**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 18855**

**Manuscript Type: TOPIC HIGHLIGHT**

2015 Advances in Gastric Cancer

**Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer**

Seshadri RA *et al.* CRS and HIPEC in gastric cancer

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**Author contribution**: Seshadri RA and Glehen O contributed equally to this paper; both authors were involved in designing the study, performing the literature research, writing and approving the final manuscript.

**Conflict-of-interest statement**: The authors have no conflict of interest to report.

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**Received:** April 28, 2015

**Peer-review started:** May 5, 2015

**First decision:** August 26, 2015

**Revised:** September 22, 2015

**Accepted:**November 30, 2015

**Article in press:**

**Published online:**

**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

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**Core tip:** Peritoneal carcinomatosis 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 peritoneal carcinomatosis and in palliating intractable ascites in gastric cancer. This review looks at the current status of HIPEC in peritoneal metastasis due to gastric cancer.

Seshadri RA, Glehen O. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer. *World J Gastroenterol* 2015; In press

**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-peritonal 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 gastric cancer 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 gastric cancer 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 gastric cancer, 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 gastric cancer- 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 gastric cancer.

**PATHOPHYSIOLOGY OF PERITONEAL CARCINOMATOSIS**

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 gastric cancer, 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 synergstic 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 gastric cancer 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 gastric cancer patients with Cy+/P0 as M1 disease[64].

Perhaps the most appealing use of HIPEC in gastric cancer 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 gastric cancer 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 synergestic 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 gastric cancer 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 gastric cancer 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 gastric cancer[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 versus 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 gastric cancer. 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 gastric cancer. Norm thermic intraoperative intraperitoneal chemotherapy (NIIC) was studied in a randomised trial in patients with advanced gastric cancer 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 gastric cancer. 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% (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)[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 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 synergestic 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 gastric cancer 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 (EUNE) on gastric cancer. In this trial, patients with high risk GC will receive 3 cycles of neoadjuvant systemic chemotherapy followed by a D2 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 gastric cancer requires a satisfactory answer to these issues.

**HIPEC FOR TREATMENT OF PERITONEAL CARCINOMATOSIS**

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 gastric cancer 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 gastric cancer 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 gastric cancer 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 Lyon. Beaujard *et al*[93] reported a phase II study of 42 patients with gastric cancer 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 gastric cancer 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 gastric cancer[103]. While intravenous docetaxel has been shown to have a good response in metastatic gastric cancer[41], there is a paucity of data regarding its use in HIPEC. A pharmacokinetic study of HIPEC using 40mg 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%.

***Neoadjuvant chemotherapy***

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/m2. Docetaxel (30 mg/m2) and cisplatin (CDDP) (30 mg/m2) were then administered by intraperitoneal 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 gastric cancer, 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 gastric cancer 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/anastamotic 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 anastamotic leaks, Piso *et al*[113] did not report any anastamotic 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 ≤ 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 ≤ 20 or > 20 (27.7 mo *vs* 6.4 mo, *P =* 0.0001). Canbay *et al*[108] identified a PCI of ≤ 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 intraperitoneal-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*[127] 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[179] 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 paracenteses[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.

**REFERENCES**

1 Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013. Available from: URL: http: //globocan.iarc.fr (accessed on Mar 1, 2015)

2 **Thomassen I**, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, Lemmens VE, de Hingh IH. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J Cancer* 2014; **134**: 622-628 [PMID: 23832847 DOI: 10.1002/ijc.28373]

3 **Abbasi SY**, Taani HE, Saad A, Badheeb A, Addasi A. Advanced gastric cancer in jordan from 2004 to 2008: a study of epidemiology and outcomes. *Gastrointest Cancer Res* 2011; **4**: 122-127 [PMID: 22368735]

4 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]

5 **Lee J**, Lim do H, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, Bae JM, Ahn YC, Sohn I, Jung SH, Park CK, Kim KM, Kang WK. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012; **30**: 268-273 [PMID: 22184384 DOI: 10.1200/JCO.2011.39.1953]

6 **Spolverato G**, Ejaz A, Kim Y, Squires MH, Poultsides GA, Fields RC, Schmidt C, Weber SM, Votanopoulos K, Maithel SK, Pawlik TM. Rates and patterns of recurrence after curative intent resection for gastric cancer: a United States multi-institutional analysis. *J Am Coll Surg* 2014; **219**: 664-675 [PMID: 25154671 DOI: 10.1016/j.jamcollsurg.2014.03.062]

7 **Roviello F**, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, De Stefano A. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg* 2003; **90**: 1113-1119 [PMID: 12945079 DOI: 10.1002/bjs.4164]

8 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]

9 **Sasako M**, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, Hiratsuka M, Tsujinaka T, Kinoshita T, Arai K, Yamamura Y, Okajima K. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; **359**: 453-462 [PMID: 18669424 DOI: 10.1056/NEJMoa0707035]

10 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

11 **Wu CW**, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, Lin HJ, Li AF, Lui WY. Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. *World J Surg* 2003; **27**: 153-158 [PMID: 12616428]

12 **Yoo CH**, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma. *Br J Surg* 2000; **87**: 236-242 [PMID: 10671934]

13 **Aoyama T**, Yoshikawa T, Hayashi T, Kuwabara H, Mikayama Y, Ogata T, Cho H, Tsuburaya A. Risk factors for peritoneal recurrence in stage II/III gastric cancer patients who received S-1 adjuvant chemotherapy after D2 gastrectomy. *Ann Surg Oncol* 2012; **19**: 1568-1574 [PMID: 22143578 DOI: 10.1245/s10434-011-2158-5]

14 **Maehara Y**, Hasuda S, Koga T, Tokunaga E, Kakeji Y, Sugimachi K. Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer. *Br J Surg* 2000; **87**: 353-357 [PMID: 10718807 DOI: 10.1046/j.1365-2168.2000.01358.x]

15 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/S0140-6736(11)61873-4]

16 **D'Angelica M**, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg* 2004; **240**: 808-816 [PMID: 15492562 DOI: 10.1097/01.sla.0000143245.28656.15]

17 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.059]

18 **Smalley SR**, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012; **30**: 2327-2333 [PMID: 22585691 DOI: 10.1200/JCO.2011.36.7136]

19 **Xiong B**, Ma L, Cheng Y, Zhang C. Clinical effectiveness of neoadjuvant chemotherapy in advanced gastric cancer: an updated meta-analysis of randomized controlled trials. *Eur J Surg Oncol* 2014; **40**: 1321-1330 [PMID: 25239442 DOI: 10.1016/j.ejso.2014.01.006]

20 **Cao J**, Qi F, Liu T. Adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis. *Scand J Gastroenterol* 2014; **49**: 690-704 [PMID: 24731211 DOI: 10.3109/00365521.2014.907337]

21 **Liang JW**, Zheng ZC, Yu T, Wang X, Zhang JJ. Is postoperative adjuvant chemoradiotherapy efficacious and safe for gastric cancer patients with D2 lymphadenectomy? A meta-analysis of the literature. *Eur J Surg Oncol* 2014; **40**: 1614-1621 [PMID: 24813809 DOI: 10.1016/j.ejso.2014.04.009]

22 **Sugarbaker PH**, Yu W, Yonemura Y. Gastrectomy, peritonectomy, and perioperative intraperitoneal chemotherapy: the evolution of treatment strategies for advanced gastric cancer. *Semin Surg Oncol* 2003; **21**: 233-248 [PMID: 14648781]

23 **Chau I**, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004; **22**: 2395-2403 [PMID: 15197201]

24 **Kim JG**, Ryoo BY, Park YH, Kim BS, Kim TY, Im YH, Kang YK. Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. *Cancer Chemother Pharmacol* 2008; **61**: 301-307 [PMID: 17429626 DOI: 10.1007/s00280-007-0476-x]

25 **Sadeghi B**, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, François Y, Vignal J, Gilly FN. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; **88**: 358-363 [PMID: 10640968 DOI: 10.1002/(SICI)1097-0142(20000115)88: 2<358: : AID-CNCR16>3.0.CO; 2-O]

26 **Yonemura Y**, Fujimura T, Nishimura G, FallaR T, Katayama K, Tsugawa K, Fushida S, Miyazaki I, Tanaka M, Endou Y, Sasaki T. Effects of intraoperative chemohyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery* 1996; **119**: 437-444 [PMID: 8644010 DOI: 10.1016/S0039-6060(96)80145-0]

27 **Pyrhönen S**, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995; **71**: 587-591 [PMID: 7533517 DOI: 10.1038/bjc.1995.114]

28 **Glimelius B**, Ekström K, Hoffman K, Graf W, Sjödén PO, Haglund U, Svensson C, Enander LK, Linné T, Sellström H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997; **8**: 163-168 [PMID: 9093725 DOI: 10.1023/A: 1008243606668]

29 **Bilici A**. Treatment options in patients with metastatic gastric cancer: current status and future perspectives. *World J Gastroenterol* 2014; **20**: 3905-3915 [PMID: 24744580 DOI: 10.3748/wjg.v20.i14.3905]

30 **Van Cutsem E**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991-4997 [PMID: 17075117 DOI: 10.1200/JCO.2006.06.8429]

31 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805 DOI: 10.1016/S1470-2045(08)70035-4]

32 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]

33 **Lordick F**, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, Kurteva G, Volovat C, Moiseyenko VM, Gorbunova V, Park JO, Sawaki A, Celik I, Götte H, Melezínková H, Moehler M. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013; **14**: 490-499 [PMID: 23594786 DOI: 10.1016/S1470-2045(13)70102-5]

34 **Yonemura Y**, Endou Y, Sasaki T, Hirano M, Mizumoto A, Matsuda T, Takao N, Ichinose M, Miura M, Li Y. Surgical treatment for peritoneal carcinomatosis from gastric cancer. *Eur J Surg Oncol* 2010; **36**: 1131-1138 [PMID: 20933363 DOI: 10.1016/j.ejso.2010.09.006]

35 **Preusser P**, Wilke H, Achterrath W, Fink U, Lenaz L, Heinicke A, Meyer J, Meyer HJ, Buente H. Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989; **7**: 1310-1317 [PMID: 2671287]

36 **Ross P**, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, Price T, Anderson H, Iveson T, Hickish T, Lofts F, Norman A. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002; **20**: 1996-2004 [PMID: 11956258 DOI: 10.1200/JCO.2002.08.105]

37 **Baba H**, Yamamoto M, Endo K, Ikeda Y, Toh Y, Kohnoe S, Okamura T. Clinical efficacy of S-1 combined with cisplatin for advanced gastric cancer. *Gastric Cancer* 2003; **6 Suppl 1**: 45-49 [PMID: 12775020 DOI: 10.1007/s10120-003-0222-y]

38 **Shirao K**, Boku N, Yamada Y, Yamaguchi K, Doi T, Goto M, Nasu J, Denda T, Hamamoto Y, Takashima A, Fukuda H, Ohtsu A. Randomized Phase III study of 5-fluorouracil continuous infusion vs. sequential methotrexate and 5-fluorouracil therapy in far advanced gastric cancer with peritoneal metastasis (JCOG0106). *Jpn J Clin Oncol* 2013; **43**: 972-980 [PMID: 24014884 DOI: 10.1093/jjco/hyt114]

39 **Hong SH**, Shin YR, Roh SY, Jeon EK, Song KY, Park CH, Jeon HM, Hong YS. Treatment outcomes of systemic chemotherapy for peritoneal carcinomatosis arising from gastric cancer with no measurable disease: retrospective analysis from a single center. *Gastric Cancer* 2013; **16**: 290-300 [PMID: 22898806 DOI: 10.1007/s10120-012-0182-1]

40 **Tamura S**, Miki H, Okada K, Takeno A, Uji K, Yoshida A, Suzuki R, Nakahira S, Egawa C, Nakata K, Okamura S, Sugimoto K, Takatsuka Y. Pilot study of a combination of S-1 and paclitaxel for patients with peritoneal metastasis from gastric cancer. *Gastric Cancer* 2010; **13**: 101-108 [PMID: 20602197 DOI: 10.1007/s10120-010-0547-2]

41 **Ishizone S**, Maruta F, Saito H, Koide N, Sugiyama A, Nakayama J, Miyagawa S. Efficacy of S-1 for patients with peritoneal metastasis of gastric cancer. *Chemotherapy* 2006; **52**: 301-307 [PMID: 17008790 DOI: 10.1159/000096002]

42 **Jacquet P**, Sugarbaker PH. Peritoneal-plasma barrier. *Cancer Treat Res* 1996; **82**: 53-63 [PMID: 8849943 DOI: 10.1007/978-1-4613-1247-5\_4]

43 **Glehen O**, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010; **116**: 5608-5618 [PMID: 20737573 DOI: 10.1002/cncr.25356]

44 **Elias D**, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dubè P, Glehen O. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 2010; **28**: 63-68 [PMID: 19917863 DOI: 10.1200/JCO.2009.23.9285]

45 **Yan TD**, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009; **27**: 6237-6242 [PMID: 19917862 DOI: 10.1200/JCO.2009.23.9640]

46 **Sugarbaker PH**. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006; **7**: 69-76 [PMID: 16389186]

47 **Iitsuka Y**, Kaneshima S, Tanida O, Takeuchi T, Koga S. Intraperitoneal free cancer cells and their viability in gastric cancer. *Cancer* 1979; **44**: 1476-1480 [PMID: 498022 DOI: 10.1002/1097-0142 (197910)44:4<1476::AID-CNCR2820440442>3.0.CO;2-R]

48 **Koga S**, Kaibara N, Iitsuka Y, Kudo H, Kimura A, Hiraoka H. Prognostic significance of intraperitoneal free cancer cells in gastric cancer patients. *J Cancer Res Clin Oncol* 1984; **108**: 236-238 [PMID: 6470030 DOI: 10.1007/BF00402474]

49 **Juhl H**, Stritzel M, Wroblewski A, Henne-Bruns D, Kremer B, Schmiegel W, Neumaier M, Wagener C, Schreiber HW, Kalthoff H. Immunocytological detection of micrometastatic cells: comparative evaluation of findings in the peritoneal cavity and the bone marrow of gastric, colorectal and pancreatic cancer patients. *Int J Cancer* 1994; **57**: 330-335 [PMID: 8168992 DOI: 10.1002/ijc.2910570307]

50 **Han TS**, Kong SH, Lee HJ, Ahn HS, Hur K, Yu J, Kim WH, Yang HK. Dissemination of free cancer cells from the gastric lumen and from perigastric lymphovascular pedicles during radical gastric cancer surgery. *Ann Surg Oncol* 2011; **18**: 2818-2825 [PMID: 21455599 DOI: 10.1245/s10434-011-1620-8]

51 **Marutsuka T**, Shimada S, Shiomori K, Hayashi N, Yagi Y, Yamane T, Ogawa M. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. *Clin Cancer Res* 2003; **9**: 678-685 [PMID: 12576435]

52 **Yu XF**, Ren ZG, Xue YW, Song HT, Wei YZ, Li CM. D2 lymphadenectomy can disseminate tumor cells into peritoneal cavity in patients with advanced gastric cancer. *Neoplasma* 2013; **60**: 174-181 [PMID: 23259786 DOI: 10.4149/neo\_2013\_023]

53 **González-Moreno S**, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: Rationale and technique. *World J Gastrointest Oncol* 2010; **2**: 68-75 [PMID: 21160924 DOI: 10.4251/wjgo.v2.i2.68]

54 **Speyer JL**, Sugarbaker PH, Collins JM, Dedrick RL, Klecker RW, Myers CE. Portal levels and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. *Cancer Res* 1981; **41**: 1916-1922 [PMID: 7214359]

55 **Sugarbaker PH**, Cunliffe WJ, Belliveau J, de Bruijn EA, Graves T, Mullins RE, Schlag P. Rationale for integrating early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. *Semin Oncol* 1989; **16**: 83-97 [PMID: 2669141]

56 **Overgaard J**. Effect of hyperthermia on malignant cells in vivo. A review and a hypothesis. *Cancer* 1977; **39**: 2637-2646 [PMID: 872062 DOI: 10.1002/1097-0142(197706)39: 6<2637: : AID-CNCR2820390650>3.0.CO; 2-S]

57 **Sticca RP**, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. *Surg Oncol Clin N Am* 2003; **12**: 689-701 [PMID: 14567025 DOI: 10.1016/S1055-3207(03)00029-2]

58 **Glehen O**, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol* 2004; **5**: 219-228 [PMID: 15050953 DOI: 10.1016/S1470-2045(04)01425-1]

59 **González-Moreno S**. Peritoneal Surface Oncology: A progress report. *Eur J Surg Oncol* 2006; **32**: 593-596 [PMID: 16603332 DOI: 10.1016/j.ejso.2006.03.001]

60 **Bando E**, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, Fushida S, Fujimura T, Nishimura G, Miwa K. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. *Am J Surg* 1999; **178**: 256-262 [PMID: 10527450 DOI: 10.1016/S0002-9610(99)00162-2]

61 **Bentrem D**, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol* 2005; **12**: 347-353 [PMID: 15915368 DOI: 10.1245/ASO.2005.03.065]

62 **Kodera Y**, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T. Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. *J Surg Oncol* 1999; **72**: 60-4; discussion 64-5 [PMID: 10518099 DOI: 10.1002/(SICI)1096-9098(199910)72: 2<60: : AID-JSO3>3.0.CO; 2-1]

63 **Yonemura Y**, Elnemr A, Endou Y, Hirano M, Mizumoto A, Takao N, Ichinose M, Miura M, Li Y. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. *World J Gastrointest Oncol* 2010; **2**: 85-97 [PMID: 21160926 DOI: 10.4251/wjgo.v2.i2.85]

64 Edge S. Cancer AJCo: AJCC cancer staging manual. 7th ed. New York: Springer, 2010

65 **Koga S**, Hamazoe R, Maeta M, Shimizu N, Murakami A, Wakatsuki T. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. *Cancer* 1988; **61**: 232-237 [PMID: 3121165 DOI: 10.1002/1097-0142 (19880115)61:2<232::AID-CNCR2820610205>3.0.CO;2-U]

66 **Fujimoto S**, Shrestha RD, Kokubun M, Kobayashi K, Kiuchi S, Konno C, Ohta M, Takahashi M, Kitsukawa Y, Mizutani M. Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced gastric cancer. *Ann Surg* 1990; **212**: 592-596 [PMID: 2241314 DOI: 10.1097/00000658-199011000-00005]

67 **Hamazoe R**, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994; **73**: 2048-2052 [PMID: 8156509 DOI: 10.1002/1097-0142 (19940415)73:8<2048::AID-CNCR2820730806>3.0.CO;2-Q]

68 **Wei G**, Fang GE, Bi JW, Shen XJ, Nie MM, Xue XC, Hua JD. Efficacy of intraoperative hypotonic peritoneal chemo-hyperthermia combined with early postoperative intraperitoneal chemotherapy on gastric cancer. *Ai Zheng* 2005; **24**: 478-482 [PMID: 15820074]

69 **Zuo Y**, Xu M, Shen D, Lu WD, Lu JF. Postoperative intraperitioneal hyperthermic chemoperfusion combined with intravenous chemotherapy for 82 advanced gastric cancer patients. *Zhonghua Zhong Liu Za Zhi* 2004; **26**: 247-249 [PMID: 15312391]

70 **Zhang GY**, Chen XC, Pan K, Xia LG, Zuo M, Zheng T. Application of hyperthermic intraoperative intraperitoneal chemotherapy in patients with gastric cancer. *Zhonghua Wei Chang Wai Ke Za Zhi* 2007; **10**: 362-364 [PMID: 17659464]

71 **Deng HJ**, Wei ZG, Zhen L, Li GX, Uang XC, Qing SH. Clinical application of perioperative continuous hyperthermic peritoneal perfusion chemotherapy for gastric cancer. *Nan Fang Yi Ke Da Xue Xue Bao* 2009; **29**: 295-297 [PMID: 19246304]

72 **Fujimura T**, Yonemura Y, Muraoka K, Takamura H, Hirono Y, Sahara H, Ninomiya I, Matsumoto H, Tsugawa K, Nishimura G. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: randomized controlled study. *World J Surg* 1994; **18**: 150-155 [PMID: 8197772]

73 **Ikeguchi M**, Kondou A, Oka A, Tsujitani S, Maeta M, Kaibara N. Effects of continuous hyperthermic peritoneal perfusion on prognosis of gastric cancer with serosal invasion. *Eur J Surg* 1995; **161**: 581-586 [PMID: 8519874]

74 **Fujimoto S**, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. *Cancer* 1999; **85**: 529-534 [PMID: 10091726 DOI: 10.1002/ (SICI)1097-0142 (19990201)85:3<529::AID-CNCR3>3.0.CO;2-9]

75 **Hirose K**, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, Kusaka Y. Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. *Oncology* 1999; **57**: 106-114 [PMID: 10461056 DOI: 10.1159/000012016]

76 **Yonemura Y**, de Aretxabala X, Fujimura T, Fushida S, Katayama K, Bandou E, Sugiyama K, Kawamura T, Kinoshita K, Endou Y, Sasaki T. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study. *Hepatogastroenterology* 2001; **48**: 1776-1782 [PMID: 11813623]

77 **Kim JY**, Bae HS. A controlled clinical study of serosa-invasive gastric carcinoma patients who underwent surgery plus intraperitoneal hyperthermo-chemo-perfusion (IHCP). *Gastric Cancer* 2001; **4**: 27-33 [PMID: 11706624 DOI: 10.1007/s101200100013]

78**Yonemura Y**, Shinbo M, Hagiwara A., Shimada S, Nakajima T, Ikeda S, Pkamura H, Hirano M, Mizuno M, Endou Y, Miura M, Mizumoto Y. Treatment for potentially curable gastric cancer patients with intraperitoneal free cancer cells. *Gastroenterological Surg* 2008; **31**: 802-812

79 **Takahashi T**, Hagiwara A, Shimotsuma M, Sawai K, Yamaguchi T. Prophylaxis and treatment of peritoneal carcinomatosis: intraperitoneal chemotherapy with mitomycin C bound to activated carbon particles. *World J Surg* 1995; **19**: 565-569 [PMID: 7676701 DOI: 10.1007/BF00294724]

80 **Yu W**, Whang I, Chung HY, Averbach A, Sugarbaker PH. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg* 2001; **25**: 985-990 [PMID: 11571980 DOI: 10.1007/s00268-001-0067-7]

81 **Sun J**, Song Y, Wang Z, Gao P, Chen X, Xu Y, Liang J, Xu H. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. *BMC Cancer* 2012; **12**: 526 [PMID: 23153379 DOI: 10.1186/1471-2407-12-526]

82 **Mi DH**, Li Z, Yang KH, Cao N, Lethaby A, Tian JH, Santesso N, Ma B, Chen YL, Liu YL. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomised controlled trials. *Int J Hyperthermia* 2013; **29**: 156-167 [PMID: 23418917 DOI: 10.3109/02656736.2013.768359]

83 **Yan TD**, Black D, Sugarbaker PH, Zhu J, Yonemura Y, Petrou G, Morris DL. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol* 2007; **14**: 2702-2713 [PMID: 17653801 DOI: 10.1245/s10434-007-9487-4]

84 **Huang JY**, Xu YY, Sun Z, Zhu Z, Song YX, Guo PT, You Y, Xu HM. Comparison different methods of intraoperative and intraperitoneal chemotherapy for patients with gastric cancer: a meta-analysis. *Asian Pac J Cancer Prev* 2012; **13**: 4379-4385 [PMID: 23167347]

85 **Coccolini F**, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. *Eur J Surg Oncol* 2014; **40**: 12-26 [PMID: 24290371 DOI: 10.1016/j.ejso.2013.10.019]

86 **Xu DZ**, Zhan YQ, Sun XW, Cao SM, Geng QR. Meta-analysis of intraperitoneal chemotherapy for gastric cancer. *World J Gastroenterol* 2004; **10**: 2727-2730 [PMID: 15309728 DOI: 10.3748/wjg.v10.i18.272]

87 **Glehen O**, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, Piaton E, Garofalo A. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. *BMC Cancer* 2014; **14**: 183 [PMID: 24628950 DOI: 10.1186/1471-2407-14-183]

88 **Roviello F**, Caruso S, Neri A, Marrelli D. Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: overview and rationale. *Eur J Surg Oncol* 2013; **39**: 1309-1316 [PMID: 24183797 DOI: 10.1016/j.ejso.2013.10.010]

89 **Fujimoto S**, Shrestha RD, Kokubun M, Ohta M, Takahashi M, Kobayashi K, Kiuchi S, Okui K, Miyoshi T, Arimizu N. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. *Ann Surg* 1988; **208**: 36-41 [PMID: 3133994 DOI: 10.1097/00000658-198807000-00005]

90 **Fujimura T**, Yonemura Y, Fushida S, Urade M, Takegawa S, Kamata T, Sugiyama K, Hasegawa H, Katayama K, Miwa K. Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. *Cancer* 1990; **65**: 65-71 [PMID: 2104572 DOI: 10.1002/1097-0142 (19900101)65:1<65::AID-CNCR2820650115>3.0.CO;2-L]

91 **Yonemura Y**, Fujimura T, Fushida S, Takegawa S, Kamata T, Katayama K, Kosaka T, Yamaguchi A, Miwa K, Miyazaki I. Hyperthermo-chemotherapy combined with cytoreductive surgery for the treatment of gastric cancer with peritoneal dissemination. *World J Surg* 1991; **15**: 530-55; discussion 530-55; [PMID: 1891941 DOI: 10.1007/BF01675656]

92 **Fujimoto S**, Takahashi M, Mutou T, Kobayashi K, Toyosawa T, Isawa E, Sumida M, Ohkubo H. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer* 1997; **79**: 884-891 [PMID: 9041149 DOI: 10.1002/1097-0142(SICI)1097-0142 (19970301)79:5<884::AID-CNCR3>3.0.CO;2-C]

93 **Sayag-Beaujard AC**, Francois Y, Glehen O, Sadeghi-Looyeh B, Bienvenu J, Panteix G, Garbit F, Grandclément E, Vignal J, Gilly FN. Intraperitoneal chemo-hyperthermia with mitomycin C for gastric cancer patients with peritoneal carcinomatosis. *Anticancer Res* 1999; **19**: 1375-1382 [PMID: 10365109]

94 **Glehen O**, Schreiber V, Cotte E, Sayag-Beaujard AC, Osinsky D, Freyer G, François Y, Vignal J, Gilly FN. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. *Arch Surg* 2004; **139**: 20-26 [PMID: 14718269 DOI: 10.1001/archsurg.139.1.20]

95 **Yonemura Y**, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N. Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. *Br J Surg* 2005; **92**: 370-375 [PMID: 15739249 DOI: 10.1002/bjs.4695]

96 **Glehen O**, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010; **17**: 2370-2377 [PMID: 20336386 DOI: 10.1245/s10434-010-1039-7]

97 **Yang XJ**, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonemura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011; **18**: 1575-1581 [PMID: 21431408 DOI: 10.1245/s10434-011-1631-5]

98 **Verwaal VJ**, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; **21**: 3737-3743 [PMID: 14551293 DOI: 10.1200/JCO.2003.04.187]

99 **Hall JJ**, Loggie BW, Shen P, Beamer S, Douglas Case L, McQuellon R, Geisinger KR, Levine EA. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. *J Gastrointest Surg* 2004; **8**: 454-463 [PMID: 15120371 DOI: 10.1016/j.gassur.2003.12.014]

100 **Scaringi S**, Kianmanesh R, Sabate JM, Facchiano E, Jouet P, Coffin B, Parmentier G, Hay JM, Flamant Y, Msika S. Advanced gastric cancer with or without peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy: a single western center experience. *Eur J Surg Oncol* 2008; **34**: 1246-1252 [PMID: 18222622 DOI: 10.1016/j.ejso.2007.12.003]

101 **Yang XJ**, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: Results from a Chinese center. *J Surg Oncol* 2010; **101**: 457-464 [PMID: 20401915 DOI: 10.1002/jso.21519]

102 **Magge D**, Zenati M, Mavanur A, Winer J, Ramalingam L, Jones H, Zureikat A, Holtzman M, Lee K, Ahrendt S, Pingpank J, Zeh HJ, Bartlett DL, Choudry HA. Aggressive locoregional surgical therapy for gastric peritoneal carcinomatosis. *Ann Surg Oncol* 2014; **21**: 1448-1455 [PMID: 24197761 DOI: 10.1245/s10434-013-3327-5]

103 **Bozzetti F**, Yu W, Baratti D, Kusamura S, Deraco M. Locoregional treatment of peritoneal carcinomatosis from gastric cancer. *J Surg Oncol* 2008; **98**: 273-276 [PMID: 18726891 DOI: 10.1002/jso.21052]

104 Yonemura Y, Canbay E, Sako S, Ishibashi H, Hirano M, Mizumoto A, Takeshita K, Takao N, Ichinose M, Liu Y, Li Y, Ikeda S, Noguchi A, Sai Y. Pharmacokinetics of docetaxel during hyperthermic intraperitoneal chemotherapy for peritoneal metastasis. *Gan To Kagaku Ryoho* 2014; **41**: 2496-2499 [PMID: 25731569]

105 **Gill RS**, Al-Adra DP, Nagendran J, Campbell S, Shi X, Haase E, Schiller D. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. *J Surg Oncol* 2011; **104**: 692-698 [PMID: 21713780 DOI: 10.1002/jso.22017]

106 **Yonemura Y**, Bandou E, Kinoshita K, Kawamura T, Takahashi S, Endou Y, Sasaki T. Effective therapy for peritoneal dissemination in gastric cancer. *Surg Oncol Clin N Am* 2003; **12**: 635-648 [PMID: 14567022 DOI: 10.1016/S1055-3207(03)00035-8]

107 **Yonemura Y**, Endou Y, Shinbo M, Sasaki T, Hirano M, Mizumoto A, Matsuda T, Takao N, Ichinose M, Mizuno M, Miura M, Ikeda M, Ikeda S, Nakajima G, Yonemura J, Yuuba T, Masuda S, Kimura H, Matsuki N. Safety and efficacy of bidirectional chemotherapy for treatment of patients with peritoneal dissemination from gastric cancer: Selection for cytoreductive surgery. *J Surg Oncol* 2009; **100**: 311-316 [PMID: 19697437 DOI: 10.1002/jso.21324]

108 **Canbay E**, Mizumoto A, Ichinose M, Ishibashi H, Sako S, Hirano M, Takao N, Yonemura Y. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. *Ann Surg Oncol* 2014; **21**: 1147-1152 [PMID: 24356799 DOI: 10.1245/s10434-013-3443-2]

109 **Lorenzen S**, Panzram B, Rosenberg R, Nekarda H, Becker K, Schenk U, Höfler H, Siewert JR, Jäger D, Ott K. Prognostic significance of free peritoneal tumor cells in the peritoneal cavity before and after neoadjuvant chemotherapy in patients with gastric carcinoma undergoing potentially curative resection. *Ann Surg Oncol* 2010; **17**: 2733-2739 [PMID: 20490698 DOI: 10.1245/s10434-010-1090-4]

110 **Hultman B**, Lind P, Glimelius B, Sundbom M, Nygren P, Haglund U, Mahteme H. Phase II study of patients with peritoneal carcinomatosis from gastric cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy. *Acta Oncol* 2013; **52**: 824-830 [PMID: 22974074 DOI: 10.3109/0284186X.2012.702925]

111 **Glehen O**, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AA, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol* 2004; **22**: 3284-3292 [PMID: 15310771 DOI: 10.1200/JCO.2004.10.012]

112 **Ströhlein MA**, Bulian DR, Heiss MM. Clinical efficacy of cytoreductive surgery and hyperthermic chemotherapy in peritoneal carcinomatosis from gastric cancer. *Expert Rev Anticancer Ther* 2011; **11**: 1505-1508 [PMID: 21999124 DOI: 10.1586/era.11.147]

113 **Piso P**, Slowik P, Popp F, Dahlke MH, Glockzin G, Schlitt HJ. Safety of gastric resections during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol* 2009; **16**: 2188-2194 [PMID: 19408049 DOI: 10.1245/s10434-009-0478-5]

114 **Sugarbaker TA**, Chang D, Koslowe P, Sugarbaker PH. Patterns of spread of recurrent intraabdominal sarcoma. In: Sugarbaker PH, editor. Peritoneal Carcinomatosis: Principles of management. Boston: Kluwer Academic, 1996: 65-78

115 **Gilly FN**, Carry PY, Sayag AC, Brachet A, Panteix G, Salle B, Bienvenu J, Burgard G, Guibert B, Banssillon V. Regional chemotherapy (with mitomycin C) and intra-operative hyperthermia for digestive cancers with peritoneal carcinomatosis. *Hepatogastroenterology* 1994; **41**: 124-129 [PMID: 8056398]

116 **Japanese research Society for Gastric Cancer**. The general rules for the gastric cancer study in surgery and pathology. 12th ed. Tokyo: Kanehara Shuppan, 1993

117 **Randle RW**, Swett KR, Swords DS, Shen P, Stewart JH, Levine EA, Votanopoulos KI. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. *Ann Surg Oncol* 2014; **21**: 1474-1479 [PMID: 23982251 DOI: 10.1245/s10434-013-3224-y]

118 **Glehen O**, Osinsky D, Cotte E, Kwiatkowski F, Freyer G, Isaac S, Trillet-Lenoir V, Sayag-Beaujard AC, François Y, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. *Ann Surg Oncol* 2003; **10**: 863-869 [PMID: 14527903 DOI: 10.1245/ASO.2003.01.018]

119 **Mohamed F**, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy: the importance of a learning curve. *Cancer J* 2009; **15**: 196-199 [PMID: 19556904 DOI: 10.1097/PPO.0b013e3181a58d56]

120 **Smeenk RM**, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg* 2007; **94**: 1408-1414 [PMID: 17631678 DOI: 10.1002/bjs.5863]

121 **Kusamura S**, Baratti D, Deraco M. Multidimensional analysis of the learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies. *Ann Surg* 2012; **255**: 348-356 [PMID: 22202584 DOI: 10.1097/SLA.0b013e3182436c28]

122 **Königsrainer I**, Horvath P, Struller F, Königsrainer A, Beckert S. Initial clinical experience with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in signet-ring cell gastric cancer with peritoneal metastases. *J Gastric Cancer* 2014; **14**: 117-122 [PMID: 25061539 DOI: 10.5230/jgc.2014.14.2.117]

123 **Koh JL**, Yan TD, Glenn D, Morris DL. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 2009; **16**: 327-333 [PMID: 19050972 DOI: 10.1245/s10434-008-0234-2]

124 **Yang QM**, Bando E, Kawamura T, Tsukiyama G, Nemoto M, Yonemura Y, Furukawa H. The diagnostic value of PET-CT for peritoneal dissemination of abdominal malignancies. *Gan To Kagaku Ryoho* 2006; **33**: 1817-1821 [PMID: 17212117]

125 **Valle M**, Garofalo A. Laparoscopic staging of peritoneal surface malignancies. *Eur J Surg Oncol* 2006; **32**: 625-627 [PMID: 16822641 DOI: 10.1016/j.ejso.2006.03.015]

126 **Sommariva A**, Zagonel V, Rossi CR. The role of laparoscopy in peritoneal surface malignancies selected for hyperthermic intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol* 2012; **19**: 3737-3744 [PMID: 22805859 DOI: 10.1245/s10434-012-2465-5]

127 **Chu DZ**, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; **63**: 364-367 [PMID: 2910444 DOI: 10.1002/1097-0142(19890115)63: 2<364: : AID-CNCR2820630228>3.0.CO; 2-V]

128 **Husain A**, Bezjak A, Easson A. Malignant ascites symptom cluster in patients referred for paracentesis. *Ann Surg Oncol* 2010; **17**: 461-469 [PMID: 19866240 DOI: 10.1245/s10434-009-0774-0]

129 **Oh SY**, Kwon HC, Lee S, Lee DM, Yoo HS, Kim SH, Jang JS, Kim MC, Jeong JS, Kim HJ. A Phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. *Jpn J Clin Oncol* 2007; **37**: 930-935 [PMID: 18211984 DOI: 10.1093/jjco/hym131]

130 **Sangisetty SL**, Miner TJ. Malignant ascites: A review of prognostic factors, pathophysiology and therapeutic measures. *World J Gastrointest Surg* 2012; **4**: 87-95 [PMID: 22590662 DOI: 10.4240/wjgs.v4.i4.87]

131 **McQuellon RP**, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Surg Oncol* 2001; **27**: 65-73 [PMID: 11237495 DOI: 10.1053/ejso.2000.1033]

132 **Shen J**, Zhu Z. Catumaxomab, a rat/murine hybrid trifunctional bispecific monoclonal antibody for the treatment of cancer. *Curr Opin Mol Ther* 2008; **10**: 273-284 [PMID: 18535935]

133 **Heiss MM**, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, Dudnichenko AS, Aleknaviciene B, Razbadauskas A, Gore M, Ganea-Motan E, Ciuleanu T, Wimberger P, Schmittel A, Schmalfeldt B, Burges A, Bokemeyer C, Lindhofer H, Lahr A, Parsons SL. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: Results of a prospective randomized phase II/III trial. *Int J Cancer* 2010; **127**: 2209-2221 [PMID: 20473913 DOI: 10.1002/ijc.25423]

134 **Facchiano E**, Scaringi S, Kianmanesh R, Sabate JM, Castel B, Flamant Y, Coffin B, Msika S. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. *Eur J Surg Oncol* 2008; **34**: 154-158 [PMID: 17640844 DOI: 10.1016/j.ejso.2007.05.015]

135 **Garofalo A**, Valle M, Garcia J, Sugarbaker PH. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. *Eur J Surg Oncol* 2006; **32**: 682-685 [PMID: 16631341 DOI: 10.1016/j.ejso.2006.03.014]

136 **Facchiano E**, Risio D, Kianmanesh R, Msika S. Laparoscopic hyperthermic intraperitoneal chemotherapy: indications, aims, and results: a systematic review of the literature. *Ann Surg Oncol* 2012; **19**: 2946-2950 [PMID: 22526907 DOI: 10.1245/s10434-012-2360-0]

137 **Valle M**, Van der Speeten K, Garofalo A. Laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) in the management of refractory malignant ascites: A multi-institutional retrospective analysis in 52 patients. *J Surg Oncol* 2009; **100**: 331-334 [PMID: 19697441 DOI: 10.1002/jso.21321]

138 **Ba MC**, Long H, Cui SZ, Tang YQ, Wu YB, Zhang XL, Tang HS, Bai SX. Multivariate comparison of B-ultrasound guided and laparoscopic continuous circulatory hyperthermic intraperitoneal perfusion chemotherapy for malignant ascites. *Surg Endosc* 2013; **27**: 2735-2743 [PMID: 23392978 DOI: 10.1007/s00464-013-2800-3]

**P-Reviewer:** Aoyagi K, Caboclo JLF, Klempner SJ

**S-Editor:** Yu J **L-Editor:** **E-Editor:**

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

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **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.

**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** | **Anastamotic 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: Inraperitoneal chemotherapy; CH: Activated carbon particles; EPIC: Early postoperative intraperitoneal chemotherapy; NIIC: Normothermic intraoperative intraperitoneal chemotherapy.

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

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year,** | **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%  Death due to Peritoneal recurrence: 10% *vs* 100% |
| Yonemura *et al*[91], 1991 | Japan | Prospective | 41 | Nil | MMC 5 µg/mL  CDDP 30 µg/mLl | 40-60 |  | 12% | 0% | 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 × 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 | USA | 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/m2 | 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/m2 ± Cisplatin 50–100 mg/m2  Oxaliplatin 360–460 mg/m2 ± irinotecan 100–  200 mg/m2 ± iv 5-FU and leucovorin  EPIC:  MMC 10 mg/m2  5-FU 600 mg/m2 | 60-120  30  Day 1  Days 2-5 | 56% | 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 | USA | 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.