Pancreatic Resection as Part of Cytoreductive Surgery in Advanced-stage and Recurrent Epithelial Ovarian Cancer – A Single-center Experience

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Abstract. *Aim: To demonstrate the efficacy of pancreatic resection as part of cytoreductive surgery for advanced-stage and recurrent epithelial ovarian cancer. Patients and Methods: Data of patients submitted to cytoreductive surgery for advanced-stage and relapsed epithelial ovarian cancer at the Dan Setlacec Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, Romania, treated between January 2002 and May 2014 were retrospectively reviewed. Results: A total of six cases were eligible for the study: one case was submitted to pancreatic resection in the context of primary cytoreduction, four cases were submitted to pancreatic resection during secondary cytoreduction, while the sixth case was submitted to distal pancreatectomy as part of tertiary cytoreduction. The early postoperative course was uneventful in four cases, while the other two developed pancreatic fistulas. In one case, the leak was managed in a conservative manner, while in the second case re-operation was required. Thirty-day mortality was zero. At the time of writing, the patient submitted to pancreatic resection during primary cytoreduction was still alive with disease at 54 months and proposed for secondary cytoreduction. The median overall survival for cases submitted to pancreatic resection in the context of secondary cytoreduction was 36.38 months, while the patient submitted to distal pancreatectomy at the moment of tertiary cytoreduction was dead of disease 10 months after surgery. Conclusion: Pancreatic resections can be safely performed in the context of cytoreductive surgery for advanced-stage and relapsed epithelial ovarian cancer, with acceptable rates of morbidity, therefore benefit in terms of survival might be achieved.*

Ovarian cancer is one of the most aggressive malignancies, being responsible for the majority of gynecological cancer-related deaths worldwide annually (1). This fact is related especially to the fact that most women are diagnosed with an advanced stage of the disease, when disseminated lesions are already present (2-5). However, the most important prognostic factor associated with improved survival is a complete R0 resection and large studies focused on the benefits of maximal debulking surgical effort (2, 4, 5). Once the benefits of R0 resection were widely demonstrated, in many centers, multidisciplinary teams comprising visceral, gynecological and oncological surgeons have been formed in order to increase the rate of complete cytoreduction even in cases presenting upper abdominal disseminated disease. While initially most studies focused on the role of liver resection as part of cytoreductive surgery, in time other parenchymatous visceral resections such as splenectomy or even pancreatectomy have been proposed in order to achieve an R0 resection (6-10).

Patients and Methods

After obtaining the Ethics Committee approval (No. 43/2015) we retrospectively reviewed data of patients submitted to surgery for advanced stage or recurrent ovarian cancer at the Dan Setlacec Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, Romania, between January 2002 and May 2014 and found six cases eligible for the study: one case who was submitted to pancreatic resection at the moment of primary cytoreduction, four cases submitted to pancreatic surgery as part of secondary cytoreduction and another patient submitted to pancreatic surgery during tertiary cytoreduction. Dates of death were obtained

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from the National Register of Population (http://depabd.mai.gov.ro). Pancreatic fistula was defined accordingly to the International Study Group of Pancreatic Fistula (ISGPF) defined as any measurable drainage from an intraoperatively or postoperatively placed drain on or after postoperative day 3, with amylase content three times the normal serum amylase level (11). Pancreatic leaks were classified according to the same study group into: grade A fistulae: transient or asymptomatic, grade B fistulae: clinically evident by symptoms which require intervention; and grade C fistulae: severe clinical manifestations and may require surgical re-exploration (11).

Results

At the time of primary cytoreduction, pancreatic resection was performed in a single case, a 55-year-old patient diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) stage IV ovarian cancer. In this case, an R0 resection including total hysterectomy with bilateral adnexectomy, total omentectomy, total peritonectomy (including diaphragmatic peritoneum), full thickness nephrectomy, pelvic and para-aortic lymph node dissection, parcelar gastrectomy, splenectomy and distal pancreatectomy were performed. Intraperitoneal chemotherapy and dissection of the peritoneal nodules were also performed. The early postoperative period was uneventful, the patient being discharged on the 13th postoperative day. The histopathological studies revealed the presence of a high-grade serous ovarian carcinoma; the patient was addressed to the oncology service where she was submitted to adjuvant chemotherapy. At the 54 month follow-up, she was alive with disease and proposed for secondary cytoreduction.

At secondary cytoreduction, pancreatectomy was carried out in four cases. Disease-free survival between the primary cytoreduction and diagnosis of relapse or re-currence of symptoms was 32 months. All patients were initially diagnosed in FIGO stage IIIC of the disease and were initially submitted to an R0 resection followed by six cycles of taxanes and platinum salt chemotherapy. In one case, four cycles of neoadjuvant chemotherapy were administered.

The main characteristics at the time of secondary cytoreduction are shown in Table I.

Postoperatively, there were two patients who developed pancreatic leaks, re-operation being needed in ore case (grade C fistula), while the second was managed conservatively (grade B fistula). In both cases, adjuvant chemotherapy was postponed for 1 month, while in the other two cases, adjuvant treatment was instituted within 30 days after surgery.

The median overall survival after secondary cytoreduction was 36.38 months, all patients being dead from disease upon completion of this study.

At the time of tertiary cytoreduction, a single patient was submitted to pancreatic resection. This was the case of a 48-year-old patient in whom tertiary cytoreduction was performed 52 months after initial diagnosis; the patient had been initially submitted to surgery for stage IIIA ovarian cancer of total radical hysterectomy with bilateral adnexectomy, omentectomy, pelvic peritonectomy, pelvic and para-aortic lymph node dissection, followed by six cycles of adjuvant chemotherapy; 34 months after ending the adjuvant chemotherapy, she was diagnosed with the first relapse and submitted to secondary cytoreduction consisting of total parietal peritonectomy; tertiary cytoreduction consisted of splenectomy, distal pancreatectomy, right colectomy, rectosigmoidial resection, cholecystectomy and parcelar diaphragmatic resection associated with dissection of the mesenteric peritoneal nodules. The histopathological examination confirmed the presence of a moderately differentiated serous adenocarcinoma. During the postoperative period, the patient developed a febrile syndrome of unknown origin, without any modification of the laboratory tests and with no imaging modifications. The patient was discharged on the 14th postoperative day and died of disease 10 months later.

Discussion

Ovarian cancer remains an aggressive disease which is usually diagnosed in an advanced stage, when multiple visceral resections are needed in order to achieve an R0 resection (2, 4, 6-10). Distant metastases originating from ovarian cancer are present at the time of diagnosis in up to 8% of cases and are expected to develop in up to 22% of patients during the course of their disease (12). Once the greater omentum is involved, upper abdominal viscera such as the stomach, pancreas, spleen or transverse colon, will be affected by contiguous tumor spread using the route of the surrounding connective structures such as the gastrocolic ligament (6). In such cases, multiple upper abdominal resections are needed in order to obtain an R0 resection.

While the most frequently associated visceral resections are bowel resections and have been widely studied in large series of cases, upper abdominal involvement is not so frequently encountered and surgical procedures involving supramesocolic viscera have recently been included in the therapeutical armamentarium against advanced-stage or relapsed ovarian cancer (2, 4, 6-13).

When it comes to pancreatic resection, it has long been considered a high-risk procedure associated with high grades of postoperative complications, especially pancreatic leakage. However, the improvement of hepato-bilio-pancreatic surgical techniques and the formation of multidisciplinary teams involving oncological gynecologists, visceral and pancreatic surgeons are responsible for the increased number of cases submitted to complete cytoreduction, even if upper abdominal tumoral burden is present.

The largest studies conducted on the subjects of efficacy and safety of ultraradical resections including pancreatic resections are summarized in the Table II.

Table I. *Characteristics of the patients submitted to pancreatic resection as part of secondary cytoreduction.*

	Patient no.			
	1	2	3	4
Age at initial diagnosis (years)	56	47	56	49
Initial FIGO stage	IIIC	IIIC	IIIC	IIIC
Histopathological subtype	Serous	Serous	Serous	Serous
Differentiation grade	G2	G2	G2	G3
No. of cycles of adjuvant CHT	6	6	6	6
DFS (months)	46	41	22	25
No. of cycles of neoadjuvant CHT	None	None	4	None
Associated visceral resection in context of secondary cytoredeuction	Left colectomy, splenectomy, distal pancreatectomy	Transverse colectomy, splenectomy, parcelar diaphragmatic resection, parcelar gastrectomy, left adrenalectomy	Distal pancreatectomy, splenectomy	Rectosigmoidectomy, distal pancreatectomy, splenectomy, right colectomy
Type of resection	R0	R0	R0	R0
Early postoperative complications	None-	None	Pleural effusion, conservative treatment, grade B pancreatic leak	Grade C pancreatic leak
Length of hospitalization (days)	14	22	19	32
Overall survival after secondary cytoreduction (months)	57.3	35.4	5.4	37.3

FIGO: International Federation of Gynaecology and Obstetrics; DFS: disease-free survival; CHT: chemotherapy.

Table II. *Efficacy and safety of pancreatic resections as part of cytoreductive surgery for advanced-stage and recurrent ovarian cancer.*

Study (Ref)	No. of patients	Recruitment period	Associated pancreatic resections	Postoperative complications related to pancreatic surgery
Eisenhauer *et al*. (5)	262	1998-2003	Distal pancreatectomy: 6 cases	-
Rafii *et al*. (10)	180	2005-2008	Distal pancreatectomy: 1 case	Necrotizing pancreatitis, re-operation, death occurred on the 30th postop. day
Chi *et al*. (1)	378	1996-2004	Distal pancreatectomy: 9 cases (4%)	-
Panici *et al*. (9)	126	2006-2014	Partial pancreatectomy: 16 cases (13.2%)	Pancreatectomy was an independent predictor of overall complications (p=0.003)
Kehoe *et al*. (7)	41	2001-2006	Distal pancreatectomy: 17 cases (41%)	Pancreatic leak occurred in 24% of cases, all of them being managed conservatively

In the study conducted by Kehoe *et al*., 17 patients diagnosed with advanced-stage ovarian, fallopian tube or peritoneal cancer were submitted to pancreatic resection in order to achieve complete cytoreduction. An optimal resection was performed in all but one case, which proved to have an unresectable tumor mass involving the diaphragmatic surface and the liver. Postoperative complications were reported in nine cases: in four cases pancreatic leaks developed and were conservatively managed, while in the other five cases, upper abdominal or pelvic abscesses were identified and submitted to percutaneous drainage but a pancreatic origin was not incriminated. Overall, the rate of pancreatic fistula in Kehoe *et al*.'s study was 24%, while the postoperative morbidity was zero (7).

Pancreatoduodenectomy as part of cytoreductive surgery for advanced-stage or relapsed ovarian cancer is even more rarely seen and is usually encountered as a case report; Beissel *et al*. reported the case of a 58-year-old patient with a history of stage I microinvasive-infiltrating ductal breast carcinoma who

was diagnosed at one-year follow-up with peritoneal carcinomatosis invading the duodenum. The preoperative biopsy revealed the presence of a stage IIIC ovarian cancer and total hysterectomy with bilateral adnexectomy, omentectomy, peritonectomy, pelvic and para-aortic lymph node dissection was performed. When performing the right para-aortic lymph node dissection, a large adenopathy involving the pancreatic head was found, therefore a pylorus-preserving pancreato-duodenectomy was also undertaken. During the early postoperative period, the patient developed a pancreatic fistula which was successfully managed conservatively (8).

However, the reported rates of pancreatic leakage after pancreatoduodenectomy or distal pancreatectomy vary widely from none up to more than 50%, with a higher incidence in cases in which pancreatic resection occurs at the pancreatic body when compared to the pancreatic neck (14, 15). This wide variation is especially related to the lack of standardization and to the lack of a widely accepted definition of pancreatic fistula. While initially pancreatic fistula was defined according to the daily pancreatic flow (daily output of at least 30 ml of fluid according to Rodriguez *et al*. (14) or daily output of 50 ml according to Grobmyer *et al*. (16), with an amylase concentration from the intraoperatively-placed drainage tube five days postoperatively three times that of serum, recently the ISGPF defined pancreatic leak as any amount of peritoneal liquid present from an intraoperatively or postoperatively placed drainage tube with amylase content three times the normal serum amylase concentration (11). According to the same study group, pancreatic leaks can be classified into three groups A-C based on their severity. According to this classification, in our study group, grade B and grade C pancreatic leaks developed, both patients being successfully managed by a conservative surgical approach.

In our study pancreatic fistula occurred in two cases (33.3%); conservative management was attempted in both cases; however, in one case, re-operation was required due to deterioration of the general and biological status of the patient.

In order to reduce the incidence of pancreatic leaks, various intraoperative or postoperative methods have been proposed, with inconsistent results. When it comes to intraoperative strategies which are able to diminish the risk of pancreatic fistula, there are authors who consider that the best option for transecting the pancreas consists of stapling transection followed by suture reinforcement of the stapler line; according to Jiminez *et al*. this surgical approach seems to reduce the rate of pancreatic leak from 40% to 0% (17). While the efficacy of suture reinforcement of the stapler line was clearly shown in Jiminez *et al*.'s study, the benefits of placement of intraperitoneal suction drainage catheters in order to reduce the risk of pancreatic leaks failed to be demonstrated (18). When it comes to the efficacy of prophylactic somatostatin administration during the early postoperative course, contradictory results have been reported (19, 20).

However, all these results in terms of diminishing the complication rate should also be regarded according to the nature of the primary tumor. While isolated pancreatic tumors can be safely removed by solely performing a distal pancreatectomy or a pancreatoduodenectomy, when it comes to pancreatic tumoral involvement in the context of advanced-stage or relapsed ovarian cancer, the surgeon often needs to perform multiple associated visceral resections, some of them involving other upper abdominal viscera, therefore the morbidity rate and other associated complications might appear to slightly vary when compared to standard surgery for isolated pancreatic tumors (7).

For example, in Hoffman *et al*.'s study regarding extended cytoreduction of intra-abdominal metastatic ovarian cancer in the left upper quadrant utilizing *en bloc* resection at the time of primary cytoreduction, six patients were included. In all these cases, the tumor was removed *en bloc* with the omentum, gastrocolic ligament and spleen; two of the patients also required partial pancreatectomy associated with partial gastrectomy. The postoperative course was uneventful in one case, while in the other case, a gastric leak requiring for reoperation developed. The authors described no specific complication related to pancreatic surgery (6).

Conclusion

Pancreatic resections can and should be performed as part of cytoreductive surgery for patients with advanced-stage or relapsed ovarian cancer. Although pancreatic fistula is a common complication after this type of surgery, this fact should not be transformed into a contraindication for pancreatic surgery in the context of advanced gynecological malignancies, a good understanding of this complication being mandatory in order to treat it successfully with minimal impact on the postoperative outcomes. Once the pancreatic fistula is assessed, the patient can be safely submitted to adjuvant chemotherapy to maximize the benefits provided by complete surgical cytoreduction.

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References

1 Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, DeMatteo R, Poynor EA, Abu-Rustum NR and Barakat RR: Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol *94*: 650-654, 2004.

2 Eisenkop SM and Spirtos NM: Procedures required to accomplish complete cytoreduction of ovarian cancer: Is there a correlation with 'biological aggressiveness' and survival? Gynecol Oncol *82*: 435-441, 2001.
3 Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA and Yeo CJ: Distal pancreatectomy: indications and outcomes in 235 patients. Ann Surg *229*: 693-698, 1999.
4 Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL and Montz FJ: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol *20*: 1248-1259, 2002.
5 Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, Jarnagin WR, DeMatteo RP, D'Angelica MI, Barakat RR and Chi DS: The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol *103*: 1083-1090, 2006.
6 Hoffman MS, Tebes SJ, Sayer RA and Lockhart J: Extended cytoreduction of intraabdominal metastatic ovarian cancer in the left upper quadrant utilizing *en bloc* resection. Am J Obstet Gynecol *197*: 209-204, 2007.
7 Kehoe SM, Eisenhauer EL, Abu-Rustum NR, Sonoda Y, D'Angelica M, Jarnagin WR, Barakat RR and Chi DS: Incidence and management of pancreatic leaks after splenectomy with distal pancreatectomy performed during primary cytoreductive surgery for advanced ovarian, peritoneal and fallopian tube cancer. Gynecol Oncol *112*: 496-500, 2009.
8 Beissel J, Kendrick M, Podratz K and Bakkum-Gamez J: Pancreaticoduodenectomy in optimal primary cytoreduction of epithelial ovarian cancer: A case report and review of the literature. Gynecologic Oncol Rep *10*: 25-27, 2014.
9 Benedetti PP, Di D, V, Fischetti M, Casorelli A, Perniola G, Musella A, Marchetti C, Palaia I, Berloco P and Muzii L: Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery. Gynecol Oncol 2015.
10 Rafii A, Stoeckle E, Jean-Laurent M, Ferron G, Morice P, Houvenaeghel G, Lecuru F, Leblanc E and Querleu D: Multi-center evaluation of post-operative morbidity and mortality after optimal cytoreductive surgery for advanced ovarian cancer. PLoS One *7*: e39415, 2012.
11 Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP and Vollmer CM Jr.: Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg *245*: 443-451, 2007.
12 Cormio G, Rossi C, Cazzolla A, Resta L, Loverro G, Greco P and Selvaggi L: Distant metastases in ovarian carcinoma. Int J Gynecol Cancer *13*: 125-129, 2003.
13 Hoffman MS, Griffin D, Tebes S, Cardosi RJ, Martino MA, Fiorica JV, Lockhart JL and Grendys EC Jr.: Sites of bowel resected to achieve optimal ovarian cancer cytoreduction: implications regarding surgical management. Am J Obstet Gynecol *193*: 582-586, 2005.
14 Rodriguez JR, Germes SS, Pandharipande PV, Gazelle GS, Thayer SP, Warshaw AL and Fernandez-del Castillo C: Implications and cost of pancreatic leak following distal pancreatic resection. Arch Surg *141*: 361-365, 2006.
15 Pannegeon V, Pessaux P, Sauvanet A, Vullierme MP, Kianmanesh R and Belghiti J: Pancreatic fistula after distal pancreatectomy: predictive risk factors and value of conservative treatment. Arch Surg *141*: 1071-1076, 2006.
16 Grobmyer SR, Pieracci FM, Allen PJ, Brennan MF and Jaques DP: Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. J Am Coll Surg *204*: 356-364, 2007.
17 Jimenez RE, Mavanur A and Macaulay WP: Staple line reinforcement reduces postoperative pancreatic stump leak after distal pancreatectomy. J Gastrointest Surg *11*: 345-349, 2007.
18 Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, Merchant N and Brennan MF: Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 234: 487-493, 2001.
19 Zeng Q, Zhang Q, Han S, Yu Z, Zheng M, Zhou M, Bai J and Jin R: Efficacy of somatostatin and its analogues in prevention of postoperative complications after pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. Pancreas *36*: 18-25, 2008.
20 Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, Campbell KA and Choti MA: Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg *232*: 419-429, 2000.

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