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TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer

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Abstract

Gastric cancer associated peritoneal carcinomatosis (GCPC) has a poor prognosis with a median survival of less than one year. Systemic chemotherapy including targeted agents has not been found to significantly increase the survival in GCPC. Since recurrent gastric cancer remains confined to the abdominal cavity in many patients, regional therapies like aggressive cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been investigated for GCPC. HIPEC has been used for three indications in GC- as an adjuvant therapy after a curative surgery, HIPEC has been shown to improve survival and reduce peritoneal recurrences in many randomised trials in Asian countries; as a definitive treatment in established PC, HIPEC along with CRS is the only therapeutic modality that has resulted in long-term survival in select groups of patients; as a palliative treatment in advanced PC with intractable ascites, HIPEC has been shown to control ascites and reduce the need for frequent paracentesis. While the results of randomised trials of adjuvant HIPEC from western centres are awaited, the role of HIPEC in the treatment of GCPC is still evolving and needs larger studies before it is accepted as a standard of care.

Key words: Gastric cancer; Peritoneal carcinomatosis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

Core tip: Peritoneal carcinomatosis (PC) associated with gastric cancer has a poor prognosis. Systemic chemotherapy is not very effective in this situation and therefore, regional therapies like cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)

have been investigated to improve the survival of these patients. HIPEC has been used as an adjuvant after curative resection, in the treatment of established PC and in palliating intractable ascites in gastric cancer. This review looks at the current status of HIPEC in peritoneal metastasis due to gastric cancer.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer in the world and the third leading cause of cancer death in both sexes worldwide, accounting for 8.8% of cancer deaths every year[1]. Peritoneal carcinomatosis (PC) occurs synchronous with the primary tumor in about 14%-43% of patients with GC and accounts for 35% of all synchronous metastasis[2,3]. It may be the sole site of synchronous metastasis in 9% of patients with GC[2].

Recurrence after curative surgery is quite common, occurring in nearly 30%-50% of patients[2,4-7]. Although locoregional recurrence is seen in only 10%-25% of patients following a D2 lymphadenectomy[4,8,9], distant metastasis still occurs in up to 25% of patients even after a D2 gastrectomy[4,5] and up to 40% in other series[7,10].

Peritoneal recurrence is seen in 10%-46% of patients after a curative surgery for GC[2,4,11-16] and it accounts for 36%-45% of all recurrences[7,11]. The peritoneum is the first/sole site of tumor recurrence after D2 gastrectomy in 12%-40% of patients[6,7,9,11,16]. While adjuvant chemotherapy[4,15], neoadjuvant chemotherapy (NAC)[10,17] and adjuvant chemoradiation[18] have all been shown to marginally improve the survival after curative surgery in GC, none of them have been shown to significantly lower the rate of distant metastases, including peritoneal recurrence[19-21] or change the patterns of recurrence[22].

The prognosis of GCPC is worse than that of other metastatic sites[23,24], with a median survival of only 3-7 mo and a 5-year survival of 0%[2,12,25,26]. In metastatic GC, although systemic chemotherapy was found to be superior to best supportive care, the median survival was improved to only 8-12 mo with conventional chemotherapy[2,27,28]. Although newer agents like S1 and docetaxel have shown some promise, the median overall survival with the current first line chemotherapy is only 8 to 14 mo[29-31], and is not greatly improved by adding targeted therapy[29,32,33].

In general, patients with GCPC have a significantly reduced probability of tumor response to chemotherapy[23,25,34] with reported rates of response being in the range of 14%-25%[35-37]. Not surprisingly, the median survival with chemotherapy in patients with only PC from GC is 9.5-12 mo[38,39]. Certain drugs like S1 and docetaxel have been reported to have a better response of 40%-56% against peritoneal disease, yet the median survival even with these drugs is only 18 mo[40,41].

The poor response of PC to systemic chemotherapy is mainly due to the presence of the "plasma-peritoneal barrier" which isolates the peritoneal cavity from the effects of intravenous chemotherapy[42]. In addition, the poor intraperitoneal blood supply and oxygenation of cancer cells, and the low apoptotic potential of such hypoxic tumor cells are also thought to be responsible for the poor response to chemotherapy[30,42]. Further, patients with PC are unlikely to tolerate the standard systemic therapy used in disseminated GC since they have a reduced metabolism and/or excretion which may increase its toxicity[38].

The ineffectiveness of systemic chemotherapy to prevent peritoneal recurrence in locally advanced GC and to provide long term survival in PC from GC has led many to explore alternate methods of prevention/treatment of PC. The belief that PC is more of a locoregional than a systemic disease[22] has led to a resurgence of interest in regional therapies like cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Currently, CRS with HIPEC is increasingly being used as a curative treatment of pseudomyxoma peritonei, peritoneal mesothelioma and selected patients with colorectal PC[43-46]. Given the natural history of GC, where nearly half of the recurrences after curative surgery is confined within the peritoneal cavity, it seems rational to apply HIPEC in the treatment strategy. HIPEC has 3 potential implications in the management of GC- one, as a prophylactic measure to prevent peritoneal recurrence after a curative gastrectomy in high risk patients; two, as a therapeutic measure in patients with established PC after CRS and; three, as a palliation in patients with intractable ascites due to extensive PC not suitable for CRS. In this review, we look at the available data on these three indications for HIPEC in GC.

PATHOPHYSIOLOGY OF PC

In order to appreciate the role of HIPEC, it is important to understand the pathogenesis of GCPC. Intra-abdominal recurrence after curative resection usually originates from intraperitoneal free cancer cells (IFCC), which in turn can occur from two potential sources: spontaneous exfoliation of cancer cells from the primary tumor, and traumatic dissemination of cancer cells as a result of the surgical trauma[22,47,48]. IFCC can be seen in up to 24% patients with stage Ⅰ and 40% patients with stage Ⅱ or Ⅲ GC[49]. The spontaneous seeding of cancer cells is more frequent in GC involving the serosal surface of the stomach since this predisposes

to exfoliation of the cancer cells. During radical surgery for GC, cancer cells are released from transected lymphatic channels, tissue at the narrow margins of resection, and tumor-contaminated blood lost in the surgical field from the cancer specimen[22,50,51]. Yu *et al*[52] observed that in a cohort of patients undergoing a D2 gastrectomy, only 24% had a positive cytology on peritoneal lavage just before the gastrectomy, whereas nearly 58% had a positive cytology in the lavage done immediately after the surgery, suggesting that surgery is responsible for dissemination of tumor cells into the peritoneal cavity. Once the cancer cells gain access to the peritoneal cavity, they spread to various areas aided by gravity, intestinal peristalsis and negative pressure due to diaphragmatic contractions.

According to the "tumor cell entrapment hypothesis" proposed by Sugarbaker *et al*[22], the IFCC which are thus spontaneously exfoliated or iatrogenically disseminated adhere to the raw area created by the surgery within minutes, and is facilitated by fibrin entrapment and assisted by cytokines released as part of the wound healing process. Cancer cells that are thus trapped in this hypoxic environment are relatively immune to the effects of systemic chemotherapy. Intraperitoneal chemotherapy (IPC) is therefore intended to clear these IFCC which persist after a curative resection.

RATIONALE FOR (HYPERTHERMIC) INTRAPERITONEAL CHEMOTHERAPY

Intraperitoneal administration of chemotherapy results in a regional dose intensification, *i.e.*, a high intraperitoneal concentration of the drug with a low plasma concentration[53]. This positive gradient of chemotherapy in the peritoneum is maintained by the plasma-peritoneal barrier. Another advantage is that the drugs administered into the peritoneal cavity are ultimately absorbed through the portal vein into the liver and may have anti-tumor effect on liver micrometastasis as well[54]. IPC is ideally given either at the time of surgery or immediately following it. The cytotoxic activity of perioperative intraperitoneal chemotherapy destroys the cancer cells within the fibrin thus produced as part of the wound healing process. However, if there is a delay in administering intraperitoneal chemotherapy, not only would the fibrin have converted to scars trapping the IFCC resulting in poor penetration of the chemotherapeutic agent into these cells, but also the adhesions that develop would result in a non-uniform distribution of chemotherapy within the peritoneal cavity[55].

Hyperthermia enhances the effects of intraperitoneal chemotherapy in two ways. The direct cytotoxic activity of hyperthermia includes impaired DNA repair, denaturation of proteins, inhibition of oxidative mechanism and increase in the lysosomal activity within the tumor cells[53,56,57]. Indirectly, it increases the cytotoxic activity of the chemotherapy by a synergistic effect. Hyperthermia increases the penetration of the drug into the tumor nodule, increases the drug uptake in the tumor cells and increases the chemosensibility of neoplastic cells[53,57,58]. Although various terminologies have been used for this method of intraoperative administration of IPC along with hyperthermia, by international consensus, the acronym HIPEC is now used as the standard nomenclature for this technique[59].

HIPEC FOR PREVENTION OF PERITONEAL RECURRENCE

The risk factors that predispose to peritoneal metastasis/recurrence in GC include advanced T stage (especially serosal involvement), advanced nodal stage, tumor size, young age, female gender, signet ring cell and diffuse-mixed histology[2,7,13]. A positive cytology in the peritoneal lavage fluid is also considered to predispose to peritoneal recurrence and a poor outcome. The 5-year survival of patients with a positive lavage cytology without macroscopic peritoneal metastasis (Cy+/P0) treated with surgery and standard systemic chemotherapy is only around 2%, similar to those with overt PC[60-62]. Nearly 81% of patients with a positive cytology (Cy+/P0) fail in the peritoneum after a curative gastrectomy compared to 45% of patients with a negative cytology (Cy-/P0)[63]. Accordingly, the 7th edition of the American Joint Committee on Cancer (AJCC) staging classifies GC patients with Cy+/P0 as M1 disease[64].

Perhaps the most appealing use of HIPEC in GC would be in a prophylactic situation, as an adjunct to a curative surgical resection in patients with a high risk of peritoneal recurrence. Not surprisingly, the majority of data related to the use of HIPEC in GC is in its role of prophylaxis against peritoneal recurrence The theoretical rationale behind this approach is that while the large volumes of diluent used in HIPEC washes out most of the intraperitoneal free cancer cells, the synergistic effect of heat and the chemotherapy destroys the remaining cancer cells.

The earliest report of the use of HIPEC as an adjuvant treatment to prevent peritoneal recurrence was by Koga *et al*[65] from Yonago, Japan in 1988. They reported two studies, the first a historical study comparing 38 GC patients with serosal invasion who underwent curative surgery followed by HIPEC using mitomycin-C (MMC) with a control group of 55 patients who underwent curative surgery without HIPEC. They found that the HIPEC group had a significantly improved 3-year survival (74% *vs* 53%, $P < 0.04$) with fewer peritoneal recurrences (36% *vs* 50%) respectively. Subsequently, they performed a randomised study in which patients were randomised to undergo curative surgery with HIPEC or only surgery. In this study also, they found that patients who received HIPEC had a trend towards a better 30

mo survival compared to the control group (83% *vs* 67%) although this was not statistically significant.

Fujimoto *et al*[66] reported a prospective study of 59 patients, 32 of whom had advanced GC without PC who underwent curative surgery. The 2-year survival of the 10 patients who received HIPEC was significantly higher than that of the 20 patients who did not (56.5% *vs* 12.9%, $P = 0.01$). While no patient in the former group developed peritoneal recurrence, 8 patients in the latter group died due to peritoneal recurrence.

In a subsequent update, the group from Yonago, Japan, reported on 82 patients who were randomised to receive HIPEC or no HIPEC after curative resection of GC[67]. IFCCs were detected in 23% and 15% of the HIPEC and control group respectively. There was a non-significant trend towards improved 5-year survival (64% *vs* 52%) and reduced death due to peritoneal recurrence (39% *vs* 59%) in the intervention group compared to the control group.

There have been various randomised controlled trials comparing HIPEC *vs* no HIPEC in patients with locally advanced GC who underwent a potentially curative resection[68-77]. A majority of them were conducted in Asian countries and have been published in Japanese and Chinese languages. A summary of the various trials published in the English literature has been provided in Table 1. Although there is some heterogeneity in these trials with respect to the drugs used, their dosage, duration of HIPEC, temperature achieved *etc*, these trials provide level 1 evidence of the ability of adjuvant HIPEC to reduce peritoneal recurrence and improve survival. The inclusion criteria in most of these trials were presence of serosal invasion and/or lymph nodal metastasis with no macroscopic peritoneal disease. Not many studies have evaluated the effects of prophylactic HIPEC in patients with Cy+/P0 GC. In a small study, Yonemura *et al*[78] reported a 5-year survival of 42% in 15 patients with Cy+/P0 disease after gastrectomy plus HIPEC.

Other variants of IPC have been used in the adjuvant treatment of GC. Normothermic intraoperative intraperitoneal chemotherapy (NIIC) was studied in a randomised trial in patients with advanced GC by Takahashi *et al*[79] who found that the 3-year survival in patients who received IP Mitomycin-C (MMC) bound to activated carbon particles after curative gastrectomy was significantly better than that of patients who underwent only surgery (66% *vs* 20%, $P < 0.01$). NIIC has also been compared to HIPEC in 2 studies[72,76], both of which showed a significant advantage of HIPEC over NIIC in terms of survival and reducing the peritoneal recurrence, especially in patients with serosal invasion and nodal metastasis.

Early post-operative intraperitoneal chemotherapy (EPIC) has also been used as an adjuvant treatment in advanced GC. Yu *et al*[80] randomised 248 patients with GC to undergo either surgery followed by intraperitoneal MMC on day 1 and 5-fluorouracil (5-FU) on days 2-5 or only surgery. The 5-year survival was significantly higher in the EPIC group compared to the surgery only group (54% *vs* 38%, $P = 0.02$). Patients with serosal invasion (5-year survival 52% *vs* 25%, $P = 0.004$) and those with nodal metastasis (5-year survival 46% *vs* 22%, $P = 0.02$) were benefited most by EPIC.

The results of these trials using prophylactic IPC have been analysed in 7 meta-analyses till date[22,81-86]. Two of these meta-analyses included only patients receiving HIPEC in the experimental arm[81,82]. Both of them did not show any significant increase in the rate of post-operative morbidity (Table 2). In a meta-analysis of 10 RCTs, Sun *et al*[81] demonstrated a significant advantage in survival with the use of HIPEC, regardless of the chemotherapy used (MMC or 5-FU) and also regardless of whether adjuvant systemic chemotherapy was used or not. In a pooled analysis of 16 RCTs, Mi *et al*[82] reported a significant improvement in the 1, 2, 3, 5 and 9-year survival and a reduction in the peritoneal recurrence rates at 2, 3 and 5 years in patients who received HIPEC compared to those who did not.

The other 5 meta-analyses included patients receiving any form of IPC including HIPEC, EPIC or NIIC. While Yan *et al*[83] and Huang *et al*[84] both reported a significant increase in the incidence of intra-abdominal abscess and neutropenia postoperatively with the use of intraperitoneal chemotherapy without any increase in the mortality, Coccolini *et al*[85] showed an increase in overall morbidity with the use of IPC. All four meta-analyses differed slightly in their findings on the survival advantage of prophylactic IPC. A survival benefit with prophylactic IPC was seen with the use of HIPEC alone or HIPEC combined with EPIC in two meta-analyses[83,84]. While NIIC was not seen to offer a significant survival advantage by Yan *et al*[83], Huang *et al*[84] showed that NIIC had a modest but significant survival advantage. The RCTs included in the subgroup analysis were slightly different in both these meta-analyses, probably explaining this difference of results. Xu *et al*[86] concluded that while any form of IPC may benefit patients after a curative resection, using hyperthermia or activated carbon particles may confer added benefits to patients. Coccolini *et al*[85] and Sugarbaker *et al*[22] did not report on the individual benefits of various forms of IP chemotherapy, but concluded that as a whole, IPC confers a survival advantage in the adjuvant setting. Peritoneal recurrence rates are reduced by nearly 50% with the use of HIPEC[81] or IPC[22,85]. The pooled rates of complications in the HIPEC arms ranged from 1.7%-3.3% (anastomotic leak), 1.4%-2.8% (bowel perforation/fistula), 2.9%-6.3% (myelosuppression), 2.6%-3.5% (adhesive ileus) and 3.1% (liver dysfunction)[81,82]. The results of these meta-analyses have been summarised in Table 2.

Huang *et al*[84] used tests of interaction to compare the different forms of IP chemotherapy and found that HIPEC did not offer a significant survival benefit over

Table 1 Published studies of prophylactic hyperthermic intraperitoneal chemotherapy in gastric cancer

Ref.	Type of study	Inclusion criteria	Treatment arms (No. of Patients)	Drugs used for IPC	Curative surgery	Complications	Post-op mortality	Survival	Peritoneal recurrence
Koga *et al*[65], 1988	RCT	Serosa+	Surgery + HIPEC (26) *vs* surgery alone (21)	MMC	100% *vs* 100%	Leak 3.1% *vs* 7.1%	NA	30 mo 83% *vs* 67%	NA
Hamazoe *et al*[67], 1994	RCT	Serosa+	Surgery + HIPEC (42) *vs* surgery alone (40)	MMC	95% *vs* 88%	Leak 4.8% *vs* 7.5%	0% *vs* 0%	5-yr 64% *vs* 52% Median survival 77 mo *vs* 66 mo	39% *vs* 59% (death due to PC)
Fujimura *et al*[72], 1994	RCT	Serosa+	Surgery + HIPEC (22) *vs* surgery + CNPP (18) *vs* surgery alone (18 controls)	MMC CDDP	NA	30% *vs* 0% (perfusion *vs* surgery 40 pts *vs* 18)	NA	3-yr 68% *vs* 51% *vs* 23% ($P < 0.01$)	9% *vs* 22% *vs* 22% (death due to PC)
Ikeguchi *et al*[73], 1995	RCT	Serosa+	Surgery + HIPEC (78) *vs* surgery alone (96)	MMC	100% *vs* 100%	1.2% *vs* 2.08%	NA	5-yr 51% *vs* 46% 5-yr 66% *vs* 44% (in 1-9 LN +)	35% *vs* 40% (death due to PC)
Fujimoto *et al*[74], 1999	RCT	Serosa+	Surgery + HIPEC (71) *vs* surgery alone (70)	MMC	94.3% *vs* 92.8%	2.8% *vs* 2.8%	0% *vs* 0%	2-yr 88% *vs* 77% 4-yr 76% *vs* 58% 8-yr 62% *vs* 49% ($P = 0.03$)	1.4% *vs* 23% ($P = 0.00008$)
Hirose *et al*[75], 1999	Prospective case control	Serosa+	Surgery + HIPEC (15) *vs* surgery alone (40)	MMC CDDP Etoposide	NA	60% *vs* 42.5%	0% *vs* 12.5%	3-yr 49% *vs* 29% 5-yr 39% *vs* 17% Median survival 33 mo *vs* 22 mo ($P = 0.01$)	26% *vs* 45%
Yonemura *et al*[76], 2001	RCT	Serosa+	Surgery + HIPEC (48) *vs* Surgery + CNPP (44) *vs* Surgery alone (47)	MMC CDDP	100% *vs* 100% *vs* 100%	19% *vs* 14% *vs* 19%	4% *vs* 0% *vs* 4%	5-yr 61% *vs* 43% *vs* 42%	13% *vs* 15% (HIPEC *vs* surgery)
Kim *et al*[77], 2001	Prospective controlled study	Serosa+	Surgery + HIPEC (52) *vs* surgery alone (51)	MMC	NA	36.5% *vs* 33.3%	NA	5-yr 33% *vs* 27% 5-yr 42% *vs* 25% (in stage ⅢB)	7.6% *vs* 25% (isolated PC)

NA: Not available, PC: Peritoneal carcinomatosis; pts: Patients; IPC: Intraperitoneal chemotherapy; MMC: Mitomycin-C; CDDP: Cisplatin.

NIIC (HR = 0.86, $P = 0.43$). However, in this meta-analysis, patients of stage Ⅰ to Ⅳ were included in the analysis, probably diluting the effect of HIPEC. Similarly, addition of EPIC to HIPEC was also not found to be beneficial (HR = 1.28, $P = 0.4$)

These results indicate that intraperitoneal chemotherapy is best delivered at the time of surgery to treat the microscopic dissemination that occurs before or during surgery[83] and that hyperthermia has a synergistic action with IPC.

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, most of these RCTs have been conducted in Asian countries and the data from the western world is scarce.

The GASTRICHIP study is a phase Ⅲ randomised European multicentre study evaluating the role of HIPEC with oxaliplatin in patients with GC who have either serosal infiltration and/or lymph nodal involvement and/or positive peritoneal cytology treated by a curative gastrectomy[87]. 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. Another trial is being conducted by the European Network of Excellence on GC. In this trial, patients with high risk GC will receive 3 cycles of neoadjuvant systemic chemotherapy followed by a D2

Table 2 Meta-analyses of trials of prophylactic hyperthermic intraperitoneal chemotherapy

Author, year, outcome measure	No. of RCTs/ No. of patients	Type of IPC	Mortality	Bone marrow suppression	Intra-abdominal abscess	Anastomotic leak	Survival	Recurrence
Xu *et al*[86], 2004, OR	11/1161	HIPEC IPC ± CH	NA	NA	NA	NA	0.51 (0.4-0.65; < 0.00001)	NA
Yan *et al*[83], 2007, HR for survival, RR for others	10/1474	HIPEC NIIC EPIC DPIC	1.03 (0.28-3.75; 0.96)	4.33 (1.49-12.61; 0.007)	2.37 (1.49-12.61; 0.004)	1.01 (0.47-2.17; 0.98)	3-yr for HIPEC 0.60 (0.43-0.83; 0.002)	Locoregional 0.84 (0.30-2.31; 0.73)
Sun *et al*[81], 2012, RR	10/1062	HIPEC	NA	1.68 (0.62-4.58; 0.3)	NA	0.52 (0.16-1.73; 0.29)	0.73 (0.64-0.83; 0.007)	Overall 0.45 (0.28-0.72; 0.001)
Huang *et al*[84], 2012, HR for survival, OR for others	10/1376	HIPEC IPC + CH EPIC NIIC	2.29 (0.66-9.63; 0.25)	6.74 (1.83-18.02; 0.003)	3.57 (1.49-8.67; 0.004)	1.04 (0.44-2.44; 0.10)	For HIPEC 0.60 (0.46-0.79; < 0.01)	Peritoneal recurrence 0.69 (0.36-1.33; 0.26)
Mi *et al*[82], 2013, RR	16/1906	HIPEC	NA	1.10 (0.53-2.29;0.8)	NA	0.86 (0.38-1.95;0.72)	5-yr 2.49 (1.97-3.14; < 0.00001)	5-yr overall 0.47 (0.39-0.56; < 0.00001)
Coccolini *et al*[85], 2014, OR	12/2145	HIPEC IPC + CH EPIC NIIC	NA	1.82 (1.29-2.57; 0.0006) Overall morbidity			3-yr 0.31 (0.20-0.47; < 0.0001) 5-yr 0.89 (0.49-1.63; 0.71)	Peritoneal recurrence 0.50 (0.37-0.68; < 0.0001)

OR: Odds ratio; HR: Hazard ratio; RR: Relative risk; HIPEC: Hyperthermic intraperitoneal chemotherapy; IPC: Intraperitoneal chemotherapy; CH: Activated carbon particles; EPIC: Early postoperative intraperitoneal chemotherapy; NIIC: Normothermic intraoperative intraperitoneal chemotherapy; DPIC: Delayed postoperative intraperitoneal chemotherapy.

gastrectomy and then randomised to receive HIPEC or no HIPEC[88].

There are still some unresolved issues in the use of HIPEC as an adjuvant treatment in GC- choice of drug, dosage, duration of treatment, addition of EPIC etc. for which there is no consensus. Widespread acceptance and adoption of prophylactic HIPEC in advanced GC requires a satisfactory answer to these issues.

HIPEC FOR TREATMENT OF PC

The earliest use of CRS and HIPEC in patients with GC who have established PC (GCPC) was reported by Fujimoto *et al*[89] in 1988. They performed extensive resection of the abdominal tumor in 15 patients with advanced GC, 9 of who had synchronous PC and/or ascites. This was followed by HIPEC using MMC at a dose of 10 μg/mL for 2 h. They also used misonidazole, a hypoxic cell sensitizer, given orally prior to the surgery. In all the 9 patients, the ascites resolved and subsequent peritoneal lavage cytology became negative. The median survival at the time of the report was 7.2 ± 4.6 mo. They concluded that extensive surgery with IPHP was a safe and well tolerated treatment for GCPC.

In 1990, Fujimoto *et al*[66] again updated their data and reported on 59 patients with advanced GC. Twenty seven patients had PC with ascites. Twenty patients underwent extensive surgery followed by IPHP whereas 7 did not undergo IPHP after surgery. The 6-mo, 1 and 2-year survival of the former cohort was 94%, 78.7% and 45% respectively whereas none of the latter cohort survived beyond 9 mo.

Fujimura *et al*[90] performed a second look operation (SLO) 2-11 mo after the first laparotomy in 12 of 31 patients with GC showing moderate to severe peritoneal dissemination who had received HIPEC with MMC and CDDP at the time of initial surgery. Four patients had complete response of the peritoneal metastasis, 1 had partial response, 3 had stable disease and 4 had progressive disease. They found that the 2-year survival of the responding patients was 50% compared to 0% survival in the non-responding patients ($P < 0.05$). The same group later updated their experience of SLO in 16 out of 41 GC patients who received HIPEC for peritoneal dissemination[91]. They found that at the SLO, 50% patients had an excellent response of the peritoneal disease and in 78% patients, the ascites had disappeared. The median overall survival was 14.6 mo and the 3 year survival was 9.8%.

In 1996, Yonemura *et al*[26], for the first time, reported a 5 year survival of 11% in a cohort of 83 patients who underwent cytoreductive surgery with HIPEC, unheard of previously in patients with peritoneal dissemination from GC.

Fujimoto *et al*[92] later reported results of aggressive surgery with HIPEC in 48 patients of GC with PC and compared it to 18 control patients who did not undergo HIPEC. The extent of peritoneal disease was classified according to the Japanese Research Society for Gastric Cancer classification (JRSGC) and accordingly, 21, 8

and 19 patients had P1, P2 and P3 disease respectively in the experimental group. The 5-year survival in the IHCP group was significantly higher than the control group (P = 0.001). HIPEC showed a survival benefit only in patients with P1 or P2 disease.

The first report from the western world on role of extensive surgery and HIPEC came from Sayag-Beaujard *et al*[93] reported a phase Ⅱ study of 42 patients with GC with peritoneal disease who underwent IPCH with MMC. The overall median survival was 10.3 mo and the 5-year survival was 8%. Subsequently, Glehen *et al*[94] reported a prospective study of 49 patients of GC with PC from the same institution. In 51% of the patients, the cytoreduction was either complete or the size of the residual nodules were < 5 mm. The overall median survival was 10.3 mo and the 5-year survival rates was 16%. A complete cytoreduction (CCR0) and a smaller volume of tumor were associated with a better survival. In patients who underwent a CCR 0/1 resection, the 5-year survival was 29.4% and the median survival was 21.3 mo.

In a large series of 107 patients reported in 2005, Yonemura *et al*[95] compared 65 patients who underwent conventional surgery followed by HIPEC for GCPC with 42 patients who had a peritonectomy as described by Sugarbaker *et al*[22] followed by HIPEC. The median survival for all 107 patients was 11.5 mo and the 5-year survival was 6.7%, but the 5 year survival for the patients who underwent peritonectomy and HIPEC was 27%. Performing a peritonectomy enabled a higher rate of complete cytoreduction and subsequently, a better survival.

The largest series of therapeutic CRS and perioperative intraperitoneal chemotherapy in GCPC was from a multi-institutional study from 15 French speaking centres in France and Belgium[96]. CRS with HIPEC (n = 150) and/or EPIC (n = 12) was performed in 159 patients with a mean PCI of 9.4. There were variations in the technique of HIPEC, drugs used and their dose, the duration of HIPEC and the intraperitoneal temperature achieved in the different institutions. The 5 year survival was 13% and median survival was 9.2 mo.

Most of the evidence for therapeutic HIPEC comes from prospective or retrospective studies. The first randomised phase 3 study of CRS and HIPEC in patients with GCPC was reported by Yang *et al*[97] from China. Sixty eight patients were randomised to receive CRS with HIPEC or CRS alone. The median PCI in both groups was 15. After a median follow-up of 32 mo, 85.3% and 97% patients had died in the experimental and control arms respectively. The 3-year survival in the CRS with HIPEC arm was 5.9% compared to 0% in the CRS alone arm. CRS with HIPEC was associated with a significantly higher median survival compared to CRS alone (11 mo *vs* 6.5 mo, P = 0.04). The authors concluded that compared to CRS alone, CRS with HIPEC is likely to increase survival by 2.6 times. The magnitude of improvement in the median survival (70%) was similar to that reported (76%) in the randomised trial of CRS and HIPEC in colorectal cancer by Verwaal *et al*[98].

The results of these and other studies[99-102] are summarised in Table 3. Various drugs have been used for HIPEC, including MMC, cisplatin, etoposide, doxorubicin *etc*. An international expert consensus favoured MMC, followed by CDDP, 5-FU and doxorubicin in that order for HIPEC in GC[103]. While intravenous docetaxel has been shown to have a good response in metastatic GC[41], there is a paucity of data regarding its use in HIPEC. A pharmacokinetic study of HIPEC using 40 mg docetaxel identified the area under curve ration (AUC) of docetaxel to be 95.12 ± 87.3 with an apparent permeability of 1.47 mm[104].

In a meta-analysis of trials examining the effectiveness of IPC in advanced GC, Cocolini *et al*[85] reported that the 1, 2 and 3-year mortality in the subset of patients with established PC significantly favoured the surgery + IPC arm when compared to the standard arm (OR = 0.25, 0.29 and 0.25, respectively) whereas there was no statistically significant difference in the 5-year mortality. The peritoneal recurrence was significantly lower in the surgery + IPC arm compared to the surgery only arm (OR = 0.29, 95%CI: 0.12-0.70, P = 0.006).

In a systematic review of 10 published studies (1 non randomised prospective controlled trial, 6 prospective and 3 retrospective series) including 441 patients who underwent CRS and HIPEC in GCPC, Gill *et al*[105] noted a median overall survival of 7.9 mo (range 6.1-9.2 mo) after HIPEC. After a complete cytoreduction, this increased to 15 mo (range 9.5-43.4 mo). The 5-year survival of all patients was 13%.

NAC

A recent advancement in the treatment of GCPC is the bidirectional/neoadjuvant intraperitoneal and systemic chemotherapy (BIPSC/NIPS), introduced by Yonemura *et al*[106]. The aims of NIPS are stage reduction, the eradication of IFCC, and an increased incidence of complete cytoreduction[63]. The procedure involves neoadjuvant intraperitoneal and systemic chemotherapy followed by CRS with HIPEC and EPIC. The rationale of this method is to reduce tumour burden before surgery with NIPS, reduce macroscopic and microscopic PC with CRS and 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[63,106].

After inserting a peritoneal port system into the abdominal cavity, the peritoneal wash cytological examination through a port was done before and after NIPS. Oral S-1 was administered for 21 d at a dose of 60 mg/m^2. Docetaxel (30 mg/m^2) and cisplatin (CDDP) (30 mg/m^2) were then administered by intraperitoneal

Table 3 Hyperthermic intraperitoneal chemotherapy in the treatment of established peritoneal carcinomatosis from gastric cancer

Ref.	Country	Type of study	No. of patients study arm	control	Drug used for HIPEC, dose	Duration (min)	Complete cytoreduction	Morbidity	Mortality	Outcome
Fujimoto *et al*[66], 1990	Japan	Prospective	20 (surgery + HIPEC)	7 (only surgery)	MMC 10 μg/mL	120	NA	NA	NA	6 mo survival: 94% *vs* 57%, $P = 0.001$ 2-yr: 45%
Yonemura *et al*[91], 1991	Japan	Prospective	41	Nil	MMC 5 μg/mL CDDP 30 μg/mL	40-60		12%	0%	Death due to Peritoneal recurrence: 10% *vs* 100% Median survival: 14.5 mo 3-yr: 28.5%
Yonemura *et al*[26], 1996	Japan	Prospective	83 (surgery + HIPEC)	Nil	MMC 30 mg CDDP 300 mg Etoposide 150 mg	60	33.7%			5-yr survival (overall: 11%, CCR0/1: 17%, CCR2: 2%) Median survival CCR0: 13.9, CCR ⩾ 1: 6.8 mo
Fujimoto *et al*[92], 1997	Japan	Prospective case-control	48 (surgery + HIPEC)	18 (only surgery)	MMC 10 μg/mL	120				1,3,5,8-yr survival (HIPEC *vs* control: 54% *vs* 11%, 42% *vs* 0%, 31% *vs* 0%, 25% *vs* 0%; $P = 0.001$) 2, 4, 8-yr survival - P1, P2, P3 - 73%, 62%, 0%; 56%, 62%, 0%; 56%, 21%, 0% (P1 *vs* P3: $P = 0.000524$; P2 *vs* P3: $P = 0.00329$). Death due to peritoneal recurrence-HIPEC *vs* control 27% *vs* 94% ($P = 7.077 \times 100^{-7}$).
Glehen *et al*[94], 2004	France	Prospective	49 (CRS + HIPEC)	Nil	MMC 40-60 mg	90	10.2%	Overall - 27% Extensive CRS - 47%	4%	Median survival (overall: 10.3 mo; CCR0/1 *vs* CCR2: 21.3 mo *vs* 6.6 mo, $P < 0.001$; Gilly Stage I/ Ⅱ PC *vs* stage Ⅲ/Ⅳ PC: 19 mo *vs* 6.6 mo, $P = 0.004$) 5-yr survival (overall: 16%, CCR0/1: 29.4%, Gilly Stage I/ Ⅱ PC: 30%)
Hirose *et al*[75], 1999	Japan	Prospective case- control	17 (CRS +HIPEC)	20 (CRS alone)	MMC 20 mg CDDP 100 mg Etoposide 100 mg	50	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 mo *vs* 6 mo 1-yr survival: HIPEC *vs* control: 44.4% *vs* 15.8%, $P = 0.04$
Hall *et al*[99], 2004	United States	Prospective case-control	34 (CRS +HIPEC)	40- no PC (only surgery)	MMC 40 mg	120	R0-21% R1-14%	35%	0%	Median survival (CRS + HIPEC): Overall: 8 mo; R0/1 *vs*, R2: 11.2 mo *vs* 3.3 mo, $P = 0.01$ 2-yr survival - R0/1 *vs*, R2-45 *vs* 8%
Yonemura *et al*[95], 2005	Japan	Retrospective	42 (peritonectomy [P] + HIPEC)	65 (conventional surgery [C] + HIPEC)	MMC 30 mg CDDP 300 mg Etoposide 150 mg	60	Overall 43.9% P + HIPEC 69% C + HIPEC 28%	Overall - 21.5% P + HIPEC- 43% C + HIPEC - 8%	Overall 2.8% P + HIPEC- 7% C + HIPEC- 0%	Median survival: Overall: 11 mo; CCR0: 15.5 mo; CCR ⩾ 1: 7.9 mo (all patients); CCR0: 19.2 mo; CCR ⩾ 1: 7.8 mo (P + HIPEC patients) 5-yr survival: overall-6.7%; P + HIPEC-27%; CCR0: 13%, CCR ⩾ 1%-2%
Scaringi *et al*[100], 2008	France	Retrospective	37 (26 with PC)	Nil	MMC 120 mg CDDP 200 mg/m^2	60-90	30.7%	27% (all patients)	3.8%	Median survival: CCR0 *vs* CCR2- 15 mo *vs* 3.9 mo, $P = 0.007$ Gilly stage 1 and 2 *vs* 3 and 4: 15 mo *vs* 4 mo, $P = 0.01$

Glehen *et al*[96], 2010	France	Retrospective	159 (CRS + HIPEC and/or EPIC)	Nil	HIPEC: MMC 30-50 mg/m^2 ± Cisplatin 50-100 mg/m^2 Oxaliplatin 360-460 mg/m^2 ± irinotecan 100-200 mg/m^2 ± iv 5-FU and leucovorin EPIC: MMC 10 mg/m^2 5-FU 600 mg/m^2	60-120 30 Day 1 Days 2-5	56.0%	27.8%	6.5%	Median survival: overall: 9.2 mo, CCR0: 15 mo 5-yr survival: overall: 13%; CCR0: 23%
Yang *et al*[101], 2010	China	Prospective	28 (CRS + HIPEC)	Nil	MMC 30 mg CDDP 120 mg	90-120	CCR0-39.2% CCR1-21.4%	14.3%	0%	2-yr survival - 43% Median survival (mo): PCI ⩽ 20 *vs* PCI > 20-27.7 *vs* 6.4, *P* = 0.0001 CCR0 *vs* CCR1 *vs* CCR2 and 3- 43 *vs* 9.5 *vs* 7.5, *P* = 0.001
Yang *et al*[97], 2011	China	Randomised controlled trial	34 (CRS + HIPEC)	34 (only CRS)	MMC 30 mg CDDP 120 mg	60-90	58.8% each arm	HIPEC *vs* control - 14.7% *vs* 11.7%	Nil	Median survival (mo): HIPEC *vs* control- 11 *vs* 6.5, *P* = 0.04 (all pts) HIPEC *vs* control: 12 *vs* 6.5, *P* = 0.02 (synchronous PC) 1,2 3-yr survival (HIPEC *vs* control): 41.2 *vs* 29.4%, 14.7 *vs* 5.9%, 5.9% *vs* 0%
Magge *et al*[102], 2014	United States	Prospective	23 (CRS + HIPEC)	Nil	MMC 40 mg	100	95.6%	52%	4.3%	Median survival: 9.5 mo 3-yr survival: 18%

MMC: Mitomycin C; CDDP: Cisplatin; CCR: Cytoreductive score; 5-FU: 5-fluorouracil; HIPEC: Hyperthermic intraperitoneal chemotherapy; CRS: Cytoreductive surgery; MMC: Mitomycin-C.

infusion on days 1-3 every 4 wk followed by a 1-wk rest period. Sequential therapy was repeated twice unless disease progression was observed. In an initial report of 79 patients, an initial positive cytology became negative in 63% of patients after NIPS, nearly half of whom eventually had a complete complete cytoreduction[107].

Recently, an updated report of 194 patients treated with this strategy of NIPS/BIPSC was published by the same group[108]. Only 152 patients out of 194 who received neoadjuvant therapy subsequently underwent CRS and HIPEC. Treatment related mortality occurred in 3.9% patients and major complications in 26%. Patients who responded to NIPS and underwent CRS and HIPEC had significantly better overall survival than those with positive cytology or peritoneal deposits for whom CRS was not performed (median survival 15.8 *vs* 7.5 mo 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. In contrast, in a prospective study of neoadjuvant systemic chemotherapy alone in resectable GC, it was reported that a positive IFCC status on lavage cytology was converted to a negative one in 37% patients after NAC while in 24% patients, an initial negative IFCC status progressed to become positive after NAC[109]. This demonstrates the effectiveness of NIPS to eradicate IFCC more effectively when compared to only systemic chemotherapy.

Hultman *et al*[110] reported a phase Ⅱ study of NAC followed by CRS with HIPEC and EPIC in patients with GCPC. Of the 18 patients recruited, 8 did not undergo surgery either due to disease progression during NAC or death due to complications of chemotherapy. Of the remaining 10 who underwent surgery, 2 had extensive small bowel involvement and did not proceed to CRS. Eight patients underwent CRS and HIPEC with a median overall survival of 14.3 mo. CCR0 was achieved in 75% (median PCI of 12) and in these patients, median OS was 19.1 mo. The postoperative mortality was 12.5% and morbidity 62.5% in the patients undergoing CRS + HIPEC + EPIC.

These results of all these studies seem to indicate that CRS with HIPEC may result in an improved survival in selected patients with GC who have established PC.

This is the only treatment modality that has resulted in 5-year survival of 25%-30%[92,94,95]. However, other important aspects of this procedure need to be kept in mind before offering this treatment to a patient. First, the results of CRS and HIPEC in GCPC are not as good as that in other peritoneal surface malignancies, especially colorectal PC[43,111]. Following CRS and HIPEC for GCPC, 50%-58% patients still develop recurrence[63,92,100] and 10%-79% patients die due to peritoneal recurrence[90,92,97]. This may be due to a more aggressive biology of GCPC, poor response to chemotherapy and retroperitoneal spread[96,112] or poor patient selection.

Second, the procedure may be associated with a considerable morbidity and mortality. Morbidity following CRS and HIPEC for GCPC can range from 3.6% to 52%[101,102] and mortality from 0%-7% (Table 3). Gill *et al*[105] in a systematic review reported an average morbidity of 21.5% and mortality of 4.8% in 10 studies. Most common complications after CRS and HIPEC are digestive fistula/anastomotic leaks, ileus, intra-abdominal abscess and hematologic toxicity[95-97,105]. Although there have been concerns that a gastrectomy performed along with HIPEC may increase the incidence of anastomotic leaks, Piso *et al*[113] did not report any anastomotic leak related to gastric resections in their series of 37 patients, 30 of whom had major gastric resections.

Therefore, it is important to strictly select patients who will benefit from this procedure. Various factors have been reported to be associated with a good outcome following CRS and HIPEC for GCPC. The most important of these would be the completeness of cytoreduction[92,94-96,108]. Since IPC cannot penetrate more than 3-4 mm, HIPEC will be ineffective against a larger residue. When complete cytoreduction is not possible, the median survival ranges from 3.3 to 8.5 mo with 5-year survival of 2% compared to median survival of 11.2 to 43.4 mo and 5-year survival of 17%-30% if complete cytoreduction is achieved (Table 3). Completeness of cytoreduction was an important prognostic factor in one of the largest series on CRS and HIPEC in GCPC, with a relative risk of 2.04[96]. Yonemura *et al*[95] reported a 2.8 fold increase in the risk of dying from the disease if an incomplete cytoreduction was done.

The extent of peritoneal carcinomatosis is another important prognostic factor for the success of HIPEC, especially in patients who undergo a complete cytoreduction. Various scoring systems to assess the extent of PC have been used in different studies. The peritoneal carcinomatosis index (PCI), developed by Sugarbaker is the most popular among them[114], the others being the Gilly score[115] and the Japanese Research Society on Gastric cancer score (JRSGC)[116]. The PCI score indirectly predicts the ability for complete cytoreduction. Yonemura *et al*[63] reported complete cytoreduction in 86%, 39% and 7% of patients with GCPC if the PCI score was $\leqslant$ 6, > 7 and > 13 respectively. 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 mo and 3 years if PCI was > 19 and > 12 respectively[96]. Yang *et al*[101] reported a significant difference in the median survival if the PCI score was $\leqslant$ 20 or > 20 (27.7 mo *vs* 6.4 mo, P = 0.0001). Canbay *et al*[108] identified a PCI of $\leqslant$ 6 to be an independent prognostic factor for survival in patients treated by bidirectional chemotherapy followed by CRS and HIPEC (HR = 2.16, 95%CI: 1.17-3.98, P = 0.013). A similar correlation between survival and extent of PC has been shown in studies using the Gilly and JSRGC scores[92,94].

The presence of preoperative ascites seems to be a poor prognostic factor, with a median survival of only 5 mo in presence of ascites compared to 15.6 mo in its absence[94]. Using a scoring system for ascites, Randle *et al*[117] found that each point increase in ascites score conferred 33% greater odds of incomplete macroscopic resection (OR = 1.33, 95 %CI: 1.14-1.55, P < 0.001).

It has been reported that the institution where the procedure is done independently predicts the survival and post-operative complications after CRS and HIPEC for GCPC[96]. 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 importance of the learning curve in reducing mortality and improving rates of complete cytoreduction has been reported by various studies. It is estimated that a learning curve of between 70 to 180 cases is needed to achieve operative proficiency, reduce complications and achieve good oncological outcomes[118-121].

The response to neoadjuvant chemotherapy is also an independent prognostic factor. While Yonemura *et al*[107] reported that a negative cytology after bidirectional chemotherapy (neoadjuvant intra-peritoneal-systemic chemotherapy protocol (NIPS) is associated with a better survival than a positive cytology (3 year survival 8.5% *vs* 0%), Canbay *et al*[108] reported that a major (grade 2/3) response to NIPS was an independent prognostic factor for survival (HR = 2.6, 95%CI: 1.17-3.98, P = 0.002). Other factors that have been found to be independent predictors for better survival after CRS and HIPEC include synchronous PC[94,97], systemic chemotherapy > 6 cycles and no serious adverse events[97] and absence of signet ring cell histology[122].

The ideal candidate for CRS and HIPEC in GCPC, therefore, would be a young patient (< 60 years) with a good performance status, PCI score < 10 with small tumor nodules, resectable primary tumor, no ascites or para-aortic lymphadenopathy, no liver/extraperioneal metastasis who has responded well to neoadjuvant chemotherapy and for whom a complete cytoreduction is possible[63,94,96,103,108].

Pre-operative staging is therefore very important to

choose patients suffering from GCPC for CRS and HIPEC by estimating the extent of PC and also identifying those patients who are likely to have unresectable disease or in whom a complete cytoreduction is not possible. This will help avoid an unnecessary laparotomy. Pre-operative imaging including a spiral CT scan or PET-CT scan is often used to stage the disease. However, the sensitivity of CT scan is low for identifying PC < 0.5 cm (11%) and detecting small bowel involvement (8%-17%)[123]. The accuracy, specificity and sensitivity of spiral CT and PET-CT in detecting PC from gastric cancer is around 78%, 94%, 39% and 87%, 94% and 73% respectively[124]. It must be kept in mind while assessing the extent of PC by radiological tests that the pre-operative PCI score estimated by radiological imaging is always lesser then the true PCI determined intra-operatively[123]. Yonemura *et al*[34] reported that only 66% of patients who were detected by CT to have a PCI of ⩽ 6 had an intraoperative PCI of ⩽ 6, whereas 41% of patients who were staged as a PCI of > 7 by CT scan had an intraoperative PCI of ⩽ 6. Thus it is difficult to identify patients with GCPC who have a favourable prognosis after CRS and HIPEC (PCI of ⩽ 6) by a pre-operative CT scan.

It is here that staging laparoscopy scores over radiology. Laparoscopy allows direct visualisation of the peritoneal cavity and can detect small volume disease which is not identified by imaging, especially over the small bowel. In addition, it allows for peritoneal lavage cytology and is associated with low morbidity. Valle *et al*[125] reported a good correlation between the laparoscopically determined PCI and the final PCI determined at laparotomy. The positive predictive value of laparoscopy for resectability of peritoneal deposits in patients undergoing CRS and HIPEC for a variety of peritoneal surface malignancies is reported to be 87%-97% and the negative predictive value 97%[126].

PALLIATIVE HIPEC

Peritoneal carcinomatosis is often complicated by debilitating malignant ascites which portends a poor prognosis, with a life expectancy of a few weeks to months[127] and also severely impairs the quality of life[128]. The treatment options include repeated paracentesis, diuretics and systemic chemotherapy which may increase the survival to 4-5 mo[129,130]. However, none of them result in a permanent resolution of the ascites. In symptomatic patients, a decrease in the intra-abdominal fluid will lead to an improved quality of life[131]. More recently, intraperitoneal administration of Catumaxomab, a rat/murine hybrid, trifunctional, bispecific (anti-epithelial cell adhesion molecule-EpCAM and anti-CD3) mAb[132], after paracentesis has been shown to significantly prolong the puncture free survival in patients with malignant ascites secondary to epithelial cell adhesion molecule (EpCAM) positive carcinomas including GC when compared to paracentesis alone[133].

HIPEC has been used to palliate GCPC associated ascites. Fujimoto *et al*[89] and Yonemura *et al*[91] had previously reported complete disappearance of ascites in patients who underwent HIPEC. More recently, few small series of laparoscopic HIPEC have been reported for palliating patients with intractable debilitating ascites from GCPC requiring repeated paracentesis[134,135]. Complete clinical regression of ascites and its related symptoms was achieved in a majority of patients without any major complications or mortality. A systematic review identified 5 studies comprising 76 patients (37 with gastric cancer) treated by laparoscopic HIPEC for ascites. The authors reported that the procedure was successful in controlling ascites 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 d[136].

Laparoscopic HIPEC may reduce operating time and hospital stay and is an ideal technique for palliative HIPEC since it does not involve major resections, anastomosis or long operating time, all of which are associated with major complications[136,137]. Recently B-ultrasound guided palliative HIPEC was shown to not only provide comparable rates of ascites remission compared to laparoscopy (93.7% *vs* 93.3% respectively)[138], but further shorten operation time and reduce hospitalisation costs.

Another approach to malignant ascites is CRS and HIPEC. From a database of 1000 CRS and HIPEC procedures, Randle *et al*[117] retrospectively analysed 299 patients with malignant ascites due to various primary intra-abdominal tumors including 20 gastric cancers. CRS with HIPEC was used to treat the ascites in these patients. However, a complete CRS was possible in only 15% patients with ascites compared to 59% in those without. Major morbidity was 25% and 30-d mortality was 5.8%. Ascites was controlled in 93% cases within 3 mo, even when a complete cytoreduction was not possible. However, survival of patients with malignant ascites improved only when the CRS was complete (median survival complete *vs* incomplete CRS 37 mo *vs* 5.6 mo, $P < 0.001$). The authors concluded that given the high rates of incomplete CRS, poor survival and not insignificant complications, for symptomatic patients with malignant ascites (other than low grade appendiceal neoplasms) in which complete cytoreduction is deemed impossible preoperatively, palliative laparoscopic HIPEC without CRS seems to be the better option.

An ongoing German study (PIPAC GA-01; clinicaltrials.gov identifier NCT01854255) is studying the clinical benefits of pressurised intraperitoneal chemotherapy (cisplatin and doxorubicin) in the form of an aerosol delivered by laparoscopy in patients with

recurrent gastric cancer.

CONCLUSION

The past two decades have seen an explosion of interest in CRS and HIPEC in gastric cancers. While there is strong evidence from Asian countries regarding the survival benefit of prophylactic HIPEC in patients with GC who are at a high risk for developing peritoneal recurrence, the role of CRS with HIPEC in GC with macroscopic PC is still evolving and needs to be addressed in large multi-institutional randomised trials. The use of bidirectional neoadjuvant chemotherapy seems to be hold promise. Palliative HIPEC may provide lasting symptomatic relief in GC patients with intractable ascites due to PC. The global impact of successful treatment or prevention of peritoneal carcinomatosis from GC could be huge, given the increasing incidence of GC worldwide and the peritoneal carcinomatosis frequently associated with it.

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