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ORIGINAL RESEARCH

Feasibility and safety of neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in patients with advanced stage ovarian cancer: a single-center experience

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Objectives: For patients with advanced ovarian cancer, neoadjuvant chemotherapy (NACT) can significantly increase the rate of optimal cytoreduction. However, this does not translate into a survival benefit. The aim of this study was to investigate the feasibility and effect of neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy (NLHIPEC).

Methods: Between March 2016 and February 2018, 14 patients with advanced ovarian cancer who were not candidates for optimal cytoreduction via primary debulking surgery (PDS) received NLHIPEC. Their clinical data were retrospectively analyzed.

Results: No patients experienced intraoperative complications during NLHIPEC. Grade 3 adverse events (AEs) were noted in two (14.3%) patients, and all patients received planned NACT without dose delay or dose reduction. Following NACT, CA125 levels <35 U/mL and <20 U/mL were observed in six (42.9%) patients and five (35.7%) patients, respectively. All patients underwent interval debulking surgery (IDS) after the last NACT cycle. After IDS, R0 resection was achieved in 10 (71.4%) patients without intraoperative injury, and one (7.1%) patient developed a grade 3 AE. During a median follow-up time of 16 months, no patients died of disease, and the median progression-free survival (PFS) was not achieved. Progression was noted in six (42.9%) patients (range, 9–21 months).

Conclusions: NLHIPEC appears to be a feasible option for ovarian cancer patients who have a low likelihood of achieving optimal cytoreduction during PDS.

Keywords: ovarian cancer, hyperthermic intraperitoneal chemotherapy, neoadjuvant, laparoscopy

Background

Among all invasive gynecologic cancers, ovarian cancer is the leading cause of death. Nearly 75% of women with ovarian cancer are diagnosed with advanced stage disease (International Federation of Gynecology and Obstetrics [FIGO] IIIC or IV) at presentation.[1] Treatment with primary debulking surgery (PDS) followed by chemotherapy has been the standard of care for ovarian cancer patients. Because each 10% increase in maximal cytoreduction is associated with a 5.5% increase in median survival, the primary aim of debulking surgery is no gross residual disease.[2] If it is difficult to achieve this aim via PDS, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) can be considered a reasonable alternative.[1] Although NACT can significantly increase the optimal cytoreduction

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rate, this does not translate into a survival benefit.[1,3,4] Therefore, novel approaches to enhance the therapeutic effects of NACT need to be explored.

The peritoneal cavity is the principal site of ovarian disease. Given that systemic chemotherapy has poor access to the peritoneum due to the plasma-peritoneal barrier, intraperitoneal chemotherapy has been proposed and validated as an effective therapy.[5,6] Intraperitoneal chemotherapy can also be delivered under hyperthermic conditions, which is termed hyperthermic intraperitoneal chemotherapy (HIPEC). Because heat can propagate the cytotoxicity of selected chemotherapeutic drugs, HIPEC in the treatment of ovarian cancer has drawn increasing interest. Recent studies have shown that HIPEC can improve the survival outcomes of ovarian cancer patients.[7,8] Considering the potential value of HIPEC, we hypothesized that it could be used in a neoadjuvant setting and might enhance the effect of NACT. The primary aim of this study was to evaluate the feasibility and primary effect of neoadjuvant laparoscopic HIPEC (NLHIPEC) in ovarian cancer patients who are not candidates for optimal cytoreduction via PDS.

Materials and methods

Patients

After Institutional Review Board (IRB) approval (#SYSEC-KY-KS-2019-018) was obtained from the Sun Yat-sen Memorial Hospital Institutional Review Board, we retrospectively identified patients who received NLHIPEC and underwent subsequent IDS for ovarian cancer at our institution between March 2016 and February 2018. Individualized treatment strategies were made by a multidisciplinary team (MDT), which consisted of three gynecologic oncologists, two pathologists and two radiologists. All patients deemed appropriate surgical candidates underwent an initial laparoscopic evaluation for pathological diagnosis and peritoneal disease assessment. The Fagotti scoring system was utilized to determine the possibility of optimal cytoreduction.[9] Patients with a Fagotti score ≥8 were offered NACT and subsequent IDS, while patients with a Fagotti score < 8 were offered PDS. Eligibility criteria to receive NLHIPEC were as follows: Fagotti score ≥8, age 18–75 years, adequate bone marrow, normal hepatic and renal function and signed informed consent. Contraindications for NHIPEC were as follows: nonepithelial or borderline histology, American Society of Anesthesiologists (ASA) score IV and extensive abdominal adhesions, active inflammation or severe comorbidities.

Technique for NLHIPEC

The NLHIPEC was started with laparoscopic evaluation. The site of the first port placement was decided at the surgeon's discretion based on imaging and clinical findings. The preferred technique for the creation of the pneumoperitoneum was via the optical access technique in the umbilical area. After induction of a CO_2 pneumoperitoneum, an additional three trocars of 5 mm were placed under direction vision in order to enable complete dissection of adhesions and a thorough inspection of the abdominal cavity. The Fagotti score was generated according to Fagotti's study, and biopsy was obtained and examined by frozen section analysis.[9] All surgical evaluation procedures were performed by a team comprising two experienced gynecologic oncologists. Following surgical evaluation and histologic confirmation of the diagnosis, four tubes were placed via the laparoscopic ports (two in the bilateral subdiaphragmatic space for use as inlet tubes and two in the pelvic cavity for use as an outlet tubes) which were used to administrate HIPEC (Figure 1). Then, HIPEC was given within 24 hrs after primary laparoscopic evaluation. The NACT regimen was paclitaxel 175 mg/m^2 administered by intravenous infusion over 3 hrs followed by cisplatin 70 mg/m^2 administered by HIPEC. A high-precision hyperthermic intraperitoneal perfusion treatment system (approved by the State Food Drug Administration of China, approval No. 2009-3260924) was utilized, which

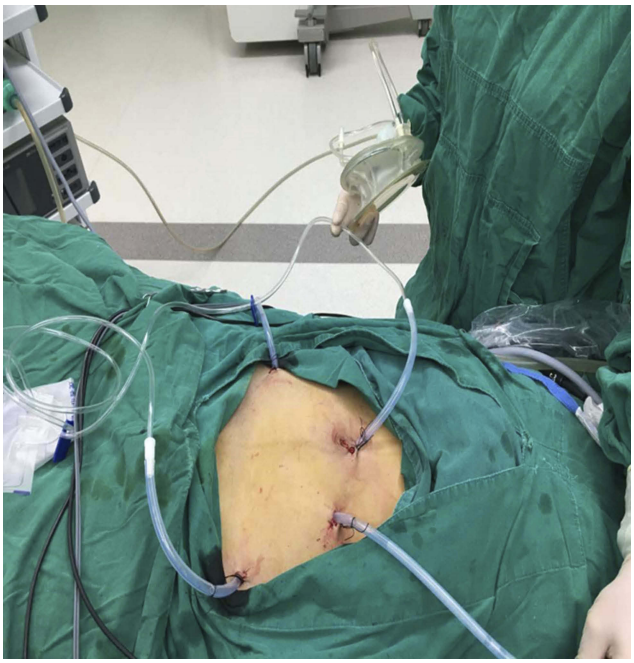

Figure 1 Placement of four tubes via the laparoscopic ports.

has a precision of ±0.10 °C for temperature control and ±5% for flow control. Cisplatin was added to 3000 mL of saline solution, which was heated and circulated at a flow rate of 300–500 mL/min. The perfusion velocity was adjusted to ensure that the entire abdomen was exposed to the perfusate (an initial velocity was 300 mL/min, and then it was increased gradually until the patient felt floated or a flow rate of 500 mL/min was achieved). An intraabdominal temperature of 43 °C was maintained and measured by the treatment system using temperature monitoring probes in the infusion and outflow catheters. The HIPEC procedure took 90 mins in total, consisting of a 30 min preheating period and a 60 min perfusion period. After HIPEC treatment, the four tubes were removed immediately to retain as much cisplatin in the abdominal cavity as possible. NLHIPEC-related adverse events (AEs) which presented within three weeks of NLHIPEC were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Following NLHIPEC, two additional cycles of NACT were planned. Both paclitaxel and platinum-based chemotherapy were given intravenously every 21 days.

Management and safety evaluation following NACT

During the NACT period, all patients were reviewed weekly, and the serum levels of CA125 were measured after each cycle of NACT. IDS was performed within four weeks after the last cycle of NACT. The result of IDS was classified using a cytoreductive completeness scoring (CCS) system, where CC-0 (R0 resection) is defined as no visible disease after cytoreduction and CC-1, 2 and 3 (CC-1+) scores (residual tumors less than 2.5 mm, between 2.5 mm and 2.5 cm, and greater than 2.5 cm, respectively) were grouped together.[10] The extent and complexity of the surgical procedures were categorized according to the score.[11] Complications that presented within two weeks of IDS were also graded according to the NCI CTCAE Version 4.0. Following IDS, all patients received at least three cycles of systemic platinum-based chemotherapy.

Statistical analysis

All statistical analyses were conducted using IBM SPSS (version 13.0, SPSS, Chicago, IL, USA). The initial data analysis was conducted by employing a descriptive statistical approach and analysis of variance. The Kolmogorov-Smirnov test was used to verify standard normal distribution assumptions of continuous variables. Survival times were calculated from the date of laparoscopic evaluation to the date of relapse, death from any reason, and last follow-up.

Results

Patient demographics

During the study period, 14 patients with a Fagotti score ≥8 received NLHIPEC. Their baseline characteristics are outlined in Tables 1 and S1. Relevant comorbidities, including cardiovascular disease, hypertension, type 2 diabetes and a history of chronic obstructive pulmonary disease and stroke, were present in five (35.7%) patients.

Safety of NLHIPEC

We did not observe any intraoperative complications during laparoscopic evaluation and HIPEC tube placement. Following NLHIPEC, no patient was admitted to the intensive care unit, and the median length of hospital stay was 2 days (range, 1–3 days). Table 2 presents AEs that manifested within three weeks of NLHIPEC. AEs of grade 4 were not observed, and AEs of grade 3 were noted in two (14.3%) patients. The most common events were neutropenia and abdominal pain. No febrile neutropenia, thromboembolic events, infection, gastrointestinal perforation or renal toxicity events were observed.

Effects of NLHIPEC

Following NLHIPEC, 9 patients with ascites at diagnosis showed ascite regression; all patients received two subsequent cycles of NACT without dose delay or dose reduction. Following the third NACT, normalization of CA125 levels was observed in six (42.9%) patients, and a CA125 level <20 U/mL was observed in five (35.7%) patients. All patients in our study received IDS within 4 weeks of the last NACT cycle. Table 3 summarizes the surgical characteristics and outcomes. Aggressive complex surgical cytoreduction (surgical complexity score ≥8) was performed in two (14.3%) patients. CC-0 was achieved in 10 (71.4%) patients. In the IDS procedure, no intraoperative injuries were recorded, and blood transfusion was required in one patient (7.1%). Following IDS, one (7.1%) patient developed grade 3 thrombosis, and no patients developed AEs of grade 4 (Table S1). During a median follow-up time of 16 months (range, 9–26 months),

Table 1 Patient and disease characteristics

Variable	
Age (years), median (range)	62 (32–76)
BMI (kg/m^2), median (range)	23.1(20.7–26.7)
Stage, n (%)	
FIGO IIIC FIGO IV	9 (64.3) 5 (35.7)
Histology, n (%)	
Serous Clear cell	13 (92.9) 1 (7.1)
ASA class, n (%)	
I-II III Comorbidity, n (%)	10 (71.4) 4 (28.6) 5 (35.7)
CA125 (median, range)	
Pre-NLHIPEC After NLHIPEC After the 3rd NACT After IDS Percent decrease (CA125 Pre-NLHIPEC − CA125 after the 3rd NACT/CA125 Pre-NLHIPEC) (%), median (range) Patients with CA125<35 U/mL following the the 3rd NACT, n (%) Patients with ascites at diagnosis, n (%)	1014 (194–6536) 298 (48–1947) 42 (10–344) 20 (7–81) 94.7 (86.3–99.4) 6 (42.9) 9 (64.3)
Fagotti score assessed by laparoscopy	
8 10 12	9 (64.3) 3 (21.4) 2 (14.3)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NLHIPEC, neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy.

Table 2 Neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy related adverse events

Adverse event	NCI-CTCAE 4.0			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	0	2	2	0
Abdominal pain	2	1	0	0
Diarrhea	1	0	0	0
Dyspnea	1	0	0	0
Vomiting	1	0	0	0
Gastrointestinal Perforation	0	0	0	0
Febrile neutropenia	0	0	0	0
Renal	0	0	0	0
Fever	0	1	0	0
Infection	0	0	0	0
Thromboembolic event	0	0	0	0

Abbreviation: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

no patient died of disease, and the median progression-free survival (PFS) was not achieved. Progression was noted in six (42.9%) patients, with PFS ranging from 9 months to 21 months (mean, 14 months). No patient developed platinum-resistant recurrence.

Discussion

The current study describes our experience of delivering NACT with a laparoscopic HIPEC technique. NLHIPEC could combine the pharmacokinetic advantages of HIPEC with the advantages of minimally invasive surgery. Hyperthermia has a direct antitumor effect, increases the penetration of chemotherapy at the peritoneal surface and augments the cytotoxic effects of platinum-based compounds.[12] Intraperitoneal chemotherapy has also been proven to improve the survival outcomes of ovarian cancer patients.[13,14] Adding hyperthermia to intraperitoneal cisplatin results in synergistic effects, which could further enhance the effect of intraperitoneal chemotherapy.[15,16] In addition, laparoscopy allows for adhesiolysis with adequate catheter placement, which results in optimal chemotherapy exposure to the peritoneal surfaces. Compared to an open approach, laparoscopy is associated with an increased abdominal pressure, which may improve drug penetration into the tumor tissue.[17] Additionally, obviating the need for nontherapeutic laparotomies could reduce postoperative discomfort, thereby decreasing the risk of delay in starting subsequent NACT.

In the present study, we administered NLHIPEC to 14 patients. No NLHIPEC-related serious AEs were noted, and NLHIPEC did not prevent the administration of subsequent NACT and IDS. In the literature, few studies on NLHIPEC in the treatment of ovarian cancer are available. However, the safety of this technique has been demonstrated in gastric cancer patients with inoperable disease. Yonemura et al reported 105 gastric cancer patients who received NLHIPEC for peritoneal metastasis.[18] Following NLHIPEC, serious AEs (grade 3 and grade 4) were noted in 4 (7.7%) patients. Although it is difficult to make a cross-study comparison, we believe that Yonemura's result is in line with ours suggesting that NLHIPEC is safe and tolerable.

Table 3 Features of surgical complexity and outcomes

Variable	
Surgical procedures, n (%)	
TH-BSO	14 (100)
Omentectomy	14 (100)
Pelvic lymphadenectomy	7 (50.0)
Paraaortic lymphadenectomy	3 (21.4)
Pelvic peritoneum stripping	11 (78.6)
Abdominal peritoneum stripping	4 (28.6)
Rectosigmoidectomy T-T nastomosis	4 (28.6)
Large bowel resection	1 (7.1)
Small bowel resection/s	6 (42.9)
Operative time (min), median (range)	240 (120–360)
Estimated blood loss (mL), median (range)	150 (50–500)
Surgical complexity score groups, n (%)	
Low	3 (21.4)
Intermediate	9 (64.3)
High	2 (14.3)
Complication grade (NCI-CTCAE 4.0), n (%)	
1	3 (21.4)
2	2 (14.3)
3	1 (7.1)
4	0
Completeness of cytoreduction, n (%)	
CC-0	10 (71.4)
CC-1+	4 (28.6)

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TH-BSO, total hysterectomy-bilateral salpingo-oophorectomy.

Following NACT, both patients with a CA125 level <35 U/mL and those with a CA125 level <20 U/mL were reported to have improved survival outcomes.[19–23] Therefore, we used these measurements as cutoff values. Of our patients, 42.9% had a CA125 level <35 U/mL, and 35.7% had a CA125 level <20 U/mL following NACT. The results are consistent with previous studies, where 17.8–57% of patients were reported to have a pre-IDS CA125 level <35 U/mL,[19,22,24–26] and 31.3–53.3% of patients had a pre-IDS CA125 level <20 U/mL.[21,23] In addition, the median percent reduction in CA125 of our cohort was 94.7% (range, 86.3–99.4), which is consistent with Mahdi's study, where the reported median percentage was 94.5% (range, 33–97.7).[21] Of note, most patients in the abovementioned studies underwent more than three cycles of NACT,[19,21,24,25] while all patients in our study received exactly three cycles of NACT. Considering that each additional cycle of NACT between 3 and 6 cycles is associated with a 4-month decrease in OS,[27] we believe that using HIPEC in a neoadjuvant setting could allow NACT to more efficiently decrease the level of CA125 and thus enhance the therapeutic effect of NACT.

Any remaining disease following IDS contains stem cells that may induce chemo-resistance, and converging evidence has highlighted the incremental survival benefit with cytoreduction to no gross residual disease.[28] Therefore, for ovarian cancer patients with advanced disease, the ultimate goal of IDS should be R0 resection. Previous randomized controlled trials (RCTs) have validated that R0 resection can be more easily achieved among NACT patients than PDS patients.[3,4,29] In these trials, NACT was administered intravenously, and the reported rate of R0 resection following NACT ranged from 39% to 55%.[3,4,29] The rate of R0 resection was 71.4% in the current study, which is much better than that in previous studies. The increased rate may be attributed to the effect of NLHIPEC.

Although NACT decreases treatment-related morbidity and mortality, many types of complicated surgical procedures are still involved in IDS. Researchers from the Mayo Clinic showed that 14.9% of ovarian cancer patients still needed to undergo high-complexity debulking surgery (surgical complexity scores ≥8) following NACT.[30] That result is in line with ours. However, 11% of their patients developed grade 3/4 complications after IDS, which is higher than the rate (7.1%) noted in our cohort. Three RCTs, EORTC/NCIC, CHORUS and JGOG0602, compared PDS with NACT followed by IDS.[3,4,29] In these trials, post-IDS death and IDS-related grade 3/4 AEs were recorded in 0.4–0.7% and 4.6–14% of NACT patients, respectively; the most common grade 3/4 AE after IDS was hemorrhage with an incidence of 4.1–6%.[3,4,29] In the present study, no IDS-related death, grade 4 AE or postoperative hemorrhage was noted; a grade 3 AE was only observed in only one (7.1%) patient. Moreover, compared with JGOG0602,[29] where blood transfusion was recorded in 52.7% of patients in the NACT group, our study indicated fewer patients (7.1%) who required blood transfusion. Given the published data and our results, we believe that NLHIPEC would not adversely affect the subsequent IDS and may even make the complicated surgical procedures much easier to perform.

NACT may increase the risk of developing platinum resistance by exposing large tumor volumes to chemotherapy, which presents a major concern in clinical settings. Previous studies have shown that NACT patients are more likely to develop platinum-resistant recurrence than

patients undergoing PDS.[31–33] In the literature, the reported incidence of platinum-resistant recurrence among NACT patients was 27.8–50%.[31,32,34] In our cohort, surprisingly, no patient experienced platinum-resistant recurrence. A possible explanation for this finding is that hyperthermia can target and eliminate cancer stem cells that drive therapy resistance and tumor recurrence.[35]

Several limitations of the current study should be acknowledged, including its small sample size, retrospective nature and limited follow-up time. In addition, peritoneal cancer index (PCI), which is a useful tool to assess tumor burden and extend of metastases, was not recorded in every patient. An efficacy analysis using PCI could not be conducted. Therefore, our results should be interpreted with caution. In addition, because of the absence of a control group, it is difficult to explore the difference between intraperitoneal NACT and NLHIPEC.

To our knowledge, this is the first study to evaluate the feasibility of NLHIPEC among ovarian cancer patients with advanced disease. Although the present study has no statistical power, the results are encouraging and suggest excellent tolerance of NLHIPEC. Moreover, we observed good disease control among our patients. The findings of the current study should be confirmed prospectively. If validated, NLHIPEC could be considered a more efficient way to deliver NACT, which may confer survival benefits for ovarian cancer patients.

Ethics

Patient data were kept to a minimum and stored in a secure manner on a database under the control of the Sun Yat-sen Memorial Hospital to which only the corresponding author has access, and patient consent to review their medical records is not required by the Sun Yat-sen Memorial Hospital Institutional Review Board. The present study was performed in accordance with the 1975 Declaration of Helsinki.

Data availability

The datasets used in the present current study are available from the corresponding author on reasonable request.

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Disclosure

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Supplementary material

Table S1 Characterization of patients

Patient number	Age	Histology	Stage	Fagotti score	CA125 before NLHIPEC	CA125 after NLHIPEC	CA125 after the 3rd NACT	CA125 after IDS	Surgical complexity score groups	R0 resection	Recurrence after primary treatment (recurrent site, time of recurrence)	Treatment of recurrence	Patient status
1	65	Serous	IIIC	10	194	49	10	7	Intermediate	Yes	No	——	NED (11 moths)
2	68	Serous	IIIC	12	803	385	43	33	Intermediate	Yes	No	——	NED (15 moths)
3	66	Serous	IIIC	8	333	61	12	13	Low	No	No	——	NED (9 months)
4	70	Serous	IV	8	989	508	135	81	Intermediate	Yes	Yes (solitary para-aortic lymph nodes; 13 months)	SCS+chemothrapy (paclitaxel +caboplatin)	NED (19 months)
5	62	Serous	IV	8	3160	1947	344	32	Intermediate	No	No	——	NED (16 months)
6	46	Serous	IIIC	8	1714	343	166	55	High	Yes	No	——	NED (16 months)
7	38	Serous	IIIC	10	1039	114	14	14	Intermediate	No	No	——	NED (21 months)
8	32	Serous	IV	8	6536	1187	40	8	Intermediate	No	Yes (solitary pelvic peritoneum, liver; 16 months)	SCS+chemothrapy (paclitaxel +caboplatin)	NED (26 months)
9	53	Clear cell	IV	8	1220	606	19	19	Low	No	Yes (extensive intraperitoneal dissemination; 9 months)	Chemothrapy (irinotecan +caboplatin)	Stable disease
10	76	Serous	IIIC	12	1669	48	14	20	Intermediate	No	Yes (pelvic peritoneum, multiple lung lesions; 14 months)	Chemothrapy (paclitaxel +caboplatin) followed by Olaparib	Partial response (24 months)

(*Continued*)

Table S1 (Continued).

Patient number	Age	Histology	Stage	Fagotti score	CA125 before NLHIPEC	CA125 after NLHIPEC	CA125 after the 3rd NACT	CA125 after IDS	Surgical complexity score groups	R0 resection	Recurrence after primary treatment (recurrent site, time of recurrence)	Treatment of recurrence	Patient status
11	62	Serous	IV	10	720	252	21	7	low	No	No	——	NED (13 months)
12	57	Serous	IIIC	8	3330	1414	240	59	High	No	No	——	NED (10 months)
13	32	Serous	IIIC	8	670	133	56	21	Intermediate	Yes	Yes (pelvic peritoneum, lung; 11 months)	Chemothrapy (paclitaxel +caboplatin)	Complete response (26 months)
14	69	Serous	IIIC	8	766	101	66	15	Intermediate	No	Yes (extensive intraperitoneal dissemination; 18 months)	Chemothrapy (paclitaxel +caboplatin)	Complete response (23 months)

Abbreviatios: NLHIPEC, neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy; NED, no evidence of disease; SCS, secondary cytoreductive surgery.