Review Article on Gastric Cancer

Intra-operative hyperthermic intraperitoneal chemotherapy for prevention and treatment of peritoneal metastases from gastric cancer: a narrative review

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Abstract: Peritoneal metastasis (PM) from gastric cancer (GC) has long been regarded as the terminal disease, lacking of effective treatments. In recent 40 years, cytoreductive surgery (CRS) plus perioperative intraperitoneal chemotherapy, including hyperthermic intraperitoneal chemotherapy (HIPEC), neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), and early post-operative intraperitoneal chemotherapy (EPIC), has been recommended as a preferred treatment option for some selected patients with GCPM. Intraperitoneal free cancer cells were recognized as the pathological cause of PM and the primary target for intraperitoneal chemotherapy. There were a lot of evidence demonstrating that HIPEC could effectively eradiate intraperitoneal free cancer cells and prolong overall survival in GCPM. However, there are still no standard HIPEC protocols. This review summarized the current HIPEC regimens used in GCPM from a literature search, trying to conclude the optimal HIPEC in GCPM, and indicate the future direction of HIPEC study. Moreover, the new data on the exploration of HIPEC in GCPM at Shijitan Hospital, Capital Medical University was shared. In conclusion, there was not enough evidence from publications and our own experience to conclude a recommended HIPEC regimen for GCPM. There is urgent need for standardizing HIPEC protocols worldwide. Accordingly, more international collaborations focusing on pharmacology and HIPEC-related parameters to generate high level evidence are essential.

Keywords: Cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy; gastric cancer (GC); peritoneal metastasis (PM)

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Introduction

Peritoneal metastasis (PM) is the most common, aggressive and lethal type of metastasis of gastric cancer (GC), in the era of standard D2 gastrectomy plus systemic chemotherapy, and has long been regarded as an incurable condition with rapidly deteriorating symptoms of refractory ascites, progressive intestinal obstruction, and uncontrollable abdominal pain (1).

Over the past four decades, significant improvements have been achieved in the field of peritoneal surface oncology. It is now generally accepted in the oncology community that in some highly selected patients peritoneal metastasis is a regional and treatable disease instead of a terminal disease (2). An integrated therapeutic package combining cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy, including hyperthermic

intraperitoneal chemotherapy (HIPEC) has been developed to treat peritoneal surface malignancies, with curative or palliative intents (3).

Recently, the Chicago Consensus on the management of GCPM recommended CRS with gastrectomy and intraperitoneal chemotherapy as the treatment for synchronous GCPM with low peritoneal cancer index following by standard chemotherapy (4). However, the drug regimen, dose, temperature, duration and other parameters of HIPEC are still not standardized.

As an established center for peritoneal surface cancer in China, with the capacity of over 200 CRS + HIPEC procedures per year, our center has long been devoted to the development, application, promotion, and education on the integrated treatment of PM from gastrointestinal and gynecological malignancies. In this review, our goal is to update our exploration of optimal HIPEC in GCPM and summarize the current HIPEC strategies from a review of the literature, trying to identify the future direction of HIPEC study in GCPM. We present the following article in accordance with the Narrative Reporting Checklist (available at http://dx.doi.org/10.21037/jgo-20-262).

Rationale for HIPEC in GCPM

Intraperitoneal free cancer cells (IFCCs) originating from spontaneous exfoliation of the primary tumour or iatrogenic dissemination at the time of surgery are the pathological cause of GCPM (5). It has been described by Yonemura *et al.* that IFCCs could invade into peritoneum through transmesothelial and translymphatic pathways (6) (*Figure 1*). In other words, IFCCs and the resulting invisible micrometastasis on peritoneal surfaces are the primary target for preventing and treating GCPM.

The presence of plasma-peritoneal barrier makes the peritoneal cavity a relatively closed space lacking blood vessels and accounting for the poor effect of intravenous chemotherapy. HIPEC is designed to exploit the function of plasma-peritoneal barrier; that is to achieve a high intraperitoneal concentration of chemotherapeutics with a low plasma concentration. This positive gradient of chemotherapy in the peritoneum will intensify its direct antitumor effect with less systemic adverse effects. Hyperthermia itself has direct detrimental effects on IFCCs and also enhances the effects of intraperitoneal chemotherapy by increasing the depth of drug penetration and the drug uptake by tumor cells (5). We reported that HIPEC will effectively eradicate IFCCs in 78% patients with peritoneal metastasis. This was determined by detecting pre- and post-HIPEC viability of IFCCs using traditional cytological assessment. However, HIPEC failed to significantly reduce the molecular markers, like CEA mRNA and CK20 mRNA (*Figure 2*) (7).

Role of HIPEC in GCPM

It has been accepted that CRS+HIPEC is a promising integrated treatment strategy for GCPM (1). There is no doubt that CRS plays a fundamental role in this comprehensive package, and the completeness of CRS is the dominant independent prognostic factor for overall survival (OS). However, HIPEC is also an essential complement, rather than an alternative technique in the treatment of GCPM. *Table 1* lists the published controlled studies comparing CRS+HIPEC versus CRS alone in GCPM (8-15), including only 1 prospective randomized control trial (RCT) and 7 retrospective analyses. Within these studies, 6 (75%) demonstrated that HIPEC could significantly prolong the OS for GCPM as compared to CRS alone. However, more well designed RCTs are urgently needed for verifying the role of HIPEC in the management of GCPM, due to the lower evidence level of the available trials. Currently, the GASTRIPEC trial (NCT02158988) is the only active multicenter RCT focusing on CRS+HIPEC in GCPM, aiming to compare the efficacy and safety of CRS with or without HIPEC using mitomycin C and cisplatin. We hope this trial may bring some new evidence into this uncertain filed.

Current HIPEC regimens in GCPM from a literature search

The optimal methodology for HIPEC remains an unsolved problem. The multiple HIPEC regimens from 29 publications are listed in *Table 2*. We could conclude the following characteristics. First, 65% (17/26) centers preferred an open technique instead of closed technique, although there was no evidence to distinguish these two methods. Moreover, the open-technique was more frequently used in Japan and China, while the closed technique was more common in USA. Second, a combined drug regimen was used more frequently than monochemotherapy. Mitomycin C in early years or more recently oxaliplatin nowadays has been used as a single

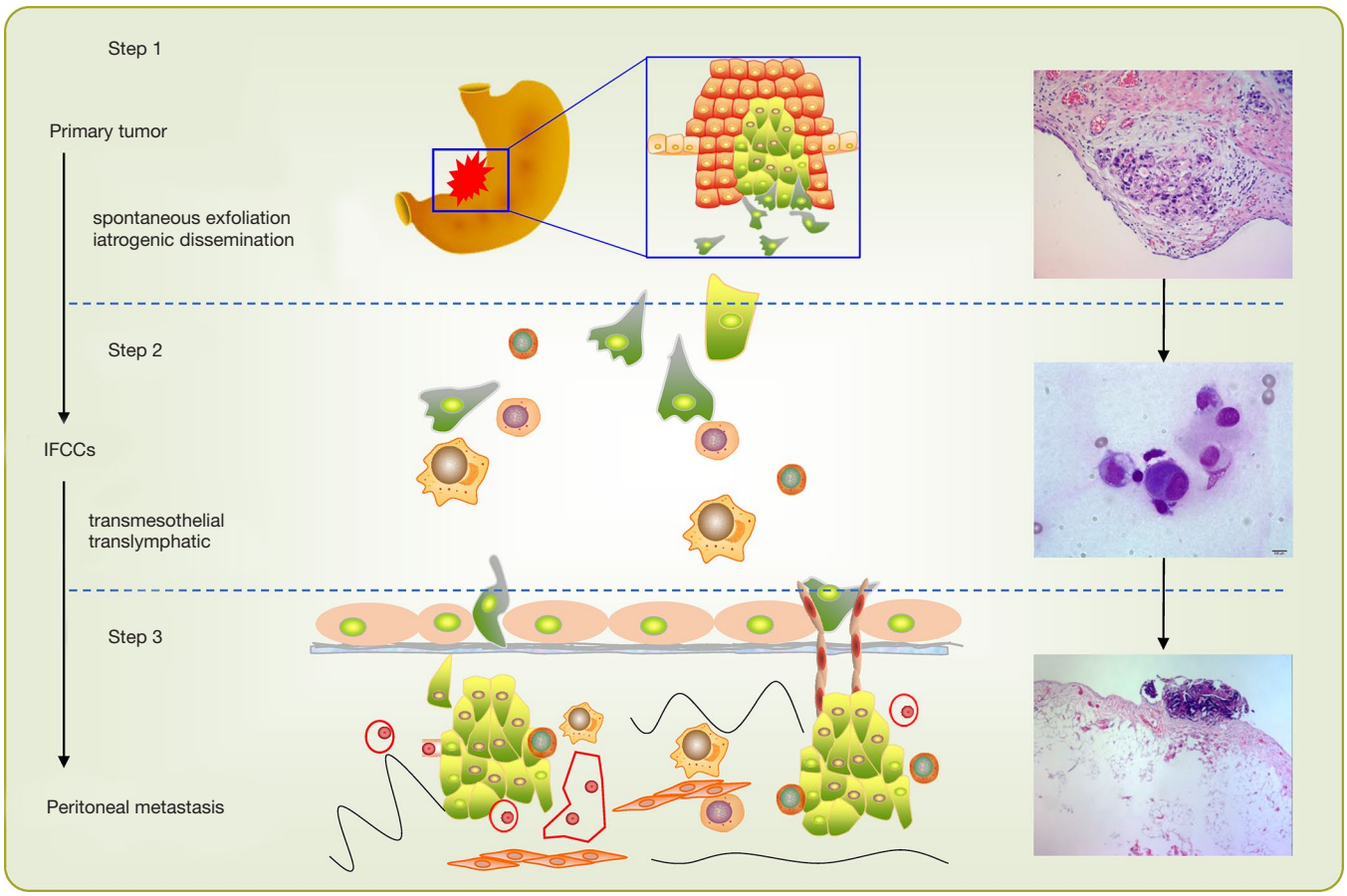

Figure 1 Mechanism of peritoneal metastasis from gastric cancer. Step 1: Cancer cell exfoliated from primary tumor, as a result of cancer invasion through serosa and/or iatrogenic dissemination during surgery. Step 2: Intraperitoneal free cancer cells (IFCCs) invade into subperitoneal space by directly interaction with mesothelium cells or through lymphatic orifices opening on peritoneal surface. Step 3: The integrity of the peritoneal-blood barrier is broken forming a favorable site for tumor proliferation. IFCCs colonize near the subperitoneal capillary, and proliferate via autocrine or paracrine stimulation by production of growth factors and neovascularization induced by angiogenic factors. The parallel pathologic image stained by HE method is shown on the right side. This figure was adapted from the original drawing of Yutaka Yonemura (6).

agent for HIPEC. The most common drug combination was cisplatin + mitomycin C ± etoposide and cisplatin + doxorubicin. Third, the dose of monochemotherapy with mitomycin C or oxaliplatin was relatively fixed. However, the dose of combined drugs varied widely. Fourth, there was no standard temperature and duration for HIPEC. The temperature of HIPEC in 29 publications ranged from 40 to 45 ℃, and the duration ranged from 30 to 120 minutes. Fifth, the flow rate, carrier solution, and other parameters were not precisely discussed in these publications. Sixth, the HIPEC regimens were relatively conservative in Asia and USA, but quite aggressive in Europe. The multicenter studies in European countries showed that the HIPEC regimens varied widely from different centers even within the same country (8,39,40).

Exploration of HIPEC in GCPM at Shijitan Hospital

In 2011, our group published the first phase III RCT comparing CRS+HIPEC or CRS alone in GCPM. In this protocol we used the open-technique for HIPEC, with 120 mg of cisplatin and 30 mg of mitomycin C at 43.0±0.5 ℃ for 60–90 minutes (10). The trial showed that such HIPEC regimens could significantly improve survival with acceptable morbidity in synchronous GCPM patients.

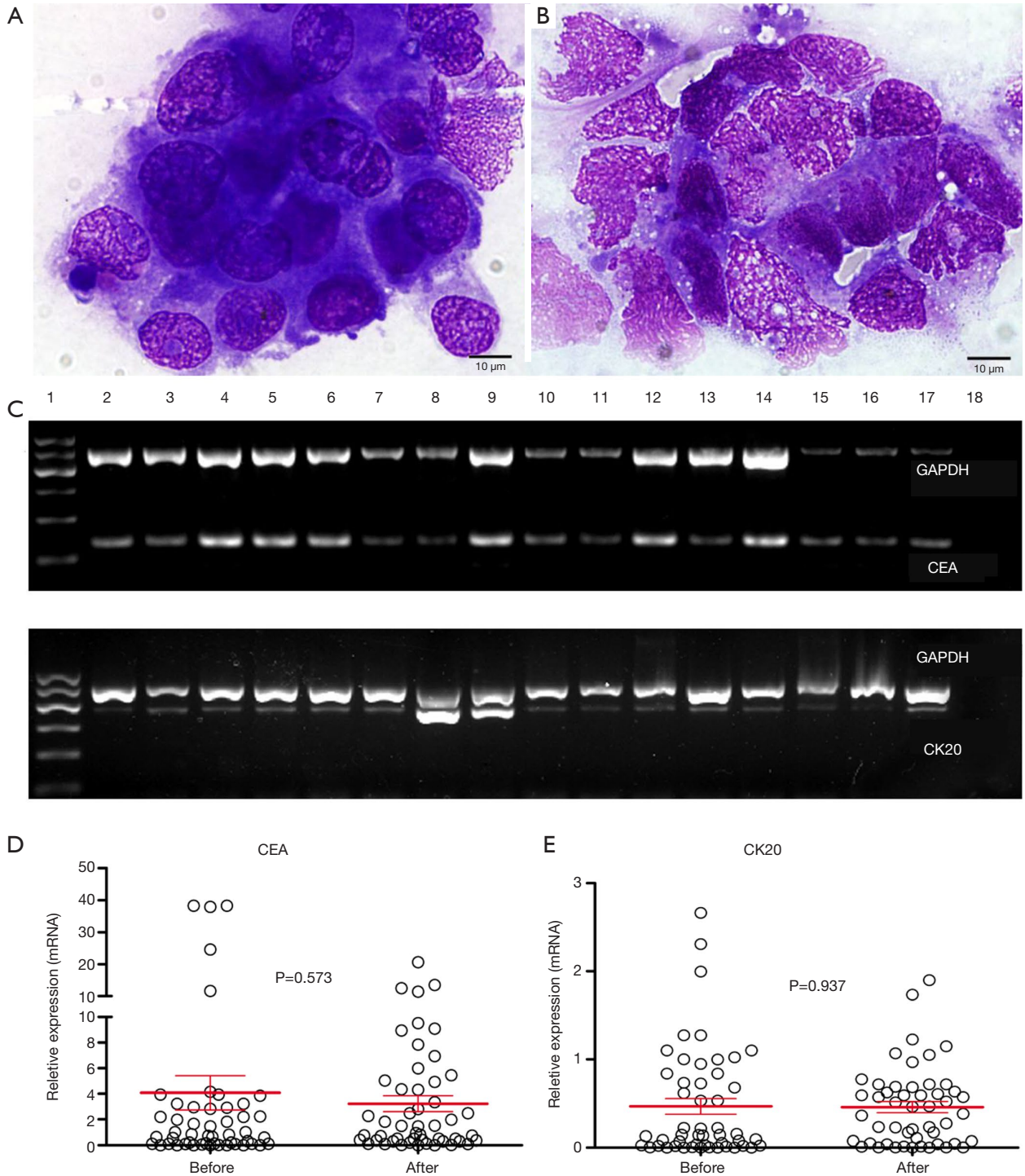

Figure 2 Assessment of hyperthermic intraperitoneal chemotherapy (HIPEC) in treating intraperitoneal free cancer cells (IFCCs) by conventional cytology (A: IFCCs before HIPEC, B: IFCCs after HIPEC) and RT-PCR method (C: Agarose gel electrophoresis of the product of CEA and CK20, D: CEAmRNA value before and after HIPEC, E: CK20 mRNA value before and after HIPEC). wright's stain, 1,000×, scale bar =10 μm in A and B. Lane 1 is a DNA maker from 100 bp (bottom) to 600 bp (top); lanes 3 to 17 are the patients' samples; lane 2 is the positive control; lane 18 is the negative control in C. Horizontal lines represent mean ± standard error in D and E.

Table 1 Publications comparing CRS+HIPEC versus CRS alone in peritoneal metastasis from gastric cancer

Reference	Design	Treatment arms [No. of pts]	Median OS	1-yr OS (%)	2-yr OS (%)	3-yr OS (%)	5-yr OS (%)	P[a]
Bonnot 2018 (8)	Retrospective	CRS + HIPEC [180] *vs.* CRS [97]	18.8 *vs.* 12.1	NR	NR	26.2 *vs.* 10.8	19.9 *vs.* 6.4	0.005
Boerner 2016 (9)	Retrospective	CRS + HIPEC [38] *vs.* CRS + SC [27]	17.2 *vs.* 11.0	71.1 *vs.* 33.3	35.8 *vs.* 16.9	24.1 *vs.* 0	6.4 *vs.* 0	0.004
Yang 2011 (10)	Prospective	CRS + HIPEC [34] *vs.* CRS [34]	11.0 *vs.* 6.5	41.2 *vs.* 29.4	14.7 *vs.* 5.9	5.9 *vs.* 0	NR	0.046
Kang 2013 (11)	Retrospective	CRS + HIPEC [16] *vs.* CRS [31]	14.6 *vs.* 8.0[b]	NR	NR	NR	NR	0.486
Zhu 2006 (12)	Retrospective	CRS + HIPEC [10] *vs.* CRS [12]	10.0 *vs.* 5.0	NR	NR	NR	NR	0.041
Hall 2004 (13)	Retrospective	CRS + HIPEC [34] *vs.* CRS [40]	8.0 *vs.* 7.8	27.0 *vs.* 41.0	23.0 *vs.* 28.0	NR	6.0 *vs.* 17.0	0.29
Hirose 1999 (14)	Retrospective	CRS + HIPEC [17] *vs.* CRS [20]	11.0 *vs.* 6.0	44.4 *vs.* 15.8	NR	NR	NR	0.114
Fujimoto 1997 (15)	Retrospective	CRS + HIPEC [48] *vs.* CRS [18]	14.1 *vs.* 8.2	54.0 *vs.* 11.0	NR	41.5 *vs.* 0	31.0 *vs.* 0	0.002

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; NR, not reported. [a]log-rank test; [b]mean value.

Thereafter, we tried lobaplatin + docetaxel combination in an open HIPEC technique. 50 mg/m^2 of lobaplatin and 60 mg/m^2 of docetaxel was each were dissolved in 3 L of normal saline. HIPEC was performed at 43.0±0.5 ℃ for 60 minutes. This regiments also showed efficacy and safety in GCPM patients (26).

However, we then changed our HIPEC regimen due to some non-medical reasons, like health economic disadvantage of lobaplatin, and short supply of mitomycin C. Lobaplatin was replaced by Cisplatin for HIPEC.

Recently, we retrospectively analyzed 125 GCPM patients treated with CRS+HIPEC at our center and investigated the impact of different HIPEC regimens on OS. The median OS for HIPEC-drug combination of cisplatin + docetaxel, lobaplatin + docetaxel, and cisplatin + mitomycin C was 12.4 (95% CI: 8.3–16.5) months, 10.9 (95% CI: 7.5–14.3) months, and 8.4 (95% CI: 3.6–13.1) months, respectively (P=0.073) (*Figure 3A*). Although, there was no significant difference among these three groups, the first two groups showed a better result in short term survival. In terms of temperature, the median OS was 10.7 (95% CI: 9.1–12.3) months in 43 ℃-HIPEC group, significantly better than 9.3 (95% CI: 6.0–12.5) months in 42 ℃-HIPEC group (P=0.030) (*Figure 3B*). In terms of duration, the median OS was 10.9 (95% CI: 7.3–14.5) months in 60-minute group, significantly better than 10.3 (95% CI: 8.1–12.4) months in 90-minute group (P=0.026) (*Figure 3C*). However, these factors showed no independently significant effect on OS.

Conclusion

Theoretically, CRS+HIPEC is designed as an integrated therapeutic package for peritoneal surface malignancies for cytologically radical resection and possible cure, with CRS for macroscopic resection of tumor nodules and HIPEC for microscopic eradication of IFCCs and micrometastasis. The recent PRODIGE 7 trial demonstrated an impressive advantage of complete CRS, but failed to verify the efficacy of HIPEC. This trial brings us a realization that we did not pay enough attention to HIPEC. It was discouraging that, we had not enough evidence from these publications and our own experience to conclude a recommended HIPEC regimen for GCPM. There is urgent need for standardizing HIPEC protocols worldwide. Accordingly, more international collaborations focusing on pharmacology and HIPEC-related parameters to generate high level evidence are essential.

Table 2 Hyperthermic intraperitoneal chemotherapy regimens in publications

Reference	Nation	No.	HIPEC regimen			
			Technique	Drug & dose	Temperature (℃)	Duration (min)
Yonemura 1991 (16)	Japan	41	Open	CDDP 300 mg + MMC 50 mg	41–43	40–60
Yonemura 1996 (17)	Japan	83	Open	CDDP 300 mg + MMC 30 mg + VP-16 150 mg	42–43	60
Fujimoto 1997 (15)	Japan	66	Closed	MMC 30–40 mg	44.5–45	120
Hirose 1999 (14)	Japan	37	Open	CDDP 100 mg + MMC 20 mg + VP-16 100 mg	41.0–44.5	NR
Fujimura 2000 (18)	Japan	15	Open	CDDP 150–250 mg + MMC 60–100 mg + VP-16 120–200 mg	42–43	60
Yonemura 2005 (19)	Japan	107	NR	CDDP 300 mg + MMC 30 mg + VP-16 150 mg	42–43	NR
Canbay 2014 (20)	Japan	194	Open	DOC 30 mg/m^2	NR	NR
Yonemura 2020 (21)	Japan	255	Open	MMC 12.5 mg/m^2 + CDDP 50 mg/m^2	42–43.5	NR
Hall 2004 (13)	USA	74	Closed	MMC 40 mg	40–41	120
Shen 2009 (22)	USA	62	Closed	MMC 40 mg	40–42.5	120
Magge 2014 (23)	USA	23	Closed	MMC 40 mg	42	100
Rudloff 2014 (24)	USA	17	Closed	L-OHP 460 mg/m^2	41	30
Zhu 2006 (12)	China	22	NR	CDDP 250–300 mg + MMC 25–30 mg	43.0±1.0	60
Yang 2010 (25)	China	28	Open	HCPT 20 mg/CDDP 120 mg + MMC 30 mg	43	90–120
Yang 2011 (10)	China	68	Open	CDDP 120 mg + MMC 30 mg	43	60–90
Kang 2013 (11)	Taiwan China	47	Open	CDDP 90–120 mg + MMC 30–40 mg + VP-16 60–80 mg	41-43	60
Wu 2016 (26)	China	50	Open	LOB 50 mg/m^2 + DOC 60 mg/m^2	43	60
Tu 2016 (27)	China	231	Closed	5-FU 1,500 mg + CDDP 100 mg	43	60
Beaujard 2000 (28)	France	42	Closed	MMC 40–60 mg	45 [41-49]	90
Glehen 2004 (29)	France	49	Closed	MMC 40–60 mg	40–43	90
Scaringi 2008 (30)	France	26	Open	CDDP 200 mg/m^2 + MMC 120 mg	41–43	90–120
Glehen 2010 (31)	France	159	Open/ Closed	CDDP 50–100 mg/m^2 + MMC 30–50 mg/m^2 or L-OHP 360–460 mg/m^2 + CPT-11 100–200 mg/m^2	40–43	60–120 or 30
Desantis 2015 (32)	France	14	Open	CDDP 50 mg/m^2/L + DOX 15 mg/m^2/L	43	60
Konigsrainer 2014 (33)	Germany	18	Open	CDDP 50 mg/m^2	42	90
Boerner 2016 (9)	Germany	103	Closed	CDDP 75 mg/m^2 + DOX 15 mg/m^2	42–43	60
Hultman 2013 (34)	Sweden	18	Open	CDDP 50 mg/m^2 + DOX 15 mg/m^2 or L-OHP 460 mg/m^2	42–44	90 or 30
Yarema 2014 (35)	Ukraine	40	NR	CDDP 75 mg/m^2 + MMC 12.5 mg/m^2	42.3±1.3	90
Muller 2014 (36)	Greece	26	Open	L-OHP 200 mg/m^2 + DOC 80 mg/m^2	NR	NR
Caro 2018 (37)	Spain	35	Open	CDDP 100 mg/m^2 + Dox 15 mg/m^2	42–43	90
Reutovich 2019 (38)	Belarus	76	Closed	CDDP 50 mg/m^2 + Dox 50 mg/m^2	42	60

MMC, mitomycin C; CDDP, cisplatin; VP-16, etoposide; L-OHP, oxaliplatin; HCPT, hydroxycamptothecine; LOB, lobaplatin: DOC, docetaxel: 5-FU, 5-Fluorouracil; DOX, doxorubicin; CPT-11, irinotecan; NR, not reported.

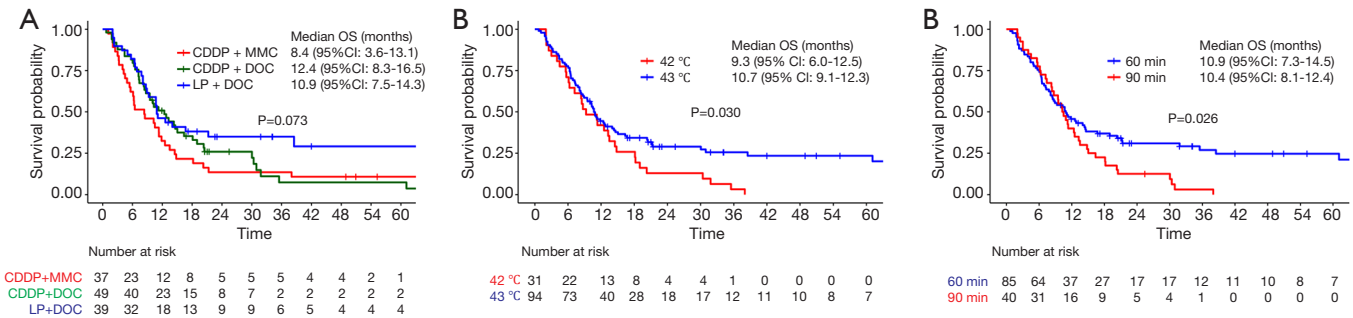

Figure 3 Kaplan-Meier curves and comparations of hyperthermic intraperitoneal chemotherapy (HIPEC) regimens: drugs (A), temperature (B) and duration (C). CDDP, cisplatin; MMC, mitomycin C; DOC, docetaxel; LP, lobaplatin.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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