Review Article

Intraperitoneal free cancer cells in gastric cancer: pathology of peritoneal carcinomatosis and rationale for intraperitoneal chemotherapy/hyperthermic intraperitoneal chemotherapy in gastric cancer

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Abstract: Peritoneal carcinomatosis (PC) is one of the most common causes of death in gastric cancer patients. Intraperitoneal free cancer cells (IFCCs) play a very important role in forming PC, but the administration of intraperitoneal chemotherapy (IPC) and/or hyperthermic intraperitoneal chemotherapy (HIPEC) could be an effective treatment for IFCCs. This review focuses on the origin of IFCCs, the mechanism of PC formatting, the rationale of IPC/HIPEC, and the current clinical trials on IPC/HIPEC to treat advanced gastric cancer patients.

Keywords: Intraperitoneal free cancer cells (IFCCs); peritoneal carcinomatosis (PC); intraperitoneal chemotherapy (IPC); hyperthermic intraperitoneal chemotherapy (HIPEC); gastric cancer (GC)

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Peritoneal carcinomatosis (PC) occurs synchronous with the primary tumor in about 14–43% of patients with gastric cancer (GC) and accounts for 35% of all synchronous metastasis (1). Moreover, metachronous PC known as peritoneal recurrence occurs in 10–46% of patients after a curative surgery for GC and accounts for 36–45% of all recurrences (1,2). The peritoneum is the first/sole site of tumor recurrence after D2 gastrectomy in 12–40% of patients (3). The prognosis of PC from GC is worse than other forms of metastases, with a median survival of only about 6 months and a 5-year survival of 0% (1,2,4).

Intraperitoneal free cancer cells (IFCCs), first exfoliating from primary tumor mass to the abdominal cavity, then attaching to peritoneal surface, and finally invading into the subperitoneal tissue to form proliferating nodules, are the most fundamental pathophysiology for both synchronous and metachronous PC (5,6).

The understanding that PC is a locoregional rather than a systemic disease has led to a resurgence of interest in regional therapies like cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC)/hyperthermic intraperitoneal chemotherapy (HIPEC) (7). Given the etiology of GC PC, it seems logic and promising to apply IPC/HIPEC as an essential component of the integrated treatment strategy.

This review focuses on the origin of IFCCs, the mechanism of PC formatting, the rationale of IPC/HIPEC,

and the current clinical trials on IPC/HIPEC to treat advanced gastric cancer patients.

Origin of IFCCs

PC usually originates from IFCCs which in turn can occur from two different sources (7-9): (I) spontaneous exfoliation of cancer cells from the primary tumor as a result of the natural course of cancer invasion; and (II) iatrogenic dissemination of cancer cells due to ineffective tumor-free technique during surgical resection.

The IFCCs positive rate in abdominal cytology increases as the tumor invades deeply from mucosa to serosa. IFCCs can be seen in up to 24% patients with stage I and 40% patients with stage II or III GC (10). Moreover, Lee *et al.* (11) found that the IFCCs positive rate is significantly correlated with T3/T4 stage and positive lymph nodes. Surgery also plays a part in dissemination of tumor cells into the peritoneal cavity. During radical surgery for GC, cancer cells are released from transected lymphatic channels, tissue at the narrow margins of resection, and tumor-contaminated blood lost in the surgical field from the cancer specimen (7,12,13).

Mechanism of PC formation

Two different processes are proposed in the formation of peritoneal dissemination, designated as "transmesothelial" and "translymphatic" metastases by Yonemura *et al*. (14). Both processes start with the dissemination and survival of IFCCs.

Transmesothelial metastasis originates from the direct attachment of IFCCs on the mesothelium. Most IFCCs attach to the mesothelial cells die off because of poor nutrient environment as the result of strong attachment to each other of the peritoneal mesothelial cells and peritoneal-blood barrier. However, once IFCCs loosely attach to the mesothelial cells with adhesion molecules like CD44, cytokines are released to contract mesothelial cells by the phosphorylation of their cell skeleton (15). As a result, IFCCs migrate directly into the submesothelial space through the cleaved space between mesothelial cells and strongly attach to the exposed basement membrane by the expression of integrin molecules (16).

After the first step, IFCCs express motility factors and matrix proteinases to degrade the peritoneal-blood barrier and invade deeper into the subperitoneal tissue (17,18). When IFCCs invade near the subperitoneal capillary, they proliferate via autocrine or paracrine loop by the production of growth factors from cancer cells or stromal cells. Furthermore, angiogenic factors like VEGF-A and VEGF-C secreted from IFCCs induce neovascularization in the subperitoneal tissue (19). As a result, the integrity of the peritoneal-blood barrier is broken to create a ready soil for establishing PC.

Translymphatic metastasis via lymphatic orifices opening on the peritoneal surface, requires fewer steps and forms PC earlier than transmesothelial metastasis. IFCCs migrate into the lymphatic orifices and proliferate in the submesothelial lymphatic space beneath the lymphatic stomatas. The distribution of lymphatic orifices on the peritoneum is uneven. There are many lymphatic orifices on the greater omentum, appendices, epiploicae of the colon, inferior surface of the diaphragm, falciform ligament, Douglas' pouch, and small bowel mesentery. Accordingly, PC occurs earlier in these places (14). In contrast, there are much fewer lymphatic stomatas on the liver capsule, the peritoneum covering the abdominal wall, or the serosal surface of small bowel and splenic capsule. These peritoneal parts are not affected until late stages of peritoneal dissemination.

Rationale for IPC/HIPEC

The presence of plasm-peritoneal barrier makes the peritoneal cavity a relatively closed space lacking blood vessels, accounting for the poor effect of intravenous chemotherapy (IVC). IPC/HIPEC is designed according to the function of plasm-peritoneal barrier, to achieve a high intraperitoneal concentration of chemotherapeutics with a low plasma concentration. Morgan *et al*. (20) found that the median peak peritoneal concentration of Gemcitabine was 1,116 folds (range, 456–1,886 folds) higher than the peak plasma level. This positive gradient of chemotherapy in the peritoneum could intensifying its direct antitumor effect and effectively eradicate IFCCs, micrometastases, and tumor nodules with less systemic adverse effects. Moreover, 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 (21).

Hyperthermia itself has direct detrimental effects on IFCCs, and also enhances the effects of IPC (22). The tolerance of normal tissue and cancer tissue to hyperthermia is different. Temperature over 43 ℃ has direct cytostatic effect on human gastric carcinoma SGC-7901 cells (23,24), colorectal carcinoma HT-29 cells (25), and ovarian SKOV-3 cells (26). Several mechanisms account for the multiple adverse effects of hyperthermia on IFCCs. First, hyperthermia causes tumor microvessel embolism at the tissue level, resulting in ischemic necrosis of tumor tissue. Second, hyperthermia disturbs cancer cell homeostasis and energy metabolism, activates the lysosomes, and destroys the cytoplasm and nucleus, directly killing cancer cells in S and M phases of the cell cycle. Third, hyperthermia also disrupts cancer cell membrane proteins at the molecular level, and interferes with the synthesis of DNA, RNA and protein. Hyperthermia enhances the effects of IPC in two ways. Firstly, hyperthermia increases the cytotoxic activity of the chemotherapy by a synergistic effect. Secondly, hyperthermia increases the penetration of chemotherapy drugs into the tumor nodule, increases the drug uptake in the tumor cells and increases the chemosensibility of neoplastic cells (27-29).

Clinical trials of IPC/HIPEC to treat gastric cancer

IPC/HIPEC has been increasingly applied in gastric cancer patients and can be categorized into three types according to the different purposes and timing of administration: neoadjuvant IPC (*Table 1*) (30-36), prophylactic IPC/HIPEC for gastric cancer patients with serosa invasion (*Table 2*) (37-53), and therapeutic IPC/HIPEC for gastric cancer patients with macroscopic PC (*Table 3*) (42,47,54-67).

Assessment methods for IPC/HIPEC

In the past, the clinical outcome was the only method to evaluate the efficacy of IPC/HIPEC. This method is the most authoritative, but it takes a very long time, which may limit the development of IPC/HIPEC. IFCCs are the recognized root pathologic cause for PC and the technique of detecting IFCCs has been developed in recent years. Ji *et al*. (5) tried to assess the efficacy of HIPEC by detecting pre- and post-HIPEC IFCCs viability using traditional cytological method and RT-PCR method. This new method makes it possible to rapidly evaluate the efficacy of IPC/HIPEC, and it can be used in routine clinical setting to evaluate patients' response to IPC/HIPEC and predict the prognosis, and in preclinical research of evaluate new chemotherapeutic agents or new treatment strategies.

Future perspectives and conclusions

From perspectives of clinical oncology, there are literally three forms of cancer metastases, i.e., lymph-route metastasis, blood-route metastasis, and peritoneal metastasis. For lymph-route metastasis, universally adopted treatment guidelines and technical standards have long been established, and surgery undoubtedly plays a major role. For blood-route metastasis, such as liver metastasis from colorectal cancer, it has also been universally accepted that that surgery is the treatment of choice for selected patients with limited liver metastases and good function reserve (68). Compared with these two types of cancer metastasis, peritoneal metastasis is the last stronghold of cancer. Confronted with such a tremendous adverse, the oncology community in whole still remains pessimistic, with palliative approaches gaining no concrete benefits other than psychologic consoling to both patients and the doctors alike.

Thanks to the groundbreaking works of the early pioneers in the field of peritoneal metastasis, the landscape is changing, slowly but steadily for the better. The first generation pioneers such as Dr. Sugarbaker (69) from the United States, Dr. Elias (70) from France, Dr. Deraco (71) from Italy, and Dr. Yonemura (72) from Japan have paved the way for the right direction. Dr. Piso (73) from Germany, Dr. Glehen (74) from France, Dr. Morris (75) from Australia, Dr. Verwaal (76) from the Netherlands, Dr. Li (77) from China and many others have also contributed enormously to push the endeavor to a new height. Currently, specialized PC treatment centers for standardized HIPEC treatments have been established in many parts of the world. A broad united front against GC PC have been established and increasingly higher levels of evidence has been obtained. It has been unequivocally proved that IPC/HIPEC is the most effective treatment strategy for GC PC, and more future work is required to promote this comprehensive treatment.

Table 1 Retrospective clinical trials from Japan about NIPC in gastric cancer

Ref.	Type of patient	No. of patients	Pre-NIPC IFCCs (%)	Post-NIPC IFCCs (%)	Treatment arms	Drugs used for IPC	Surgery rate (%)	Curative surgery	Survival outcomes
Yonemura *et al*. (30) 2006	PC	61	63.9	27.9	NIPS + surgery	DOC 40 mg + CBDCA 150 mg	49.2	Complete CRS 50% (in 30 patients)	Median OS: 14.4 *vs.* 18.0 *vs.* 9.6 mo (overall *vs.* surgery *vs.* no surgery)
Yonemura *et al*. (31) 2009	PC	79	82.2	63.0	NIPS + surgery	DOC 30 mg/m^2 + CDDP 30 mg/m^2	57.7	Complete CRS 78% (in 41 patients)	Median OS: 1.70 *vs.* 0.88 yr; 1-yr OS: 67.4% *vs.* 35.9%; 2-yr OS: 40.0% *vs.* 20.4% (surgery *vs.* no surgery)
Ishigami *et al*. (32) 2010	PC	40	70.0	10.0	NIPS	PTX 20 mg/m^2	NR	NR	Median OS: 22.5 mo; 1-yr OS: 78%; 2-yr OS: 46%
Fujiwara *et al*. (33) 2012	PC	18	100.0	22.0	NIPS + surgery	DOC 40–60 mg/m^2	88.9	D2 lymphadenectomy 25% (in 16 patients)	Median OS: 24.6 mo; 1-yr OS: 76%; 2-yr OS: 54%
Imano *et al*. (34) 2012	PC	35	NR	NR	NIPC + NIVC + surgery	PTX 80 mg/m^2	62.9	R0 resection 100% (in 22 patients)	Median OS: 21.3 *vs.* 29.7 *vs.* 14.7 mo; 1-yr OS: 68.6% *vs.* 77.3% *vs.* 53.8%; 2-yr OS: 45.7% *vs.* 63.6% *vs.*15.4% ; 5-yr OS: 13.7% *vs.* 21.8% *vs.* 0% (overall *vs.* surgery *vs.* no surgery)
Fushida *et al*. (35) 2013	PC	27	81.5	14.8	NIPS + surgery	DOC 60 mg/m^2	51.9	R0 resection 21% (in 14 patients)	Median OS: 16.2 mo; 1-yr OS: 70.4%; 2-yr OS: 33.4%
Peng *et al*. (36) 2015	cT4aN0-3 M0	37	0.0	0.0	NIPC + NIVC + surgery	PTX 80 mg/m^2	100.0	R0 resection 100%	3-yr OS: 78.0%; 5-yr OS: 74.9%; 3-yr DFS: 75.2%; 5-yr DFS: 67.3%

NIPS, neoadjuvant intraperitoneal and systemic chemotherapy; IFCCs, intraperitoneal free cancer cells; IPC, intraperitoneal chemotherapy; PC, peritoneal carcinomatosis; DOC, docetaxel; CBDCA, carboplatin; CRS, cytoreductive surgery; OS, overall survival; CDDP, cisplatin; PTX, paclitaxel; NR, not reported; NIPC, neoadjuvant intraperitoneal chemotherapy; NIVC, neoadjuvant intravenous chemotherapy; DFS, disease free survival.

Table 2 Prophylactic IPC/HIPEC for gastric cancer patients with serosa invasion with or without IFCCs

Ref.	Country	Type of study	IFCCs positive rate	Treatment arms [No. of patients]	Drugs used for IPC	Curative surgery	Post-op morbidity	Post-op mortality	Survival outcomes	Peritoneal recurrence
Koga *et al*. (37) 1988	Japan	RCT	NR	Surgery + HIPEC [26] *vs*. surgery alone [21]	MMC 64–100 mg	100% *vs*. 100%	Leak 3.1% *vs*. 7.1%	NR	30-mo OS rate: 83% *vs*. 67%	NR
Hamazoe *et al*. (38) 1994	Japan	RCT	NR	Surgery + HIPEC [42] *vs*. surgery alone [40]	MMC 10 mg/mL	95% *vs*. 88%	Leak 4.8% *vs*. 7.5%	0% *vs*. 0%	Median OS: 77 *vs*. 66 mo; 5-yr 64% *vs*. 52%	39% *vs*. 59%
Fujimura *et al*. (39) 1994	Japan	RCT	NR	Surgery + HIPEC [22] *vs*. surgery + CNPP [18] *vs*. surgery alone [18]	MMC 30 mg + CDDP 300 mg	NR	30% *vs*. 0% (perfusion *vs*. surgery)	0%	1-yr OS: 95% *vs*.81% *vs*.43%; 2-yr OS: 89% *vs*.75% *vs*.23%; 3-yr OS: 68% *vs*. 51% *vs*. 23%	9% *vs*. 22% *vs*. 22%
Ikeguchi *et al*. (40) 1995	Japan	RCT	17.9% *vs*. 20.8%	Surgery + HIPEC [78] *vs*. surgery alone [96]	MMC 80–100 mg/m^2	100% *vs*. 100%	1.2% *vs*. 2.08%	NR	5-yr OS: 51% *vs*. 46%	35% *vs*. 40%
Fujimoto *et al*. (41) 1999	Japan	RCT	18.3% *vs*. 11.4% (after laparotomy)	Surgery + HIPEC [71] *vs*. surgery alone [70]	MMC 10 mg/mL	94.3% *vs*. 92.8%	2.8% *vs*. 2.8%	0% *vs*. 0%	2-yr OS: 88% *vs*. 77%; 4-yr OS: 76% *vs*. 58%; 8-yr OS: 62% *vs*. 49%	1.4% *vs*. 23%
Hirose *et al*. (42) 1999	Japan	Prospective case control	NR	Surgery + HIPEC [15] *vs*. surgery alone [40]	MMC 20 mg + CDDP 100 mg + VP16 100 mg	NR	60% *vs*. 42.5%	0% *vs*. 12.5%	Median OS: 33 *vs*. 22 mo; 3-yr OS: 48.9% *vs*. 28.8%; 5-yr OS: 39.1% *vs*. 17.3%	26.7% *vs*. 45%
Yonemura *et al*. (43) 2001	Japan	RCT	NR	Surgery + HIPEC [48] *vs*. surgery + CNPP [44] *vs*. surgery alone [47]	MMC 30 mg + CDDP 300 mg	100% *vs*. 100% *vs*. 100%	19% *vs*. 14% *vs*. 19%	4% *vs*. 0% *vs*. 4%	5-yr OS: 61% *vs*. 43% *vs*. 42%	12.5% *vs*. 20.5% *vs*. 14.9%
Kim *et al*. (44) 2001	Korea	Prospective case control	NR	Surgery + HIPEC [52] *vs*. surgery alone [51]	MMC 40 mg	NR	36.5% *vs*. 33.3%	NR	5-yr OS: 32.7% *vs*. 27.1%	7.6% *vs*. 25%
Shimada *et al*. (45) 2002	Japan	Retrospective	100%	Surgery + EPIL + IPC [7] *vs*. surgery + IPC [7] *vs*. surgery alone [8]	CDDP 100 mg	NR	NR	NR	2-yr OS: 57.1% *vs*. 14.3% *vs*.0%	100% *vs*.85.7% *vs*.42.9%
Newman *et al*. (46) 2005	United states	Prospective	NR	Neoadjuvant chemotherapy + surgery + IPC [32]	FUDR 3 g + CDDP 60 mg/m^2	86.2%	34.5%	6.9%	Median OS: 36.5 mo	21.9%

Table 2 *(continued)*

Table 2 *(continued)*

Ref.	Country	Type of study	IFCCs positive rate	Treatment arms [No. of patients]	Drugs used for IPC	Curative surgery	Post-op morbidity	Post-op mortality	Survival outcomes	Peritoneal recurrence
Zhu *et al*. (47) 2006	China	Prospective case control	NR	Surgery + HIPEC [42] *vs.* surgery alone [54]	MMC 30 mg + CDDP 300 mg	73.8% *vs.* 66.7%	23.1% *vs.*12.1%	0%	Mean OS: 60.85±4.27 *vs.* 42.90±3.67 mo; 2-yr OS: 83.0% *vs.* 63.7%; 4-yr OS: 70.5% *vs.* 52.1%; 6-yr OS: 67.9% *vs.* 37.7%	10.3% *vs.* 34.7%
Brenner *et al*. (48) 2006	United States	Prospective	NR	Neoadjuvant chemotherapy + surgery + IPC [38]	FUDR 1,000 mg/m^2 + LV 240 mg/m^2	84.20%	32% IPC, 10% surgery	0%	Median OS: 30.3 mo; 3-yr OS: 45%	21.9%
Kuramoto *et al*. (49) 2009	Japan	RCT	100%	Surgery + EPIL + IPC [30] *vs.* surgery + IPC [29] *vs.* surgery alone [29]	CDDP 100 mg	100%	NR	NR	Median OS: 35 *vs.* 16 *vs.* 15 mo; 5-yr OS: 43.8% *vs.*4.6% *vs.* 0%	40.0% *vs.*79.3% *vs.* 89.7%
Imano *et al*. (50) 2011	Japan	Prospective	100%	Surgery +EPIC [10]	PTX 80 mg/m^2	100%	10%	NR	Median OS: 1,151 days; 2-yr OS: 70%; 3-yr OS: 56.0%	NR
Yarema *et al*. (51) 2014	Ukraine	Retrospective case control	NR	Surgery + IPC [19] *vs.* surgery alone [19]	MMC 12.5 mg/m^2 + CDDP 75 mg/m^2	NR	NR	NR	Median OS: 22.5±6.5 *vs.* 12±1.3 mo; 1-yr OS: 100% *vs.* 52.6%	11.1% *vs.* 73.7%
Kwon *et al*. (52) 2014	Korea	Prospective case control	NR	Surgery + EPIC [65] *vs.* surgery alone [180]	MMC 10 mg/m^2 + 5-FU 700 mg/m^2	–	10.8% *vs.* 8.9%	NR	5-yr OS: 53.1% *vs.* 29.7%	32.2% *vs.* 18.5%
Kodera *et al*. (53) 2016	Japan	RCT	35.9% *vs.* 27.3%	Surgery + IPC [39] *vs.* surgery+ IVC [44]	PTX 60 mg/m^2	51.3% *vs.* 59.1%	14% *vs.* 11%	0% *vs.* 1%	NR	–

IPC, intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; IFCCs, intraperitoneal free cancer cells; NR, not reported; MMC, mitomycin C; OS, overall survival; CNPP, chemonormothermic peritoneal perfusion; CDDP, cisplatin; VP16, etoposide; EPIL, extensive postoperative intraperitoneal lavage; FUDR, floxuridine; EPIC, early postoperative intraperitoneal chemotherapy; PTX, paclitaxel; 5-FU, 5-fluorouracil; IVC, intravenous chemotherapy.

Table 3 Therapeutic IPC/HIPEC in the treatment of macroscopic PC from gastric cancer

Ref.	Country	Type of study	Treatment arms [No. of patients]	Drugs used for IPC/HIPEC	Duration (min)	Morbidity	Mortality	Outcome
Yonemura *et al*. (54) 1991	Japan	Prospective	Surgery + HIPEC [41]	MMC 5 μg/mL + CDDP 30 μg/mL	40–60	12.0%	0%	Median OS: 14.5 mo; 3-yr: 28.5%
Yonemura *et al*. (55) 1996	Japan	Prospective	Surgery + HIPEC [83]	MMC 30 mg + CDDP 300 mg	60	NR	NR	1-yr OS: 43.0%; 5-yr OS: 11.0%
Fujimoto *et al*. (56) 1997	Japan	Prospective case-control	Surgery + HIPEC [48] *vs.* surgery alone [18]	VP16 150 mg + MMC 10 μg/mL	120	NR	NR	1-yr OS: 54.0% *vs.* 11.0%; 3-yr OS: 42.0% *vs.* 0%; 5-yr OS: 31.0% *vs.* 0%; 8-yr OS: 25.0% *vs.* 0%
Hirose *et al*. (42) 1999	Japan	Prospective case-control	CRS +HIPEC [17] *vs.* CRS alone [20]	MMC 20 mg + CDDP 100 mg + VP16 100 mg	50	35.2% *vs.* 20.0%	5.8% *vs.* 0%	Median OS: 11 *vs.* 6 mo; 1-yr OS: 44.4% *vs.* 15.8%
Glehen *et al*. (57) 2004	France	Prospective	CRS +HIPEC [49]	MMC 40–60 mg	90	27.0%	4.0%	Median OS: 10.3 mo; 5-yr OS: 16.0%
Hall *et al*. (58) 2004	United States	Prospective case-control	CRS +HIPEC [34] *vs.* surgery alone [40]	MMC 40 mg	120	35.0%	0%	Median OS: 8 mo; 1-yr OS: 36.0%; 2-yr OS: 26.0%; 5-yr OS: 12.0% (all patients)
Yonemura *et al*. (59) 2005	Japan	Retrospective	Peritonectomy + HIPEC [42] *vs.* conventional surgery + HIPEC [65]	MMC 30 mg + CDDP 300 mg + VP16 150 mg	60	43.0% *vs.* 8.0%	7.0% *vs.* 0%	Median OS: 11 mo; 5-yr OS: 6.7% (all patients)
Zhu *et al*. (47) 2006	China	Prospective case control	Surgery + HIPEC [10] *vs.* surgery alone [12]	CDDP 50 μg/mL + MMC 5 μg/mL	60	NR	0%	Median OS: 10 *vs.* 5 mo
Cheong *et al*. (60) 2007	Korea	Prospective	Surgery + EPIC [154]	5-FU 500 mg/m^2 + CDDP 40 mg/m^2	60	22.7%	2.6%	Median OS: 11.4 mo; 5-yr: 12.2%
Scaringi *et al*. (61) 2008	France	Retrospective	CRS +HIPEC [26]	MMC 120 mg + CDDP 200 mg/m^2	60–90	27.0%	3.8%	Median OS: 6.6 mo (all patients); CC0 *vs.* CC ≥1: 15 *vs.* 3.9 mo

Table 3 *(continued)*

Table 3 *(continued)*

Ref.	Country	Type of study	Treatment arms [No. of patients]	Drugs used for IPC/ HIPEC	Duration (min)	Morbidity	Mortality	Outcome
Glehen *et al*. (62) 2010	France	Retrospective	CRS + HIPEC and/or EPIC [159]	HIPEC: MMC 30–50 mg/m^2 + CDDP 50–100 mg/m^2; or OX 360–460 mg/m^2 ± irinotecan 100–200 mg/m^2 ± i.v. 5-FU and leucovorin; EPIC: MMC 10 mg/m^2 + 5-FU 600 mg/m^2	60–120	27.8%	6.5%	Median OS: 9.2 mo; 5-yr OS: 13%
Yang *et al*. (63) 2010	China	Prospective	CRS + HIPEC [28]	MMC 30 mg + CDDP 120 mg	90–120	14.3%	0%	1-yr OS: 78.6%; 2-yr OS: 42.8%
Yang *et al*. (64) 2011	China	RCT	CRS + HIPEC [34] *vs.* CRS alone [34]	MMC 30 mg + CDDP 120 mg	60–90	14.7% *vs.* 11.7%	NR	Median OS: 11.0 *vs.* 6.5 mo; 1-yr OS: 41.2% *vs.* 29.4%; 2-yr OS: 14.7% *vs.* 5.9%; 3-yr OS: 5.9% *vs.* 0%
Magge *et al*. (65) 2014	United States	Prospective	CRS + HIPEC [23]	MMC 40 mg	100	52.0%	4.3%	Median OS: 9.5 mo; 3-yr OS: 18%
Rudloff *et al*. (66) 2014	United States	RCT	CRS + HIPEC [9] *vs.* chemotherapy alone [8]	OX 460 mg/m^2	30	11.0%	NR	Median OS: 11.3 *vs.* 4.3 mo
Wu *et al*. (67) 2016	China	Prospective	CRS + HIPEC + IPC [50]	LOB 50 mg/m^2 + DOC 60 mg/m^2; IPC: LOB 50 mg/m^2 + DOC 60 mg/m^2	60	23.0%	0%	Median OS: 14.3 mo; 1-yr OS: 58%; 2-yr OS: 40%; 3-yr OS: 32%

IPC, intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; PC, peritoneal carcinomatosis; MMC, mitomycin C; CDDP, cisplatin; OS, overall survival; NR, not reported; VP16, etoposide; CRS, cytoreductive surgery; 5-FU, 5-fluorouracil; CC, completeness of cytoreductive; EPIC, early postoperative intraperitoneal chemotherapy; OX, oxaliplatin; LOB, lobaplatin; DOC, docetaxel.

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Footnote

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