

Original Article



Distal pancreatectomy with splenectomy for the management of splenic hilum metastasis in cytoreductive surgery of epithelial ovarian cancer

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ABSTRACT

Objective: Distal pancreatectomy with splenectomy may be required for optimal cytoreductive surgery in patients with epithelial ovarian cancer (EOC) metastasized to splenic hilum. This study evaluates the morbidity and treatment outcomes of the uncommon procedure in the management of advanced or recurrent EOC.

Methods: This study recruited 18 patients who underwent distal pancreatectomy with splenectomy during cytoreductive surgery of EOC. Their clinicopathological characteristics and follow-up data were retrospectively analyzed.

Results: All tumors were confirmed as high-grade serous carcinomas. The median diameter of metastatic tumors located in splenic hilum was 3.5 cm (range, 1 to 10 cm). Optimal cytoreduction was achieved in all patients. Eight patients (44.4%) suffered from postoperative complications. The morbidity associated with distal pancreatectomy and splenectomy included pancreatic leakage (22.2%), encapsulated effusion in the left upper quadrant (11.1%), intra-abdominal infection (11.1%), pleural effusion with or without pulmonary atelectasis (11.1%), intestinal obstruction (5.6%), pneumonia (5.6%), postoperative hemorrhage (5.6%), and pancreatic pseudocyst (5.6%). There was no perioperative mortality. The majority of complications were treated successfully with conservative management. During the median follow-up duration of 25 months, nine patients experienced recurrence, and three patients died of the disease. The 2-year progression-free survival and overall survival were 40.2% and 84.8%, respectively.

Conclusion: The inclusion of distal pancreatectomy with splenectomy as part of cytoreduction for the management of ovarian cancer was associated with high morbidity; however, the majority of complications could be managed with conservative therapy.

Keywords: Cytoreductive Surgery; Distal Pancreatectomy; Morbidity; Ovarian Epithelial Cancer; Splenectomy; Treatment Outcome

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<http://orcid.org/0000-0003-4569-6454>**Conflict of Interest**

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

INTRODUCTION

Ovarian cancer is a leading type of life-threatening malignancy and accounts for over 140,000 deaths per year worldwide [1]. Cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment for ovarian cancer. Prospective clinical trials and retrospective studies have revealed that optimal cytoreduction improves survival and that postoperative residual disease is one of the most prominent prognostic parameters [2-4]. To achieve optimal cytoreduction, the use of extensive upper abdominal surgery has become widely accepted by gynecologic oncology surgeons [5].

The splenic hilum occupies a relatively low position in the left upper quadrant of the abdomen when a patient is in the supine position. In advanced epithelial ovarian cancer (EOC), tumor cells in ascites may travel to and implant in this region. Thus, during cytoreductive surgery for primary or recurrent EOC, metastasized tumors in the splenic hilum are occasionally encountered. These metastases may be difficult to dissect from the pancreatic tail and spleen. In such cases, removal of the pancreatic tail and spleen is required to achieve complete resection of the metastatic tumor for optimal reduction. However, this surgical procedure is rarely performed because surgeons tend to have limited experience with the proximal anatomy and limited knowledge of the associated morbidity and mortality. To date, limited retrospective studies of small case series presenting the incidence of pancreatic fistula following splenectomy and distal pancreatectomy have been published [6-8]. More studies are needed to evaluate the benefits and risks of performing this procedure for the management of splenic hilum metastasis during cytoreductive surgery of advanced and recurrent EOC. At Fudan University Shanghai Cancer Center (FUSCC), gynecologic oncology subspecialists have been performing this surgical procedure in collaboration with upper gastrointestinal surgeons since 2008. As experience with the procedure has increased, gynecologic oncologists have begun performing the surgery independently. The present study presents our clinical experiences associated with the procedure over the past 6 years.

MATERIALS AND METHODS

1. Patients

The current study was performed retrospectively and was approved by our center's Institutional Review Board (SCCIRB-090371-2). Cytoreductive surgeries were carried out for approximate 4,100 patients with advanced or recurrent EOC at FUSCC between April 2009 and September 2015. During this period, 91 splenectomies without indication for distal pancreatectomy were performed. A total of 18 consecutive patients, who underwent distal pancreatectomy with splenectomy, were recruited in this study. Their clinicopathologic characteristics, operation data, and postoperative events were obtained by reviewing inpatient medical records. Disease progress and recurrence and survival data were obtained from outpatient medical records. The patients were followed up until October 31, 2015. The histopathologic features of the metastatic tumors found in the splenic hilum were reviewed by the pathologist (X. Shen).

2. Surgical techniques

After dissection of perisplenic ligaments and short gastric vessels, the splenic artery and vein were isolated and separately ligated. Distal pancreatic tissue was carefully dissected to isolate the major pancreatic duct to the greatest extent possible. The major pancreatic duct

was ligated or sutured separately if visible. The pancreatic tail, spleen and metastatic tumors within the splenic hilum were removed *en bloc*. About 5% to 30% of distal pancreases were dissected. The transected end of the pancreas was sewn in the way of interrupted mattress suture using 4–0 absorbable sutures. After suturing, one to three drainage tubes were placed around the remaining pancreas.

3. Postsurgical observation and management

A broad-spectrum antibiotic combined with an agent against anaerobic bacteria, such as cefuroxime plus metronidazole, were tripped intravenously in the first and second postoperative days. Octreotide (0.1 mg) was injected subcutaneously every 8 hours in the first 5 days for seven patients. Amylase in drainage fluids was tested every second day to monitor pancreatic fistula. The patients began to eat fluid diet after the first flatus. The peripancreatic drainage tubes were removed if the following prescriptions were satisfied: (1) the patients had no fever and no upper abdominal pain after diet; (2) there was no fluid in drainage tubes for more than 1 day or the value of amylase in drainage fluid was normal. The patients begin systematic chemotherapy when they had normal diet and their Eastern Cooperative Oncology Group (ECOG) performance status score was no more than 2.

4. Statistical analysis

Disease stage was defined according to the 2014 The International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer staging guidelines. Optimal cytoreduction of EOC was defined as <1 cm residual tumor volume. Pancreatic fistula was defined and classified according to International Study Group of Pancreatic Fistula criteria [9]. Descriptive statistics were employed in this study. Inter-group comparisons were performed using Fisher exact test. Progression-free survival (PFS) and overall survival (OS) were assessed using the Kaplan-Meier method. PFS was defined as the interval between cytoreductive surgery and recurrence or progression of the disease, and OS was defined as the interval between surgery and death. Significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinicopathological characteristics

The median age of the 18 enrolled patients was 54.5 years (range, 39 to 75 years). Nine patients underwent distal pancreatectomy with splenectomy for primary EOC, and the remaining nine patients underwent the procedure for recurrent disease. The ECOG performance status of the patients were 0 or 1. Metastatic tumors in the splenic hilum were preoperatively identified via computed tomography in eight patients and via positron emission tomography/computed tomography in seven patients (**Fig. 1A, B**, respectively). In the remaining three patients, preoperative radiology did not reveal metastatic tumors in the splenic hilum. FIGO staging, serum cancer antigen 125 levels, and histological subtypes of the tumors are shown in **Table 1**.

2. Surgical parameters

Table 2 depicts the surgical parameters associated with the primary group and the recurrent group patients. Widely disseminated carcinomas in the abdominopelvic cavity were found in all nine patients with primary disease and in three of the patients with recurrent disease. These patients underwent extensive upper-abdominal, middle-abdominal, lower-abdominal,

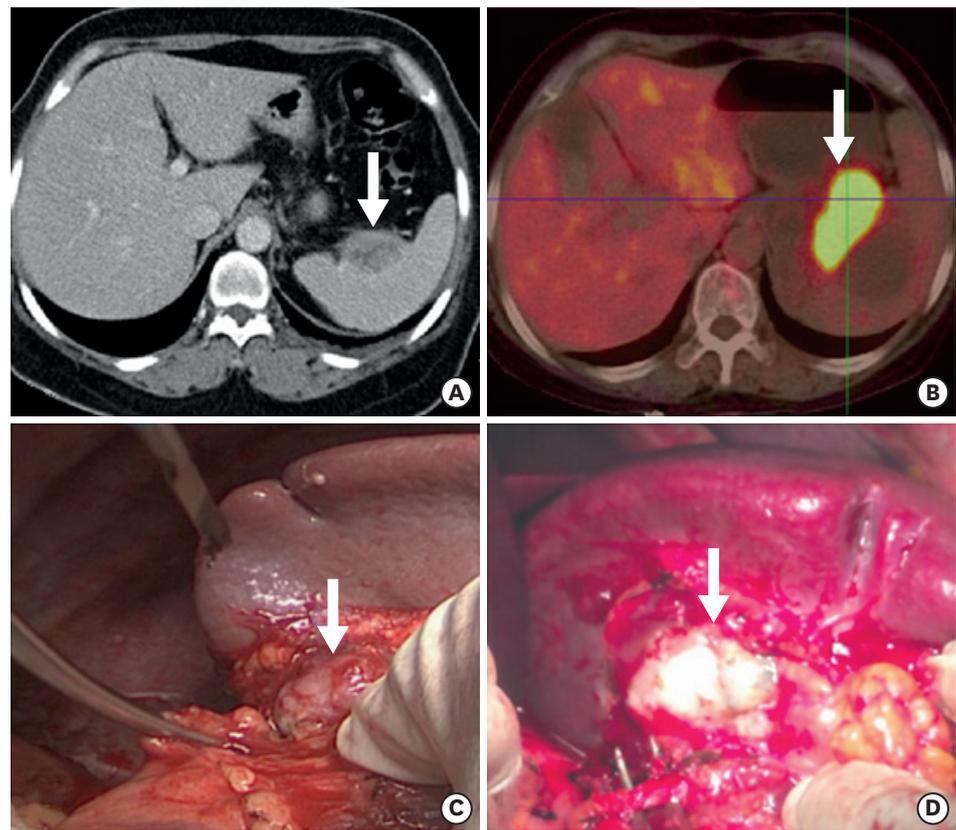


Fig. 1. Metastatic tumors at splenic hilum in a patient with primary ovarian serous carcinoma. (A) Computed tomography (CT) scan; (B) positron emission tomography scan, CT; (C, D) gross appearance during debulking surgery.

or retroperitoneal cytoreductive surgeries, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, distal pancreatectomy with splenectomy, bowel resection, appendectomy, stripping of the diaphragm or other peritoneal surfaces, pleural tumor resection, pelvic and para-aortic lymphadenectomy, or groin lymphadenectomy. Localized tumors in the spleen and pancreas were explored in the remaining six patients with recurrent disease. All 18 patients underwent distal pancreatectomy with splenectomy. The median surgical duration was 3.0 hours (range, 1.0 to 5.2 hours). Seven patients experienced blood loss of a volume greater than 1,000 mL. Ten patients underwent blood transfusions with a median volume of 1,150 mL (range, 500 to 1,800 mL). Eight patients required postoperative Intensive Care Unit admission. The median hospitalization period following surgery was 9 days (range, 6 to 17 days). The median interval from surgery to adjuvant chemotherapy was 18 days.

3. Residual disease

The median diameter of the metastatic tumors found within the splenic hilum was 3.5 cm (range, 1 to 10 cm) (**Fig. 1C, D**). Histological examination confirmed the presence of capsular and parenchymal tumors in the spleen and/or pancreas. All 18 patients achieved optimal cytoreduction, with microscopic residual disease in 11 patients, residual tumors less than 0.5 cm in diameter in four patients, and residual tumors between 0.5 and 1 cm in diameter in three patients. The residual carcinomas were located in the porta hepatis, small bowel mesentery, intestinal wall, and thoracic cavity.

Distal pancreatectomy in advanced ovarian cancer

Table 1. Clinicopathologic characteristics of the 18 patients

Parameter	Value
Diseases status	
Primary diseases	9 (50.0)
Recurrent diseases	9 (50.0)
Cytoreductive surgery	
Primary	9 (50.0)
Secondary	8 (44.4)
Tertiary	1 (5.6)
FIGO stage for primary diseases	
IVB	4 (44.4)
IIIC	5 (55.6)
Initial FIGO stage for recurrent diseases	
IIIC	6 (66.7)
IIIB	1 (11.1)
IIIA	1 (11.1)
IIB	1 (11.1)
Splenic hilum metastasis diagnosed by radiology	
Yes	15 (83.3)
No	3 (16.7)
Serum CA-125 (U/L)	
Primary diseases	1,193 (119–5,000)
Recurrent diseases	119 (10.6–391)
Histological subtype	
High-grade serous carcinoma	18 (100)

Values are presented as number (%) or median (range).

CA-125, cancer antigen 125; FIGO, The International Federation of Gynecology and Obstetrics.

Table 2. Surgical parameters in the primary group and recurrent group patients

Parameter	Primary group (n=9)	Recurrent group (n=9)
Volume of ascites (mL)	2,000 (200–7,000)	0 (0–100)
Diameter of metastatic tumors located in splenic hilum (cm)	4.5 (3–10)	2 (1–10)
Disease burdens		
Widely disseminated carcinomas	9 (100)	3 (33.3)
Localized tumors	-	6 (66.7)
Surgical time (hr)	4.8 (2.6–5.2)	2.0 (1.0–4.0)
Blood loss (mL)	1,500 (300–3,500)	200 (100–800)
Blood transfusion (mL)	1,200 (0–1,800)	0 (0–700)
Residual tumor (cm)		
Microscopic	3 (33.3)	8 (88.9)
<0.5	3 (33.3)	1 (11.1)
0.5–1	3 (33.3)	0
Pancreatic parenchyma invasion*	2 (22.2)	5 (55.6)
Splenic parenchyma invasion*	3 (33.3)	7 (77.8)
Duration of hospitalization after surgery (day)	13 (6–17)	8 (6–13)
Interval from surgery to chemotherapy (day)	15 (9–24)	14 (8–47)
Postoperative complications	5 (55.6)	3 (33.3)

Values are presented as number (%) or median (range).

*In remaining patients, metastatic tumors adhered to pancreatic capsule and spleen and cannot be divided from pancreatic tails and spleen. Distal pancreatectomy with splenectomy was performed to avoid damage of pancreatic capsule and to reduce unexpected pancreatic fistula.

4. Postoperative complications

Eight patients (44.4%) suffered from postoperative complications, including pancreatic fistula, pleural effusion and atelectasis, encapsulated effusion in the left upper quadrant, intra-abdominal infection, hemorrhage, pneumonia, pancreatic pseudocyst, and intestinal obstruction (**Table 3**). There was no perioperative mortality. One patient experienced a large postoperative hemorrhage because of splenic vein bleeding; this patient underwent re-exploration. All other complications were successfully treated using conservative management. Pancreatic fistula occurred in four patients (22.2%): three of the patients had grade A pancreatic fistulas with transient biochemical evidence and no clinical symptoms,

Table 3. Complications related to distal pancreatectomy and splenectomy

Postoperative complication	No.	Treatment
Severe complication*		
Postoperative hemorrhage	1	Re-exploration and hemostasis
Pancreatic fistula (grade B)	1	Prolonged intra-abdominal drainage
Left pleural effusion and atelectasis	1	Thoracentesis
Intestinal obstruction	1	Gastrointestinal decompression
Mild complication†		
Pancreatic fistula (grade A)	3	Observation
Encapsulated effusion in the left upper quadrant	2	Observation
Intra-abdominal infection	2	Antibiotics
Pneumonia	1	Antibiotics
Pancreatic pseudocyst	1	Observation
Bilateral pleural effusion (mild)	1	Albumin injection
Reactive thrombocytosis and leukocytosis	18	Observation or heparin injection

*Required special intervention. †Required pharmacotherapy or observation only.

and the remaining patient had a grade B pancreatic fistula and required prolonged intra-abdominal drainage and hospitalization. Transient reactive thrombocytosis and leukocytosis were observed in all of the patients; however, no related adverse clinical consequences were observed. No cases of clinically apparent new onset diabetes or uncontrollable infection were observed following surgery through the end of the study.

5. Follow-up data

All patients were treated with six to eight cycles of postoperative platinum-based chemotherapy. The median follow-up duration was 25 months (range, 3 to 68 months). Nine patients (50.0%) experienced recurrence of EOC after distal pancreatectomy and splenectomy. Three patients died of the disease, and 15 patients were still alive at the end of the study. The 2-year PFS and OS were 40.2% and 84.8%, respectively (**Fig. 2**).

DISCUSSION

Over 70% of patients with EOC initially present at an advanced stage. The majority of these cases have upper abdominal metastasis. The necessity of performing upper abdominal surgery in such cases has been increasingly accepted by gynecologic oncologists. Splenic hilum metastasis is not rare in cases with metastasis in the left upper quadrant of the abdomen. As pancreatectomy and splenectomy can significantly increase postoperative morbidity [10] and because the associated complications can cause serious and even fatal consequences [11,12], the vast majority of gynecologic surgeons choose to leave these metastatic tumors alone. In such cases, optimal cytoreductive surgery is impossible. Thus, it is necessary to assess the risks and benefits of performing these surgical procedures as a component of cytoreductive surgery for the treatment of primary and recurrent EOC. The present study is the largest series published to date that specifically addresses distal pancreatectomy with splenectomy for the management of splenic hilum metastasis during cytoreductive surgery of EOC.

Splenic hilum metastasis of EOC has been considered an obstacle to optimal cytoreduction in most institutes. In recent years, various preoperative prediction models for optimal and suboptimal cytoreductive surgeries have been used to evaluate newly diagnosed advanced EOC. Tumor extension into the spleen or pancreas is a predictor of suboptimal cytoreduction in all models. However, optimal cytoreduction rates during upfront surgeries vary among

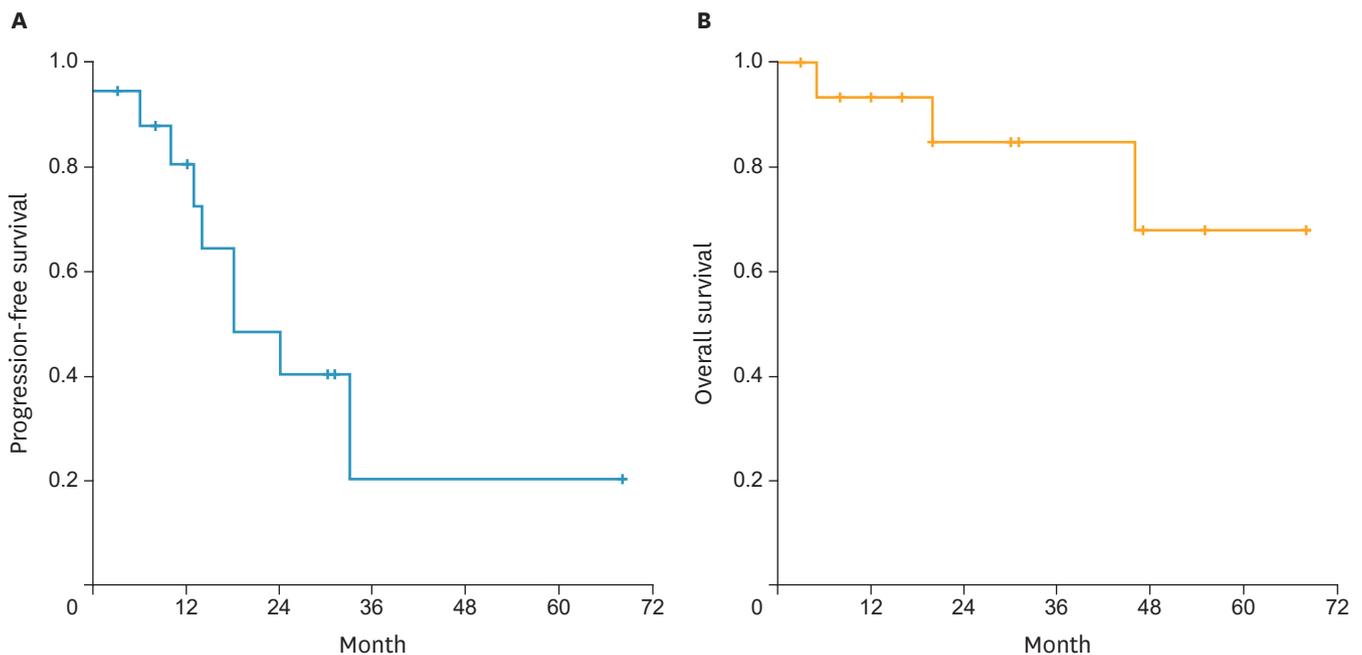


Fig. 2. Survival analysis of the 18 patients by Kaplan-Meier method. (A) Progression-free survival, (B) overall survival.

institutes and surgeons. Distal pancreatectomy and splenectomy are now being performed in some institutes. Gynecologic oncology surgeons at Memorial Sloan Kettering Cancer Center (MSKCC) began performing this procedure in 2001 and presented their experiences in 2009 [8]. Similar to these surgeons, we began performing this procedure with the aid of upper gastrointestinal surgeons to help overcome the associated learning curve.

The surgeons at our institute agree that removal of the pancreatic tail and spleen is appropriate in EOC patients with splenic hilum metastasis in cases in which these patients can achieve optimal cytoreductive results following this procedure. However, in patients with unresectable bulky tumors, it is not worth conducting such a high-risk procedure. Thus, the decision to perform this procedure should be made after careful exploration of the abdominopelvic cavity and after assessment of the resectability of tumors present in the pelvis, middle-abdomen and upper-abdomen. The procedure can be performed after the removal of all bulky tumors located in other anatomic structures. In the present study, the median diameter of the tumors resected from the splenic hilum was 3.5 cm, and all of the patients achieved optimal cytoreduction after distal pancreatectomy and splenectomy. Some of the patients presented with residual disease (less than 1.0 cm) in the porta hepatis or thoracic cavity. Other patients had small, disseminated tumors in the small bowel mesentery and intestinal wall. At present stage, tumors in these anatomic regions are considered to be unresectable.

The postoperative morbidity associated with distal pancreatectomy and splenectomy was high (44%). However, the majority of these complications were mild and just required pharmacotherapy or observation only. Pancreatic leakage was the most common complication associated with distal pancreatectomy. The incidence of this complication is approximately 25% according to previous studies and the current study [6]. Only one out of 18 patients had a grade B pancreatic fistula and no patients had grade C fistula in our series. All the patients with pancreatic fistula in the current study recovered after conservative treatment; these treatments included prolonged drainage, late recovery of oral intake and total parenteral

nutrition or the use of octreotide therapy (**Table 3**). To prevent its occurrence and reduce its damage, the gynecologic oncology surgeons at MSKCC utilize vascular staplers to seal the tail of the pancreas [8]. Diener et al. [14] suggested that stapler closure did not reduce the rate of pancreatic fistula compared to hand-sewn closure for distal pancreatectomy. In our opinion, separate ligation of the major pancreatic duct may be helpful in preventing the development of grade B or C pancreatic fistulas. Adequate peripancreas drainage may be useful to reduce the life-threatening adverse effects associated with pancreatic fistula.

Other severe complications related to distal pancreatectomy and splenectomy are relatively low (as shown in **Table 3**). No cases of postoperative clinical diabetes were observed after partial removal of the pancreas in the current study. King et al. [13] suggested that the rate of new onset diabetes after distal pancreatectomy is minimal. Thrombocytosis and leukocytosis were observed in all of the patients. However, overwhelming post-splenectomy infection (OPSI) was not observed in this series of patients. It has been reported that the majority of OPSI cases occur in infants and children. Intra-abdominal infection without intestinal perforation is easily controlled by the administration of broad-spectrum antibiotics. Encapsulated effusion or the development of asymptomatic pancreatic pseudocyst does not always require special intervention, as the majority of such complications disappear spontaneously. Left pleural effusion and atelectasis were treated by catheterization. When treating these complications, systemic chemotherapy was delayed in only one of the 18 patients.

Because of the limited cases number and the limited duration of our follow-up, the survival benefits of distal pancreatectomy with splenectomy cannot be assessed in the current study. However, evidence has shown that aggressive resections of upper-abdominal metastatic tumors may not only improve survival but also enhance quality of life [5,15].

In conclusion, performing distal pancreatectomy with splenectomy during cytoreductive surgery is associated with a high morbidity rate; however, the majority of associated complications can be managed using conservative therapy. Metastasis to the splenic hilum is likely not an insuperable obstacle for optimal cytoreductive surgery of EOC.

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