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Original Article

Quality of life outcomes from the randomized trial of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery for primary ovarian cancer (KOV-HIPEC-01)

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ABSTRACT

Objective: To investigate the health-related quality of life (HRQOL) related to hyperthermic intraperitoneal chemotherapy (HIPEC) following primary or interval cytoreductive surgery for primary ovarian cancer.
Methods: Between 2010 and 2016, a total of 184 patients were randomly assigned to receive cytoreductive surgery with HIPEC (n=92) or without HIPEC (n=92). Quality of life (QOL) assessment was evaluated at baseline (before surgery); on postoperative day 7; after the 3rd and 6th cycle of adjuvant chemotherapy; and at 3, 6, 9, and 12 months after randomization. Patient-reported QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC-QLQ-C30), ovarian cancer questionnaire modules (QLQ-OV28), and the MD Anderson Symptoms Inventory (MDASI).
Results: Of the 184 patients enrolled, 165 (83/92 in the HIPEC group and 82/92 in the control group) participated in the baseline QOL assessment. There were no statistically significant differences in functional scales and symptom scales in QLQ-C30; symptom scales, including gastrointestinal symptoms QLQ-OV28; and severity and impact score in MDASI between the 2 treatment groups until 12 months after randomization.
Conclusion: HIPEC with cytoreductive surgery showed no statistically significant difference in HRQOL outcomes. Thus, implementation of HIPEC during either primary or interval cytoreductive surgery does not impair HRQOL.

Trial Registration: ClinicalTrials.gov Identifier: NCT01091636

Keywords: HIPEC; Ovarian Cancer; Quality of Life

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: K.J.H., L.M.C.; Data curation: K.J.H., L.D.E., L.Y.; Formal analysis: K.J.H., L.D.E., C.Y.J., P.S.Y., L.M.C.; Investigation: L.Y., H.H.I., C.Y.J., C.S.J., P.S.Y., L.M.C.; Methodology: K.J.H., L.D.E.; Resources: L.M.C.; Supervision: C.S.J., P.S.Y., L.M.C.; Visualization: K.J.H.; Writing - original draft: K.J.H., H.H.I., L.M.C.; Writing - review & editing: K.J.H., L.Y., H.H.I., C.Y.J., C.S.J., P.S.Y., L.M.C.

Synopsis
Quality of life was assessed during a randomized phase III trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in stage III–IV ovarian cancer. HIPEC with primary or interval cytoreductive surgery demonstrated no statistically significant difference in health-related quality of life outcomes.

INTRODUCTION

Ovarian cancer is one of the highest lethal diseases in gynecologic cancers [1-3]. Most patients with ovarian cancer are diagnosed at an advanced stage with peritoneal carcinomatosis, followed by standard treatment of cytoreductive surgery and platinum-based chemotherapy [4]. Although 75%–80% of patients respond to initial treatment, the recurrence rate is high at 80%, requiring additional active treatment modalities, including surgery and systemic treatment [5-7].

Three large, multicenter, randomized controlled studies conducted by the Gynecologic Oncology Group (GOG) demonstrated that intraperitoneal (IP) chemotherapy confers improved median progression-free survival (PFS) and overall survival (OS) in advanced epithelial ovarian cancer with minimal residual tumor compared to intravenous chemotherapy [4-6]. However, IP chemotherapy has not been widely accepted as a front-line treatment for ovarian cancer owing to regimen toxicity and IP port-related complications, resulting in a low completion rate of planned chemotherapy [8,9]. As an alternative locoregional chemotherapy delivery method, hyperthermic IP chemotherapy (HIPEC) has been investigated in primary and recurrent ovarian cancers in recent years [10-14].

The current randomized phase III trial of HIPEC after primary and interval cytoreductive surgery in stage III–IV ovarian cancer (KOV-HIPEC-01) showed no OS benefit in terms of PFS and OS [15]. But, subgroup analysis of patients with HIPEC following interval cytoreductive surgery showed improvement in PFS and OS.

To date, the first study of health-related quality of life (HRQOL) analysis after HIPEC was reported from a randomized trial of HIPEC in patients with stage III ovarian cancer who received neoadjuvant chemotherapy [16]. With the concern of a higher frequency of grade 3 or worse late postoperative complications, particularly hematological complications, when HIPEC is added during cytoreductive surgery, as shown in the PRODIGE 7 trial [17], this study aimed to investigate HRQOL in patients after cytoreductive surgery and HIPEC and compare it with patients without HIPEC.

MATERIALS AND METHODS

1. Study design and patients

The study was a single-blinded randomized controlled trial that compared the outcomes of cytoreductive surgery plus HIPEC and cytoreductive surgery alone. Patients with stage III–IV epithelial ovarian cancer who achieved optimal cytoreduction were enrolled in this trial and randomized in a 1:1 allocation ratio. The details of the trial have been reported in the previous article [15].

The primary endpoint of the trial was PFS. HRQOL was a secondary endpoint in the trial, which was analyzed using the same data cut-off as the primary intention-to-treat analysis. Written informed consent was obtained from all the enrolled patients. The Institutional Review Board of the National Cancer Center approved the trial protocol (NCCCTS-06-222) and registered at ClinicalTrials.gov (NCT01091636).

2. Quality of life assessment plan

HRQOL was assessed using 3 questionnaires: the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC-QLQ-C30), ovarian cancer questionnaire modules (QLQ-OV28), and the MD Anderson Symptoms Inventory (MDASI). These self-administered questionnaires were assessed at the following 8 time points: before randomization, on postoperative day 7, after 3 cycles of adjuvant chemotherapy, after 6 cycles of adjuvant chemotherapy, and at 3, 6, 9, and 12 months after treatment. Questionnaires submitted after disease recurrence or after the data cut-off were excluded from the HRQOL analysis.

The QLQ-C30 comprises 15 questions on the global health scale, functional status (physical, role, emotional, cognitive, and social), and symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). In addition, we calculated the summary score of the EORTC-QLQ-C30 from the 13 scales, excluding the financial impact scale and global health scale, according to the scoring manual (3rd edition) [18].

The QLQ-OV28 consists of 28 questions evaluating 6 categorized symptoms and 4 single-item symptoms (abdominal/GI symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal symptoms, body image, attitudes to disease/treatment, and sexuality) [19].

The MDASI comprises 2 scoring system categories: symptom severity and activity interference. The symptom severity score assesses the 13 symptoms at their worst in the last 24 hours with 0 to 10 numerical scales (pain, fatigue, nausea, disturbed sleep, distress or feeling upset, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness, or tingling) [20]. Symptom Interference scores 6 items that have interfered with daily activities (general activity, mood, work, relations with others, and enjoyment of life).

3. Statistical analysis

For baseline patient characteristics, the characteristics of the Intention to treat population and the quality of life (QOL) population were summarized, respectively. All QOL analyses were restricted to patients who completed the baseline QOL assessment. At each time point, the completion rate of the questionnaire was calculated. Demographic variables were compared between the intention-to-treat population and the HRQOL questionnaire participants.

A mixed-effects model with autoregressive (AR1) working correlation matrix was used in the analysis to include the case of no response at the time point, excluding the baseline. In addition, the mixed-effects model was used to compare changes in QOL over time according to the implementation of HIPEC. Additionally, HRQOL analyses were performed for the primary cytoreductive surgery and interval cytoreductive surgery subgroups.

All statistical analyses were performed using SAS 9.4 version (SAS Institute Inc., Cary, NC, USA). A 2-sided p-value less than 0.05 (2-sided) was considered statistically significant.

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RESULTS

1. Baseline characteristics

Between March 2010 and January 2019, 184 patients were randomly assigned to the HIPEC and control groups. Of these, 165 participated in the HRQOL questionnaire (**Fig. 1**). A total of 937 HRQOL questionnaires were collected, and 40 submitted forms were excluded because their time points were after recurrence or data cut-off.

Clinicopathological characteristics are presented in **Table 1**. No significant differences were observed between the treatment groups in age, stage, histology, performance status, prior use of neoadjuvant chemotherapy, and combined bowel resection. High-grade serous ovarian carcinoma was the most frequent histology (92.4% in the HIPEC group and 85.9% in control group), and bowel resection was performed in 79.4% and 73.9% of the HIPEC group and the control group, respectively.

2. Compliance

At each assessment point, the number of patients who answered with HRQOL questionnaire is shown in **Table 2**. The completion rate of HRQOL assessment at randomization was 89.1% (82 of 92 patients) in the control group and 90.2% (83 of 92 patients) in the HIPEC group. Four assessments until 6 cycles of adjuvant chemotherapy were valid in 79.7% (51 of 64 patients) of the control group and 88.4% (61 of 69 patients) of the HIPEC group. At the last time point of completion of all 8 assessments, validity was maintained at 89.5% (34 of 38 patients) in the control group and 81.0% (34 of 42 patients).

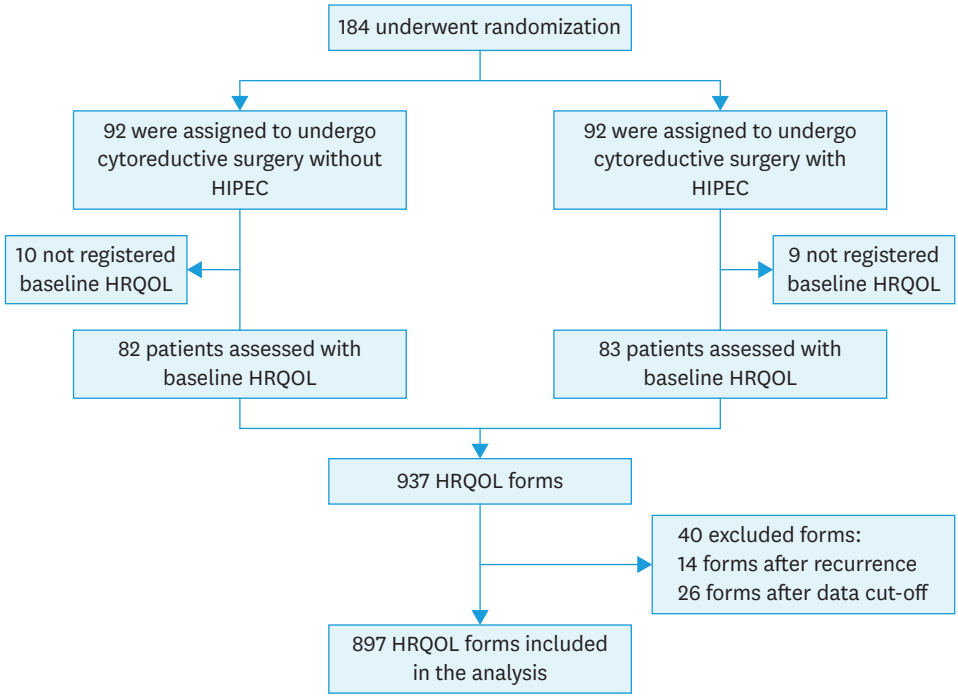

Fig. 1. CONSORT diagram for HRQOL assessment in KOV-HIPEC-01 trial.
HIPEC, hyperthermic intraperitoneal chemotherapy; HRQOL, health-related quality of life.

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Table 1. Patient characteristics

Variable	Intention to treat population			QOL population			Intention to treat population vs. QOL population
	Non-HIPEC (n=92)	HIPEC (n=92)	p-value	Non-HIPEC (n=82)	HIPEC (n=83)	p-value	p-value
Age (yr)			0.336*			0.447*	0.908*
Mean ± SD	54.0±9.7	53.1±9.7		54.0±10.1	53.2±9.6		
Median (Min–Max)	53.5 (25.0–72.0)	52.0 (28.0–74.0)		53.5 (25.0–72.0)	52.0 (28.0–74.0)		
Stage			0.175†			0.133†	0.775†
III	51 (55.4)	60 (65.2)		46 (56.1)	56 (67.5)		
IV	41 (44.6)	32 (34.8)		36 (43.9)	27 (32.5)		
Histology			0.228‡			0.202‡	1.000‡
Serous	79 (85.9)	85 (92.4)		70 (85.4)	76 (91.6)		
Endometrioid	5 (5.4)	3 (3.3)		5 (6.1)	3 (3.6)		
Clear cell	4 (4.4)	0 (0)		4 (4.9)	0 (0)		
Others	4 (4.4)	4 (4.3)		3 (3.7)	4 (4.8)		
Neoadjuvant chemotherapy			0.179†			0.483†	0.561†
No	49 (53.3)	58 (63.0)		48 (58.5)	53 (63.9)		
Yes	43 (46.7)	34 (37.0)		34 (41.5)	30 (36.1)		
Bowel resection			0.384†			0.447†	0.651†
No	24 (26.1)	19 (20.7)		23 (28.0)	19 (22.9)		
Yes	68 (73.9)	73 (79.4)		59 (72.0)	64 (77.1)		
ECOG performance			0.294†			0.129†	0.337†
0	51 (55.4)	58 (63.0)		48 (58.5)	58 (69.9)		
1	41 (44.6)	34 (37.0)		34 (41.5)	25 (30.1)		

ECOG, European Cooperative Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; QOL, quality of life; SD, standard deviation.
*Wilcoxon rank sum test; †Chi-squared test; ‡Fisher's exact test.

Table 2. Summary of questionnaire compliance at each assessment point

Assessment point	No. of patients (%)	
	Non-HIPEC (valid/expected)	HIPEC (valid/expected)
Patients enrolled	92	92
Before randomization	82/92 (89.1)	83/92 (90.2)
POD 7	81/82 (98.8)	75/83 (90.4)
After 3 cycles of adjuvant chemotherapy	62/74 (83.8)	68/76 (89.5)
After 6 cycles of adjuvant chemotherapy	51/64 (79.7)	61/69 (88.4)
3 mon after treatment	50/60 (83.3)	54/66 (81.8)
6 mon after treatment	41/51 (80.4)	46/54 (85.2)
9 mon after treatment	38/47 (80.9)	37/48 (75.5)
12 mon after treatment	34/38 (89.5)	34/42 (81.0)

HIPEC, hyperthermic intraperitoneal chemotherapy; POD, postoperative day.

3. HRQOL outcomes

QLQ-C30

No statistically significant difference in the QLQ-C30 summary score was found between the HIPEC and control groups over time (p=0.56). The QLQ-C30 summary score declined perioperatively but improved shortly after 3 cycles of adjuvant chemotherapy (**Fig. 2**). Similarly, the global health status (p=0.82) and functional scales of the QLQ-C30 were not significantly different between the 2 treatment groups. Physical and role function scores improved after surgery compared with baseline and declined until 12 months after treatment. On the other hand, emotional, cognitive and social functional scales declined more shortly after surgery than the baseline score 12 months after the end of adjuvant chemotherapy (**Fig. S1A**). The categories of symptom scales showed no statistical difference between the 2 groups, and their scores were highest on postoperative days 7 and declined throughout the time points (**Fig. S1B**).

QLQ-OV28

In the QLQ-OV28, patients showed higher scales of peripheral neuropathy and other chemotherapy side effects after 6 cycles of adjuvant chemotherapy than in the perioperative

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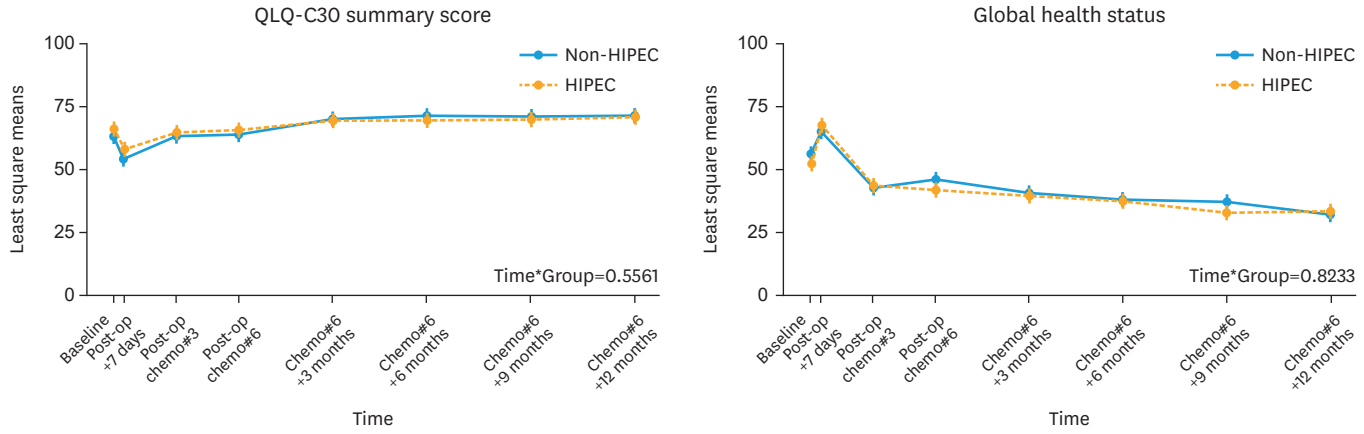

Fig. 2. Overall plots of summary score and global health status of EORTC QLQ-C30.
EORTC, European Organization for Research and Treatment of Cancer; HIPEC, hyperthermic intraperitoneal chemotherapy; QLQ-C30, quality of life questionnaire core 30.

period. For any scale of the QLQ-OV28, there was no statistically significant difference in the HRQOL (**Fig. 3A**).

MDASI

Both modules of symptom severity and impact were statistically insignificant between the 2 groups (**Fig. 3B**).

Detailed results including least square means and standard errors of 3 QOL values including QLQ-C30, QLQ-OV28, and MDASI are described in **Table S1**. Additionally, results of subgroup analyses of HRQOL in primary cytoreductive surgery and interval cytoreductive surgery are shown in **Fig. S2A and S2B** respectively. Full details are described in **Tables S2** and **S3**. Both subgroups showed no clinically relevant or statistically significant differences between the HIPEC and control groups.

DISCUSSION

The current trial showed improved PFS and OS with the addition of HIPEC to interval cytoreductive surgery compared to the control group [15]. As a secondary endpoint of the trial, we aimed to evaluate the impact of HIPEC administration during cytoreductive surgery on HRQOL. Subsequently, there was no difference in the overall HRQOL between the 2 treatment groups. Similarly, there was no difference in the subgroup analysis results between the primary cytoreductive surgery and interval cytoreductive surgery groups.

As the implementation of HIPEC requires surgical intervention similar to IP chemotherapy, there are concerns about additive postoperative toxicities and inferior HRQOL when HIPEC is applied [21-23]. In the case of a GOG randomized phase III trial (GOG 172) [8], treatment with IP cisplatin and paclitaxel plus intravenous paclitaxel in stage III epithelial ovarian cancer disrupted the overall physical and functional HRQOL until 6 months after IP chemotherapy. In particular, neurotoxicity-related symptoms persist for 12 months after IP chemotherapy [21]. However, HIPEC is a single-course treatment that lasts for 80–90 minutes, and there is no disadvantage in terms of port-related toxicities or inconvenience. Accordingly, even if HIPEC has a potential risk factor for hyperthermia with a high concentration of chemotherapy that can

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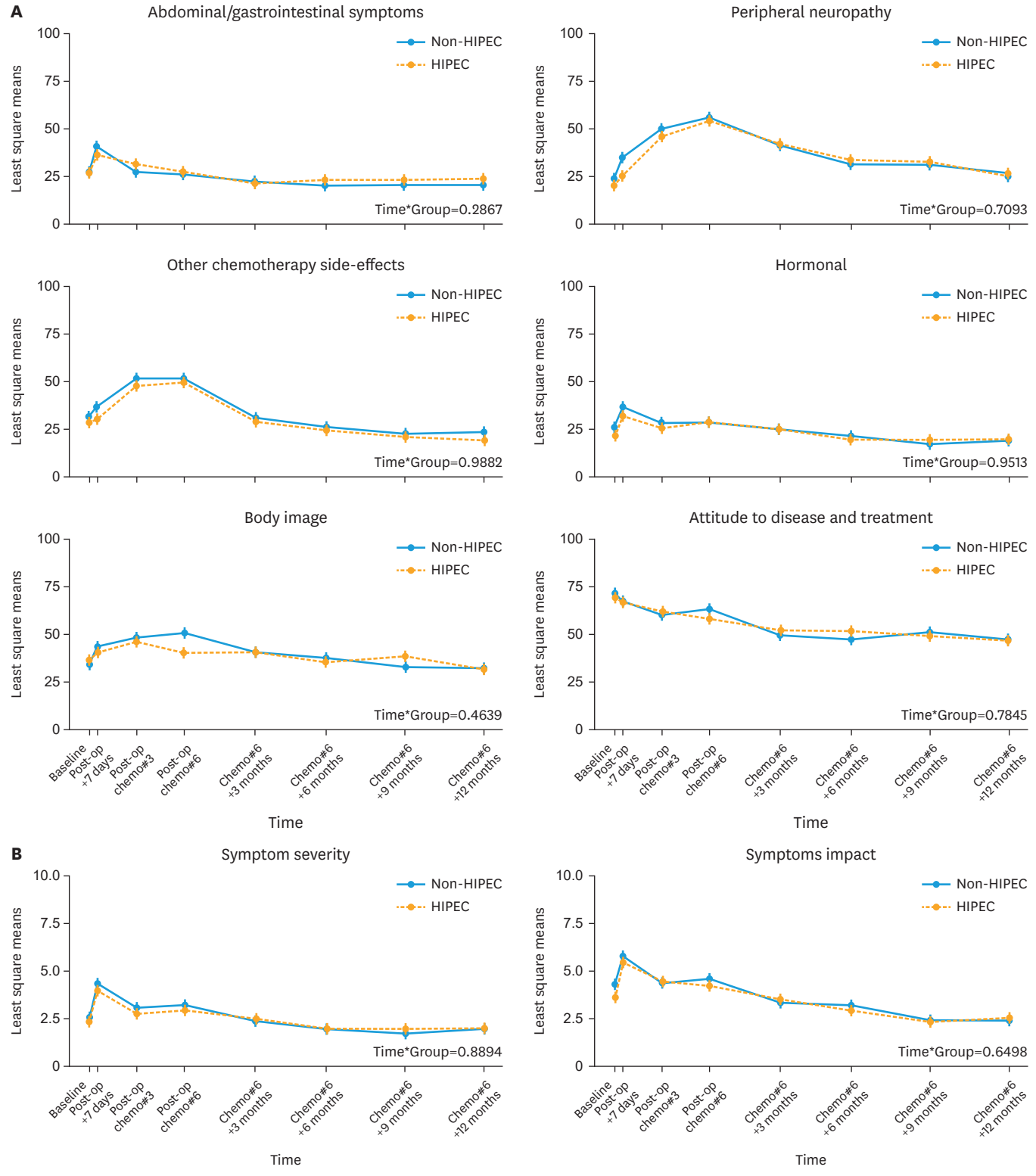

Fig. 3. Overall plots of EORTC QLQ-OV28 and MDASI. (A) Overall plots of EORTC QLQ-OV28. (B) Overall plots of MDASI.
EORTC, European Organization for Research and Treatment of Cancer; HIPEC, hyperthermic intraperitoneal chemotherapy; MDASI, MD Anderson Symptoms Inventory; QLQ-OV28, quality of life questionnaire ovarian cancer questionnaire modules.

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cause perioperative complications [14,24], there is no apparent exacerbation of HRQOL that lasts for 3–6 months after HIPEC. Notably, neurotoxicity-related and gastrointestinal symptoms had similar trajectories, irrespective of HIPEC.

Previous studies on HRQOL related to HIPEC consistently presented similar outcomes to the control group in several types of malignancies [16,25-27]. Koole et al. [16] reported that patients who were assigned to a phase III randomized controlled trial (OV-HIPEC-01) to receive interval cytoreductive surgery with or without HIPEC in stage III ovarian cancer had no significant statistical difference in HRQOL between treatment groups. Notably, physical and functional HRQOL fluctuated during cytoreductive surgery until 3 cycles after adjuvant chemotherapy but recovered back to the baseline HRQOL score.

The present study has several strengths. First, we investigated HRQOL, and subjects were randomly assigned to the trial groups. Second, this study investigated the difference between the interval cytoreductive surgery group that underwent 3 cycles of neoadjuvant chemotherapy and the primary cytoreductive surgery group for the first time. However, this study had some limitations. First, as HRQOL questionnaire at the immediate postoperative period was not assessed, this study couldn't assess the short-term effect of HIPEC on HRQOL. Second, the study had erratic missing data at each time point, and it might have a potential bias in HRQOL trajectories because patients with severe comorbidities are less likely to submit questionnaires at a longer time point. However, the compliance rate of questionnaires in both groups were not different, so this fact might neutralize the bias. Moreover, the current study collected 3 types of questionnaires at each visit, which might increase the respondent burden, one of the disturbance factors of compliance [28].

In conclusion, HIPEC with cytoreductive surgery demonstrated no statistically significant difference in HRQOL outcomes when compared with that in the control group. Based on the results of this study, HIPEC implementation during interval cytoreductive surgery could be considered a primary treatment option.

SUPPLEMENTARY MATERIALS

Table S1

Results of least square mean and standard errors of quality of life questionnaires (EORTC QOL-C30, EORTC QOL-OV28, MSASI)

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Table S2

Results of least square mean and standard errors of quality of life questionnaires in subgroup analysis of primary cytoreductive surgery (EORTC QOL-C30, EORTC QOL-OV28, MSASI)

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Table S3

Results of least square mean and standard errors of quality of life questionnaires in subgroup analysis of interval cytoreductive surgery (EORTC QOL-C30, EORTC QOL-OV28, MSASI)

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Fig. S1
Functional and symptom scales of EORTC QLQ-C30.

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Fig. S2
Subgroup analyses of summary score of EORTC QLQ-C30, physical function score of EORTC QLQ-C30, and scores of peripheral neuropathy after HIPEC with primary cytoreductive surgery or interval cytoreductive surgery

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