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**Combined laparoscopic spleen-preserving distal pancreatectomy and islet autotransplantation for benign pancreatic neoplasm**

**Balzano *et al*.** Surgical treatment of benign pancreatic neoplasm

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**Abstract**

**AIM:** To evaluate the safety and feasibility of laparoscopic spleen-preserving distal pancreatectomy (LSPDP) with autologous islet transplantation (AIT) for benign tumors of the pancreatic body-neck.

**METHODS**: Three non-diabetic, female patients (age 37, 44, 35 years, respectively) were candidate to surgery, between May and September 2011, because of pancreatic body/neck cystic lesions. The planned operation was a LSPDP associated with AIT from the normal pancreas distal to the neoplasm. Islets isolation was performed on the residual pancreatic parenchyma after frozen section examination of the margin. Purified autologous islets were infused in the portal vein by percutaneous transhepatic approach the day after surgery.

**RESULTS:** The procedure was successfully performed in all the three cases, and the spleen was preserved along with its vessels. Mean operation time was 283 ± 52 min and average blood loss was 133 ± 57 mL. Residual pancreas weight was 33, 22, 30 g and 105.200, 40.390, 94.790 islet equivalents were isolated, respectively. Surgical complications occurred in one patient (grade A pancreatic fistula). Postoperative stay was 6, 6, and 7 d, respectively. Histopathological evaluation revealed mucinous cystic neoplasm in cases 1 and 3, serous cystic neoplasm in patient 2. No postoperative insulin administration was needed. One patient developed a transient partial portal thrombosis 2 mo after islet infusion. Patients are insulin independent at a mean follow up of 8 ± 2 mo.

**CONCLUSION:** Combination of LSPDP and AIT is feasible and could be effective to minimize the surgical impact for benign neoplasm of pancreatic body-neck.

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**Key words:** Pancreas; Benign neoplasm; Laparoscopy; Minimally invasive treatment; Spleen preservation; Pancreatogenic diabetes; Autologous islet transplantation

**Core tip:** The article describes for the first time a combination of techniques to reduce all possible consequences of pancreatic resection for benign/borderline neoplasm located at the pancreatic body-neck. The procedure combines laparoscopy, spleen preservation and islet autotransplantation. Laparoscopic approach reduces the access trauma of an extensive surgery. The spleen preservation avoids infectious and haematologic complication related to splenectomy. Islet Auto transplantation could reduce the incidence of pancreatogenic diabetes after resection.

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**INTRODUCTION**

Distal pancreatectomy (DP) is the standard operation for borderline pancreatic tumors located in the body-neck of the pancreas[1,2]. Spleen preservation is indicated in such cases in order to reduce immunologic and haematologic impairment[3].

Although there are no prospective randomized studies, there is agreement regarding the feasibility and efficacy of the laparoscopic approach compared to the open procedure[3-10].

DP is associated with the risk of post-surgical diabetes, ranging from 5% to 42%, related with the amount of resected parenchyma[11-15]. Autologous islet transplantation (AIT) is effective in the prevention of post-surgical diabetes, by rescuing the endocrine component of the non-neoplastic resected pancreas[16,17].

Minimizing the surgical damage is a challenging goal, especially in patients with a long life-expectancy. In the setting of benign neoplasm of pancreatic body-neck, this goal could be totally achieved by the combination of laparoscopic technique, spleen preservation and AIT; such approach has not been reported yet. In this report, we describe three patients affected by pancreatic cystic neoplasm of the body-neck, successfully treated by laparoscopic spleen-preserving distal pancreatectomy (LSPDP) and AIT.

**MATERIALS AND METHODS**

***Patient 1***

A 37 years old woman underwent computerized tomography (CT) scan because of persistent postprandial abdominal pain. CT-scan revealed a 4 cm cystic lesion in the body of the pancreas suspected for mucinous cistadenoma (Figure 1A). Plasma carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels were within normal range. Fine needle ago biopsy, performed by endoscopic utrasounds, the presence of mucinous fluid associated to epithelial cells without signs of displasia.

***Patient 2***

A 44 years old woman presented with an abdominal epigastric mass associated with nausea and mild pain since 2 months. CT-scan showed a 10 cm cystic lesion of the pancreatic body (Figure 1B). There were no mural nodules nor contrast-enhancement of the cyst wall. Plasma CEA and CA 19-9 values were normal.

***Patient 3***

A 35 years old woman underwent CT-scan because of left-sided renal colic. As a collateral finding, a pancreatic cystic lesion was described. Abdominal magnetic resonance imaging (MRI) showed a 5 cm unilocular cyst of the pancreatic neck suspected for mucinous cistadenoma, with 1.5 cm intramural nodule (Figure 1C). Plasma CEA level was normal while CA 19-9 was elevated (421 UI/mL). A careful evaluation of MR images showed no involvement of the surrounding pancreatic parenchyma, with a well demarcated capsule of the cystic lesion and no dilation of the main pancreatic duct.

***Surgical technique***

The patient is placed in supine split legs position with the surgeon standing between the legs. A total of four trocars are used. After establishing laparoscopic access, the gastrocolic omentum is divided, accessing the lesser sac. In patient 2 (cyst diameter 10 cm) the cyst was emptied to allow adequate exposition of the splenic vessels. A retropancreatic tunnel is accomplished anterior to the superior mesenteric vein, exposing the splenic vein. The inferior border of the pancreatic body is mobilized from right to left. The splenic artery is identified close to its origin and freed from its pancreatic adhesions. The gland is transacted (about two centimetres to the right of the neoplasm) by single application of a linear stapling device (ECHELON FLEXTM Powered ENDOPATH® Stapler). The splenic vessels are then skeletonised, proceeding towards the splenic hilum. Specimen is extracted by endocatch through Pfannenstiel incision. The specimen is transected distal from the lesion with 1 cm safety margin (Figure 2). A frozen section examination of this margin is performed, and the organ processed for islet isolation. In the three patients the same surgical procedure, described above, was performed.

***Islets isolation***

Islets isolation process is performed by automated method as previously described[18,19]. Briefly, pancreatic duct is perfused by collagenase solution. After parenchymal distension, the organ is digested and islets are freed from the exocrine tissue. Using a COBE machine the islets are purified.

***Islets re-infusion***

Under ultrasound guidance using a percutaneous transhepatic approach islets are infused into the right portal vein.

***Islets function follow-up and metabolic assessment***

Capillary blood glucose was measured four times per day during postoperative hospital stay. Mixed Meal Tolerance test was performed 1 mo after transplantation. Fasting serum C-peptide, insulin, and hemoglobin A1c were measured 15 d and at 1, 2, 3, 6 mo after transplantation.

**RESULTS**

Operations were performed laparoscopically, with no conversion; the spleen was preserved along with the splenic vessels. Average blood loss was quantified as 133 ± 57 mL. Mean operative time was 283 ± 52 min. Intraoperative frozen section examination of the pancreatic margin was normal. In patient 3, due to cyst characteristics and CA 19-9 elevation, an intraoperative frozen section examination of the cyst wall was performed to rule out malignancy. Pathological evaluation showed a mucinous cystoadenoma for patients 1 and 3, and a serous cystodenoma for patient 2. No major complication occurred during the operation nor in early postoperative period. Patient 3 developed a grade A pancreatic fistula (ISGPF definition[20]); surgical drain was removed on 36 postoperative day. Hospital stay was 6, 6 and 7 d, respectively.

Weight of the processed pancreatic parenchyma was 30, 22, 33 g for patients 1-3, respectively. After isolation process 94.790, 40.390, 105.200 islet equivalents (IEs) were obtained at final counting while absolute islet number was 268.000, 95.000, 274.800 respectively. IE per kilogram of body weight (IE/kg) were 1528, 553, 1696, respectively. Portal vein pressure remained stable after islet infusion. No bleeding occurred after islet infusion and regular portal system patency was documented the day after reinfusion. No postoperative insulin administration was needed. One month after surgery patient 3 was diagnosed with partial portal vein thrombosis by Doppler ultrasound, and was treated with low-molecular weight heparin. Metabolic assessment showed normal insulin production during the follow-up. C-peptide values were comparable to preoperative values and remained substantially stable in the follow-up (Figure 3A). Fasting glucose remained stable after transplantation compared to pre-transpant level (Figure 3B). The 3 patients are insulin independent at a median follow-up of 8 ± 2 mo.

**DISCUSSION**

Traditionally, DP is associated with splenectomy and it is performed through a wide incision. For borderline neoplasm of the body-neck, the removal of a significant healthy portion of the gland is required with consequent risk of pancreatogenic diabetes.

LSPDP may be a paradigm of the surgical evolution towards minimizing the operative short- and long-term impact. The mainstays of this procedure are the reduction of access trauma through laparoscopy, the avoidance of immunologic and haematologic long-term consequences of splenectomy, and the improvement of postoperative glycemic control by AIT. Advantages of laparoscopy have not been proved by any randomized trial comparing laparoscopic versus laparotomic DP yet. However, several studies showed the benefits of the laparoscopic approach and no difference between the two procedures in terms of complication have been reported[4-6,21-23] .

In our case series no conversion was needed, mean surgical time was 266 ± 37 min, and, despite of the need for an AIT, hospital stay was 6-7 d. Grade A fistula occurred in one of the three patients.

Splenectomy may result in long-term immunological and haematological impairment[24-26]. Spleen-preservation is therefore indicated for patient undergoing distal pancreatic resection for benign and low-grade malignant lesion[23]. Moreover, after spleen preservation, a reduction of early postoperative complications, especially infective morbidity, has been reported[27].

The incidence of new-onset diabetes after DP is probably underestimated: a retrospective study on 125 non-diabetic patients reported a minimal rate of postoperative diabetes (7.5% when excluding patients with chronic pancreatitis)[15]. Patient with chronic pancreatitis have an increased risk (up to 42%) of developing diabetes after distal pancreatic resection because the endocrine function of the organ is already impaired[12]. However analysis of diabetes onset in hemipancreatectomized living-donors for pancreas transplantation showed an unexpectedly high rate of glucose metabolism impairment: 25% of donors had overt diabetes or glucose intolerance[28] and 40% had abnormalities of glucose metabolism 3-10 years after donation[29].

To encompass this problem, median pancreatectomy has been proposed as a surgical strategy for the treatment of benign neoplasm of the pancreatic body-neck[30-33]. However, with respect to DP, median pancreatectomy has a higher risk of pancreatic fistula (50%)[32,34].

Islet autotransplantation is an alternative to median pancreatectomy to preserve the endocrine function of distal pancreas, without increasing the fistula risk. Ris *et al*[17] performed open DP and AIT succesfully in 25 patients within a 17-year period. At a median follow-up of 90 mo, all the patients were insulin independent[17].

In our case series, we isolated pancreatic islet from the resected pancreas and re-infuse them, preserving endocrine function and mantaining euglycemia in the early and late post-operative period. The expected complications of the transhepatic islet infusion are low, mainly related to minor intra-and perihepatic bleeding and transient portal thrombosis[35,36]. One of three patients was diagnosed with partial intrahepatic thrombosis one month after islet infusion, successfully treated by low molecular weight heparin therapy.

When a conservative operation is planned, accurate consideration has to be made about the possibility of unsuspected malignancy. Indeed, the reported rate of malignancy in three large series of spleen-preserving DP published in 2012, was < 1% (two out of 213 overall patients)[23,37,38]. In case of suspicion of malignancy endoscopic ultrasonography can provide a more accurate description of the lesion morphology, allowing to perform fine needle aspiration (FNA) for cytologic evaluation of the cyst fluid or of the solid component of the cyst wall. The dissemination risk of endoscopic FNA in presumed benign lesion was never reported, but even in case of pancreatic malignancy, endoscopic FNA is considered not to increase the risk of peritoneal dissemination[39].

A further concern regards the possibility of occult malignancy in the “normal” pancreas segment to be processed for AIT. Pre- and intraoperative work up is essential to select adequate cases for autotransplantation. In our protocol the presence of any multifocal pancreatic neoplasm at preoperative imaging or intraoperative evaluation, including multifocal benign intraductal-papillary mucinous neoplasm or a diagnosis (suspected or ascertained) of Multiple Endocrine Neoplasm is an exclusion criterion. In the retrospective study carried out by Ris *et al*[17] 3 mm have been considered safe to obtain a safety margin as demonstrated by the postoperative follow up. In 90 mo median follow-up all the patients were disease free. In our short series pancreatic specimens were sent for frozen section analysis of the margin, with a margin of 1 cm. Further, in patient 3, owing to the preoperative findings, a frozen section examination of the cyst wall was performed to look for the mural nodule and rule out malignancy before islet infusion.

The ultimate goal of this technique is to reduce the morbidity of extended pancreatic resection, required for patients with benign pancreatic tumour, occurring at the body-neck site. The minimally invasive treatment with the preservation of the spleen and the vessels in association with AIT may provide an improvement in early and late postoperative quality of life. However, while laparoscopic DP is becoming largely performed, very few institutions may offer an islet producing facility. Besides the referral of patients to specific institutions, the creation of a network with neighboring hospitals should be considered to provide access to AIT to a wider amount of patients candidates to this procedure[17].

To our knowledge this is the first study demonstrating feasibility and safety of the minimally invasive spleen preserving left pancreatectomy combined with autologous islet transplantation. A larger patient series is needed to confirm the metabolic advantages of the technique.

**COMMENTS**

***Background***

Benign pancreatic lesion of the pancreatic neck could require extensive surgery. The widespread use of laparoscopic has considerably reduced the surgical direct trauma. Spleen preservation in such non-malignant cases has reduced the infectious morbidity of the standard procedure. However with distal pancreatectomy a considerable portion of the gland is removed, possibily leading to pancreatogenic diabetes. Islet auto transplantation is a promising strategy in reducing the risk of diabetes onset after pancreatic resection.

***Research frontiers***

This article could be important for the future evolution of minimally invasive procedures in pancreatic surgery.

***Innovations and breakthroughs***

Laparoscopy has already reduced the surgical trauma on patients. However metabolic consequences (pancreatogenic diabetes) as results of pancreatic resection could be lifelong. Islet autotransplantation has demonstrated to be effective in the control of metabolic impairment after pancreatic resection. Main goal of this technique is to provide a combination of the minimally invasive treatment and improvement of long term metabolic outcome.

***Applications***

The procedure has been demonstrated to be feasible. A larger patient series is needed to confirm the metabolic advantages of the technique.

***Terminology***

Autologous islet transplantation is a procedure in which the endocrine component of the pancreas (Langherans islet) is preserved by a laboratory isolation process. The islet are then usually infused into the portal system by percutaneous transhepatic approach.

***Peer review***

Interesting small series of autotransplantation in pancreatic partial resection for benign neoplasm.

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**Figure 1 Abdominal** **computed tomography scan.** A: Abdominal computed tomography (CT) scan showing a 4 cm pancreatic cystic lesion of neck in patient 1; B: Abdominal CT scan showing a 10 cm pancreatic cystic lesion of the body in patient 2; C: Abdominal magnetic resonance imaging showing a 4, 6 cm cystic lesion of the neck in patient 3. Arrows mark~~s~~ the cystic lesion (A-C).

**Figure 2 Specimen after distal pancreatic resection.** A:Arrow marks the cystic lesion, interrupted line mark the site of transaction; B: Transection of the pancreas distal from the lesion; C: Spared pancreatic parenchyma.

**Figure 3 Fasting C-Peptide (A) and fasting glycemia (B) remained stable and comparable with respect to pretransplant value, respectively.** Values are expressed as mean standard error of the mean. preop: Preoperative value; preinfu: C-Peptide value after resection and before islet re-infusion; POD: Post operative day.