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Total parietal peritonectomy in primary debulking surgery for advanced ovarian cancer

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ABSTRACT

The object of this study is to evaluate the clinical safety and efficacy of total parietal peritonectomy (TPP) in primary debulking surgery (PDS) for advanced ovarian cancer. This retrospective single-center study analyzed 16 patients with FIGO stages IIIC-IVB epithelial ovarian cancer who underwent TPP in PDS and achieved macroscopically complete resection between April 2015 and June 2016. The median age of 16 patients was 52.5 years old. 12 were in stage IIIC and 4 were in stage IV.

Regarding intraoperative complications, unintended diaphragm perforation was observed in two patients. Regarding postoperative complications (Clavien–Dindo classification grade 3–5) before the adjuvant chemotherapy, lymph cysts occured in 3 patients, intra-abdominal abscess in 3, ileus in 2, pancreatic fistula in 1 and temporary kidney failure in 1. Regarding postoperative complications (grade 3–5) after the initiation of adjuvant chemotherapy, diaphragmatic hernia occured in 1 patient, ileus in 2 and intra-abdominal abscess in 2. Except 1 patient who relapsed approximately one month from surgery and died, the other 15 patients overcamed complications and recovered without problems in daily life. This analysis was conducted 3 years after all patients underwent PDS, with the 3-year progression-free and overall survival of 62.5% (95% confidence interval [CI], 34.9–81.1) and 87.5% (95 %CI, 58.6–96.7), respectively.

Based on the above results, TPP in PDS may improve the prognosis compared to previous reports such as LION trial. On the other hand, complications may increase. Therefore, further studies are necessary on its safety and efficacy.

1. Introduction

Ovarian cancer is the most life-threatening gynecologic cancer. Approximately 60% of ovarian cancers are diagnosed in FIGO stages III-IV (Cancer Research UK, 2020; Torre et al., 2018). Although the response rate of first-line treatment is high, the recurrent rate is also very high; 62% within 3 years at post-treatment in stages III-IV (Heinz et al., 2006). The 3-year overall survival (OS) rate in stages III/IV was approximately 45% (Torre et al., 2018).

The standard first-line treatment strategy for advanced ovarian cancer are roughly divided into two: primary debulking surgery (PDS) followed by chemotherapy and interval debulking surgery (IDS) after a neoadjuvant chemotherapy (NAC). Chemotherapy is a platinum-based combination therapy with paclitaxel. Whether PDS or IDS, the maximal diameter of residual tumor after debulking surgery significantly correlates with the prognosis. Patients with no residual tumor (complete surgery) in PDS shows the best prognosis (Kehoe et al., 2015).

Almost all patients with advanced ovarian cancer have extensive peritoneal dissemination from the pelvis to upper abdomen. Complete surgery often requires highly invasive procedures such as systematic pelvic and *para*-aortic lymphadenectomy (PPaLND), intestinal resection, splenectomy, and distal pancreatectomy. In addition, parietal peritonectomy is an indispensable procedure to reduce residual tumor and improve the prognosis. In LION trial, a phase III trial that evaluates the efficacy of PPaLND for advanced ovarian cancer in patients who underwent complete resection in PDS, approximately 90% of patients underwent parietal peritonectomy, resulting in nearly 100% complete surgery rate (Harter et al., 2019). However, the 3-year progression-free

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survival (PFS) was approximately 34% in this trial, which was still insufficient.

The most common site of first recurrence of ovarian cancer is peritoneum. Sinukumar et al. reported that microscopic residual disease was observed in 23.3% of the normal looking peritoneum in IDS (Sinukumar et al., 2019). Even if the tumor is completely removed macroscopically by surgery or chemotherapy, it can remain at the peritoneum microscopically. Therefore, we hypothesized that we can improve the prognosis by total parietal peritonectomy (TPP), i.e., removing the parietal peritoneum not only in the disseminated area but also in the macroscopically non-disseminated area. However, there are few reports about TPP in PDS, its safety and efficacy have not yet been established.

2. Materials and methods

2.1. Patients

A total of 16 patients treated at Jikei University Kashiwa Hospital between April 2015 and July 2016 were retrospectively examined (Fig. 1). The inclusion criteria for TPP at that time were as follows.

(i) Patients with newly diagnosed epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer of advanced FIGO stages IIIB-IVB and had macroscopic dissemination in the upper abdomen.
(ii) We additionally performed TPP when we achieved complete surgery in PDS.
(iii) With good Eastern Cooperative Oncology Group (ECOG) performance score (0–2).

Exclusion criteria were as follows.

(i) Stage IIIA: it involves retroperitoneal lymph node metastasis or microscopic dissemination to the upper abdomen, which cannot be diagnosed during surgery.
(ii) Unresectable metastasis such as diffuse dissemination to the small intestinal mesentery and multiple lung or liver metastasis.
(iii) When operated by surgeons who were not proficient in TPP surgical techniques.

Use of patient information in this study has been approved by our institution's ethics committee.

2.2. Procedure of TPP

We defined the colored parts as a resection range of TPP. The parietal peritoneum was divided into 9 compartments (Fig. 2).

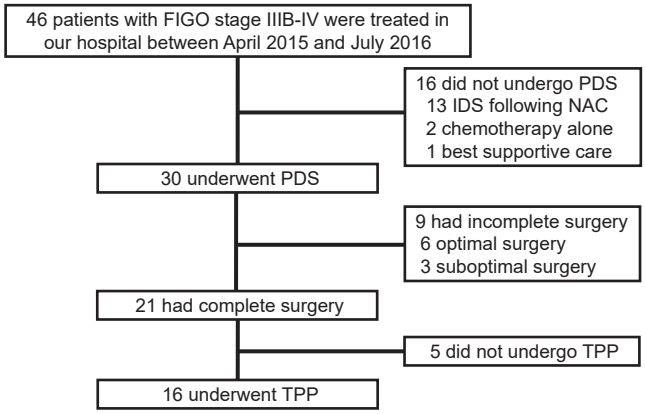

Fig. 1. Enrollment.

1,2: Subdiaphragm (right and left)

We strip the peritoneum from the hypochondriac abdominal wall and the diaphragm. At the right side, the liver is needed to be mobilized to completely resect the subdiaphragmatic peritoneum. When stripping the peritoneum is difficult due to the tumor infiltration to the diaphragm, partial diaphragm full-thickness resection is necessary.

3: Morrison's pouch

We strip the peritoneum from the anterior surface of the duodenum through the anterior surface of the right kidney toward the lower edge of the liver. Liver mobilization is also important in this procedure.

4, 5: Lumbar region (right and left)

We strip the peritoneum from the abdominal wall of lumbar region through the paracolic gutter toward the outer edge of the ascending colon on the right side and descending colon on the left side. Actually, the visceral peritoneum of ascending and descending colon mesentery are stripped. Both colons are mobilized by this procedure.

6,7: Pelvic wall (right and left)

We strip the peritoneum from the low abdominal wall through the pelvic side wall toward the bilateral edges of the rectum. The complete ureter mobilization from the peritoneum is necessary during this procedure.

8: Bladder

This procedure is performed after mobilizing the bladder from the pubic bone. Warm saline is generally injected into the bladder to avoid bladder injury. Then, we strip the peritoneum from the bladder while pulling the inflated bladder. The lateral umbilical ligament is a good landmark.

9: Douglas' pouch

This is very narrow area between the rectum and the uterus. When performing a low anterior resection, this part is unintentionally resected by removing the uterus and rectum in one piece. Otherwise, we strip the peritoneum from the vaginal posterior wall toward the rectum.

2.3. Statistical analysis

We evaluated the prognosis according to PFS and OS rates at 3 years since all patients underwent PDS. PFS and OS at 3 years were estimated using the Kaplan–Meier method. PFS was defined as the time from PDS to the date of recurrence or last follow-up. OS was defined as the time from PDS to the date of last follow-up or death. No patients were lost to follow-up. All statistical analyses were performed using EZR (Kanda, 2013).

3. Results

3.1. Patient characteristics (Table 1)

Out of 3 patients with stage IVB consisted of 1 inguinal lymph node metastasis, 1 inguinal lymph node and spleen metastasis, and 1 direct infiltration into the pleura through the diaphragm.

Intestinal resection was performed in all patients, and ileostomy or colostomy was created in seven of them. We performed intestinal resection when there is macroscopic dissemination to the intestine. Whether or not to create a stoma determined based on the distance between the anus and the rectal anastomosis by the colorectal surgeon. PPaLND to the renal vein level was also performed in all patients. The median blood loss was 3,975 (510–9,000) mL, and the median surgery duration was 564 (258–776) min. 15 patients entered the ICU postoperatively and median length of stay was 4 (1–11) days. Seven patients continued to be ventilated after surgery and median duration was 3 (1–7) days.

The median time from surgery to chemotherapy was 31 (13–99) days excluding one patient who died before chemotherapy. They underwent adjuvant chemotherapy with dose-dense TC (paclitaxel/carboplatin) or dose-dense TC plus bevacizumab (15 mg/kg of body weight, given every

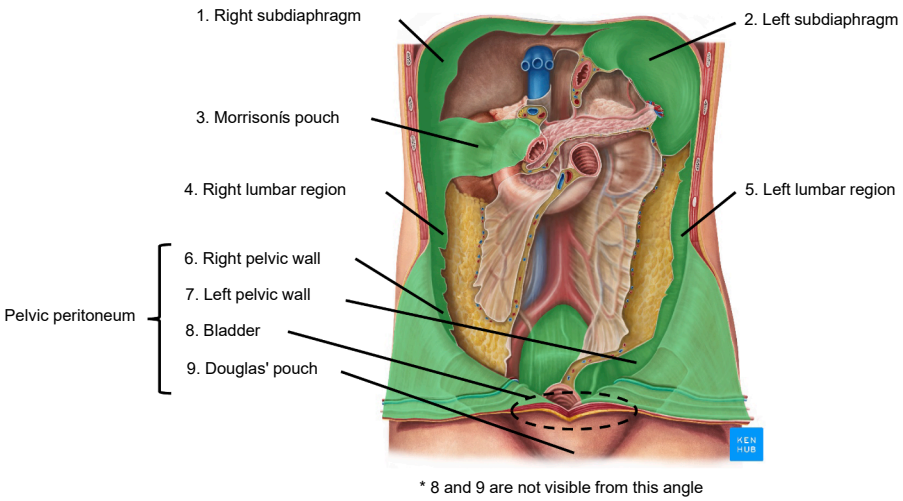

Fig. 2. Definition of peritoneal compartments (©Kenhu).

3 weeks for 5 cycles from second cycle of dose-dense TC, continued for 16 additional cycles unless for a particular reason).

3.2. Intraoperative complications

We encountered 2 cases of unintended diaphragm perforation. There is a risk of diaphragm perforation while stripping ting the subdiaphragmatic peritoneum. In either case, an absorbable suture was used for suturing to close the perforation, and no symptom occurred in the perioperative period. Other complications were not seem to be related to TPP directly.

3.3. Postoperative complications

We used Clavien–Dindo classification ver.2.0 to evaluate the severity of postoperative complications. We showed only severe complications of Grade 3–5 (Table2). Early postoperative complications were defined as those recorded before the adjuvant chemotherapy, whereas late postoperative complications were defined as those that occurred after the initiation of adjuvant chemotherapy. Complications caused by chemotherapy were excluded.

Table 1
Patient characteristics.

	N = 16
Median age(range) –yr.	52.5 (41–71)
Median follow-up -month	39 (41–71)
FIGO Stage-no.	
IIIC	12
IVA	1
IVB	3
Histological type -no.	
High grade serous	13
Endometrioid grade 3	1
Clear cell	1
Low grade serous	1
Surgical procedure -no.	
Hysterectomy, bilateral salpingo-oophorectomy, omentectomy	16
Intestinal resection	16
Ileostomy or colostomy	7
Pelvic and *para*-aortic lymphadenectomy	16
Splenectomy	7
Partial hepatectomy	2
Distal pancreatectomy	2
Partial diaphragm full-thickness resection	1
Partial cystectomy	1
Adjuvant chemotherapy -no.	
Dose-dense TC	6
Dose-dense TC + bevacizumab	9

Table 2
Postoperative complications.

	Grade 3	Grade 4	Grade 5
Early (before adjuvant chemotherapy) –no.			
Lymph cysts	3		
Intra-abdominal abscess	3		
Ileus	2		
Anastomotic leak	1		
Pancreatic fistula	1		
Kidney failure		1	
Late (during or after adjuvant chemotherapy) –no.			
Intra-abdominal abscess	3		
Ileus	2		
Diaphragmatic hernia		1	

In the early period, 3 patients had severe lymph cysts that required peritoneal puncture after removing the intra-abdominal drain. Intra-abdominal abscess that required CT-guided drainage was also observed in 3 patients. One patient developed renal failure and required hemodialysis, which the nephrologist diagnosed as drug-induced. Although it took 99 days, her renal function recovered and initiate adjuvant chemotherapy. One patient developed paralytic ileus, however she recovered with conservative treatment.

One patient who underwent distal pancreatectomy developed pancreatic fistula and intra-abdominal abscess on postoperative day 3 (POD3). We administered antibiotics and performed CT-guided drainage. The inflammation tended to improve gradually, adjuvant chemotherapy was scheduled to be started. However, bilateral malignant pleural effusion appeared and increased rapidly, resulting in atelectasis. Therefore, she needed oxygen administration and chest tube drainage. In addition, innumerable liver metastases appeared in both lobes and grew rapidly, she developed severe liver dysfunction. As a result, her general condition gradually got worse and she died on POD50.

In the late period, one patient had left diaphragmatic hernia and gastric perforation 24 months after the first operation. The left-side diaphragm was perforated, and the stomach fundus was caught in the hole and became necrotic due to ischemia. Gastric contents leaked into the left thoracic cavity from the stomach perforation. Emergency surgery was performed, and the diaphragm and stomach perforation were repaired. She was discharged 35 days after the first emergency surgery.

Regarding 4 patients with ileus, 2 recovered with conservative treatment, whereas the other 2 required surgery to release the adhesion.

Except for 1 patient who died, the other 15 patients overcame complications and recovered without problems in daily life.

3.4. Prognosis

During the observation period, 7 patients relapsed and 2 of them died. The 3-year PFS and OS were 62.5% (95% confidence interval [CI], 34.9–81.1 and 87.5% (95% CI, 58.6–96.7), respectively (Fig. 3).

Regarding the sight of first recurrence, lymph node was observed in 5 patients, peritoneum in 4, and distant metastasis to parenchymal organs in 3 (Table3).

4. Discussion

Surgical treatment for advanced ovarian cancer changed from the era of aiming at making the maximal residual tumor diameter of < 1 cm as the optimal surgery to the era of aiming at the absence of macroscopic residual tumor as the complete surgery.

Of the total peritoneal area, the parietal peritoneum accounts for only 20% (Albanese et al., 2009). It is technically difficult to remove the visceral peritoneum which accounts for the remaining 80%, so that TPP cannot prevent peritoneal recurrence completely. However, when there is no macroscopic dissemination in the peritoneum, the probability of no microscopic dissemination (negative predictive value) is reported to be as low as 48.4% for the parietal peritoneum and as high as 80.4% for the visceral peritoneum in IDS (Bhatt et al., 2020). In other words, there is a high probability that the parietal peritoneum has occult disease. Therefore, we considered that TPP could contribute to the further improvement of the prognosis by removing even the microscopic residual tumor on the parietal peritoneum. To the best of our knowledge, our study is the first report that examined the safety and efficacy of TPP in PDS in multiple patients.

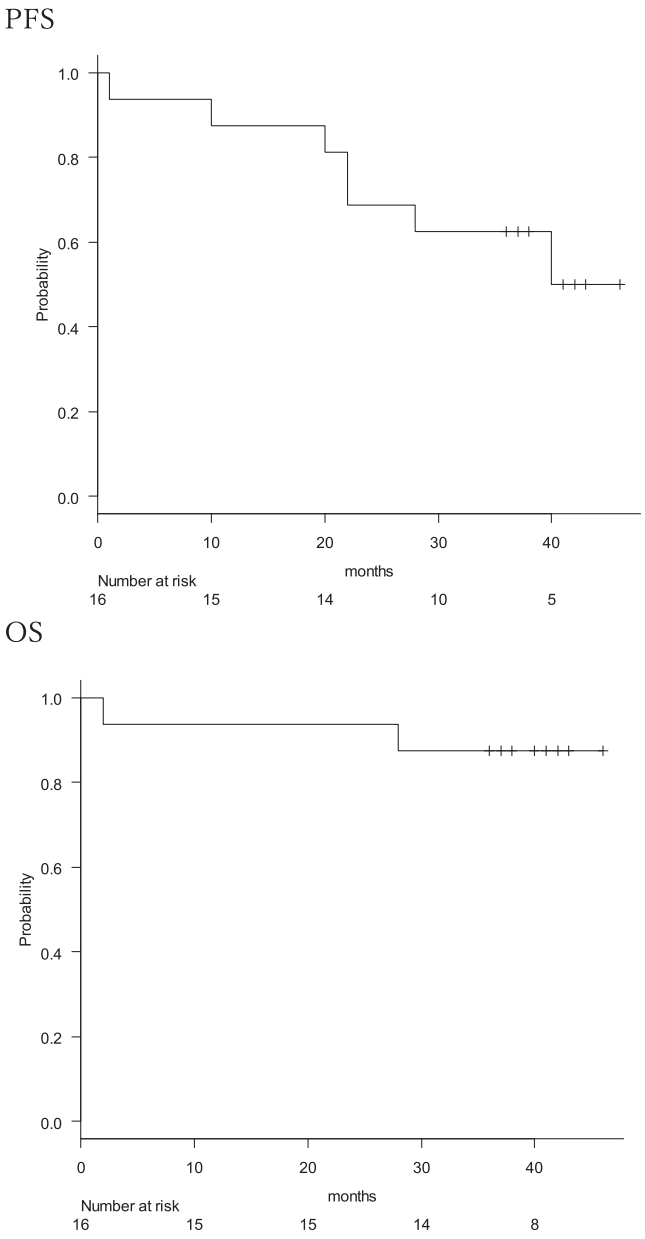

Fig. 3. Progression-free survival, Overall survival.

Regarding safety, several characteristic complications were observed. We encountered many patients who developed lymph cysts and subsequent intra-abdominal abscess. This is because PPaLND was performed in all patients, and absorption of lymphatic leakage was reduced due to the absence of the peritoneum. However, LION trial showed that patients with advanced ovarian cancer and no clinically positive lymph nodes who underwent macroscopically complete resection did not benefit from PPaLND. Therefore, recently we omit PPaLND when we perform TPP, lymph cysts no longer occur and intra-abdominal abscess significantly reduced.

Diaphragmatic hernia was an unexpected severe complication. During her first surgery, we perforated the both- sides diaphragm during peritonectomy and sutured with absorbable suture. However, we should have used non-absorbable suture. Diaphragmatic hernia does not occur on the right side due to the presence of the liver, so that we should be more careful when stripping left subdiaphragmatic pritoneum than the right side.

Although the main cause is bilateral malignant pleural effusion and multiple lung metastasis that appeared immediately after PDS, we took very seriously the loss of one patient during the perioperative period. If she had undergone NAC, she might not have died so early. This is a limitation of PDS.

On the other hand, the results of the efficusy were interesting. In this study, the 3-year PFS and OS were 62.5% and 87.5%, which tended to be higher than those previously reported. In LION trial, which has the same conditions as this study in terms of complete surgery in PDS, the 3-year PFS and OS were approximately 34% and 62%, respectively. (Harter et al., 2019).

We know that the most common site of first recurrence of ovarian cancer is peritoneum. Amate P et al. reported that in the advanced stage, 75% of recurrences involved the peritoneum and 40% were confined to the peritoneum, and nodal recurrences were noted in 38% (Amate et al., 2013). However, the most common site of recurrence was not peritoneum in this study. Moreover, recurrence confined to peritoneum was not observed. This may be due to the removing microscopic dissemination on the parietal peritoneum by TPP, which reduced or delayed peritoneal recurrence and improved the prognosis.

After all, treatment of advanced ovarian cancer depends on how to control peritoneal dissemination. Some clinical trials for intraperitoneal chemotherapy (IP therapy) and hyperthermic chemotherapy (HIPEC), the new treatment methods devised to reduce peritoneal dissemination, have already been conducted. TPP is one of those attempts.

Of course, this study has a number of limitations. The number of cases is very small and retrospective studies cannot escape selection bias. Also, many serious complications were observed in this study. Therefore, we cannot say that this study established the safety and efficacy of TPP.

In order to verify the safety and efficacy of TPP, a prospective study with a larger number of cases is needed. It is expected that complications can be reduced compared to this study by omitting PPaLND.

Table 3
Recurrent cases.

Case	Histological type	Stage	PFS (month)	Sight of first recurrence			Status at last follow-up
				Peritoneal dissemination	Site of lymph node	Other	
1	HGS	IIIC	40	Yes	Angular incision	No	AWD
2	HGS	IVA	28	No	No	Brain	AWD
3	HGS	IIIC	22	Yes	Pelvis	No	AWD
4	HGS	IIIC	22	Yes	Supraclavicular fossa, PAN	No	AWD
5	HGS	IVB	20	No	Inguinal region, PAN	No	AWD
6	Clear cell	IVB	10	Yes	Mediastinum, axilla	Pleura	DOD
7	Em G3	IIIC	1	No	No	Liver, Pleura	DOD

HGS: high grade serous, Em G3: endometrioid Grade 3, PAN: *para*-aortic lymph node, AWD: alive with disease, DOD: died of disease.

Informed consent

We have obtained informed consent from our patients and approval of our institution's ethics committee.

CRediT authorship contribution statement

Kota Yokosu: Conceptualization, Investigation, Writing - original draft. **Hiroshi Tanabe:** Conceptualization, Supervision. **Shogo Nomura:** Data curation. **Hirokazu Ozone:** Resources. **Motoaki Saito:** Writing - review & editing. **Hirokuni Takano:** Writing - review & editing. **Aikou Okamoto:** Writing - review & editing.

Declaration of Competing Interest

All the authors have no conflicts of interest associated with this publication, and there has been no financial support for this work. This has been reviewed and approved by our institution's Conflict of Interest Management Committee.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2021.100805.

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