

## Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Where are we?

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### Abstract

Peritoneal surface malignancies are generally associated with poor prognosis. In daily clinical routine, systemic chemotherapy is still considered the only reasonable therapy despite of encouraging results of cytoreductive surgery (CRS) along with intraperitoneal hyperthermic chemotherapy (HIPEC). The Achilles heel of CRS and HIPEC is appropriate patient selection and precise surgical technique preventing patients from excessive morbidity and mortality. Given these findings, new concepts of second look surgery for high risk patients allow detection of peritoneal spread ahead of clinical symptoms or presence of peritoneal masses reducing perioperative morbidity. In addition, personalized intraperitoneal chemotherapy might further improve outcome by appreciating individual tumor biology. These days, every physician should be aware of CRS and HIPEC for treatment of peritoneal surface malignancies. Since there is now sufficient data for the superiority of CRS and HIPEC to systemic chemotherapy in selected patients, our next goal should be providing this strategy with minimal morbidity and mortality even in the presence of higher tumor load.

### INTRODUCTION

In Peritoneal surface malignancies (PSM), tumor location is restricted to the abdominal cavity as opposed to systemic metastatic disease. In the past, the majority of PSM patients underwent systemic chemotherapy which was associated with poor quality of life and was ineffective with respect to prolonging survival.

Thanks to the pioneer work of Professor Paul Sugarbaker, a proactive surgical approach termed cytoreductive surgery (CRS), aiming for maximal tumor resection, along with hyperthermic intraperitoneal chemotherapy (HIPEC) evolved into a highly relevant treatment option for selected patients with limited peritoneal spread of various tumor entities<sup>[1-3]</sup>. The rationale for this particular approach is the restriction of tumor dissemination to the peritoneal compartment justifying a radical surgical procedure followed by HIPEC.

Although there is now evidence for the superiority of

CRS and HIPEC to systemic chemotherapy, this strategy has not made its way into clinical routine since peritoneal spread is still considered as stage IV cancer when surgical resection is not an option any more. However, there was a similar thinking for colorectal liver metastasis for a long time. Now, surgery represents the main strategy even though its superiority has never been proven in a randomized phase III trial.

If cytoreductive surgery is scheduled, proactive surgery achieving total or almost total (remaining nodules < 2.5 mm) cytoreduction has to be the main aim. In addition, hyperthermic intraperitoneal chemotherapy is administered for eradication of microscopic residual disease. The most frequently cited paper on this topic was published by Verwaal *et al.*<sup>[4,5]</sup> who first proved the benefit of this multimodal approach in a phase III trial comparing patients with colorectal cancer undergoing CRS and HIPEC followed by systemic chemotherapy with systemic chemotherapy. Up to now, there are several reports on long term survival if radical resection was performed<sup>[4-7]</sup>. Other entities for which this treatment is accepted are pseudomyxoma peritonei and mesothelioma<sup>[8]</sup>. For selected patients with ovarian and gastric cancer this option can be offered with good results<sup>[9-12]</sup>.

Since survival does not significantly differ between completeness of cytoreduction CC0 or CC1, an oncologic resection with wide resection margins seems not necessary in this content except for primary gastrointestinal cancer with peritoneal carcinomatosis PC.

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## INTERDISCIPLINARY CONCEPT

The implementation of many new centers for PSM could mean that more and more patients are asking for this therapeutic option. However, the perioperative setting has to be established first rather than the surgical one. An experienced radiologist is mandatory to assess preoperative tumor load and to rule out contraindications such as diffuse infiltration of the small bowel or extraperitoneal disease. The anaesthesiologists, nurses and HIPEC technicians should visit centers and participate in workshops for HIPEC before initiating the program. Lastly, the medical oncologist becomes more and more important because there are numerous different intraperitoneal as well as pre- and postoperative chemotherapy regimens. The founding of a peritoneal surface malignancy group which meets regularly has had a great impact on scientific discussion between surgeons, radiologists, anaesthesiologists. In addition, this facilitates the initiation of clinical multi-center and experimental studies.

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## HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

In most cases, intraperitoneal chemotherapy is administered after cytoreductive surgery and completion of intestinal anastomoses, either immediately intraoperatively (HIPEC) or early postoperatively (EPIC). Technically,

this chemotherapy can be applied to an open or closed abdomen which varies between the different centers.

The rationale of HIPEC is the synergistic cytotoxic effect of heat, ideally 42-43 degree Celcius, and the chemotherapeutic agent itself on tumor cells.

There are various concepts varying in duration of exposition, in combination with for example intraoperative intravenous therapy and in type of the administered chemotherapy.

The effect of hyperthermic intraperitoneal chemotherapy itself has never been proven in a randomized controlled trial and is still the focus of ongoing investigations. Nevertheless, there are numerous data of how HIPEC might work and most surgeons, medical oncologists and last but not least patients believe in the effect of local chemotherapy.

The rationale for applying intraoperative chemotherapy under hyperthermic conditions is improving both tissue as well as tumor oxygenation by vasodilation enhancing the cytotoxic effect of chemotherapeutic agents. So far, however, nobody has demonstrated an effect on hyperthermia on tissue oxygenation and there is no data whether this putative effect on pO<sub>2</sub> (oxygen) might be sustained throughout the entire HIPEC period. As learned from wound healing research, supplemental oxygen during HIPEC might further enhance cytotoxicity since it has been shown to increase tissue oxygen tension. In addition of thinking about the best timing for HIPEC, HIPEC in combination with supplemental oxygen could be a worthwhile option in the future.

Another future important issue could be testing chemotherapeutic sensitivity to improve the cytotoxic effect of HIPEC. Such particular tests already exist for ovarian cancer with respect to platinum resistance<sup>[13,14]</sup>. This further strengthens the need for personalized intraoperative chemotherapy regimens.

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## NEOADJUVANT CHEMOTHERAPY

A quite high percentage of patients is not eligible for cytoreductive surgery at the time of surgical exploration. Therefore, tumor downsizing by systemic chemotherapy and subsequent surgery might be an option. In liver surgery, the concept of secondary resection after chemotherapy, both intravenous as well as regionally, is accepted and response to preoperative chemotherapy can be considered as a prognostic factor<sup>[15-17]</sup>. In PSM, neoadjuvant chemotherapy might also aid in categorizing patients in responders and non-responders with responders being more likely to profit from CRS and HIPEC. One limitation is the difficulty to evaluate response to chemotherapy since computed tomography (CT) or positron emission tomography (PET)/CT often do not sufficiently show tumor spread. One ongoing phase II trial in Germany addressing perioperative chemotherapy is the COMBATAC trial (multimodality treatment including neoadjuvant and adjuvant chemotherapy with cetuximab and CRS and HIPEC).

## ORGAN PRESERVING CYTOREDUCTIVE SURGERY

Radical cytoreduction is many times associated with multivisceral resection because of diffuse organ infiltration. When performing cytoreductive surgery, the surgeon should, however, aim for preserving as many organs as possible. Moreover, the surgeon should leave as much as possible behind but without any oncological compromise. This approach seems quite unfamiliar to surgeons who do not deal with peritoneal metastases. In many cases, the small/large bowel can be preserved when addressed with patience for meticulous tumor resection since tumor nodules are mainly located on the peritoneal surface and can be removed without opening the bowel in most cases unless there is infiltrative growth.

From an oncologic point of view, a radical oncologic colon resection, except in primary colorectal cancer with peritoneal spread is not necessary in our opinion.

The surgical expertise should ideally include a broad surgical spectrum especially colorectal surgery. One technical challenge is certainly the liver hilus with the sulcus rex, sulcus arancii and segment 1 region which is very demanding to dissect with the risk of biliary or vascular damage when a certain experience in liver surgery is helpful.

## SECOND LOOK SURGERY

Peritoneal carcinomatosis index (PCI), representing intraabdominal tumor load is a prognostic factor for survival. The lower the PCI, the better the prognosis maybe also due to the fact that a complete cytoreduction becomes more likely. Clinical signs of peritoneal metastases are often not specific and current imaging methods often do not detect small tumor nodules<sup>[18,19]</sup>. Given these findings, a second look protocol with a re-laparotomy within one year of colorectal surgery in high risk patients was proposed. The high risk patient for developing PSM suffers from either a perforated tumor or a local peritoneal spread at the time of primary surgery. Current data revealed quite a high percentage of PSM in those patients.

The second look protocol was firstly described by Elias *et al*<sup>[20]</sup>. Predicting the development of PSM in high risk patients is certainly a mile stone in the treatment of peritoneal metastases<sup>[20]</sup>. Although this approach is proactive, it may further prolong survival in those patients.

The administration of HIPEC even in a patient without macroscopic peritoneal disease needs further to be elucidated in randomized trials but seems to be promising so far. The “ProphyloCHIP” trial (Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus “in Principle” HIPEC in Colorectal Patients) run by Prof Elias is addressing this particular point. In this randomised phase III trial, colorectal cancer patients at risk to develop PC receive standard adjuvant chemotherapy after curative resection. After having excluded recurrent disease within 6 mo of follow-up they are randomised to either surveil-

lance alone or explorative laparotomy and HIPEC. With this proactive approach, disease free and overall survival may be increased.

## CONCLUSION

With newer imaging modalities such as PET/CT and PET/magnetic resonance tomography a better location of the tumor may be realized in future. Pro-active second look surgery, as far as there is no optimal imaging method, realizes the anticipation of diffuse peritoneal spread.

Making “unresectable patients” resectable is one challenging goal of neoadjuvant chemotherapy protocols in the future.

Using new protocols including intraperitoneal antibodies or even intraperitoneal virotherapy in patients with unresectable disease may further improve results.

Lastly and most importantly, a dedicated surgeon, an experienced anaesthesiologist and cooperating medical oncologists are mandatory to achieve excellent results and develop new concept in the treatment of peritoneal metastases.

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