From what is known so far, pseudomyxoma peritonei and peritoneal carcinomatosis of colon cancer are the best indications for peritonectomy and HIPEC. There is weak evidence that patients with gastric cancer, ovarian cancer, sarcoma and mesothelioma may benefit from peritonectomy, so that the indication for this approach should be very carefully and individually evaluated. Patients with peritoneal carcinomatosis of hepato-biliary and pancreatic origin are no candidates for this therapeutic regimen.

When considering peritonectomy and HIPEC it is of utmost importance to identify those patients who may benefit most from the procedure. For that reason patients' selection is a therapeutic prerequisite.

Scoring systems

Although preoperative diagnostic work-up including computed tomography may identify patients suitable for such an extensive surgical approach (6), the indication for peritonectomy and HIPEC is most often validated during surgical exploration. Nevertheless, selection criteria should be fulfilled to perform peritonectomy and HIPEC (Tableau 1).

Apart from these selection criteria, the Peritoneal Cancer Index (PCI) and the Completeness of Cytoreduction Score (CCS) are valuable tools with respect to description of tumor spread, determining resectability and the extent of resection as well as prognosis (8,9). For the PCI, it was found that more than 20 points represent a relative contraindication for peritonectomy and HIPEC (10), while a CCS of zero (no visible tumor left) is associated with the best prognosis (11). Critically, however, it has to be acknowledged that these scoring systems may allow a good classification of resectability, but all are not validated and - most important - are influenced by the subjective impression and experience of the surgeon.

Operative Technique

For peritonectomy, usually a median laparotomy, occasionally extended by subcostal right/left incisions, is required to get best exposure of all quadrants of the abdomen. Thereafter, the PCI is determined and the possibility of achieving a CCS score of 0 is evaluated. In general, multivisceral resections of various extent are necessary (Tableau 2).

Peritonectomy of the parietal peritoneum is performed in all 4 quadrants of the abdominal cavity when indicated (Fig 1). A

Colorectal	79%
Omentectomy	61%
Cholecystectomy	47%
Partial resection of the diaphragm	35%
Splenectomy	31%
Small bowel resection	29%
Liver resection	21%
Gastric resection	21%
(left) pancreatic resection	15%
Partial bladder resection	15%
Hysterectomy	11%

Table 2: Extend of resection in peritonectomy - Own data of 160 resections.



Figure 1: Specimen of parietal peritonectomy.

selective approach in case of limited peritoneal disease is justified. Quite often, parietal peritonectomy is combined with organ resection to establish an en-bloc resection (Fig 2). Immediately after peritonectomy, HIPEC is performed. In the own strategy, HIPEC is performed for 90 min. with 42 °C at the open abdomen in the so-called Arena-Technique (Fig 3a and 3b).

Currently, many issues regarding the best way for HIPEC are still unsolved. This refers to the length of the chemotherapy (30 versus 60 versus 90 min.), the optimal temperature, its performance at the open or closed abdomen as well as the optimal drugs. In the own patients, Mitomycin C is used for colon peritoneal carcinomatosis, while cisplatin is applied in other malignancies.

Morbidity and Mortality

According to a literature review the overall mortality of peritonectomy and HIPEC is approximately 3% with a range from 0-17%, while the morbidity is around 30% (12). These data, however, require a closer look. First of all, the definition of morbidity is subjective. In almost all studies, many papers differentiate between minor and major morbidity, the latter one defined as major complications requiring re-operation or ICU admission or interventional radiology (13). This differentiation appears as an attempt to mask the real figures of perioperative morbidity. From the own experience there is hardly any patient who does not experience some kind of postoperative disturbances, a fact, which does not surprise in light of the extensive procedure. Despite the high morbidity, however, postoperative mortality does not significantly differ from other major established oncological resections such as esophagectomy or pancreatectomy, so that peritonectomy should be considered at the same level as the above mentioned operations.

Prognosis

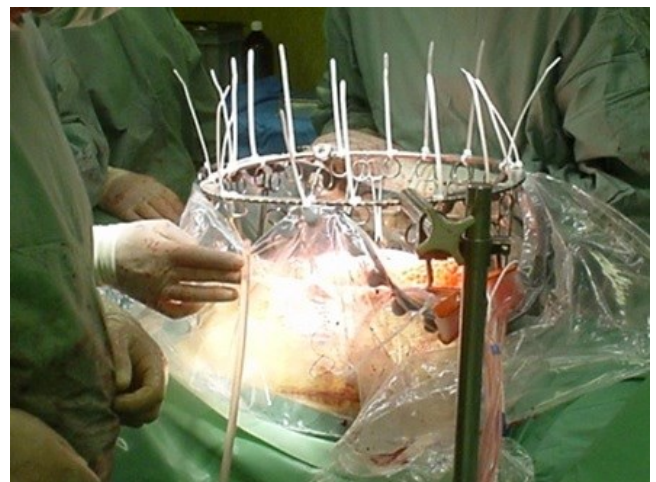
In a just published series of 1000 patients treated with peritonectomy and HIPEC the overall 10-year-survival was nearly 20% with peritoneal carcinomatosis due to appendiceal malignancies being better than any other cancer type (14). Already ten years ago, Verwaal and coworkers reported a 5-year-survival of 20% for peritoneal carcinomatosis of colorectal cancer, and this survival reached a plateau (15). Similar data could be retrieved just recently (11,16-18), demonstrating that in colorectal cancer, long-term survival may be possible even in case of peritoneal carcinomatosis. According to these results, differentiated carcinomas have a much better prognosis than undifferentiated lesions. With respect to the PCI, it was found that patients with a PCI ≤ 10 had a significantly better survival of 40% at five years than patients with a higher



Figure 2: Peritonectomy en-bloc with splenectomy in case pseudomyxoma peritonei.

PCI-score. For gastric cancer, the PCI score with promising long-term survival was even lower (≤ 6). Even similar figures could be found in the large French trial for colorectal cancer (18). These PCI-related survival data question the cut-off, at which peritonectomy is useful. The recent studies suggest, that the former recommendation of 20 PCI-points as a contraindication may no longer be valid and that indeed a much smaller score should be considered. Additionally, patients with any kind of small bowel involvement should no longer be candidates for peritonectomy and HIPEC.

Figure 3a and 3b: HIPEC at the open abdomen.



Conclusion

Due to the challenge «Peritoneal Carcinomatosis», peritonectomy and HIPEC as a potentially curative approach to a usually fatal disease have gained increasing interest in recent years. Peritonectomy and HIPEC require a strict patients' selection and a precise indication, e.g. pseudomyxoma peritonei and colon cancer, perhaps gastric cancer, in order to achieve a CCS-0 status. Open questions need to be addressed in the next years. This refers to the length of HIPEC (30 vs 60 vs 90 min), open vs. closed intraperitoneal chemotherapy, optimal temperature and optimal drug selection. Additionally, a re-evaluation of the PCI regarding cut-off for resection seems necessary because the actual data show, that patients with $</= 10$ points (colon cancer) and $</= 6$ points (gastric cancer) benefit most from this procedure. Although hard and reliable facts are still lacking, a prognostic benefit is demonstrated in numerous studies: Selected patients may have a 5y survival of 20% - a glimmer of hope! The operative procedure requires substantial individual and institutional experience to keep morbidity and mortality as low as possible, but may be as high as 50-80% and 3-10% respectively. It also raises the question, how many centers are necessary to meet patients' interests. Furthermore, due to advancements in systemic chemotherapy comparative effectiveness studies are needed to precisely determine the value of peritonectomy and HIPEC.

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