

# Retrospective Analysis of Total Parietal Peritonectomy Without Systematic Lymphadenectomy for Advanced Epithelial Ovarian Cancer

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**Abstract.** *Background/Aim:* Total parietal peritonectomy (TPP) is a surgical procedure used for complete resection of microscopic peritoneal dissemination. This study analyzed the perioperative complications that developed when omitting systematic lymphadenectomy from TPP. *Patients and Methods:* We retrospectively analyzed perioperative complications in epithelial ovarian cancer patients with stage IIIB-IVB who underwent TPP during primary and interval cytoreductive surgeries between April 2018 and October 2021. *Results:* Thirty-three patients were enrolled in the study. The median patient age was 62 years. Of 31 patients (94%) with stage IIIC/IV disease, 24 (73%) had high-grade serous carcinoma. The median operative time and blood loss were 447 min and 2,831 ml, respectively. Complete tumor resection was performed in 30 patients (91%). Only five patients underwent partial lymphadenectomy for clinical metastatic lymph nodes. Further, grade 3 complications were observed in seven (21%) patients, and there were no fatal events in this study. Three patients (9%) had ureteric injuries, which was the most frequent complication in this study. Only one patient developed an intra-abdominal infection due to ascites. In this case, partial para-aortic and pelvic lymphadenectomies were performed. *Conclusion:* TPP

*without systematic lymphadenectomy reduces the frequency of perioperative complications associated with ascites.*

Advanced epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies in developed countries (1, 2). The mainstay of treatment for EOC is cytoreductive surgery with the aim of macroscopically complete resection of all visible tumor (3). Complete tumor resection during cytoreductive surgery results in significantly improved prognosis (4-6). However, complete cytoreductive surgery is more difficult and complicated for patients with high tumor loads because it frequently requires resection of gynecological organs together with other organs, including the intestinal tract and upper abdominal organs (7-10). It has been known widely that primary cytoreductive surgery (PCS) and high tumor burden patients have higher risk of perioperative morbidity than interval cytoreductive surgery (ICS) and early stage EOC (11-13). Although extended surgery was performed for EOC, some patients underwent incomplete surgery for residual tumor after PCS or neoadjuvant chemotherapy followed by ICS. Some articles have reported that the complete tumor resection rate at the leading centers is <70% (14-16). The LION trial provides some insight into the type of surgical procedures necessary for complete surgery. Although the LION clinical trial aimed to evaluate the efficacy of systematic lymphadenectomy (LNx) during PCS in EOC, it enrolled only eligible patients who underwent macroscopically complete resection. All surgical procedures in the LION study, except hysterectomy, bilateral salpingo-oophorectomy, and omentectomy, were parietal peritonectomy, with a frequency of approximately 90% (9). Peritonectomy plays an essential role in achieving complete cytoreductive surgery. Recently, several studies have reported resection of peritoneal dissemination as a new surgical method by resecting the entire parietal peritoneum. Mualllen *et al.* reported total retroperitoneal en bloc resection of multivisceral-peritoneal packet (TROMP operation), a novel surgical technique based on a total retroperitoneal approach to

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remove the parietal peritoneum with no-touch isolation and resection technique for all infiltrated organs (en bloc) (17). Notably, this novel surgical procedure was performed in all patients with PCS. In general, comprehensive PCS in patients with high tumor burden results in a high rate of perioperative complications (18-20). The TROMP operation increased the complete tumor resection rate to 87.9% without increasing blood loss, perioperative complications, or the duration of surgery compared with conventional PCS without TROMP operation. Moreover, Kota *et al.* reported total parietal peritonectomy (TPP), a surgical technique similar to the TROMP operation approached through the retroperitoneal cavity, which may improve the prognosis compared with conventional cytoreductive surgical methods (21). However, these techniques slightly increased the rates of perioperative infection, pneumonia, anastomotic leaks, and wound dehiscence compared with conventional surgical procedures (not statistically significant). Both studies concluded that the problem appears to lie in peritonectomy with TPP obstructing the absorption of perioperative ascites by the peritoneum, resulting in various perioperative complications due to ascites accumulation. At our facility, we performed TPP for patients with EOC at the time of PCS and ICS. Additionally, systematic lymphadenectomy (LNx) is not performed for patients with EOC because the LION clinical trial revealed that systematic LNx in EOC patients who had undergone intra-abdominal macroscopically complete resection was not associated with longer overall or progression-free survival compared to no LNx (9). To the best of our knowledge, there are few articles regarding the perioperative complications of PCS and ICS with TPP for EOC. Moreover, no study has focused on perioperative complications of TPP without systematic LNx. The present retrospective study focused on the frequency of perioperative complications associated with TPP without systematic LNx during PCS and ICS.

## Patients and Methods

This study was approved by the Institutional Review Board of the Institute of National Cancer Center East Hospital (2021-329). Informed consent was obtained in the form of an opt-out option on the website.

We reviewed the medical records of patients who underwent TPP for EOC at the time of PCS or ICS at our hospital between April 2018 and October 2021. The decision criteria for PCS or neoadjuvant chemotherapy (NAC) were determined by the gynecological oncology team based on the patient's condition, preoperative imaging, or the findings of staging laparoscopy. Although the number of cycles of NAC for ICS was not specified, preoperative chemotherapy was administered until complete surgery was determined to be possible using preoperative imaging before ICS. The surgical indications for TPP were defined as stage IIIB or higher cases in which complete surgery was determined to be possible intraoperatively. Patients with an Eastern Cooperative Oncology Group performance status of  $\geq 2$ , serious cardiac or

respiratory disease, or hepatic or renal dysfunction were excluded from TPP. We did not perform systematic LNx for EOC regularly. We performed lymphadenectomy only for grossly apparent metastatic lymph nodes that were detected intraoperatively or preoperatively. The main aim of this study was to evaluate the surgical outcomes and perioperative complications in EOC patients who underwent TPP without systematic LNx. The following parameters were assessed: patient characteristics, surgical outcomes, and perioperative complications. Perioperative morbidity and mortality were defined as any adverse event occurring until the initial perioperative chemotherapy. We used the Clavien-Dindo classification version 2.0 to evaluate the severity of complications.

Statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Jichii Medical University, Saitama, Japan) (22). Continuous variables were compared using unpaired t-tests. Categorical variables are presented as absolute numbers and/or percentages and were compared using the chi-square test. Statistical significance was set at a *p*-value of  $<0.05$ .

## Results

Overall, 93 patients with stage IIIB-IVB EOC were admitted to our facility during the study period. Among them, 33 patients who underwent PCS and ICS with TPP were enrolled in this study. Regarding the timing of cytoreductive surgery, 19 patients (58%) had PCS and 14 (42%) had ICS. The characteristics of all patients and each cytoreductive surgery are summarized in Table I. The median age was 62 years (range=23-74 years), and 31 patients (94%) had stage IIIC or IV disease. There were no significant differences in age, follow-up period, cancer type, stage, or histology between the PCS and ICS groups. The age of the PCS group tended to be lower than that of the ICS group. The histological types were as follows: 24 patients (73%) had high-grade serous carcinoma, two (6%) had endometrioid carcinoma, two (6%) had clear-cell carcinoma, and four patients had other types (three patients, low-grade serous carcinoma; one patient, mixed carcinoma). The surgical characteristics of all patients and each cytoreductive surgery are summarized in Table II. The median operative time was 447 min (range=214-632 min) and median operative blood loss was 2,831 ml (range=340-6,477 ml) in all patients. There was no significant difference in the operative time and operative blood loss between the two cytoreductive surgeries. Moreover, complete tumor resection was performed on 30 patients (91%), optimal surgery (residual tumor  $<1$  cm) on 2 patients (6%), and suboptimal surgery (residual tumor  $\geq 1$  cm) on only one patient (3%). Of the two optimal surgeries, one patient had a 3-mm residual tumor in the mesentery and one had a 1-mm residual tumor in the mesentery and lesser mesentery. In addition, the suboptimal surgery case had 1-cm residual lesions in the liver and mesentery. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Additionally, bowel resection was performed on 22 patients (67%), and three of the patients underwent total colectomy and 21 underwent diversion of ileostomy to a stoma.

Table I. Patient characteristics.

	Total	PCS	ICS	<i>p</i> -Value
Case (no.)	33	19	14	
Age at first diagnosis (year)	62 (23-74)	61 (23-71)	65.5 (39-74)	0.12
Follow-up period (months)	15 (3-44)	17 (3-41)	10 (4-44)	0.53
Cancer type				
Ovarian cancer	19 (58%)	13 (68%)	6 (43%)	0.07
Fallopian cancer	2 (6%)	2 (11%)	0 (0%)	
Primary peritoneal cancer	12 (36%)	4 (21%)	8 (57%)	
FIGO stage (2014)				
IIIB	2 (6%)	2 (11%)	0 (0%)	0.28
IIIC	16 (49%)	7 (36%)	9 (64%)	
IVA	4 (12%)	2 (11%)	2 (14%)	
IVB	11 (33%)	8 (42%)	3 (22%)	
Histology				
High-grade serous	25 (76%)	12 (63%)	13 (93%)	0.37
Endometrioid	2 (6%)	1 (5%)	1 (7%)	
Clear	2 (6%)	2 (11%)	0 (0%)	
Mucinous	0 (0%)	0 (0%)	0 (0%)	
Other	4 (12%)	4 (21%)	0 (0%)	
CA125 (U/ml) [median (range)]	759 (55-15,197)	559 (55-15,197)	1112 (206-11,633)	0.18

Values are presented as median (range) or number (%). PCS: Primary cytoreductive surgery; ICS: interval cytoreductive surgery.

In bowel resection, there were three total colectomy patients; two in the PCS group and one in the ICS group. In our study, patients who previously underwent ileostomy were treated with stoma closure after the completion of adjuvant chemotherapy and confirmation of complete remission. Of the 21 patients who underwent stoma diversion, 13 patients had already undergone ileostomy closure, excluding those who had undergone adjuvant chemotherapy and total colorectal resection. In addition to the subdiaphragmatic peritoneum, partial diaphragmatic full-thickness resection was performed in five cases (15%). There were no patients with systemic LN<sub>x</sub>, but three patients underwent bilateral pelvic and para-aortic partial LN<sub>x</sub> for only grossly apparent metastatic lymph nodes, and two patients underwent partial LN<sub>x</sub> only for pelvic lesions. The median surgical complexity score was 9 (range=5-15), and the details of each complexity score group included 10 patients (30%) in the intermediate group and 23 patients (70%) in the high group. The frequency of high surgical complex scores in the PCS group was higher than that in the ICS group; however, there was no statistically significant difference. Compared with PCS and ICS, all partial LN<sub>x</sub> patients had PCS, and the rate of bowel resection was higher in the PCS group than in the ICS group.

Perioperative complications (grade 3) are summarized in Table III. Grade 3 complications were observed in seven (21%) patients, and there were no mortality events after surgery. More than one grade 3 complication was observed in three patients. The rate of complications was higher with PCS than with ICS. Ureteric injury was the most frequent

complication. Although these ureteric injuries caused renal dysfunction, renal function improved after recovery procedures (ureteral stent or nephrostomy) and is currently within normal function. Gastrointestinal anastomotic leak occurred in only two patients, one of whom required reoperation and one recovered with drainage only. In terms of abdominal infection and ascites, one patient developed intra-abdominal infection due to ascites. In this case, partial LN<sub>x</sub> was performed for pelvic and para-aortic lesions. The patient was treated with computed tomography-guided drainage and antibiotics. Only one other case had complications of pleural effusion, necrotizing fasciitis, ileus, and delayed gastric emptying.

## Discussion

To the best of our knowledge, this is the first study to show the characteristics and frequency of TPP complications in EOC without systematic LN<sub>x</sub>. Few studies have reported the perioperative outcomes and complications of TPP, including PCS and ICS for EOC, with two studies on PCS performing systematic LN<sub>x</sub> and one study on ICS for suspicious metastatic lymph node resection only (17, 21, 23). In previous reports, TPP was found to be an effective surgical technique for EOC because it increases the rate of complete tumor resection without increasing blood loss and perioperative complications (17). Especially, Gynecologic Oncology Group 182 trial showed that the diaphragm is the most common localization

Table II. *Surgical characteristics in total patients and each cytoreductive surgery*

	Total	PCS	ICS	p-Value
Case (no.)	33	19	14	
Operation time (min)	447 (214-632)	467 (301-619)	517 (214-632)	0.17
Operation blood loss (ml)	2,831 (340-6,477)	3,252 (340-6,747)	2,051 (676-6,107)	0.15
Residual tumor				
No residual	30 (91%)	17 (90%)	13 (93%)	0.67
<10 mm	2 (6%)	1 (5%)	1 (7%)	
≥10 mm	1 (3%)	1 (5%)	0 (0%)	
Surgical procedure				
Hysterectomy, BSO	33 (100%)	19 (100%)	14 (100%)	
Omentectomy	33 (100%)	19 (100%)	14 (100%)	
Pelvic LNx*	5 (15%)	5 (26%)	0 (0%)	
Para-aortic LNx*	3 (9%)	3 (16%)	0 (0%)	
Bowel resection	22 (67%)	15 (79%)	7 (50%)	
Resection of small intestine	8 (24%)	6 (32%)	2 (14%)	
Resection of large intestine	22 (67%)	15 (79%)	7 (50%)	
Diverting stoma	21 (63%)	14 (74%)	7 (50%)	
Liver resection	2 (6%)	2 (11%)	0 (0%)	
Cholecystectomy	2 (6%)	2 (11%)	0 (0%)	
Splenectomy	11 (33%)	7 (37%)	4 (29%)	
Distal pancreatectomy	2 (6%)	0 (0%)	2 (14%)	
Diaphragmatic partial resection	5 (15%)	2 (11%)	3 (21%)	
Surgical complexity score	9 (5-15)	8.5 (5-15)	8.5 (5-12)	0.10
Intermediate (4-7)	10 (30%)	4 (21%)	6 (43%)	0.34
High (≥8)	23 (70%)	15 (79%)	8 (57%)	
Period from cytoreductive surgery to adjuvant chemotherapy (days)	45 (28-80)	45 (28-80)	47 (29-59)	0.80

Values are presented as median (range) or number (%). BSO: Bilateral salpingo-oophorectomy; LNx: lymphadenectomy; PCS: primary cytoreductive surgery; ICS: interval cytoreductive surgery. \*Indicates that grossly metastatic lymph nodes were resected in our study.

for residual tumor after cytoreductive surgery (24). Upper abdominal peritonectomy from extraperitoneal approach constitutes a technique safely applied in EOC with diaphragm dissemination (25). Moreover, this procedure may improve EOC (21); however, Muallem *et al.* reported that the rate of all grade perioperative infection (23%) was higher, but not significantly, in TPP compared to conventional cytoreductive surgery (10.4%). They attributed the increased rate of infection to splenectomy and/or systematic LNx (17). Additionally, Yokosu *et al.* indicated that TPP increased the incidence of lymph cysts (19%) and subsequent intra-abdominal infection (23%) due to decreased absorption of ascites caused by the loss of peritoneum (21). The combined use of systematic LNx with TPP is suspected to be associated with an increased risk of complications associated with ascites, which may accumulate due to perioperative lymphatic leakage. In one ICS article, although only suspicious metastatic lymph nodes were targeted for resection, LNx was performed in 90% of the patients. In these cases, the most frequent complication was perioperative ascites that required aspiration (23). Therefore, it is important to clarify the relationship between TPP and complications with systematic LNx in addition to developing a conventional TPP into an even safer TPP. The causes of these ascites

complications were based on the following: The lumen of the lymphatic lacunae is irregularly shaped, with a wide lumen under the diaphragm and parietal peritoneum, and lymphatic vessels open from the lymphatic lacunae into the spaces between the mesothelial cells. This opening of the lymphatic vessels is called lymphatic stoma, through which ascites enters the lymphatic vessels. Lymphatic stoma of the entire abdominal parietal peritoneum is obstructed following TPP, and the ability of the peritoneum to absorb ascites from the peritoneal wall is reduced, resulting in lymphatic fluid accumulation (26, 27). This study showed that TPP without systematic LNx reduced the rate of perioperative complications with regards to perioperative abdominal infection and ascites compared with previous studies (Table IV). In our study, there were overlapping cases of ascites and intra-abdominal infection in which the patients had grossly metastatic lymph nodes intraoperatively and underwent partial LNx. It can, therefore, be presumed that TPP without systematic LNx reduces the risk of perioperative ascites, intra-abdominal infection, and lymphatic cyst.

However, the surgical strategy for LNx in EOC patients has been discussed. Two RCTs investigated the efficacy of systematic LNx during PCS in EOC (9, 28). Both RCTs

Table III. Perioperative complication in total patients and each cytoreductive surgery.

	Total (n=33)	PCS (n=19)		ICS (n=14)	
		LNx (n=5)	No LNx (n=14)	LNx (n=0)	No LNx (n=14)
	Grade 3	Grade 3	Grade3	Grade 3	Grade 3
Total event	11 (36%)	4 (80%)	5 (36%)	0 (0%)	3 (21%)
Ureteric injury	3 (9%)	1 (20%)	1 (7%)	0 (0%)	1 (7%)
Gastrointestinal anastomotic leak	2 (6%)	0 (0%)	2 (14%)	0 (0%)	0 (0%)
Intra-abdominal abscess	1 (3%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
Ascites	1 (3%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
Ileus	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Pleura effusion	1 (3%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
Delayed gastric emptying	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Necrotizing fasciitis	1 (3%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)

Values are presented as number (%). More than one grade 3 complication was observed in three patients. There were no cases of grade 4 or 5 complications. LNx: Lymphadenectomy; PCS: primary cytoreductive surgery; ICS: interval cytoreductive surgery.

Table IV. Comparison of perioperative complications between this study and other studies.

	Total	PCS			ICS	
	Our study	Our study	Other study 1	Other study 2	Our study	Other study 3
Case (no.)	33	19	47	16	14	50
Ureteric injury	3 (9%)	2 (11%)	0 (0%)	1 (6%)	1 (7%)	0 (0%)
Gastrointestinal anastomotic leak	2 (6%)	2 (11%)	4 (9%)	1 (6%)	0 (0%)	0 (0%)
Pleura effusion	1 (3%)	1 (5%)	17 (36%)	1 (6%)	0 (0%)	0 (0%)
Infection	1 (3%)	1 (5%)	11 (23%)	6 (38%)	0 (0%)	0 (0%)
Ascites	1 (3%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	5 (10%)
Necrotizing fasciitis	1 (3%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ileus	1 (3%)	0 (0%)	2 (4%)	4 (25%)	1 (7%)	1 (2%)
Delayed gastric emptying	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Pneumonia	0 (0%)	0 (0%)	5 (11%)	0 (0%)	0 (0%)	0 (0%)
Wound dehiscence	0 (0%)	0 (0%)	5 (11%)	0 (0%)	0 (0%)	0 (0%)
Neurologic complication	0 (0%)	0 (0%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)
Sepsis	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	2 (4%)
Postoperative hemorrhage	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (4%)
Lymph cyst	0 (0%)	0 (0%)	0 (0%)	3 (19%)	0 (0%)	0 (0%)
Pancreatic fistula	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Diaphragmatic hernia	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Ileostomy-related complications	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

Values are presented as number (%). Study 1 included complications of all grades, whereas our study and studies 2 and 3 included complications of more than grade 3. LNx: Lymphadenectomy; PCS: primary cytoreductive surgery; ICS: interval cytoreductive surgery.

showed that systematic LNx did not contribute to survival, but systematic LNx increased the frequency of perioperative complications, including longer operative time, increased blood loss, higher incidence of perioperative infection, lymph cyst at discharge, and increased repeat laparotomy rate. In particular, the LION trial included only patients who underwent complete resection for intra-abdominal disease and had clinically negative lymph node metastasis. The LION trial showed that 55.7% of the patients in the systematic LNx

group had pathologic lymph node metastases, and it was presumed that the no systematic LNx group had a similar frequency of pathologic lymph node metastases. Additionally, there is no definitive evidence that chemotherapy is effective in cases of grossly apparent lymph node metastasis (29, 30). This evidence suggests that pathologic lymph node metastasis does not have an effect on prognosis; therefore, the surgical strategy in PCS is to resect only grossly metastatic lymph nodes after complete intra-abdominal surgery in EOC. No

RCTs have examined the efficacy of systematic LNx during ICS; however, several retrospective studies have shown the efficacy and complications of systematic LNx for ICS. Seidler *et al.* reported a review article that included six retrospective studies that showed the same trend as PCS. This indicates that systematic LNx may not be associated with improved survival in lymph node-negative patients (31). In addition, all series highlight the importance of complete macroscopic surgery for the intra-abdominal cavity and confirm that macroscopic residual disease is the main prognostic factor. Moreover, the incidence of perioperative complications associated with LNx increased in ICS. In our study, grossly apparent metastatic lymph nodes could not be detected in ICS patients intraoperatively; therefore, not all patients with ICS underwent partial LNx. There were no perioperative complications associated with ascites in the ICS group. Therefore, it is the most effective strategy to remove grossly apparently metastatic lymph nodes during PCS and ICS. However, in our study, three of the five patients who underwent partial LNx developed perioperative intra-abdominal infection associated with ascites, including all grades. Although it should be noted that even partial LNx carries the risk of perioperative ascites and associated infection, omitting LNx in the absence of clinically apparent metastatic lymph nodes is expected to reduce intra-abdominal infection associated with ascites in TPP.

This study has some limitations. First, this retrospective study contained only a small number of cases. Second, the median follow-up period of 15 months was insufficient for prognostic evaluation. A phase 2 study is currently being designed to reveal the perioperative complications and prognosis of TPP without systematic LNx compared with conventional cytoreductive surgery without TPP and systematic LNx.

## Conclusion

This retrospective study revealed that TPP without systematic LNx reduces the frequency of perioperative complications associated with ascites. However, grossly metastatic lymph nodes should be resected with partial LNx because there is insufficient evidence that they are affected by chemotherapy. Although partial LNx does not include systematic LNx, it should be considered a complication of LNx.

## Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

## Authors' Contributions

SO and HT contributed to data analysis, data collection, and manuscript writing. YK and KY contributed to data collection and analysis.

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