Indian J Surg Oncol (June 2016) 7(2):198–207
DOI 10.1007/s13193-016-0502-8

REVIEW ARTICLE

The Role of Hyperthermic Intraperitoneal Chemotherapy in Gastric Cancer

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Received: 7 January 2016 / Accepted: 28 January 2016 / Published online: 2 February 2016

Abstract Peritoneal metastasis, either synchronous or metachronous, is commonly seen in gastric cancer. It is associated with a poor prognosis, with a median survival of less than one year. The outcomes are not significantly improved by the use of systemic chemotherapy. We review the relevant literature on the role of HIPEC in gastric cancer. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been used in three situations in gastric cancer. Besides its role as a definitive treatment in patients with established peritoneal metastasis (PM), it has been used as a prophylaxis against peritoneal recurrence after curative surgery and also as a palliative treatment in advanced peritoneal metastasis with intractable ascites. While prophylactic HIPEC has been shown to reduce peritoneal recurrence and improve survival in many randomised trials, palliative HIPEC can reduce the need for frequent paracentesis. Although CRS with HIPEC has shown promise in increasing the survival of selected patients with established PM from gastric cancer, larger studies are needed before this can be accepted as a standard of care.

Keywords Gastric cancer · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Peritoneal carcinomatosis

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Introduction

Gastric cancer (GC) is the fifth most common cancer in the world and the third leading cause of cancer related death in both sexes worldwide [1]. Peritoneal metastasis (PM) at presentation is seen in about 14–43 % of patients with GC [2, 3]. The peritoneum may be the sole site of synchronous metastasis in nearly 10 % of patients with GC [3] and the first/sole site of tumor recurrence after curative surgery in 12–40 % of patients [4–7]. Although adjuvant and/or neoadjuvant treatment [8–11] can improve the survival after curative surgery in GC, it does not significantly reduce the rate of peritoneal recurrence [12–14].

The median survival of patients with PM from gastric cancer is only 3 to 7 months [3, 15, 16], which is worse than that of patients with other sites of metastatis [17, 18]. The median overall survival in metastatic gastric cancer with current first line chemotherapy is only 8 to 14 months [19, 20] and even the use of targeted therapies does not result in long-term survival [20, 21]. The median survival with chemotherapy in patients with only PM from gastric cancer is 9.5 to 12 months [22, 23]. Peritoneal metastasis in gastric cancer responds poorly to systemic chemotherapy [16, 18, 24]. This is due to the presence of the "plasma-peritonal barrier" [25]. The inability of systemic chemotherapy to provide long-term survival coupled with the belief that peritoneal recurrence remains confined to the abdomen [26] has prompted investigators to explore regional therapies. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is currently being used as a curative treatment in pseudomyxoma peritonei, peritoneal mesothelioma and selected patients with colorectal PM [27, 28]. It seems logical to use CRS & HIPEC in gastric cancer, since nearly half of the recurrences after curative surgery are confined within the peritoneal cavity. HIPEC has been used in three different situations in the

management of gastric cancer- in an adjuvant setting to prevent peritoneal recurrence after a curative gastrectomy in high risk patients, as a definitive treatment in patients with established PM after CRS, and to palliate patients with intractable ascites due to extensive peritoneal dissemination. In this article, we review the current role of CRS & HIPEC in gastric cancer.

Rationale for HIPEC

Peritoneal recurrence after a curative resection for gastric cancer is thought to originate from intraperitoneal free cancer cells (IFCC), which in turn arise from two potential sources: spontaneous exfoliation of cancer cells from the primary tumor from the serosal surface, and iatrogenic dissemination of cancer cells as a result of the surgical trauma [26, 29]. Sugarbaker et al. proposed the "tumor cell entrapment hypothesis" [26], according to which the IFCC adhere to the surgical raw area within minutes- a process facilitated by fibrin entrapment and assisted by cytokines released as part of the wound healing mechanism. This hypoxic environment renders the trapped cancer cells relatively immune to the effects of systemic chemotherapy.

Intraperitoneal administration of chemotherapy results in a positive gradient of chemotherapy in the peritoneum. This regional dose intensification ie- a high intraperitoneal concentration of the drug with a low plasma concentration is maintained by the plasma-peritoneal barrier [30]. Hyperthermia synergistically enhances the effects of intraperitoneal chemotherapy by both direct cytotoxic action (impaired DNA repair, denaturation of proteins and increase in the lysosomal activity within the tumor cells) and indirect cytotoxic effects (increased penetration of the drug into the tumor nodule and increased drug uptake in the tumor cells) [30, 31]. Intraperitoneal chemotherapy is best delivered either at the time of surgery or immediately following it since the cytotoxic activity of perioperative intraperitoneal chemotherapy destroys the cancer cells within the fibrin produced as part of the wound healing process. Delayed administration of intraperitoneal chemotherapy not only results in poor penetration of the chemotherapeutic agent into the cells trapped in the scar but also in a non-uniform distribution of chemotherapy within the peritoneal cavity due to adhesions [32].

HIPEC for Prevention of Peritoneal Recurrence

The most attractive use of HIPEC in gastric cancer would be in an adjuvant sitting after a curative surgical resection in patients with a high risk of peritoneal recurrence. The rationale behind this prophylactic approach is twofold- while the large volumes of fluid used during HIPEC dilutes the intraperitoneal free cancer cells, the synergestic effect of heat and the chemotherapy destroys the residual cancer cells. The risk factors for peritoneal metastasis/recurrence in gastric cancer include advanced T stage, advanced nodal stage, signet ring cell or diffuse type histology, tumor size, young age and female gender [3, 6, 33]. A positive peritoneal lavage cytology also predisposes to peritoneal recurrence. Upto 80 % of patients with a positive cytology (Cy+/P0) have a peritoneal recurrence after a curative gastrectomy compared to 45 % of patients with a negative cytology (Cy−/P0) [34]. The 5-year survival of these patients (Cy+/P0) treated with surgery and adjuvant systemic chemotherapy is only around 2 %, similar to those with established PM [35, 36].

The use of HIPEC to prevent peritoneal recurrence was first reported in 1988 by Koga et al. They observed a significant improvement in the 3-year survival (74 % vs 53 %, $p < 0.04$) and reduction in peritoneal recurrence (36 % vs 50 %) in patients who received prophylactic HIPEC after a curative gastrectomy compared to those who did not [37]. Since then, there have been many randomised trials comparing prophylactic HIPEC versus no HIPEC in patients with locally advanced GC who underwent a potentially curative resection. The trials from English literature have been summarised in Table 1. Most of these trials included patients who had serosal invasion and/or lymph nodal metastasis without macroscopic peritoneal disease. The role of prophylactic HIPEC in patients with Cy+/P0 gastric cancer has been reported only in one study, in which a 5-year survival of 42 % was achieved in 15 patients with Cy+/P0 disease who underwent gastrectomy followed by HIPEC [45]. There is considerable heterogeneity in these trials with respect to the drugs used and their dose, duration of HIPEC etc.

Several meta-analyses of the trials using prophylactic intraperitoneal chemotherapy have been published. While two of these meta-analyses included only patients receiving HIPEC in the experimental arm [46, 47] the others included patients receiving other forms of intraperitoneal chemotherapy besides HIPEC, like early post-operative intraperitoneal chemotherapy (EPIC) and normothermic intra-operative intraperitoneal chemotherapy (NIIC) [48–51]. Intraperitoneal chemotherapy, including HIPEC reduced the peritoneal recurrence rates by nearly 50 % [47, 50]. Mi et al. [46] observed that HIPEC was associated with a significant improvement in the survival rate at 3 years (hazard ratio (HR)-2.63; 95%CI 2.17 to 3.20; $p < 0.00001$), 5 years (HR-2.49; 95%CI 1.97 to 3.14; $p < 0.00001$), and 9 years (HR-2.14;95%CI 1.38 to 3.32; $p = 0.0007$) and a significant reduction in recurrence rate at 2 years (RR-0.42; 95%CI 0.29 to 0.61; $p < 0.00001$), 3 years (RR-0.35; 95%CI 0.24 to 0.51; $p < 0.00001$) and 5 years (RR-0.47; 95%CI 0.39 to 0.56; $p < 0.00001$). Sun et al. reported a significant survival advantage with the use of HIPEC (RR 0.73, 95 % CI 0.64-0.83, $p < 0.0001$) and a significant reduction in peritoneal recurrence (RR 0.45, 95 % CI 0.28-0.72, p0.001) [47]. The two meta-analyses including only HIPEC trials did not show any significant increase in the risk of bone

Table 1 Randomised studies of prophylactic HIPEC in gastric cancer

Author	Treatment arms	No. of patients	Drugs used	Complications	Post-op Mortality	Peritoneal Recurrence	Survival
Koga et al. [37]	Surgery with HIPEC Vs surgery alone	47	MMC	Leak 3.1 % vs 7.1 %	NA	NA	30 month 83 % vs 67 %
Fujimura et al. [38]	Surgery with HIPEC Vs surgery with CNPP Vs surgery alone (controls)	58	MMC CDDP	30 % vs 0 %[#]	NA	9 % vs 22 % vs 22 %*	3-year 68 % vs 51 % vs 23 % ($p < 0.01$)
Hamazoe et al. [39]	Surgery with HIPEC Vs surgery alone	82	MMC	Leak 4.8 % vs 7.5 %	0 % vs 0 %	39 % vs 59 %*	5-year 64 % vs 52 % Median survival 77 vs 66 months
Ikeguchi et al. [40]	Surgery +withHIPEC Vs surgery alone	174	MMC	1.2 % vs 2.08 %	NA	35 % vs 40 %*	5-year 51 % vs 46 % 5-year 66 % vs 44 % (in 1–9 LN +)
Hirose et al. [41]	Surgery with HIPEC Vs surgery alone	55	MMC CDDP Etoposide	60 % vs 42.5 %	0 % vs 12.5 %	26 % vs 45 %	3-year 49 % vs 29 % 5-year 39 % vs 17 % Median survival 33 vs 22 months ($p = 0.01$)
Fujimoto et al. [42]	Surgery with HIPEC Vs surgery alone	141	MMC	2.8 % vs 2.8 %	0 % vs 0 %	1.4 % vs 23 % ($p = 0.00008$)	2- year 88 % vs 77 % 4-year 76 % vs 58 % 8-year 62 % vs 49 % ($p = 0.03$)
Kim et al. [43]	Surgery with HIPEC vs surgery alone	103	MMC	36.5 % vs 33.3 %	NA	7.6 % vs 25 % (isolated PC)	5-year 33 % vs 27 % 5-year 42 % vs 25 % (in stage IIIB)
Yonemura et al. [44]	Surgery with HIPEC Vs Surgery with CNPP vs Surgery alone	139	MMC CDDP	19 % vs 14 % vs 19 %	4 % vs 0 % vs 4 %	13 % vs 15 %[†]	5-year 61 % vs 43 % vs 42 %

NA- not available, PC-peritoneal carcinomatosis, MMC-mitomycin-c, CDDP- cisplatin, CNNP- continuous normothermic peritoneal perfusion

*death due to PC, [#] perfusion vs surgery alone, [†] (HIPEC vs surgery)

marrow suppression (relative risk (RR) 1.10–1.68) or anastamotic leak (RR 0.52-0.86). The pooled rates of complications in the HIPEC arms ranged from 1.7 %-3.3 % (anastamotic leak), 1.4 %-2.8 % (bowel perforation/fistula), 2.9 %-6.3 % (myelosuppression), 2.6 %-3.5 % (adhesive ileus) and 3.1 % (liver dysfunction) [46, 47].

In contrast, three other meta-analyses [48–50] reported a significant increase in the incidence of morbidity including, especially intra-abdominal abscess and neutropenia with the use of intraperitoneal chemotherapy without any increase in the mortality. A survival benefit with prophylactic intraperitoneal chemotherapy was seen with the use of HIPEC alone or combined with EPIC in two meta-analyses [48, 49]. While Coccolini et al. [50] reported that intraperitoneal chemotherapy confers a survival advantage in the adjuvant setting, Xu et al. [51] concluded that while any form of intraperitoneal chemotherapy may benefit patients after a curative resection, using hyperthermia or activated carbon particles may confer added benefit to patients.

An ongoing phase III randomised European multicentre study (GASTRICHIP) is evaluating the role of HIPEC in patients with gastric cancer who have either serosal infiltration and/or lymph nodal involvement and/or positive peritoneal cytology treated by a curative gastrectomy [52]. The primary aim of the study is the 5-year overall survival while the secondary outcome measures include the recurrence free survival, patterns of recurrence, quality of life and morbidity.

In summary, adjuvant HIPEC used as prophylaxis against peritoneal recurrence in patients with high risk GC (serosal invasion or nodal metastasis) is safe, significantly improves the survival and reduces the risk of peritoneal recurrence. However, an international consensus is required on many issues like choice of the drug, dosage, duration of treatment, addition of EPIC etc. before prophylactic HIPEC in advanced gastric cancer becomes widely accepted.

HIPEC for Treatment of Peritoneal Metastasis

The use of CRS & HIPEC in treating patients with gastric cancer who have established PM was reported by Fujimoto et al. in 1988 [53]. Fifteen patients with advanced GC, 9 of whom had synchronous PM and/or ascites, underwent extensive resection followed by HIPEC using mitomycin-C (MMC) at a dose of 10 μg/ml for 2 h in conjunction with oral misonidazole, a hypoxic cell sensitizer, given prior to the surgery. Ascites resolved in all the 9 patients and subsequent peritoneal lavage cytology turned negative. They concluded that extensive surgery with HIPEC was a safe and well tolerated treatment for PM from gastric cancer. This data was later updated in 1990 where the authors reported a 2-year survival of 45 % in 20 patients who underwent extensive surgery followed by HIPEC compared to 0 % in 7 patients who did not receive this treatment [54].

Many other studies of CRS & HIPEC as a therapeutic option in patients with PM from gastric cancer have been published (Table 2). Most of these are prospective case control studies or retrospective studies. The first long term survival (11 % 5-year survival) with the use of HIPEC in PM from gastric cancer was reported in 1996 by Yonemura et al. in a cohort of 83 patients who underwent cytoreductive surgery with HIPEC [15]. Subsequently, Glehen et al. reported a prospective study of 49 patients with PM from gastric cancer treated with CRS & HIPEC. The overall median survival was 10.3 months and the 5-year survival rate was 16 % [57]. One of the largest series of therapeutic CRS and perioperative intraperitoneal chemotherapy for PM from gastric cancer was a prospective multi-institutional study from France and Belgium in which HIPEC was performed in 150 patients while 12 patients received EPIC [59]. The 5 year survival was 13 % and median survival was 9.2 months for the entire cohort.

The importance of surgical technique of CRS was highlighted by Yonemura et al. who compared 65 patients who underwent conventional surgery followed by HIPEC for PM from gastric cancer with 42 patients who had a peritonectomy as described by Sugarbaker et al. followed by HIPEC [58]. While the 5-year survival was 6.7 % in all patients, it was 27 % in the patients who underwent peritonectomy and HIPEC demonstrating that the technique of cytoreduction is also an important factor in achieving good results.

Surprisingly, unlike in the adjuvant setting, very few randomised studies have been conducted to evaluate the role of CRS & HIPEC in established PM from gastric cancer. The first randomised phase 3 trial was reported by Yang et al. from China [60]. Sixty eight patients of gastric cancer with PM were randomised to receive either CRS & HIPEC or CRS alone. The median PCI in both groups was 15. The 3-year survival in the CRS & HIPEC arm was 5.9 % compared to 0 % in the CRS alone arm. Patients treated with CRS & HIPEC had a significantly higher median survival compared to those treated by CRS alone (11 vs 6.5 months, $p = 0.04$). The authors reported a 70 % improvement in the median survival which is close to that reported in the Dutch randomised trial of CRS & HIPEC in colorectal cancer (76 %) [61].

A systematic review of 10 published studies comprising 441 patients who underwent CRS & HIPEC for PM from gastric cancer reported a 5-year survival of 13 %. The median overall survival was 7.9 months (range 6.1–9.2 months) which increased to 15 months (range 9.5–43.4 months) if a complete cytoreduction was achieved [62]. A meta-analysis evaluating the effectiveness of intraperitoneal chemotherapy in advanced GC, reported that the 3-year mortality in patients with established PM significantly favoured the surgery with intraperitoneal chemotherapy arm when compared to the standard arm (odds ratio (OR) = 0.25) whereas there was no statistically

Table 2 Published studies of therapeutic HIPEC in gastric cancer

Author	Type of study	No. of patients	Control arm	Drug used for HIPEC, Dose	Complete cytoreduction	Morbidity	Mortality	Survival
Fujimoto et al. [54]	Prospective	27	only surgery	MMC 10 μg/ml	NA	NA	NA	6 month survival- 94 vs 57 %, $p = 0.001$ Death due to Peritoneal recurrence- 10 vs 100 %
Yonemura et al. [55]	Prospective	41	Nil	MMC 5 μg/ml CDDP 30 μg/ml	NA	12 %	0 %	Median survival-14.5 months 3-year 28.5 %
Yonemura et al. [15]	Prospective	83	Nil	MMC 30 mg CDDP 300 mg Etoposide 150 mg	33.7 %	NA	NA	5-year survival - overall-11 % (CCR0/1–17 %, CCR2- 2 %)
Fujimoto et al. [56]	Prospective case-control	66	only surgery	MMC 10 μg/ml	NA	NA	NA	3-year & 5-year survival (HIPEC vs control- 42 vs 0 % & 31 vs 0 %; $p = 0.001$) Death due to peritoneal recurrence- HIPEC vs control 27 vs 94 % ($p = 7.077 \times 100^{-7}$).
Hirose et al. [41]	Prospective case-control	37	CRS alone	MMC 20 mg CDDP 100 mg Etoposide 100 mg	HIPEC vs control- 29.4 vs 15 %	HIPEC vs control- 35.2 vs 20 %	HIPEC vs control- 5.8 vs 0 %	Median survival: HIPEC vs control-11 vs 6 months 1-year survival: HIPEC vs control-44.4 vs 15.8 %, $p = 0.04$)
Glehen et al. [57]	Prospective	49	Nil	MMC 40-60 mg	10.2 %	Overall-27 %	4 %	Median overall survival -10.3 months (CCR0/1 vs CCR2- 21.3 vs 6.6 months, $p < 0.001$; Gilly Stage I/II PC vs stage III/IV PC- 19 vs 6.6 months, $p = 0.004$)) 5-year overall survival -16 % (CCR0/1–29.4 %)
Yonemura et al. [56]	Retrospective	107*	conventional surgery + HIPEC	MMC 30 mg CDDP 300 mg Etoposide 150 mg	Overall 43.9 % Study arm- 69 % Control- 28 %	Overall - 21.5 % Study arm- 43 % control- 8 %	Overall 2.8 % Study arm- 7 % Control- 0 %	5-year survival: overall-6.7 %; study arm-27 %; CCR0-13 %, CCR ≥ 1–2 % (overall) Median survival: CCR0/ CCR ≥ 1: 15.5 months/ 7.9 months (all patients); CCR0/CCR≥: 19.2 months/ 7.8 months (study arm)
Glehen et al. [57]	Retrospective	159	Nil	HIPEC: MMC 30–50 mg/m^2 ± CDDP 50–100 mg/m^2 Oxaliplatin 360–460 mg/m^2 ± irinotecan 100–200 mg/m^2 ± I.V. 5-FU EPIC: MMC 10 mg/m^2 5-FU 600 mg/m^2	56 %	27.8 %	6.5 %	5-year survival: overall-13 %; CCR0-23 % Median survival:9.2 months
Yang et al. [60]	Randomised controlled trial	68	only CRS	MMC 30 mg CDDP 120 mg	58.8 % each arm	HIPEC vs control- 14.7 vs 11.7 %	Nil	Median survival (months): HIPEC vs control- 11 vs 6.5, $p = 0.04$ (all pts) 2-year, 3-year survival (HIPEC vs control): 14.7 vs 5.9 %, 5.9 vs 0 %

MMC-mitomycin-c, CDDP- cisplatin, 5-FU- 5-fluorouracil, *study arm- peritonectomy with HIPEC

significant difference in the 5-year mortality [50]. The surgery with intraperitoneal chemotherapy arm had a significantly lower risk of peritoneal recurrence compared to the surgery only arm (OR = 0.29; 95 % CI = 0.12–0.70; $p = 0.006$).

Again, there is a lot of heterogeneity in the reported studies of therapeutic HIPEC with respect to the technique, drugs used and their dose, the duration of HIPEC and the intraperitoneal temperature achieved. Various drugs have been used for HIPEC, including MMC, cisplatin (CDDP), etoposide, doxorubicin etc. An international expert consensus favoured MMC, followed by CDDP, 5-fluorouracil and doxorubicin in that order for HIPEC in gastric cancer [63].

Nips

The bidirectional / neoadjuvant intraperitoneal and systemic chemotherapy (BIPSC/NIPS), introduced by Yonemura et al. [64] is a treatment schedule that aims at stage reduction, eradication of IFCC, and an increase in the incidence of complete cytoreduction [34]. The rationale of this method is to reduce tumour burden before surgery with NIPS, reduce macroscopic and microscopic PM with CRS & HIPEC and finally eradicate residual intraperitoneal cancer cells before the development of adhesions using EPIC. By simultaneously administering intravenous and intraperitoneal chemotherapy, the cancer cells are attacked both from the peritoneal cavity and from subperitoneal blood vessels [34, 64].

Details of this technique have been published elsewhere [65]. In short, after inserting a peritoneal port system into the abdominal cavity, oral S-1 is administered for 21 days at a dose of 60 mg/m2. An intraperitoneal infusion of docetaxel (30 mg/m2) and CDDP (30 mg/m2) is given on days 1–3 every 4 weeks followed by a 1-week rest period. Sequential therapy is repeated twice unless there is disease progression. Recently, an updated report of 194 patients treated with NIPS was published, of whom only 152 patients subsequently underwent CRS & HIPEC [66]. The morbidity and mortality were 26 % and 3.9 % respectively. Patients who responded to NIPS and underwent CRS & HIPEC had a significantly better overall survival than those for whom CRS was not performed (median survival 15.8 vs. 7.5 months and 5-years survival rates of 9.3 vs. 0 %, respectively). A complete response to NIPS was seen in 23 % patients. In 69 % patients, a positive cytology before starting NIPS was converted to a negative cytology after NIPS. However, no patient with an initial negative cytology was converted to a positive cytology after NIPS.

These results of all these studies seem to indicate that CRS & HIPEC may result in an improved survival in selected patients with gastric cancer who have established PM. This is the only treatment modality in patients with PM from gastric cancer that has resulted in a 5-year survival of 25–30 % [56–58]. However, CRS & HIPEC for PM from gastric cancer seems to be less effective when compared to other peritoneal surface malignancies, especially colorectal PM [28, 67]. Nearly 50–58 % patients still develop recurrence [34, 56, 68] and 27–79 % patients die due to peritoneal recurrence [56, 61]. Moreover, the procedure may be associated with a considerable morbidity and mortality. A systematic review reported an average morbidity of 21.5 % and mortality of 4.8 % in 10 studies [62]. Most common complications after CRS & HIPEC are digestive fistula/anastamotic leaks, ileus, intra-abdominal abscess and hematologic toxicity [58–60, 62]. Therefore, it is important to strictly select patients who will benefit from this procedure.

One of the most important factors associated with a good outcome following CRS & HIPEC for PM from gastric cancer is the completeness of cytoreduction [56–59, 66]. A complete cytoreduction followed by HIPEC is associated with a median survival of 11 to 43 months and a 5-year survival of 17–30 % when compared to an incomplete cytoreduction (median survival 3.3–8.5 months and 5-year survival of 2 %) (see Table 3). The extent of peritoneal carcinomatosis is another important prognostic factor for the success of HIPEC, especially in patients who undergo a complete cytoreduction, and the most commonly used score to assess it is the peritoneal carcinomatosis index (PCI). Yonemura et al. reported complete cytoreduction in 86 % of patients if the PCI score was ≤6 compared to 7 % if the PCI score was >13 [34]. A multicentre European study reported that in patients who had a complete cytoreduction, the PCI score was the only independent factor predicting survival, with no patient surviving beyond 6 months and 3 years if PCI was >19 and >12 respectively [59]. In patients treated by bidirectional chemotherapy followed by CRS & HIPEC, a PCI of ≤6 was found to be an independent prognostic factor for survival (HR = 2.16 95 % CI = 1.17–3.98, $p = 0.013$) [66].

The outcome of CRS & HIPEC also depends on the institutional experience [59]. In an European multicentre study, it was seen that the 5-year survival of patients in institutions with <3 years of experience was 8 % compared to 16 % in institutions with >11 years of experience. The response to neoadjuvant chemotherapy is another independent prognostic factor. After a NIPS protocol, a negative cytology has been shown to be associated with a better survival than a positive cytology (3 year survival 8.5 % vs 0 %) [65], and a major (grade 2/3) response has a better outcome than a lesser (HR = 2.6, 95 % CI = 1.17–3.98, $p = 0.002$) [66]. The other factors that have been found to predict a better survival after CRS & HIPEC include synchronous PM [57, 60], systemic chemotherapy >6 cycles and no serious adverse events [60] and absence of signet ring cell histology [69] and absence of ascites [57]. The ideal candidate for CRS & HIPEC in PM from gastric cancer, therefore, would be a young patient (<60 years) with a good performance status, PCI score < 10 with a resectable primary tumor, no ascites or para-aortic

lymphadenopathy, no liver/extraperioneal metastasis, who has a good response to neoadjuvant chemotherapy and for whom a complete cytoreduction is possible [34, 59, 63, 66].

Pre-operative evaluation plays an important role in identifying those patients with gastric cancer who are likely to have unresectable peritoneal disease or in whom a complete cytoreduction is not possible, thus avoiding an unnecessary laparotomy. Although a spiral CT scan or PET-CT scan is often used to stage the disease, their accuracy is only around 78 % and 87 % respectively [70]. The pre-operative PCI score estimated by radiological imaging is often lower than the true PCI determined intra-operatively [71]. In one study, 34 % of patients who were detected by CT to have a PCI of ≤6 had an intraoperative PCI of >6 [24]. A staging laparoscopy, however, allows direct visualisation of the peritoneal cavity and can detect small volume disease which is not identified by imaging, especially over the small bowel [72]. Staging laparoscopy has a positive and negative predictive value of 87–97 % and 97 % respectively in assessing the resectability of peritoneal deposits in patients undergoing CRS & HIPEC for a variety of peritoneal surface malignancies [73].

HIPEC for Palliation

Debilitating ascites due to PM not only indicates a poor prognosis [74] but also has a negative impact on the quality of life [75]. None of the treatment options including repeated paracentesis, diuretics and systemic chemotherapy result in a permanent resolution of the ascites. Earlier reports of complete disappearance of ascites in patients with PM from gastric cancer who underwent HIPEC suggest its efficacy in this clinical setting [53, 55]. Recently, laparoscopic HIPEC has been used to palliate patients with intractable ascites requiring repeated paracenteses [76, 77]. This approach led to a complete clinical regression of ascites in a majority of patients. In a systematic review including 76 patients (37 with gastric cancer) from 5 studies treated by laparoscopic HIPEC for ascites, ascites was controlled successfully in 95 % of cases. There were no major complications, the incidence of minor complications was 7.6 % and the mean hospital stay ranged from 2.2 to 23 days [78]. Laparoscopic HIPEC may reduce operating time and hospital stay and is an ideal technique for palliative HIPEC [78, 79]. Cytoreductive surgery and HIPEC for palliation of ascites is not a good option since complete cytoreduction is possible in a small proportion of patients, the complications rates are high and the survival is not greatly improved [80]. In patients with recurrent gastric cancer, the clinical benefits of pressurised intraperitoneal chemotherapy (cisplatin and doxorubicin) in the form of an aerosol delivered laparoscopically is being evaluated in an ongoing German study (PIPAC GA-01; clinicaltrials.gov identifier NCT01854255).

Conclusion

Evidence from randomised trials, predominantly from Asian countries, suggest that prophylactic HIPEC in patients with GC who are at a high risk for developing peritoneal recurrence can reduce peritoneal recurrence and improve survival. Laparoscopic palliative HIPEC may provide lasting symptomatic relief in patients with advanced peritoneal dissemination from gastric cancer who have intractable ascites. CRS & HIPEC, including NIPS, in patients with established PM from gastric cancer, has shown encouraging results in selected patients. However, its role is still evolving and currently it cannot be recommended outside of a clinical trial protocol. Selection of patients is critical to achieve good results in this clinical setting.

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