Ex Vivo Resection and Autotransplantation for Pancreatic Neoplasms

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KEYWORDS
- Pancreas • Pancreatic tumors • Ex vivo resection • Autotransplantation
- Mesenteric root involvement • SMA involvement

KEY POINTS
- Ex vivo resection and autotransplantation is a technique derived from multivisceral and intestinal transplantation whereby tumor-infiltrated organs are removed en bloc and preserved in the cold, followed by tumor resection and reimplantation of the remaining viscera.
- Advantages of ex vivo resection include tumor removal in a bloodless field while minimizing the risk of ischemic injury to the involved organs.
- Access to the mesenteric root is greatly facilitated with ex vivo resection, and allows for safe reconstruction of major vasculature while preserving visceral integrity.
- Certain low-grade, non-adenocarcinomatous pancreatic neoplasms involving the mesenteric vessels where aggressive surgical resection would be warranted, may benefit from ex vivo resection.
- Although ex vivo resections have been performed for pancreatic adenocarcinomas with major arterial involvement, the associated morbidity is significant and benefit remains unclear.

INTRODUCTION
Pancreatic neoplasms are a heterogeneous group of tumors arising from the pancreas with distinct and varied clinical profiles.1 Although pancreatic adenocarcinoma remains by far the most common and deadliest of these, there are several low-grade or benign neoplasms that may benefit from aggressive, curative resection.2,3 Due to the proximity of the pancreas to major abdominal vasculature, these tumors can sometimes infiltrate these vessels and preclude complete or safe resection by conventional surgical technique. Ex vivo resection and autotransplantation, whereby...
tumor-laden viscera are explanted and reimplanted following tumor removal in cold preservation, allows the possibility of complete resection and vascular reconstruction while minimizing organ injury and obviating the need for allotransplantation. Ex vivo surgery was first described in 1963 for the reimplantation of a kidney following a high ureteral injury. In 1988, Rudolf Pichlmayr and colleagues successfully described the first ex vivo tumor resection for large liver neoplasms located at the confluence of the hepatic veins. Although radical pancreatectomy with vascular reconstruction had been previously performed for tumors invading the mesenteric vessels, further experience in multivisceral transplantation led to the first successful description of ex vivo resection and intestinal autotransplantation for a large fibroma located in the head of the pancreas invading the mesenteric root by Andreas Tzakis and colleagues. Since then, more than 40 cases of ex vivo tumor resection and intestinal autotransplantation have been reported worldwide for tumors involving the superior mesenteric vessels, and 32 of these involved pancreatic neoplasms. Additionally, our institution has reported 2 multivisceral ex vivo resections with combined liver, intestinal, and pancreas autotransplantation for pancreatic tumors involving both the superior mesenteric artery (SMA) and the celiac axis.

The technique of ex vivo surgery, which involves the explantation of all tumor-associated organs and tumor removal in cold preservation, allows for safe and complete resection or separation of critical vascular structures while minimizing ischemic organ injury. Exposure to these mesenteric vessels is also significantly improved in a bloodless field, where the organ bloc can be flipped over and easily manipulated. Most importantly, ex vivo surgery can help facilitate the safe reconstruction of critical vasculature while ensuring visceral preservation. For certain pancreatic tumors, this technique could help prevent the need for allotransplantation and its associated morbidities.

The ideal candidate for ex vivo surgery is a patient with a low-grade or benign yet symptomatic mass involving the mesenteric vessels that is not feasible with conventional surgical or vascular reconstructive techniques. Symptoms are often nonspecific, but patients can present with abdominal pain, difficulty eating, and signs of intestinal or biliary obstruction, or of portal hypertension. Several pancreatic tumor types have been successfully resected using ex vivo techniques with excellent long-term outcomes, including pancreatic fibromas, desmoid tumors of the pancreas, solid pseudopapillary tumors, pancreatic neuroendocrine tumors, ganglioneuromas, serous cystadenocarcinomas, inflammatory myofibroblastic tumors, and hemangioendotheliomas.

Most of these tumors are located at the head of the pancreas and therefore amenable for pancreaticoduodenectomy. A few occur diffusely throughout the entire gland, and require total pancreatectomy to achieve complete resection.

The benefit of ex vivo resection in patients with pancreatic adenocarcinoma involving the SMA is unclear. Although surgical resection of all gross disease has traditionally been the best hope for long-term survival, aggressive surgery for disease that has already spread to encase the mesenteric arteries is controversial. In a meta-analysis by Mollberg and colleagues, patients who underwent arterial reconstruction during pancreatectomy exhibited higher perioperative mortality and poorer 1-year and 3-year survival compared with patients who underwent pancreatectomy without vascular reconstruction or with venous reconstruction only. However, patients who underwent arterial reconstruction were associated with longer survival than patients with locally advanced disease who did not undergo pancreatectomy altogether.

For patients with locally advanced pancreatic adenocarcinoma, ex vivo resection can theoretically provide a means to completely resect all gross disease, including the involved vasculature. But due to the high likelihood of micrometastatic disease at the time of diagnosis, tumors that have already encased the SMA would almost
invariably recur despite the degree of resection. This is supported by data available for patients who have undergone ex vivo resection for adenocarcinoma with limited long-term survival. We currently do not advocate for the routine use of ex vivo techniques for patients with pancreatic adenocarcinoma. For younger patients with stable disease involving the SMA despite neoadjuvant therapy who still wish to pursue surgery, discussions must be held weighing the benefits and risks of major surgery for an incurable disease, and the potential for significant life-long morbidity.

PREOPERATIVE EVALUATION

Patients with pancreatic neoplasms amenable for ex vivo resection will require a complete medical evaluation before surgery. Every patient should be evaluated by a multidisciplinary team experienced in both autotransplantation and allotransplantation. Specialists should include a surgeon, medical oncologist, gastroenterologist, nutritionist, nurse coordinator, physical therapist, and a social worker. Comorbidities, exercise tolerance, cardiopulmonary status, and availability of psychosocial support must all be considered when evaluating a candidate for ex vivo resection.

Management of the patient’s specific tumor type also should be discussed in the multidisciplinary setting. Preoperative tissue biopsies can usually be obtained using minimally invasive techniques, and are valuable in establishing a diagnosis and guiding chemotherapeutic options.

Neoadjuvant chemoradiation should be considered before ex vivo surgical resection as appropriate. Preoperative procedures, such as biliary stenting or transjugular intrahepatic portosystemic shunting also should be considered.

High-quality cross-sectional imaging with computed tomography angiography is necessary for surgical planning. The tumor can be assessed in relation to adjacent vessels, which is critical in guiding the strategy for vascular reconstruction. Positron emission (PET) and Magnetic resonance imaging (MRI) may be helpful in further delineating tumor anatomy and ruling out distant metastases unclear on computed tomography imaging.

SURGICAL TECHNIQUE

Due to the heterogeneity and anatomic variability of pancreatic tumors requiring ex vivo resection techniques, specific surgical techniques have not been standardized. Careful and meticulous planning with high-quality cross-sectional imaging is always necessary to modify the surgical approach to each tumor.

Pancreaticoduodenectomy with Ex Vivo Intestinal Resection and Autotransplantation

Pancreaticoduodenectomy with intestinal autotransplantation is generally reserved for pancreatic tumors that encase the SMA, or involve the distal superior mesenteric vein (SMV) branches. The general approach and technical considerations are described as follows.

Abdominal exploration and mobilization

The initial exploration and mobilization of the abdominal contents is similar to the standard open pancreaticoduodenectomy. A vertical midline incision from the xiphoid process to below the umbilicus with a right subcostal extension will usually facilitate generous exposure of the abdominal cavity. The entire peritoneum is thoroughly explored to assess for evidence of tumor spread. The liver surface is first examined and palpated to check for abnormal lesions. Although modern cross-sectional imaging is highly sensitive in detecting liver metastases, intraoperative ultrasound can be used to
assess the liver parenchyma for questionable imaging findings and biopsied if necessary. If there is evidence of hepatic disease in the setting of certain neoplasms (i.e., nonfunctional pancreatic neuroendocrine tumors), the lesions are again assessed for resectability. In circumstances in which there is high preoperative concern for metastatic spread precluding surgical resection, staging laparoscopy can be performed before laparotomy. In addition, the omentum and bowel are checked for disease spread.

Once the decision is made to proceed with resection, a full right medial visceral rotation is performed, mobilizing the right colon off its peritoneal attachments and exposing the retroperitoneal contents, part of the duodenum, and pancreatic head. Often there are extensive adhesions from prior surgeries or radiation and must be carefully taken down. The lesser sac is opened to further expose the head of the pancreas and tumor. The transverse colon is transected to form the distal end of the intestinal autograft and dissected off the duodenum to complete the exposure of the mesenteric vessels as they run posteriorly behind the pancreas.

The hepatoduodenal ligament is then dissected in the usual fashion, exposing the common bile duct, common hepatic artery, and gastroduodenal artery (GDA). After confirmation of normal hepatic arterial anatomy, the GDA is test clamped and divided, revealing the portal vein beneath. A traditional cholecystectomy is then performed and the common bile duct is transected and gently clamped. The antrum of the stomach is divided, forming the proximal end of the organ bloc for removal. The pancreas is then assessed for resection. Often because of extensive mesenteric vessel involvement, it may be difficult or impossible to create a tunnel between the pancreas and SMV. The pancreas is transected and margins are sent for frozen pathologic analysis in the appropriate setting (Fig. 1). If the entire pancreas is to be removed, the spleen is

![Fig. 1. Transection of the pancreas before small bowel explant. D, duodenum; P, pancreas; S, stomach; SR, stomach remnant.](image)
concomitantly mobilized and splenic artery and vein identified for ligation. The SMA is now identified and encircled. With the remaining attachments taken down, the entire tumor-multivisceral bloc is mobilized and suspended by the 2 mesenteric vessels (Fig. 2). The artery and vein are then clamped and divided, and the viscera are removed and immediately flushed with organ preservation solution via the SMA. For certain tumors involving the portomesenteric junction, proximal transection of the portal vein necessitates reconstruction of the splenic vein either with creation of a splenorenal shunt, or via anastomosis to an interposition autologous vein graft.

An alternative approach to intestinal autotransplantation is the isolation of a segment of small bowel in the manner of the living donor intestinal transplant procurement. At the time of exploration, a segment of uninvolved small bowel (usually mid-jejunum or distal ileum) is isolated on a single vascular pedicle distal to the tumor region. The vessels are preserved and its associated bowel and mesentery are transsected. This segment is removed first and flushed in cold preservation solution as a means of ensuring a usable portion of healthy small bowel for autotransplantation, without risk of injury during tumor resection. Isolation of a single vascular pedicle often limits the length of small bowel preserved to approximately 200 cm, although segments greater than 100 cm are probably enough to safely sustain the patient without the need for long-term parenteral nutrition.

**Back-table resection and reconstruction**

After the tumor-multivisceral bloc is preserved on ice (Fig. 3), the mesenteric vasculature is examined in relation to the tumor and resection is performed while carefully preserving the uninvolved vessels and its associated bowel. The SMA is traced distally, identifying the first jejunal branches, which may need to be removed if involved with tumor. The ileocolic artery is also identified and preserved if possible.

Fig. 2. Skeletonizing the mesenteric vessels in preparation for bowel explant. PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
If additional length on the artery is required for implantation, a segment of internal iliac artery may be harvested. The SMV is similarly traced and resected to obtain a tumor-free margin. Occasionally, 2 or more segments of mesenteric vein branches may need to be reconstructed to form a new venous outflow tract. The left internal jugular vein may be harvested to facilitate this reconstruction. Once vascular reconstruction is complete, the vessels are carefully checked for leaks to minimize bleeding after reperfusion, and the autograft is flushed with albumin and brought back to the operating field (Fig. 4). During back-table resection and preparation of the autograft, a second “recipient” team performs hemostasis, completion lymphadenectomy, vascular shunting, or intraoperative radiation, as appropriate (Fig. 5).

Reimplantation and Reconstruction
Once the autograft is brought to the field, it is checked for vessel orientation and positioned without any mesenteric twisting. Heparin is administered and the arterial anastomosis is performed with graft implantation onto the SMA stump or infrarenal aorta. Subsequently, the reconstructed venous conduit is anastomosed to the portal vein or directly onto the vena cava. The graft is then reperfused and hemostasis performed (Fig. 6). Intestinal viability is evaluated visually or with indocyanine green fluorescence angiography and additional bowel resected if perfusion is inadequate.

The gastrointestinal tract is reestablished in a manner similar to the standard pancreaticoduodenectomy. The proximal jejunal limb is brought up and a pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy are created in the usual fashion. An alternative to the pancreaticojejunostomy is the pancreaticogastrostomy, which may be the preferred reconstructive method in this procedure, as it avoids
anastomosing pancreas to reperfused bowel. Distally, the ileum or ascending colon, depending on the remaining length of the autograft, is reconnected to the left colon. If an ileocolonic anastomosis is created, a Santulli-type “chimney” ileostomy is performed proximal to the side-to-end anastomosis. Otherwise, a standard loop ileostomy can be brought up if a colocolonic anastomosis is formed. A gastrostomy tube is placed if long-term enteral nutritional support is anticipated.

Fig. 4. The prepared intestinal autograft after tumor resection. The SMA and SMV are seen here and used for implantation.

Fig. 5. The “empty abdomen” with small bowel explanted. Clamps have been placed on the SMA and SMV stumps. The pancreatic tail is seen. PANC, pancreas.
If there is concern for inadequate graft perfusion or the patient is hemodynamically unstable, the abdomen can be temporarily closed and brought back for a second-look laparotomy with completion of the gastrointestinal reconstruction at that time. As an alternative, the distal end of the autograft can be brought up as a terminal enterostomy, leaving a long colonic Hartmann-type stump that can be reversed after full recovery.

Pancreaticoduodenectomy with Ex Vivo Liver Resection and Autotransplantation

For low-grade or benign tumors of the pancreatic head invading the hepatic hilum, pancreaticoduodenectomy with ex vivo resection and reconstruction of the hilum with liver autotransplantation can be performed (Fig. 7). We have previously described a case of a pancreatic head ganglioneuroma diffusely infiltrating the hepatoduodenal structures, causing complete portal vein, SMV, and splenic vein thrombosis and bile duct obstruction that was removed using this technique.\textsuperscript{13}

Due to massive venous collaterals from mesenteric thrombosis, a mesocaval shunt with an autologous jugular vein graft, as well as a distal splenorenal shunt, were first created to decompress the portal system. The liver was then completely dissected off the vena cava and pancreaticoduodenal mobilization performed with stomach, jejunum, and pancreas transections. After the division of the common hepatic artery and the hepatic veins, the entire multivisceral bloc was flushed and preserved in the cold via the portal vein.

The tumor was carefully dissected off the hepatic hilum ex vivo in a bloodless field. The left hepatic artery was completely encased with tumor, so a left lateral...
hepatectomy was performed at this time. The patient remained stable during this anhepatic phase, supported with the mesocaval and splenorenal shunts.

Once the tumor was completely removed, the right lobe was reimplanted by taking down the mesocaval shunt and connecting it to the portal vein. The right hepatic artery was anastomosed to the common hepatic artery stump and the liver was reperfused. The gastrointestinal tract was then reestablished with a pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy.

Pancreatectomy with Multivisceral Ex Vivo Resection and Combined Liver/Intestine Autotransplantation

Certain pancreatic tumors encasing both the celiac artery and SMA may be amenable to ex vivo tumor resection and autotransplantation of the liver and intestine. We have previously described this multivisceral ex vivo procedure for an inflammatory myofibroblastic tumor involving most of the pancreas, as well as a hemangiendothelioma of the pancreatic head, both encasing the celiac artery and SMA.10 The techniques of this complex procedure are developed from experience performing multivisceral transplantations. Strategies for vascular and gastrointestinal reconstruction are highly dependent on tumor size, location, and involvement of adjacent structures, and must be individualized with careful preoperative planning.

At the time of exploration, the abdominal viscera are fully mobilized as previously described to expose the tumor and its involvements. The gastrointestinal tract is divided at the gastroesophageal junction and at the transverse colon. The kidneys are usually left in situ, unless there is tumor involvement. Using techniques similar to that of multivisceral transplant procurement, the stomach, pancreas, spleen, small bowel, and proximal colon are mobilized en bloc. The liver is dissected off the vena cava to the level of the major hepatic veins, and the entire multivisceral bloc is lifted out after the ligation of the SMA and celiac arteries. If portions of the vena cava or aorta

Fig. 7. Diagram of pancreaticoduodenectomy with liver ex vivo tumor resection. (A) The visceral bloc containing the pancreatic tumor invading the hepatic hilum. (B) The liver, pancreatic head and duodenum are removed and preserved in cold preservation leaving the intestines in situ (C). (D) The tumor is resected (E), leaving only part of the liver behind for implantation. (F) The tumor-free lobe of the liver is reimplanted. (From Matsuoka N, Weiner JI, Griesemer AD, et al. Ex vivo pancreatectoduodenectomy and liver autotransplantation for pancreatic head tumor with extensive involvement of the hepatoduodenal ligament. Liver Transpl 2015;21(12):1554; with permission.)
are involved with tumor, segments of these great vessels can be removed as well with the organs and reconstructed with synthetic graft. In these cases, venovenous or venoarterial bypass should be considered but is usually not necessary.

Because of both SMA and celiac arterial involvement, total pancreatectomy generally must be performed. Depending on the level of tumor invasion and parenchymal sparing, islet cells potentially could be harvested for autotransplantation. If the distal pancreas is spared from tumor, it is possible to reimplant the pancreatic tail and spleen in the groin with drainage into the bladder.

After flushing the organ bloc with preservation fluid via the SMA and celiac artery, the tumor is resected ex vivo. The strategy of tumor removal is highly variable and dependent on its vessel and organ involvement. Organs deemed unsalvageable are removed, and can include the stomach, spleen, pancreas, segments of small bowel, and segments of the liver. Vascular reconstruction poses a significant challenge and often relies on the use of both autologous grafts from the jugular and saphenous veins, as well as synthetic grafts. With some creativity, the splenic and gastric vessels also can be used for hepatic arterial reconstruction, especially in the setting of variant anatomy.

Owing to the general location of pancreatic tumors requiring multivisceral ex vivo resection, the organs are usually detached and implanted separately. The liver is implanted first, with reconnection to the vena cava or synthetic conduit. A renoportal anastomosis is created to establish portal flow via a jugular vein graft, before the small bowel is autotransplanted. The reconstructed hepatic artery is then reconnected to the existing celiac artery stump or the synthetic aortic graft. Once the liver is perfused, the small bowel is brought to the field and implanted, with the reconstructed mesenteric artery connected to the aorta and mesenteric vein to the side of the renoportal anastomosis. As previously mentioned, a spared distal pancreas and spleen is amenable for implantation. In our experience, the splenic artery and vein can be anastomosed to the iliac vessels in the pelvis and the pancreas is connected to the bladder. Once the organs are reperfused, intestinal continuity is restored with an esophagojejunostomy, hepaticojejunostomy, and ileocolostomy.

**POSTOPERATIVE MANAGEMENT**

Due to the complex and invasive nature of these procedures, multidisciplinary management in the postoperative phase is crucial. Patients are transferred to the intensive care unit for hemodynamic monitoring. They typically remain intubated, especially if a second-look laparotomy is planned. Laboratory values and hemodynamic parameters are carefully trended with a low threshold for reexploration if there is concern for inadequate graft perfusion. Doppler ultrasound is performed postoperatively to examine the patency of the hepatic and mesenteric vasculature.

Once the hematocrit has stabilized or there is low concern for bleeding, a heparin drip is initiated. Although there is no standardization for timing of initiation, we typically start a low-dose heparin drip intraoperatively if the field appears hemostatic, and uptitrate over the next 24 to 48 hours. Sublingual aspirin is usually started as well, particularly when synthetic grafts are used. Insulin is administered as needed, especially in the setting of total pancreatectomy. Total parenteral nutrition is begun 3 to 4 days after surgery and continued until the patient can be supported entirely on enteral nutrition. Intra-abdominal drains are left in place until output is minimal and a pancreatic or bile leak has effectively been ruled out. Intestinal output is generally higher with shorter intestinal autografts and may require parenteral hydration and the use of antimotility agents. When the patient is tolerating enteral feeding without need for parenteral nutrition, the stoma can be evaluated for closure, usually within 2 to 3 months.
COMPLICATIONS

Ex vivo resection for pancreatic tumors is associated with significant morbidity and is subject to the same complications as pancreaticoduodenectomy, including pancreatic fistulae, bile leak, significant bleeding, intra-abdominal infection, delayed gastric emptying, and wound complications. The most devastating complications specific to intestinal or multivisceral autotransplantation relate to loss of the autograft from vessel thrombosis or dissection. Early suspicion of graft loss and prompt surgical exploration is necessary to prevent irreversible ischemia of the autograft. Doppler ultrasound and close laboratory and clinical monitoring can aid in the detection of these complications. There is no proven method for prevention, but until more evidence becomes available, we routinely anticoagulate all patients after autotransplantation and use autologous vessel grafts for reconstruction when possible. Postoperative arterial anastomotic disruption causing massive hemorrhage is another serious complication after autotransplantation and is likely related to a concomitant pancreatic fistula. It is our preference to perform a pancreaticogastrotomy when possible, as limited evidence supports lower fistula rates when compared with a pancreaticojejunostomy. In addition, we would avoid performing this anastomosis on reperfused bowel. Long-term complications of the vascular reconstruction relate to vessel stenosis and venous thrombosis, which may be amenable to endovascular intervention.

Other major complications relate to delayed graft function, especially in shorter intestinal autografts. During ex vivo resection, every effort is made to preserve an adequate length of bowel to support sufficient enteral absorption. The recovery process becomes more challenging with shorter autografts, as intestinal absorption is decreased, leading to higher rates of dehydration and a longer dependence on parenteral nutrition. Due to the neoplastic tendencies of teduglutide, its use in managing short-bowel syndrome in these patients is not currently recommended. Patients who are unable to be weaned off parenteral nutrition should be considered for intestinal allotransplantation in the appropriate setting.

SUMMARY

There are several low-grade pancreatic tumors whose biology permits the use of aggressive surgery to achieve a curative resection. Tumors that are deemed unresectable by conventional techniques due to mesenteric vessel involvement may benefit from ex vivo tumor resection and autotransplantation to allow complete resection while minimizing ischemic organ injury. Ex vivo techniques also facilitate wide exposure of the major vessels and allow for complex vascular reconstruction. Despite the excellent oncologic outcomes when used for these neoplasms, the procedure carries substantial morbidity and a high complication rate. But for patients who were otherwise offered total enterectomy and allotransplantation or told that their tumor was unresectable, ex vivo resection may offer them a hope for cure.

REFERENCES


