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Microscopic diseases remain in initial disseminated sites after neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and primary peritoneal cancer

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ABSTRACT

Objective: This study aimed to evaluate the presence of pathological residual tumor (pRT) in each initial disseminated site after neoadjuvant chemotherapy (NACT) to assess the appropriate surgical margins during interval debulking surgery (IDS) for a favorable prognosis.
Methods: This prospective descriptive study included patients with stage IIIC–IV epithelial ovarian, fallopian tubal, and peritoneal cancer. One hundred eleven patients underwent diagnostic exploratory laparotomy, and their initial intra-abdominal dissemination statuses were recorded. Any tumor >1 cm in diameter found during the exploratory laparotomy was resected during IDS even if it was macroscopically invisible after NACT. The pRT rate after NACT and negative predictive value (NPV; probability that sites with macroscopically invisible tumors have no pRT) during IDS were assessed in each disseminated site.
Results: A median of 5 NACT cycles were performed. Sites with a high incidence of pRT and low NPV included the rectosigmoid colon (71.4%, 38.6%), transverse mesentery (70.3%, 50.0%), greater omentum (68.3%, 51.7%), right diaphragm (61.9%, 48.1%), paracolic gutters (61.1%, 50.0%), and vesicouterine pouch (56.6%, 50.0%). Organs/tissues with a high incidence of pRT featured a low NPV. The median progression-free survival and overall survival in this cohort were 27.7 and 71.9 months, respectively.
Conclusion: Even if a disseminated site >1 cm in diameter before NACT is invisible during IDS, microscopic disease remains present within it. The appropriate surgical margins for IDS with a favorable prognosis could be secured by resecting a lesion of >1 cm before NACT even if it is invisible during IDS.

Keywords: Residual Disease, Minimal; Debulking Surgical Procedures; Surgical Margins; Ovarian Cancer

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INTRODUCTION

Complete resection of macroscopic tumors without residual disease is an important prognostic factor of survival outcomes in advanced ovarian cancer [1-3]. However, only one-third of patients undergo complete resection during primary debulking surgery (PDS) [4] and receive its benefits. Compared with patients with low tumor loads, those with high tumor loads are at an increased risk of perioperative complications because they require a complex surgical procedure, including an upper abdominal operation [5]. This may lead to decreased complete resection rates during PDS.

To increase the complete resection rate and decrease the perioperative complication rate, neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) was introduced to patients with advanced or unresectable ovarian cancer as well those with poor performance status. A phase III trial to compare PDS with NACT-IDS proved that the survival outcomes of NACT-IDS were not inferior to those of PDS [6,7]. NACT allowed peritoneal diseases to shrink or disappear, which simplified complicated surgical procedures and reduced the perioperative complication rate [5,8,9]. Since then, NACT-IDS has been a treatment option for patients with bulky stage IIIC–IV ovarian carcinoma.

However, some issues remain to be resolved regarding the treatment of NACT-IDS. First, large tumors may develop drug resistance when exposed to NACT [10,11]. Patients who undergo NACT-IDS are reportedly more likely to develop platinum-resistant relapse [12] and have an increased risk of death within 2 years as compared with those who undergo PDS [13]. Furthermore, a meta-analysis reported that one additional course of NACT decreases survival time by 4.1 months [14]. Second, residual tumor size is related to the survival outcomes of PDS, but its role in IDS remains unclear. Two phase III trials that compared PDS with IDS introduced the idea of an optimal surgical criterion (i.e., residual disease ≤1 cm) and conducted a survival analysis using this criterion for IDS [6,7]. Although the prognosis of optimal surgery in PDS is inferior to that of complete surgery, the prognosis is relatively favorable. However, the prognosis of optimal surgery in IDS is not significantly different from that of suboptimal surgery. Several studies reported that complete surgery is important to achieve better survival outcomes in IDS [15-18]. Third, if IDS is performed after favorable responses are obtained in NACT, many macroscopically disseminated lesions in the abdomen will disappear, consequently shrinking the extent of resection. This shrinking may cause microscopically viable cancer cells to remain within the tissue [19]. This is why the prognosis of patients with complete resection during IDS was comparable with that of patients with suboptimal cytoreduction during PDS [20]. However, studies on microscopic diseases in patients indicated for IDS are lacking. Therefore, we evaluated microscopic diseases after NACT in initial disseminated sites to determine the appropriate IDS surgical margins defined as the extent of resection.

MATERIALS AND METHODS

1. Study design and patients
This prospective descriptive study provides details of pathological residual tumor (pRT) after NACT with aggressive surgery. This study aimed to investigate the rate of pRT after NACT in each disseminated site where the tumor was >1 cm before NACT and determine the progression-free survival (PFS) and overall survival (OS) of patients who underwent resection

of tumors sized >1 cm before NACT even if they were macroscopically invisible during IDS. We prospectively evaluated 260 consecutive patients who were surgically diagnosed as having stage III–IV epithelial ovarian, fallopian tubal, or peritoneal cancer according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging criteria [21] at our institution between January 2008 and December 2017. Of the patients, 111 who underwent PDS were excluded because they had a favorable performance status and were eligible for complete resection. We excluded another 18 patients who were ineligible for exploratory laparotomy because of poor performance status. Among the remaining 131 patients who underwent exploratory laparotomy before NACT, 20 did not undergo IDS because of disease progression during NACT. Thus, 111 patients who underwent exploratory laparotomy followed by NACT-IDS were enrolled in this study (**Fig. 1**). The pRT rate after NACT (C/A in **Figs. 1** and **2A**) and negative predictive value (NPV; probability that sites with macroscopically invisible tumors have no pRT, C/B in **Figs. 1** and **2B**) during IDS were assessed in each disseminated site. This study was approved by the Institutional Review Board of Chiba University (approval No. 2961).

2. Indications for NACT

The indications for NACT were determined at the initial laparotomy because preoperative assessment for the extent of disease was often under- or overestimated by imaging modalities, such as computed tomography, magnetic resonance imaging, and positron emission tomography. The indications for NACT were as follows: disseminated tumor burden was too high to achieve complete cytoreduction; gastrectomy, resection of the hepatic hilum or head of the pancreas, massive intestinal resection, or total colectomy was required; and/or massive ascites caused coagulopathy. Patients in poor general condition (performance status ≥3 or ileus) were excluded from this study.
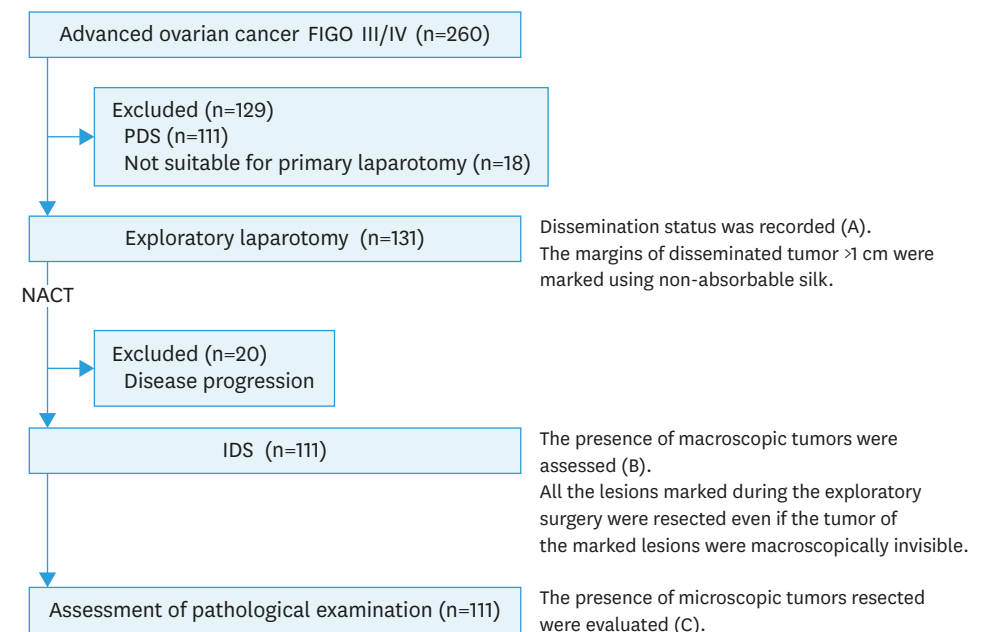

Fig. 1. Study population and design.
pRT after NACT (C/A see **Fig. 2A**) and NPV at IDS macroscopic findings (C/B see **Fig. 2B**) were assessed.
FIGO, International Federation of Gynecology and Obstetrics; PDS, primary debulking surgery; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NPV, negative predictive value; pRT, pathological residual tumor.
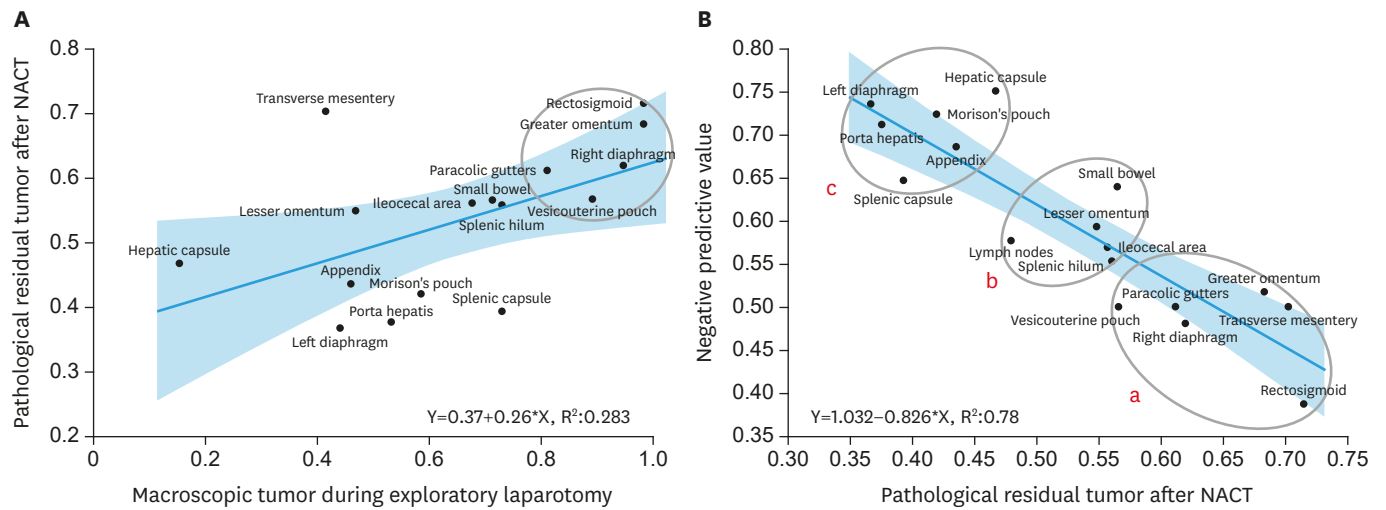
Fig. 2. (A) Association of macroscopic tumor positive ratios on exploratory laparotomy and pRT after NACT. The incidences of dissemination and pRT after NACT during exploratory laparotomy positively correlated. The sites with high incidence rates of initial dissemination and a high incidence of pRT after NACT (circled) included the rectosigmoid colon, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch. (B) Association between pRTs after NACT and NPV. The incidence of pRT after NACT and that of the NPVs showed a negative correlation. Tumor sites can be categorized into 3 groups as follows: (a) those with a high incidence of pRT after NACT and a low incidence of NPV (rectosigmoid colon, transverse mesentery, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch); (b) those with a relatively high incidence of pRT after NACT and a high incidence of NPV (ileocecal area, splenic hilum, small bowel, lesser omentum, and lymph nodes); and (c) those with a low incidence of pRT after NACT and a high incidence of NPV (hepatic capsule, appendix, Morison's pouch, splenic capsule, porta hepatis, and left diaphragm).
The blue line and colored area indicate the regression line and average confidence interval, respectively.
NACT, neoadjuvant chemotherapy; NPV, negative predictive value; pRT, pathological residual tumor.

3. Treatment protocol

The treatment protocol was as follows: during the exploratory laparotomy, we performed a salpingo-oophorectomy, partial omentectomy, or peritoneal biopsy to confirm the diagnosis. We then observed the abdominal cavity and recorded in detail the dissemination status in the medical charts. If disseminated tumors were >1 cm, both ends of the margins were marked using non-absorbable 3-0 black silk (**Supplementary Fig. 1**). An implantable port system (Bard Port-Ti®; Medicon Inc., Osaka, Japan) was placed in the abdominal cavity to perform the peritoneal washing cytology during NACT and to evaluate peritonitis carcinomatosa in the abdominal cavity.

NACT consisting of weekly paclitaxel (80 mg/m²/week intravenous) and carboplatin (area under the curve=2–3/week intravenous) was performed until IDS. Bevacizumab (15 mg/kg/3 weeks) was also used once it received approval for treatment of ovarian cancer in November 2013 in Japan.

IDS was performed under the following 2 conditions: 1) when the serum CA-125 level decreased to ≤15 IU/mL and the peritoneal washing cytology become negative, or 2) when the serum CA-125 level stopped decreasing when the peritoneal washing cytology remained positive. This is because a serum CA-125 level ≤15 IU/mL and negative washing cytology at IDS are prognostic factors for the patients who underwent IDS and are also predictors for the achievement of complete resection at IDS [22]. The serum CA-125 level may not reflect the extent of peritoneal carcinomatosis when it decreases to less than 35 U/mL after chemotherapy [23,24]. Even with a serum CA-125 ≤35 IU/mL after NACT, we experienced that carcinomatosis remained and complete resection was impossible. Thus, we performed peritoneal washing cytology in addition to serum CA-125 to evaluate peritoneal carcinomatosis during NACT.

During IDS, all the lesions marked during the exploratory surgery were resected even if the tumor of the marked lesions were macroscopically invisible. As it was easy to resect, the peritoneum (in the diaphragm, vesicouterine pouch, ileocecal area, paracolic gutters, transverse mesentery, and Morison's pouch) was resected during IDS, regardless of the size of each disseminated tumor observed in the peritoneum during exploratory laparotomy. Each IDS, including gastrointestinal and upper abdominal surgeries, was performed by gynecologic oncologists.

4. Assessment of surgical specimens

The excised specimens were macroscopically and microscopically examined for the presence or absence of disease. Immunohistochemistry (cytokeratin, p53, CD68, and CD31) was also performed in some cases if differentiation between cancer, mesothelial, and endothelial cells, and macrophage was required. From each patient, tissue samples for the microscopic examination were collected from 17 sites, including the rectosigmoid (rectouterine pouch and rectosigmoid colon), vesicouterine pouch, ileocecal area, appendix, small bowel (small intestine and mesentery), greater omentum, paracolic gutters, transverse mesentery, Morison's pouch, porta hepatis, hepatic capsule, right diaphragm, lesser omentum, splenic hilum, splenic capsule, left diaphragm, and lymph nodes (para-aorta and pelvic). A median of 58 slides (interquartile range [IQR]=40–65) were prepared for each patient for microscopic examination. The relationship between the intraperitoneal macroscopic initial diseases identified during exploratory laparotomy and the pRT identified after NACT was examined. The microscopic examination results were confirmed by 2 pathologists (T.K. and M.K.).

5. Statistics

Kaplan-Meier survival curves were used to estimate PFS and OS. Two-sided log-rank tests were used to compare the subgroups. Cox proportional-hazards regression analysis were used to univariable and multivariable analysis on PFS. Significance level of the test results was set at 0.05. The median PFS and OS were also calculated along with their 95% confidence intervals (CIs).

RESULTS

1. Patient characteristics

Table 1 shows the patients' characteristics. Sixty-two patients (56%) had stage IIIc and 49 patients (44%) had stage IV carcinoma. The primary tumor sites included the ovary (n=51; 46%), fallopian tube (n=51; 46%), and peritoneum (n=9; 8%). High-grade serous carcinoma (n=99; 89%) was the most common histological type. One hundred seven patients (96%) had a high disease score [25]. The median ascites volume during the exploratory laparotomy was 2,900 mL (IQR=475–2,960 mL). The median interval between exploratory laparotomy and start of chemotherapy was 6 days (IQR=4–7). A median of 5 NACT cycles (IQR=4–7) were performed. Sixty patients received bevacizumab concomitantly during NACT, and a median of 3 bevacizumab administration cycles (IQR=2–4) were completed during NACT.

The median CA-125 value was 1,240 IU/mL (IQR=588–2,960 IU/mL) before exploratory laparotomy and 12 IU/mL (IQR=8.8–21.9) before IDS. The peritoneal cancer index [26] was 19 (IQR=14–22) at the time of the exploratory laparotomy and 4 (IQR=2–8) at the time of IDS.

Complete resection (residual tumor=0 cm) was achieved in 104 patients (94%); optimal resection (residual tumor of ≤1 cm), in 5 (5%); and suboptimal resection (residual tumor

Table 1. Patients' characteristics (n=111)

Characteristic	No. of Patients
Age	
Median age (yr)	62 (51–70)
FIGO stage	
IIIC	62 (55.9)
IV	49 (44.1)
Primary site	
Ovary	51 (45.9)
Fallopian tube	51 (45.9)
Peritoneum	9 (8.1)
Histology	
Serous carcinoma, high grade	99 (89.2)
Serous carcinoma, low grade	2 (1.8)
Clear cell carcinoma	4 (3.6)
Carcinosarcoma	3 (2.7)
Endometrioid carcinoma	2 (1.8)
Poorly differentiated carcinoma	1 (0.9)
Performance status	
0–1	61 (55.0)
2–4	50 (45.0)
Disease score	
Low	2 (1.8)
Moderate	2 (1.8)
High	107 (96.4)
Ascites at exploratory laparotomy (mL)	2,900 (475–5,045)
CA-125 (IU/mL)	
At exploratory laparotomy	1,240 (588–2,960)
At interval surgery	12 (8.8–21.9)
Peritoneal cancer index	
At exploratory laparotomy	19 (14–22)
At interval surgery	4 (2–8)
NACT cycle	5 (4–7)
Interval between exploratory laparotomy and chemotherapy (day)	6 (4–7)
Adjuvant chemotherapy cycle	6 (6–6.5)
Bevacizumab introduced to NACT	
Bevacizumab introduced to NACT	64 (57.7)
Cycle	21 (12–21)
Bevacizumab NOT introduced to NACT	47 (42.3)
Peritoneal cytology during IDS	
Positive	33 (29.7)
Suspicious	4 (3.6)
Negative	74 (66.7)
Surgical complexity score	13 (11–15)
Low (0–3)	3 (2.7)
Moderate (4–7)	9 (8.1)
High (8–18)	99 (89.2)
Surgical procedures during IDS	
Rectosigmoid colectomy	105 (94.6)
Vesicouterine peritonectomy	99 (89.2)
Greater omentectomy	82 (73.9)
Right diaphragm peritonectomy	105 (94.6)
Splenectomy	79 (71.2)
Lymphadenectomy	96 (86.5)
Completeness of resection (cm)	
0	104 (93.7)
≥0.1 and ≤1	5 (4.5)
>1	2 (1.8)

Values are presented as median (IQR) or number of patients (%).
FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; IQR, interquartile range; NACT, neoadjuvant chemotherapy.

of >1 cm) in 2 (2%). Ninety-nine patients (89%) underwent a surgery with a high surgical complexity score [27].

2. Macroscopic tumors in exploratory laparotomy

Findings obtained from the 111 patients during their exploratory laparotomies revealed that organs that developed macroscopic dissemination in >90% of patients were the rectosigmoid colon (98%), greater omentum (98%), and right diaphragm (95%; **Table 2**).

3. pRT after NACT

Macroscopic diseases were found in 84 patients (75.7%). Microscopic diseases were found in 18 patients (16.2%). Pathological complete response after NACT was achieved in only 9 patients (8.1%). Tissues and organs were resected from 1,150 sites during IDS; among them, pRT was found in 643 patients (55.9%). Each site had a different pRT rate that ranged from 36.6% (15/41) to 71.4% (75/105). The sites with a high incidence rate of pRT included the rectosigmoid colon (71.4%), transverse mesentery (70.3%), greater omentum (68.3%), right diaphragm (61.9%), paracolic gutters (61.1%), vesicouterine pouch (56.6%), and ileocecal area (56.0%; **Table 2**). A positive correlation was found between the incidence of dissemination found during exploratory laparotomy and the incidence of pRT after NACT (**Fig. 2A**). The sites with a high incidence of both initial dissemination and pRT after NACT were the rectosigmoid colon, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch.

4. NPV of the macroscopic findings obtained during IDS

Despite the presence of dissemination during exploratory laparotomy, tissues and organs in 786 (68%) of 1,150 sites were confirmed as macroscopically undetectable during IDS. Of these sites, 334 (42.5%) had a pRT (**Supplementary Fig. 2**). Therefore, the overall NPV of the tissues and organs was 57.5%. The NPV markedly differed between sites, ranging
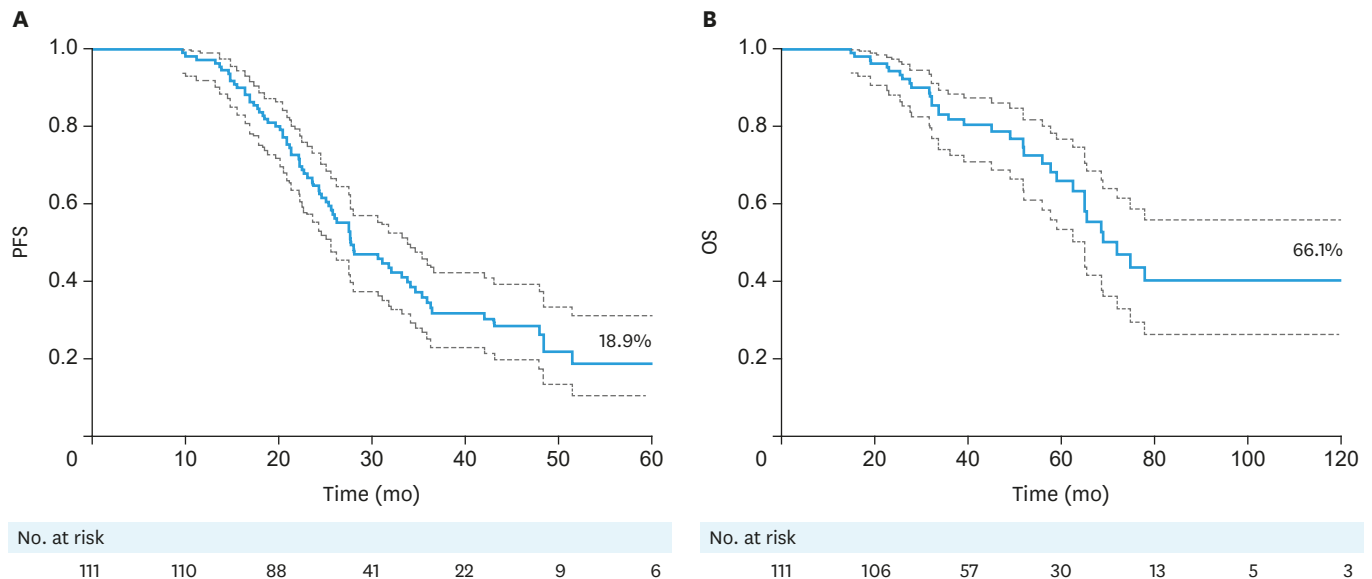

Fig. 3. PFS and OS of the 111 patients who received IDS in this study.
The solid lines indicate the estimated survival curves, and the dotted lines represent 95% CIs. (A) Median PFS: 27.7 months (95% CI=25.2–33.7). (B) Median OS: 71.9 months (95% CI=62.4–not reached).
CI, confidence interval; IDS, interval debulking surgery; OS, overall survival; PFS, progression-free survival.

Table 2. Peritoneal implants during exploratory laparotomies and IDSs in this study (n=111)

Organ/tissues	Exploratory laparotomy			No. patient who underwent the resection*	Findings on the IDS						Summary		
	No. Pt. who underwent the initial laparotomy (a)	No. of macroscopic diseases (b)	Percent of macroscopic diseases (b/a)		Macroscopic finding			No macroscopic finding			No. of Pt. with pathological tumor (d+f)	Percent of pRT after NACT (=[d+f]/[c+e])	NPV (=[e−f]/e)
					No. of Pt. (c)	Pathological tumor (d)	Percent of pathological tumor (c/d)	No. of Pt. (e)	Pathological tumor (f)	Percent of pathological tumor (f/e)			
Rectosigmoid	111	109	98.20%	105	61	48	78.70%	44	27	61.40%	75	71.40%	38.60%
Greater omentum	111	109	98.20%	82	53	42	79.20%	29	14	48.30%	56	68.30%	51.70%
Right diaphragm	111	105	94.60%	105	26	24	92.30%	79	41	51.90%	65	61.90%	48.10%
Vesicouterine pouch	111	99	89.20%	99	21	17	81.00%	78	39	50.00%	56	56.60%	50.00%
Paracolic gutters	111	90	81.10%	90	24	22	91.70%	66	33	50.00%	55	61.10%	50.00%
Splenic hilum	111	81	73.00%	79	28	22	78.60%	51	22	43.10%	44	55.70%	56.90%
Splenic capsule	111	81	73.00%	79	11	7	63.60%	68	24	35.30%	31	39.20%	64.70%
Small bowel	111	79	71.20%	62	26	22	84.60%	36	13	36.10%	35	56.50%	63.90%
Ileocecal area	111	75	67.60%	75	28	21	75.00%	47	21	44.70%	42	56.00%	55.30%
Morison's pouch	111	65	58.60%	62	15	13	86.70%	47	13	27.70%	26	41.90%	72.30%
Porta hepatis	111	59	53.20%	56	11	8	72.70%	45	13	28.90%	21	37.50%	71.10%
Lesser omentum	111	52	46.80%	42	15	12	80.00%	27	11	40.70%	23	54.80%	59.30%
Appendix	111	51	45.90%	46	11	9	81.80%	35	11	31.40%	20	43.50%	68.60%
Left diaphragm	111	49	44.10%	41	7	6	85.70%	34	9	26.50%	15	36.60%	73.50%
Transverse mesentery	111	46	41.40%	37	19	17	89.50%	18	9	50.00%	26	70.30%	50.00%
Hepatic capsule	111	17	15.30%	15	11	6	54.50%	4	1	25.00%	7	46.70%	75.00%
Lymph nodes	111	NA	NA	96	18	13	72.20%	78	33	42.30%	46	47.90%	57.70%
All organ/tissues				1,150	385	309	80.30%	786	334	42.50%	643	55.90%	57.50%

IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NPV, negative predictive value; pRT, pathological residual tumor; Pt., patient.
*Excluding patients who underwent resection of some organs/tissues during exploratory laparotomies.

from 38.6% (17/44) to 75.0% (3/4). The sites that had a low NPV were the rectosigmoid (38.6%), right diaphragm (48.1%), vesicouterine pouch (50.0%), paracolic gutters (50.0%), transverse mesentery (50.0%), and greater omentum (51.7%), whereas those with an NPV of ≥70% were the hepatic capsule (75.0%), left diaphragm (73.5%), Morison's pouch (72.3%), and porta hepatis (71.1%; **Table 2**). A negative correlation was observed between the incidence of pRT after NACT and NPV (**Fig. 2B**). This means that the organs that had a high incidence of pRT after NACT, namely the rectosigmoid colon, transverse mesentery, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch, showed characteristics of a low NPV (<60%).

5. Survival outcome and perioperative complications

The median follow-up time was 40.3 months (IQR=27.3–60.8 months). The median PFS was 27.7 months (95% CI=25.2–33.7). The median OS was 71.9 months (95% CI=62.4–not reached; **Fig. 3**). When the analysis was conducted in June 2019, 71 of the 111 patients had experienced a recurrence. Specifically, the patterns of recurrence were platinum-resistant relapse (platinum free interval [PFI] <6 months) in 5 patients (7.0%), partial sensitive relapse (PFI=6–12 months) in 10 patients (14.1%), and sensitive relapse (PFI ≥12 months) in 56 patients (78.9%).

Severe perioperative complications (grade ≥IIIb according to the Clavien-Dindo classification [28]) occurred in 6 patients (5.4%, grade IIIb: leakage of rectosigmoid colon anastomosis in 3, ureteral leakage in 1, and pancreatic fistula in 1; and grade IV: intraabdominal bleeding in 1).

6. Comparison of PFS in this study and historical approaches

To clarify that prognosis improved when a lesion >1 cm before NACT was resected during IDS whether it was visible or not, a further analysis was performed. Among the patients in whom complete resection was achieved during IDS in our hospital, the prognosis of those treated during 2008–2017 (this study period) was compared to those treated during 2000–2007 (before this study period). Patients treated in our hospital during 2000–2007 were included as the control group because a lesion of >1 cm before NACT was not resected during IDS when the lesion became invisible. Surgical complexity score, complete resection rate, and bevacizumab administration rate in patients treated during 2008–2017 were significantly higher than those treated during 2000–2007 (**Table 3**). The median PFS among patients in whom complete resection was achieved during IDS was longer in patients treated during 2008–2017 than in those treated during 2000–2007 (20.3 months [95% CI=14.6–46.1], 30.5 months [95% CI=25.7–34.0]; log-rank test, p=0.273; Wilcoxon test, p=0.012, **Supplementary Fig. 3**). A multivariate Cox proportional-hazards regression analysis indicated that treatment period (hazard ratio [HR]=0.56; 95% CI=0.35–0.90) and bevacizumab administration (HR=0.64; 95% CI=0.41–0.99) were independent prognostic factors of PFS (**Supplementary Table 1**), although 64 (58%) of 111 patients treated during 2008–2017 received bevacizumab.

7. PFS according to number of cycles and pathological response to NACT

The PFS was not different between the patients with <6 cycles of NACT and with ≥6 cycles (**Supplementary Fig. 4A**). Moreover, the pathological response to NACT (macroscopic disease, microscopic disease, or pathologically complete response) did not affect PFS (**Supplementary Fig. 4B**).

Table 3. Comparisons of clinical measures between 2000–2007 and 2008–2017

Characteristic	2000–2007 (n=36)	2008–2017 (n=111)	p value
Age			0.763
Median age (yr)	62 (52–69)	62 (51–70)	
FIGO stage			0.175
IIIC	25 (69.4)	62 (55.9)	
IV	11 (30.6)	49 (44.1)	
Primary site			<0.001
Ovary	32 (88.9)	51 (45.9)	
Fallopian tube	1 (2.8)	51 (45.9)	
Peritoneum	3 (8.3)	9 (8.1)	
Histology			0.141
Serous carcinoma, high grade	31 (86.1)	99 (89.2)	
Serous carcinoma, low grade	0 (0.0)	2 (1.8)	
Clear cell carcinoma	1 (2.8)	4 (3.6)	
Carcinosarcoma	1 (2.8)	3 (2.7)	
Endometrioid carcinoma	0 (0.0)	2 (1.8)	
Mucinous carcinoma	2 (5.6)	0 (0.0)	
Poorly differentiated carcinoma	0 (0.0)	1 (0.9)	
Mixed carcinoma	1 (2.8)	0 (0.0)	
CA-125 (IU/mL)			
At exploratory laparotomy	1,602 (740–3,316)	1,240 (588–2,960)	0.474
At interval surgery	19.2 (10.0–50.6)	12 (8.8–21.9)	0.012
Bevacizumab			<0.001
Bevacizumab administration	0 (0.0)	64 (57.7)	
Cycle	-	21 (12–21)	
Bevacizumab NOT administration	36 (100.0)	47 (42.3)	
Surgical complexity score	2 (2–4)	13 (11–15)	<0.001
Low (0–3)	23 (63.9)	1 (0.9)	<0.001
Moderate (4–7)	11 (30.6)	6 (5.4)	
High (8–18)	2 (5.6)	104 (93.7)	
Surgical procedures during IDS			-
Rectosigmoid colectomy	10 (27.8)	105 (94.6)	
Vesicouterine peritonectomy	0 (0)	99 (89.2)	
Greater omentectomy	32 (88.9)	82 (73.9)	
Right diaphragm peritonectomy	0 (0)	105 (94.6)	
Splenectomy	0 (0)	79 (71.2)	
Lymphadenectomy	9 (25.0)	96 (86.5)	
Completeness of resection (cm)			<0.001
0	20 (55.6)	104 (93.7)	
≥0.1 and ≤1	11 (30.6)	5 (4.5)	
>1	5 (13.9)	2 (1.8)	

Values are presented as median (IQR) or number of patients (%).
FIGO, the International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; IQR, interquartile range.

DISCUSSION

This study is the first to report that the incidence of pRT after NACT differed significantly among the disseminated sites (range, 36.6%–71.4%). The sites with a high incidence of initial dissemination, namely the rectosigmoid colon, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch, had a high pRT rate after NACT. We further showed that the presence of microscopic disease decreased the NPV, which also differed remarkably among the sites (range, 38.6%–75.0%). The incidence of pRT after NACT and the NPV had a negative correlation. The sites with a high incidence of initial dissemination become invisible during IDS. Moreover, we showed that, despite a median 5 NACT cycles (i.e., late IDS), the survival outcomes of patients treated with this study protocol were favorable compared to

those treated before the introduction of this protocol in our hospital on historical analysis. The appropriate surgical margins for IDS can be secured by resecting a lesion that is >1 cm in diameter before NACT, even if it is not visible during IDS. Our study may lead to a change in perspective regarding IDS surgical margins. The downside of IDS is that disseminated lesions disappear macroscopically after successful chemotherapy, making resection of microscopic residual tumors impossible. Ideally, the target extent of resection should be set to remove not only tumors that are macroscopically visible during IDS but also those identified on the basis of the initial disease spread status.

Despite the median of 5 NACT cycles in this study, many residual diseases were present both macroscopically and microscopically. The incidence of pRT after NACT differed widely among disseminated sites. The greater omentum and colon (rectosigmoid colon and transverse mesentery) were less responsive to NACT. The sites with high incidence rates of initial dissemination and pRT after NACT included the rectosigmoid colon, greater omentum, right diaphragm, paracolic gutters, and vesicouterine pouch. Our study results support the argument that the role of NACT is to shrink rather than eradicate tumors [29].

By using initial exploratory laparotomy records, our study showed that macroscopic findings of IDS were not associated with pRT. Macroscopic complete resection during IDS does not automatically indicate the complete removal of pathological diseases. Similarly, Hynninen et al. [19] recently discussed that the use of NACT made it difficult to evaluate the extension of disseminations; consequently, microscopic diseases are left unresected. They also reported that the NPV was highest in the peritoneal surfaces of the paracolic gutters and the pelvis during IDS. It is unclear why the NPV frequencies varied among sites. Lim et al. [30] speculated that these small residual diseases might have some cancer stem cells. We understand that even if complete resection is macroscopically successful in traditional IDS, microscopic residual disease remains and can lead to a subsequent recurrence.

In our study, both PFS and OS in the 111 patients who underwent NACT-IDS according to our treatment protocol were favorable (27.7 and 71.9 months, respectively), with a low complication rate. Moreover, 78.9% of the patients who underwent IDS had a platinum-sensitive recurrent disease in this study. Meanwhile, a phase III study showed PFS and OS of 12 and 30 months, respectively, in the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) trial [6], and 12.0 and 24.1 months, respectively, in CHORUS study [7]. Our treatment protocol of keeping records of lesions >1 cm during exploratory laparotomy allowed us to resect invisible diseases during IDS, with comparable prognosis as optimal PDS. Resection of lesions >1 cm before NACT gave a favorable prognosis for patients with macroscopic and microscopic disease comparable to patients with pathological complete response regardless of pathological response to NACT. Our result differed from those of other reports that patients with poor pathological response to NACT had poor prognosis [31]. We believe that the increased number of NACT cycles does not induce drug resistance [10]; rather, it causes more lesions to become macroscopically invisible, allowing unresected pathological disease to remain on site, which leads to drug resistance.

In this study, the rate of severe perioperative complications was low (5.4%). We did not resect a lesion <1 cm before NACT in the liver surface, portal triad, and colon other than the rectum during IDS. Tumors ≥1 cm before NACT in these lesions usually shrink after NACT, and the extent of surgical resection could consequently narrow. As a result, surgical procedures that

have high morbidity rates are not required during IDS. For example, tumors that require total colectomy if removed at PDS can be removed using low anterior resection with right or left hemicolectomy at IDS. Similarly, tumors that require liver segmentectomy if removed at PDS can be removed using wedge resection at IDS, while tumors that require resection of the portal triad if removed at PDS can be removed with resection of the ligamentum teres hepatis at IDS. Not requiring surgical procedures with high morbidity rates during IDS is one of the benefits of NACT that can reduce the incidence of complications.

We believe laparotomy is the best method to evaluate and mark disseminated tumors throughout the abdominal cavity. This is because tumors may be present at sites that are difficult to find with a laparoscope or may be found by palpation only. If the sole purpose of identifying disseminated tumors before NACT is to detect unresectable lesions, laparoscopy may be sufficient. However, laparoscopic evaluation may be insufficient for the resection of tumors >1 cm before NACT during IDS. In several clinical studies of laparoscopic evaluation or surgery, the number of sites to be evaluated by laparoscopy is small [32]. In other reports of laparoscopic evaluations before IDS, complete resection was achieved in only 51%–58% of patients who were judged to not have unresectable tumors by laparoscopy [33]. These results suggest that it is difficult to identify all disseminated tumors throughout the abdominal cavity.

Our study had some limitations. First, when abdominal disseminations were severe and unobservable during the exploratory laparotomy, the observation data of these sites were defined as missing data. In particular, the transverse colon and ileocecal lesions were unobservable when the omental cake was massive. Similarly, nodules of the splenic hilum were sometimes unclear during exploratory laparotomy. Second, patients who had resectable omental nodules underwent their resection during the exploratory laparotomy. Thus, regarding the omentum, only patients who could not undergo omental resections during exploratory laparotomy were included in this study. Third, as most of the disseminated tumors in the small intestinal mesentery were ≤1 cm in diameter and the disseminated nodules were too numerous to mark using 3–0 black silk, we did not perform an extensive intestinal resection. Whether disseminated sites of ≤1 cm will disappear after NACT remains unclear in this study. Fourth, the choice of PDS or NACT-IDS depends on the criteria in each institution, which affects the incidence rate of residual tumors after NACT. Finally, although the appropriate resection line for IDS was not explicitly proved in this observational study, a randomized clinical study is needed to define the appropriate resection margin on the basis of our present findings.

The strength of our study was that the first-line treatment policy and the selection criteria of PDS or NACT-IDS were consistent throughout the study period. In this study, 99 patients (89%) underwent IDS with high surgical complexity scores. The evaluation of exploratory abdominal laparotomies and IDS performed for all 111 patients were conducted by 2 gynecological oncologists (S.T. and K.N.) consistently. A median of 58 slides, a larger number than those in previous similar studies, were prepared for the pathological examination of each patient [19].

In conclusion, the role of NACT is to shrink rather than eradicate tumors [29]. Aggressive surgery using a resection line based on the initial disease during IDS leads to favorable survival outcomes [30]. As we previously reported, the benefit of NACT is not that it decreases perioperative complications by reducing surgical complexity. Rather, it decreases

perioperative complication rates without reducing surgical complexity [34]. The treatment strategy of this study is feasible and has continued in daily practice in our hospital.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Uni- and multivariate analyses of PFS for historical approaches

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Supplementary Fig. 1
Representative cases of the markings on the margins of the tumor using non-absorbable 3–0 black silk. (A) Markings of a tumor at the transverse colon mesentery on both ends of the margins using non-absorbable 3–0 black silk. (B) Markings of tumors disseminated massively around the ileum end on the oral margin. The black arrowhead indicates non-absorbable 3–0 black to be marked 50 cm from the ilium end at the oral edge of the tumors. We marked both ends of the margins of the tumor >1 cm before NACT using non-absorbable 3–0 black silk. We put markings on the right and left of normal lesions a few millimeters away from the tumor's edge. Regarding the markings for the small and large intestines, we marked the oral and anal edges of the tumors disseminated to the intestinal serosa. By marking both ends of the tumor margins, the original excision margin is secured by resecting the area between the marks, even if the tumor shrinks after NACT and the markings are moved.

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Supplementary Fig. 2
Microscopic residual tumor resides in the right diaphragm after NACT. After NACT, no macroscopic dissemination was observed in the right diaphragm, but right diaphragm stripping was performed. (A) Histological images (original magnification ×1.25). The black arrowhead indicates the surface layer of the diaphragmatic peritoneum, and the dotted line indicates tumors deep inside the diaphragmatic peritoneum. The surface of the diaphragmatic peritoneum is fibrotic and contains no tumor cells. (B) Histological images (original magnification ×10). A microscopic residual tumor remains deep inside the diaphragmatic peritoneum.

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Supplementary Fig. 3
(A) Median PFS: 20.3 months (95% CI=14.6–46.1) in 2000–2007, 30.5 months (95% CI=25.7–34.0) in 2008–2017, log-rank test, p=0.273; Wilcoxon test, p=0.012. (B) Median OS: 75.6 months (95% CI=40.8–95.4) in 2000–2007, 71.9 months (95% CI=64.9– not reached) in 2008–2017, log-rank test, p=0.467; Wilcoxon test, p=0.426.

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Supplementary Fig. 4
Comparison of PFS of number of cycles and pathological response to the NACT. (A) The cycle of NACT, median PFS: <6 cycles, 32.0 months (95% CI=25.9–35.8); ≥6 cycles, 25.2 months

(95% CI=22.1–30.5), log-rank test, p=0.212; Wilcoxon test, p=0.10). (B) The pathological response after NACT, median PFS: macroscopic disease, 27.7 months (95% CI=23.6–31.0); microscopic disease, 25.4 months (95% CI=21.2–42.0); pCR, 34.6 months (95% CI=15.1–not reached), log-rank test, p=0.301; Wilcoxon test, p=0.375).

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