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To cite this article: Karol Polom, Luigi Marano, Giandomenico Roviello, Roberto Petrioli, Riccardo Piagnerelli, Lorenzo de Franco, Daniele Marrelli & Franco Roviello (2015): Evolution and emerging future of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion in gastric cancer: From treating the incurable to preventing recurrence, International Journal of Hyperthermia, DOI: [10.3109/02656736.2015.1111432](https://doi.org/10.3109/02656736.2015.1111432)

To link to this article: <http://dx.doi.org/10.3109/02656736.2015.1111432>



Published online: 15 Dec 2015.



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REVIEW ARTICLE

Evolution and emerging future of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion in gastric cancer: From treating the incurable to preventing recurrence

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Abstract

The number of new gastric cancer (GC) cases is decreasing, and these patients have longer survival thanks to new oncological treatments. In advanced GC a common evolution of this neoplasm is peritoneal metastases (PM). In the past this finding meant no chance for cure. However, today, using high quality operations and HIPEC, we are able to increase the number of patients treated with curative intention. New options in the diagnosis of PM, tumour susceptibility for different drugs, importance of quality of life, usage in ascites treatment, diagnostic tools in image-guided surgery, new targeted therapies and analysis of currently ongoing trials are presented together with today's knowledge of HIPEC efficacy in order to evaluate gastric PM. HIPEC is an effective tool in the treatment of selected patients with PM from GC. Together with new diagnostic options such as targeted therapies, HIPEC may improve the prognosis of these patients, not only by treating clinically manifest carcinomatosis, but also in the prophylactic setting, addressing occult peritoneal seeding.

Keywords

Ascites, gastric cancer, intraperitoneal chemotherapy, HIPEC, near infrared fluorescence, targeted therapies

History

Received 24 September 2015
Revised 13 October 2015
Accepted 19 October 2015
Published online 15 December 2015

Introduction

Gastric cancer and peritoneal metastases

Close to one million new gastric cancer (GC) cases have been estimated to have been diagnosed in 2012, accounting for 6.8% of all cancers [1]. Currently, stomach cancer is the fifth most common cancer worldwide, shifting from its spot as the most common malignancy in the last 40 years. In spite of this change, this neoplasm is the third leading cause of death associated with cancer (723 000 deaths) [1].

GC metastases can be categorised by how they spread in the body: via the lymphatic system to the lymph nodes, via the haematic system to distant organs, and by dissemination to the peritoneal cavity – known as peritoneal metastasis (PM). Stomach cancer has the highest rate of peritoneal recurrence of all gastrointestinal cancers. It has been shown that PM is a more common way of GC dissemination than distant metastasis as PM is observed in other malignancies. Okines et al. showed that GC PM associated deaths are seen 53–60% of the time, which is markedly higher than in cases of distant metastases for example 40% for hepatic metastases [2].

Some studies reported clinical and pathological factors associated with peritoneal recurrence: T3 and T4 tumours, positive peritoneal wash, lymph node invasion, signet ring cell pathology, diffuse infiltrative growth pattern, and a reaction of the primary scirrhous-type tumour [3–9].

The impact of systemic chemotherapy in PM of GC origin is minimal. In cases with distant metastases, a short duration response rate is about 43% and the response for PM cases is less than 14% [10,11]. The reasoning for this is a barrier between blood and peritoneum that prevents high concentrations of intravenous drugs in the peritoneal layer [10].

PM during an abdominal examination is observed in 10–20% of patients who are scheduled for surgery, and up to 40% of stage III GC [12,13]. A second problem is that half of patients treated with curative intent will develop a future recurrence in the form of PM; 40–60% of advanced GC patients were observed to have PM and died because of PM recurrence, despite the fact that extensive surgery including D2 lymph node dissection had been performed [14–16].

Evidence of hyperthermic intraperitoneal chemotherapy usage in gastric cancer peritoneal metastases

GC hyperthermic intraperitoneal chemotherapy (HIPEC) studies focus on the indications for treatment of PM. Glehen et al. presented one of the largest groups of 159 patients in their

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multi institutional French study [17]. The centre effected with specialised team and radicality in case of cytoreductive surgery (CRS) (completeness of the cancer resection – CCR 0 resection) were independent prognostic factors in multivariate analysis, and only patients with complete cytoreduction had a chance of curative treatment. Even in the group of patients submitted to CCR 0, only patients with a PCI score lower than 13 were suitable to benefit from this treatment. They also underlined the fact that no patients lived longer than 6 months in cases where the PCI score was higher than 19. A Japanese study by Yonemura et al. was performed on 107 patients [18]. Five-year survival was 6.7%, and in cases of CRS with HIPEC, 5-year survival was raised up to 27%. For patients with complete and incomplete residual tumour resection, median survival time was 15.5 months and 7.9 months, respectively. The independent prognostic factors were completeness of cytoreduction and peritonectomy. From our own studies we proved that serosal involvement, Lauren histotype and peritoneal cytology are the most important risk factors for peritoneal recurrence after GC surgery [9,19].

Currently we can follow the data from five meta-analyses [20–24]. The first meta-analysis by Yan et al. reported a significant improvement in survival in patients after HIPEC or HIPEC together with early post-operative intraperitoneal chemotherapy [20]. They stated that HIPEC is associated with higher rates of intra-abdominal abscess and neutropenia. This meta-analysis also underlined the usage of HIPEC in GC PM for the first time, based on strong evidence, especially as it is complementary to adjuvant oncological treatment. The limitation of this technique is restricted by extension of the disease and possibility of radical surgery of GC spread. Other important evidence from meta-analysis by Mi et al. is based on results from 16 RCTs. They showed better survival rate at 1, 2 and 3 years, but also at 5 and 9 years [21]. In the Mi et al. study only HIPEC trials were analysed [21]. Usage of HIPEC was not associated with a higher rate of anastomotic leakage, ileus, bowel perforation, myelosuppression, gastrointestinal reaction or hypohepatia, but with a higher rate of abdominal pain [21]. In the meta-analysis by Sun et al. based on 10 RCTs, a significant improvement in the group with HIPEC was shown [22]. Additionally, after usage of HIPEC, a lower number of peritoneal recurrences were seen, without higher rate of complications. These three studies analysed prophylactic HIPEC in GC [20–22]. The latest meta-analysis showed that surgery with intraperitoneal chemotherapy (IPC) (no matter the type) improves 1-, 2- and 3-year mortality, 2- and 3-year mortality in patients who had regional lymph node metastases, and 1-, 2-year mortality in patients with serosal infiltration [23]. No difference in 5-year survival rate was seen. This meta-analysis underlined the role of IPC on nodal metastases.

All studies lead to the result that HIPEC procedure in the case of GC PM is only possible in a small fraction of patients with limited PM and complete resectability of disease (CCR 0/1). Currently no benefit is seen in the case of macroscopic tumour residue.

Mortality and morbidity in HIPEC

The use of intraperitoneal chemotherapy in the case of malignant peritoneal spread was first proposed more than

60 years ago using a nitrogen mustard [25]. In 1980, Spratt was the first to propose maximal cytoreductive surgery with HIPEC as a treatment option for a recurring peritoneal pseudomyxoma [26]. Initial reports from post-operative mortality and morbidity were not encouraging [27]. Building on past experience and careful patient selection, a French study from 25 centres based on 1290 patients presented a mortality rate of 4.1%, and a morbidity of grade 3 and 4 complications of 34% [17]. A study by Chua et al. showed similar results with 3% mortality rate and 43% morbidity [28]. These results, as well as similar results from other centres, suggest that after a learning curve phase and in the hands of an experienced surgeon, complete cytoreductive surgery and HIPEC should be used without fear of high rates of post-operative complications.

Quality of life

CRS and HIPEC combine an extensive surgical approach with the influence of chemotherapy given during the surgical procedure. Both are responsible for a high rate of post-operative morbidity. This has led to the suggestion that this procedure reduces health-related quality of life (HQL) [29,30]. Worse results of HQL for PM patients are also related to the stage of the primary disease, as well as the effect of palliative chemotherapy. A study presented by McQuellon et al. used different scales to monitor health outcome after CRS and HIPEC [31]. HQL and pain improved in 12 months. Physical functioning improved at 6 months. Interestingly, 32% of patients reported depressive symptoms at the baseline; after 3 months, 19% were depressed; and after 6 and 12 months, the number was 24% [31]. In a paper by Tsilimparis et al. based on European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, physical and role functions recovered significantly at 6 months and were the same as at the 24 month measurement [32]. Emotional function rose from low values to the baseline in 12 months. Cognitive and social functions slowly recovered during the follow-up. The most influencing factors on HQL such as fatigue, diarrhoea, dyspnoea and sleep disturbances were improved after 6 months. Importantly, as the aggressive treatment received a positive result from an oncological point of view, in the second year patients had better HQL than before operation. Zenasni et al. reported a good HQL in 67% of patients after CRS and HIPEC [33]. Worse results were observed in relation to future prospects and sexual functioning. A reduction of HQL after CRS and HIPEC should not disqualify this technique from clinical usage since 6–12 months after CRS and HIPEC, most of the HQL elements recover to the preoperative level.

Chemoresponse assay

In HIPEC, the chemotherapy drug has the possibility to make direct contact with tumour cells. As the drug mostly stays in the abdominal cavity, its dose can be increased without fear of high systemic exposure. Similar tumours, however, do not respond to intraperitoneally administered drugs as well as they do in the case of systemic chemotherapy [34]. A good solution to this problem seems to be a chemoresponse assay. Using this system we can characterise the sensitivity and

resistance of many chemotherapeutic agents. This is not a standard tool that may replace standard chemotherapy. In the paper by Bhagwandin et al., 27 patients that were planned for CRS and HIPEC underwent *in vitro* drug-sensitive testing using ChemoFx assay [35]. The sensitivity (63%) was not satisfactory, and results did not correlate with final oncological outcomes such as progression-free survival (PFS), and overall survival (OS). Another point is that there was no correlation between *in vitro* drug sensitivity and pathological result with preoperative chemotherapy management. Currently we need more studies on this interesting issue, especially as more new drugs are available for HIPEC; however, for now it seems that this tool is not useful for HIPEC drug selection.

HIPEC in management of malignant ascites

A PM associated with malignant ascites indicates a very poor prognosis, with survival from weeks to a few months. CRS-HIPEC is effective in ascites control in 93% of patients presenting with malignant ascites, even in situations where complete PM resection is not possible. The effect was seen no matter the primary tumour origin, time, type of drug chemoperfusion, and ascites score [36]. Additionally, the ascites resolution was independent from extension of CRS and is probably just an effect of HIPEC. It seems that HIPEC may be used as a palliative treatment in the case of malignant ascites [37]. With modern palliative chemotherapy, life expectancy is no longer than 4–5 months [38]. The problem of ascites are distension and dyspnoea which are handled for a short time with paracentesis, but the effect is temporary and leads to a decrease in the quality of life of these patients. Currently the treatment is only palliative [39]. A survival benefit in the case of ascites with PM is observed only in patients with complete cytoreduction [36]. It seems that HIPEC is a promising tool in dealing with malignant ascites. Patients presenting malignant ascites in majority cases will not get a complete cytoreduction, and ascites itself impedes the correct scoring of PM. To summarise, we need to underline that the concept of using HIPEC in the presence of ascites has been recognised as a contraindication for CRS/HIPEC with curative intent for several tumours such as colorectal, gastric and recurrent ovarian cancer PM. HIPEC for palliation of malignant ascites needs to be taken into consideration for very specific cases. Future studies are needed to prove its effectiveness, keeping in mind not only survival benefit, but especially improvement in quality of life.

The new option of using HIPEC in treatment of advanced gastric cancer

Based on current knowledge, HIPEC is effective in treatment of only limited PM and only in situations of complete surgical resection of all tumour deposits. New ongoing clinical studies focus on prevention of the disease, not on treating the incurable [2]. The new therapeutical options for treating GC are rapidly being explored [40–42]. Currently some interesting trials are being performed with valuable patient groups: one such trial is a phase II trial performed by a German team (HIPEC_Stomach), trial number NCT01683864. The investigation consists of patients with GC (TNM stage \geq T2 < T4)

without proven metastases (TNM stage M0), with and without involved regional lymph nodes (TNM stage +N/–N) and positive cytology in preoperative abdominal lavage. The preventive utility of HIPEC might be of highest importance, especially as patients with positive tumour cell cytology lavage can develop PM in the near future in up to 80% of patients. Conversely, patients with advanced GC but without tumour cells in peritoneal lavage will develop PM in only 40% of cases. The French group GASTICHIP phase III multicentre trial (NCT01882933), recruiting patients with advanced GC (T3, T4 and/or N+ and/or with positive peritoneal cytology) will give a curative gastrectomy with D2 lymphadenectomy in one arm and the same treatment with HIPEC in the second arm. This will help to get an answer about preventive application of HIPEC in peritoneal cytology positive patients as well as in peritoneal cytology negative patients. One possibility is that the future of HIPEC lies not in treatment, but in prevention of PM in high-risk patients. A similar study is being performed by a Chinese group (NCT02240524). A Spanish non-randomised phase II multicentre trial (NCT01342653) will try to find the effects of intraperitoneal infusion of chemotherapy administered simultaneously with intravenous treatment in a preoperative setting. After neoadjuvant treatment, CRS and HIPEC with intravenous chemotherapy during operation will be performed, and after operation, adjuvant chemotherapy is the last phase. A completed phase II study, currently without published results, has been performed in Sweden (NCT01379482). They proposed patients with PM from GC undergo neoadjuvant chemotherapy, then HIPEC with CRS, and afterwards, post-operative adjuvant chemotherapy. A trial from the MD Anderson Cancer Center in the USA (NCT02092298) recruited patients for laparoscopic HIPEC performed 2–8 weeks after completion of systemic neoadjuvant chemotherapy in a group of patients with positive peritoneal lavage cytology, or carcinomatosis on diagnostic laparoscopy/laparotomy. In a recent study by Bokemeyer et al., catumaxomab was administered intraoperatively and post-operatively in resectable advanced GC after neoadjuvant setting [43]. This phase II study was created to evaluate the safety and efficacy of this antibody. Complications were observed in 33% of patients. The most common ones were pulmonary infection (17%) and anastomosis insufficiency (11%) which required a surgical approach. The 4-year disease-free survival was 38% and overall survival was 50%. These findings suggest that this drug might find a place in randomised multicentre trials.

Detection of peritoneal metastases

The most important factor in selecting an appropriate treatment for GC patients is staging of the disease. The extent of the peritoneal spread is of the highest importance. Even today, with very sensitive radiological tools, diagnostic laparoscopy is still important for detection of subradiological disease; in addition, peritoneal lavage cytology can be performed as well. The importance of pretreatment laparoscopy was proven, as up to about a third of patients presented PM, even though in radiological tests it was not visible [44]. In the pretreatment analysis, a peritoneal cytology also plays an important role. Patients that present a positive result in the

peritoneal lavage cytology mimic stage IV of the disease [45]. Peritoneal lavage sensitivity has improved as highly sensitive molecular diagnostics such as an enzyme immunoassay, reverse transcription polymerase chain reaction, and virus-guided imaging are used. All of them have been developed to detect minute cancer cells in the peritoneal cavity. The conventional cytological examination of the peritoneal lavage is still the main tool for diagnosis of PM, but these new approaches could serve as a complementary tool in the near future [46,47].

A new imaging modality is available using near infrared fluorescence (NIRF). This image-guided tool using fluorophores has gained vast interest among different medical disciplines such as surgery, oncology, urology, and many others [48–56]. In the case of performing CRS and HIPEC, it might be used in the safe visualisation of important structures such as ureters [48]. On the other hand, NIRF technology was used by van Dam et al. for the first time in humans in intraoperative tumour-specific fluorescence imaging of ovarian cancer PM [57]. Overexpression of a folate receptor α in ovarian cancer has been proposed as a target for a fluorophore. Targeted tumour-specific fluorescence imaging was employed. More spots were visualised than with the naked eye. The authors also stated that this image-guided surgical approach in CRS and HIPEC operations might be of the highest value: it may guide the surgeon to a more efficient cytoreduction, which ultimately improves the oncological outcome of the patient due to complete removal of all tumour deposits – even the smallest ones. To define the most suitable target, van Oosten et al. developed a novel target identification method for colon cancer: TASC [58]. In the future, perhaps tumour-targeted imaging probes will be in daily use to visualise and offer targeted individualised therapies. Clinical trials are being held to evaluate NIRF technology in improving detection of PM in different cancers (NCT02032485, NCT01982227). An interesting mouse model study was performed by Ito et al. that visualised PM in GC using multimodality imaging combined with NIRF-guided visualisation with antibodies against CEA or EGFR, in conjunction with indocyanine green (ICG) [59]. They also added three-dimensional fluorescence imaging to assess the exact localisation of metastasis in mouse peritoneal cavities. Another display of NIRF-guided PM detection was made by Hoshino et al. using liposomal synthesised ICG liposomal derivate [60]. The laparoscopic NIRF camera on a pig model clearly showed an improved visualisation of PM.

Another fluorescent dye used in clinical practice that is visualised in a different light wavelength is 5-aminolevulinic acid (5-ALA). During laparoscopy for GC cases Murayama et al. [61], as well as Kishi et al. [62], demonstrated its usefulness in improving the staging of the disease; Kishi et al. reported that during staging laparoscopy 5-ALA detected peritoneal spread in 21% of patients who previously were not found to have had PM using laparoscopy alone [62].

Targeted therapies

Just as when targeted drugs started a new age in modern oncology some time ago, PM treatment can look forward to new pharmaceutical possibilities [63,64]. In the case of

malignant ascites, we can use Cetumaxomab – a trifunctional non-humanised monoclonal antibody. It works as a locoregional immunotherapy against EpCAM+ tumour cells in the peritoneal cavity. In a study by Heis et al., patients with malignant ascites had statistically longer puncture-free survival as they received catumaxomab, and a better survival trend was observed [65]. The drug-related symptoms were pyrexia, nausea, vomiting, and abdominal pain. Importantly, aggravation in HQL was delayed.

Trastuzumab

Monoclonal antibody against human epidermal growth factor 2 (HER-2) is used with success in HER-2 positive breast cancers, and also in advanced GC [66–68]. It was proved that the primary and metastatic tumours present 95–98% compatibility of primary and metastatic GC [69]. The randomised TOGA trial demonstrated that patients with positive human epidermal receptor 2 (HER-2) tumours may benefit from chemotherapy combined with the monoclonal antibody trastuzumab, in terms of progression-free survival (PFS) and OS [70]. However, HER2 over-expressing tumours represent roughly 20% of the total number of GC [70–73]. From this point of view it seems to be effective to use this kind of antibody intraperitoneally. An ongoing American phase I study is using radioactive elements releasing sufficient amounts of energy to destroy tumour cells by combining an isotope with trastuzumab antibody (^{212}Pb -TCMC-trastuzumab) (NCT01384253). The target for the drug will be PM in intraperitoneal cavity. A peritoneal catheter will be positioned and the drug will be given intravenously. The intraperitoneal administration of trastuzumab was documented in the case report of PM with HER-2 overexpression by Berretta et al. where weekly administration to intraperitoneal cavity after paracentesis occurred [70].

Anti-angiogenesis therapies

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). This factor is involved in angiogenesis and vascular penetrability enhancing PM dissemination and malignant ascites. VEGF is markedly elevated in the peritoneal cavity with malignant ascites and leads to increasing endothelial cell permeability [63]. An encouraging paper from MD Anderson Cancer Center on the treatment of unresectable appendiceal epithelial neoplasm using bevacizumab was recently presented [74]. Bevacizumab is currently approved for the treatment of colon, lung, breast, ovarian, endometrial and clear cell renal carcinoma in a metastatic setting. Unfortunately, based on the reported results, bevacizumab is currently not an option for GC patients with unresectable or metastatic tumours. Elevated concentration of bevacizumab is observed in malignant ascites patients when given as an oncological treatment. Therefore, future trials are awaited to assess a possible role of intraperitoneal bevacizumab in GC patients. Finally, ramucirumab, a human IgG1 monoclonal antibody and VEGFR-2 antagonist has been recently approved by the US Federal Drug Administration as a second line treatment in patients with advanced or metastatic GC or gastroesophageal junction cancers who progressed on fluoropyrimidine-or platinum-containing

first-line chemotherapy. However, data for ramucirumab's effects on malignant ascites by GC is lacking.

Conclusions

To date, the most important prognostic factor of successful treatment is the completeness of surgical cytoreduction together with HIPEC. This highlights the need for optimal patient selection criteria. First, patients at high risk for PM must be identified. Serosal involvement of the GC, a diffuse histotype, and positive peritoneal washing are known factors that increase the chance of PM. This is a group of highest importance for prevention. We can also use new diagnostic options where image-guided surgery using NIRF seems to play a big role in the future, together with targeted tools that may help in better estimation of the cancer spread.

In the near future, the standardisation of surgical procedures and HIPEC techniques, integrated with new anti-cancer drugs and new bidirectional chemotherapy protocols combining neoadjuvant, intraperitoneal and systemic chemotherapy in a tailored approach is awaited [75–77]. The other way of improvement in survival of GC patients seems to be the prevention of PM. Many new trials are ongoing and we eagerly wait for the results that may change the current usage of HIPEC in GC multimodal treatment.

Declaration of interest

The authors have no conflict of interest or financial ties to disclose. All authors contributed equally to this work. The authors alone are responsible for the content and writing of the paper.

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