TOPIC HIGHLIGHT

Tricks and tips in pancreatoduodenectomy

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Abstract

Pancreaticoduodenectomy (PD) is the standard surgical treatment for tumors of the pancreatic head, proximal bile duct, duodenum and ampulla, and represents the only hope of cure in cases of malignancy. Since its initial description in 1935 by Whipple *et al*, this complex surgical technique has evolved and undergone several modifications. We review three key issues in PD: (1) the initial approach to the superior mesenteric artery, known as the artery-first approach; (2) arterial complications caused by anatomic variants of the hepatic artery or celiac artery stenosis; and (3) the extent of lymphadenectomy.

Core tip: The "artery-first approach" prioritized the dissection of the origin of the superior mesenteric artery (SMA), allowing complete lymphadenectomy, safe dissection of the SMA, and accurate identification of the most frequent anatomic variations such as a hepatic artery originating in the SMA. It has been demonstrated that patients with intraoperative arterial complications have longer operative time, higher transfusion rate and more postoperative complications. Another controversial issue is the extent of lymphadenectomy in the pancreaticoduodenectomy. The randomized trials published do not recommend radical lymphadenectomy as a standard approach for pancreatic ductal adenocarcinoma.

Pancreaticoduodenectomy (PD) is the standard surgical treatment for tumors of the pancreatic head, proximal bile duct, duodenum and ampulla, and represents the only hope of cure in cases of malignancy[1-3]. Since its initial description in 1935 by Whipple *et al*[4], this complex surgical technique has evolved and, although the mortality rate has been reduced by regionalizing interventions in high volume centers[1,3], morbidity remains high, with a rate close to 40%[5,6]. Various modifications of the classical PD have been proposed to reduce morbidity [7].

We review three key issues in PD: (1) the initial approach to the superior mesenteric artery (SMA), known as the artery-first approach; (2) arterial complications caused by anatomic variants of the hepatic artery (HA) or celiac artery stenosis; and (3) the extent of lymphadenectomy.

ARTERY-FIRST PANCREATODUODENECTOMY

It has been shown that the superior mesenteric vein (SMV) can be safely resected, the only contraindication being arterial involvement[8,9]. With the classical dissection

approach, the infiltration of the SMA is often identified at the end of the operation, obliging the surgeon to resect; this often results in a resection with positive margins[8]. The objective of PD is a R0 resection, because free margins are relevant to prognosis[10]. However, up to 20% of PD have R1 resection; the most frequently invaded margin is the peripancreatic retroperitoneal margin[11], representing 3-4 cm of tissue surrounding the origin of the SMA behind the SMV[12].

In 2003, Pessaux *et al*[13] presented a modification of the dissection of the retroportal pancreatic lamina which prioritized the dissection of the origin of the SMA, allowing complete lymphadenectomy, safe dissection of the SMA and accurate identification of anatomic variations such as a HA originating in the SMA. In 2006, the same authors[8] described a technique that they termed the "SMA-first approach", which encompasses a liberal kocherization to expose the origin of the SMA just above the point where the left renal vein crosses the aorta, and in which the dissection is started caudally along the vessel. Approximately 1-2 cm from the origin of the SMA, an anomalous right HA (RHA) may be identified; if so, it is left intact and the dissection of the SMA continues caudally to the 3rd-4th part of the duodenum. The front aspect of the SMA is dissected from the mesouncinate, at which point the invasion of the SMA can be identified and the surgery finished[8]. The origin of the superior and inferior pancreaticoduodenal arteries (IPDA) can be identified and ligated when they enter the pancreatic head and the uncinate process respectively, reducing congestion and bleeding from the pancreatic head[9].

Since the initial description, Pessaux *et al*[8] have reported several surgical techniques and approaches, all termed "artery-first". All these techniques prioritize artery dissection to identify arterial involvement, and thus assess whether the tumor is resectable before taking the irreversible step to operate[9].

Posterior approach

Pessaux *et al*[8] described the posterior approach to the SMA, indicated for resection of posteromedial tumors of the head and neck and periampullary tumors extending from the body to the head of the pancreas[9]. This procedure allows early dissection of the posterior pancreatic capsule and identification of SMA involvement and an anomalous RHA, and also facilitates *en bloc* resection of the portal vein (PV)/SMV if they are involved[1]. Its disadvantage is that it is difficult to perform in patients presenting with peripancreatic inflammation and adhesions around the pancreatic head[9], and also in obese patients[14].

Inferior supracolic/anterior approach

Hirota *et al*[15] described PD using a "no-touch isolation technique", to avoid compression of the tumor and the spread of malignant cells within the abdominal cavity. The tumor is wrapped in Gerota's fascia and the retroperitoneal margin dissected along the right side of the SMA and the abdominal aorta. The stomach can be retracted

cranially to expose the pancreatic neck and, before it is sectioned, to raise its lower edge in order to assess the resectability of the tumor[9]. It is considered a useful technique for tumors of the lower edge of the pancreas and facilitates retroperitoneal dissection, especially in locally advanced tumors receiving neoadjuvant therapy[9].

"Hanging maneuver"

Pessaux *et al*[12] described an approach that combined the posterior and anterior technique, which they termed the "hanging maneuver". It has subsequently been used by other authors[11]. A tape is passed around the SMA from its origin in the aorta to its exit point in the mesentery, thus lifting up the peripancreatic retroperitoneal tissue. The traction exerted on the tape by the assistant pulls the retroperitoneal pancreatic tissue to the right, improving the exposure of the SMA and facilitating dissection at the origin of all its proximal branches, and leaving both hands of the surgeon free to control the bleeding[11,12,14]. The authors recommend this approach especially in patients with preoperative suspicion of involvement of the SMA, in patients receiving neoadjuvant therapy for locally advanced disease, in obese patients, and when the RHA originates in the SMA[12].

Inferior infracolic/mesenteric approach

Weitz *et al*[10] described the infracolic approach from the transverse mesocolon. To identify the origin of the SMA, after a modified Kocher maneuver, the small intestine is moved to the right and the peritoneum is opened parallel to the root of the mesentery on the left of the proximal jejunum and the duodenojejunal flexure. Then, the posterior part of the SMA is dissected, trying to preserve the nerves on the left side in order to avoid postoperative diarrhea. The SMV and SMA are identified from an inframesocolic position, and the dissection continued cranially. On the right side of the SMA, the anomalous or accessory RHA may be identified and the IPDA located, facilitating its early ligation and reducing bleeding[9]. Weitz *et al*[10] believe that this technique is especially useful in patients with locally advanced tumors and suspected infiltration of the SMA at the origin of the aorta or malignant tumors in the uncinate pancreas, but it is difficult to perform in obese patients and if the origin of the SMA is high.

Right/medial uncinate approach

Hackert *et al*[16] presented a modification of PD for early SMA dissection consisting of a retrograde dissection of the pancreatic head in the caudo-cranial direction. The proximal jejunum is dissected and the first jejunal loop is moved to the right of the mesenteric root in order to initiate pancreatic dissection in the uncinate process and to perform pancreatic transection in the last surgical stage. Previously, Shukla *et al*[17] described the dissection of the uncinate process from the mesenteric vessels, facilitating tumor removal and demonstrating the involvement of these vessels early during surgery. This approach is recommended in uncinate tumors and in cases with suspected involvement of the SMV or SMA[2]. Another advan-

tage of this approach is the early ligation of the IPDA, but it does not allow early identification of an anomalous RHA[9].

Left-posterior approach

Kurosaki *et al*[18] presented the "left-posterior approach" in which the superior mesenteric vessels are dissected first, clockwise from the left. This technique allows *en bloc* dissection of the superior mesenteric pedicle, provides a clear understanding of the anatomy in order to detect an aberrant RHA, and predicts the involvement of the margins in the SMA level prior to performing PD. It consists of a kocherization of the duodenum, pushing the proximal jejunum to the left and sectioning the first and second jejunal arteries at the origin of the SMA; while the proximal jejunum is pushed leftwards, the SMA rotates counterclockwise for correct dissection of the posterior and right faces of the SMA, allowing early ligation of the IPDA. The first jejunal vein is then revealed, which is the landmark for dissection; as the lower part of the pancreatic head is moved leftwards the SMV appears, the first jejunal vein is transected, and the SMV is dissected. The proximal jejunum is then moved to the right of the mesenteric pedicle allowing dissection of the connective tissue remaining on the anterior side of the SMA. This technique may be useful in tumors of the posterior part of the head of the pancreas or the uncinate process[9].

Superior approach

This approach is useful for resection of tumors on the upper edge of the pancreas or when involvement of the common HA (CHA), or of the surrounding lymph nodes, is suspected[9]. The hepatoduodenal ligament is dissected to expose the CHA and the gastroduodenal artery, with dissection from right to left to perform lymphadenectomy in this area. Subsequently the pancreas is retracted caudally, dissection proceeds caudally as far as the celiac trunk, and the origin of the SMA and the lymphatic tissue surrounding it is dissected. This technique is difficult to perform in patients presenting a low origin of the SMA[9].

Comparative studies of the different approaches

Several authors have compared these approaches with classical PD. Figueras *et al*[3] compared classical PD with the posterior artery-first approach, reporting a reduction in complications and hospital stay, while Dumitrascu *et al*[1] found no significant differences in hospital stay, early morbidity, mortality, or overall survival. Shrikhande *et al*[2] compared classical PD with the "uncinate artery-first approach" and found no evidence of significant differences in blood loss, operative time, margin involvement, lymph node yield, or complications.

Comparing conventional PD with the left posterior approach, Kurosaki *et al*[18] found no differences in operative time, blood loss or hospital stay, but reported a lower rate of recurrence and improved survival with the left posterior approach. They also recorded an increase in frequency and degree of diarrhea in patients treated with

the left posterior approach, but this was controlled with antidiarrheal drugs.

Most authors agree that artery-first PD is useful in patients in whom an anomalous origin of the RHA or an accessory HA leaving the SMA is suspected. It allows early assessment of arterial involvement and thus of tumor resectability, especially in patients receiving chemotherapy and/or radiotherapy in whom tumor status is difficult to determine using computed tomography (CT), and in patients with borderline resectable disease[9].

Whichever approach is used, the standardization of "artery-first" PD will be important in reducing the number of R1 resections and in increasing survival[14].

ARTERIAL COMPLICATIONS DURING PANCREATODUODENECTOMY

Morbidity rates in PD remain high. Arterial complications are one of the possible sources of morbidity[19]. This problem has received little attention to date: some reports suggest that these complications occur only in 3%-4% of PD[19], but this seems excessively low given that various arteries around the pancreas are put at risk during dissection, arterial anomalies are frequent, and atherosclerosis can occlude arterial vessels[19]. When atherosclerosis occurs, morbidity is higher[19]. In this section, we review the most frequent arterial complications during PD: problems related to anatomical variations of the HA and celiac axis stenosis.

Hepatic artery anatomical variations

Rates of anatomical variations in the hepatic arterial system may be as high as 45%[20,21]. A thorough knowledge of HA anatomy is essential; in the presence of HA anatomical variations (HAAV), accidental ligation may occur during PD, provoking hepatic necrosis, ischemic biliary injury or an anastomotic fistula[6,20-24].

Preoperative assessment of peripancreatic vascular patterns using imaging methods is crucial for surgeons[22]. Multidetector CT is the method of choice, and multidimensional reconstruction may be very useful[6,21-23,25]. Angiography is no longer needed[20].

Several classifications of HAAV have been proposed (Covey, Hiatt, Koops and Michels)[6,20,22,23]. The most frequently described HAAV are an anomalous RHA from the SMA (10%-21%), a displaced left HA (LHA) from the left gastric artery (4%-10%), displaced RHA and LHA, an accessory RHA and/or LHA (1%-8%), a displaced CHA from the SMA or aorta (0.4%-4.5%), and quadrifurcation of the HA itself[20,23].

In the largest study carried out to date, which included 5002 abdominal CT, the crucial data regarding identification of HAAV during PD were the following: only 0.13% of patients with CHA originating in the celiac axis (normal anatomy) had a retroportal or transpancreatic course; CHA originating in the aorta always had a normal course, and CHA coming from the SMA might show different relations with the pancreas (supra, trans or infrapancreatic) and the PV and SMV (pre or retroportal and

pre or post SMV)[25].

The most important HAAV that the surgeon must bear in mind during PD are accessory RHA and displaced or accessory CHA, both arising from the SMA[23].

Dieplaced or accessory RHA arising from the SMA (10%-21%) is the variation that is most often identified during PD[6,20-23]. This vessel passes lateral to and behind the PV and can be felt by palpation, but it may also pass behind or through the pancreas[6,22,23]. Displaced or accessory CHA arising from the SMA, known as the hepato-mesenteric trunk, is the second most frequent variation (2%-3%)[6,20] and its course is variable[20,23].

On encountering an HAAV during PD, the possible options for intraoperative management are ligation, dissection and traction away from the site of dissection, or division and anastomosis[6,20,23]: (1) the main problem with ligature of the displaced RHA is liver necrosis[20]. The ligation of accessory vessels usually has fewer clinical implications[23]. Preoperative clamping of the artery to be ligatured and post-ligature control of the flow of the non-ligated arteries is advisable[20]; (2) dissection and traction procedures are only possible in certain HAAV and tumors located in the ampulla. The procedure may be technically demanding; cancer cells may spread and there may be postoperative bleeding[20]; and (3) reconstruction of the HAAV may increase the risk of postoperative bleeding if pancreatic fistula develops[20]. Besides, there is no consensus among pancreatic surgeons regarding the desirability of arterial resections during PD.

Early in every PD, a conscious attempt should be made to define the vascular anatomy. However, in the standard approach, dissection of an HAAV coming from the SMA is usually performed late, when bleeding reduces its exposure[6]. When SMA dissection is performed first, the exposure of the HAAV is better, particularly the RHA or a CHA originating from the SMA or aorta[6,13,21].

In vessels that lie within the head of the pancreas there are several options. One is the division of the pancreas to preserve the vessel, but this is not recommended in cases of malignancy[22]. If detected preoperatively, an embolization may be performed. If identification is intraoperative, the possible technical options are ligature after temporary clamping of the vessel and checking the hepatic flow using Doppler or division and anastomosis[20,23].

In conclusion, the presence of HAAV complicates PD and their preoperative diagnosis using CT is essential. The most frequent HAAV are displaced RHA or CHA from the SMA. The artery-first approach seems to obtain a better identification of HAAV. Several technical options (ligature in the case of accessory arteries, dissection and traction or vascular reconstruction) may be performed during PD. Patients with intraoperative arterial complications have longer operative time, higher transfusion rate, and more postoperative complications[19].

Celiac artery stenosis
Celiac artery occlusion or stenosis (CAS) is frequently present (12%-50%) but it is usually of no clinical sig-

nificance due to collateral pathways[26-28]. CAS has been reported in 2%-7.6% of patients undergoing PD[23]. In these patients, upper abdominal organs are at risk of necrosis from ischemia because PD resection involves the collateral vessels (the gastroduodenal and pancreatico-duodenal arteries)[19,24,26-28].

The cause of CAS may be vascular (mainly arterio-sclerosis) or non-vascular: compression of the median arcuate ligament (MAL) or invasion by tumor or lymph nodes[23,26,27]. Sugae *et al*[27] proposed a morphological grading of celiac axis stenosis (A, B and C) by MAL compression according to stenosis grade and duration, distance from the aorta, and collateral pathways.

To maintain correct blood supply after PD in patients with CAS, a detailed preoperative assessment is essential[23,26,27]. The best method for defining CAS and its etiology is multidetector CT[24,27].

The treatment options are tailored to stenosis grade and etiology of CAS, but preserving collateral pathways during PD is essential[26,27]. Placing arterial preoperative stenting before PD is a valid therapeutic option especially in severe cases of CAS unrelated to MAL compression[24,26,27]. When CAS is caused by MAL compression, surgical division of the MAL is performed during PD. After division, blood flow should be restored by Doppler or palpation[23,26,27]. Gaujoux *et al*[24] only consider MAL division when the intraoperative clamping test of the gastroduodenal artery is positive. Revascularization should be performed (arterial anastomoses or bypass grafting) if MAL division does not improve perfusion, or in other selected cases[24,27].

If CAS is not diagnosed and treated during PD, there may be severe complications during the postoperative period[24]. Muros *et al*[28] showed that patients with CAS presented more serious complications (pancreatic fistula and hemoperitoneum) and more reoperations.

EXTENDED LYMPHADENECTOMY FOR PANCREATIC HEAD ADENOCARCINOMA
Pancreatic ductal carcinoma has an incidence of lymph node invasion of more than 70%[29-31]. Though many different multimodal therapy regimens have been used, long-term survival has seen little improvement, with a median survival of about 18 mo and a 5-year survival after curative resection of 6%-20%[32-34].

The multivariate analysis of Nimura's randomized study identified lymph node involvement and vascular resection as independent factors for poor prognosis[35]. A recent study also found the lymph node ratio to be a better prognostic factor than the total number of infiltrated lymph nodes.

In view of the high frequency of lymph node involvement, the high incidence of local recurrence, and the relationship between survival and node level of invasion published in some studies[34], numerous attempts have been made to increase survival by means of a more radical local resection and by extended lymphadenectomy

of the most frequently affected lymph nodes (anterior and posterior pancreaticoduodenal nodes, periaortic, and those of the SMA and the celiac trunk)[35,36]. The first report was published in 1977 by Fortner[37], who described "regional pancreatectomy" in which an extended lymphadenectomy with vascular and perineural mesenteric resection was associated with the PD. Since then, several studies have tried to increase survival with extended radical lymphadenectomy (ELA), which has been protocolized in many centers in Japan since the late 1990s. Ishikawa *et al*[38] in 1998, and Manabe *et al*[39] in 1999, published two non-randomized studies with 5-year survival rates of 28% and 33%, respectively. Several prospective non-randomized studies have been published showing a significantly higher number of lymph nodes removed in patients with ELA, but without any influence on survival. However, these studies presented higher morbidity in the form of diarrhea associated with the circumferential dissection around the SMA[40,41]. The design of these studies was heterogeneous, with different adjuvant chemotherapy regimens and different definitions of surgical radicality.

Four prospective randomized studies comparing standard lymphadenectomy (SL) *vs* extended lymphadenectomy had been published by 2005 (Pedrazzoli *et al*[32] in 1998, Yeo *et al*[29] in 2002, Nimura *et al*[30] in 2004, and Farnell *et al*[33] in 2005). All these studies applied different adjuvant chemotherapy regimens. Pedrazzoli *et al*[32] administered intraoperative radiotherapy, and Yeo *et al*[29] and Farnell *et al*[33] postoperative chemoradiotherapy. As in the previous studies, the number of lymph nodes removed was significantly higher and the operative time significantly longer with ELA.

Yeo *et al*[29] found a significantly higher rate of complications with ELA, mainly due to a greater frequency of delayed gastric emptying and pancreatic fistula (29% in SL *vs* 43% in ELA). Nimura *et al*[30] recorded severe diarrhea in 48% of patients with ELA. There was no difference in postoperative stay (range between 11 and 23 d). These randomized studies showed no significant differences in mean and long term survival between standard and extended lymphadenectomy. In-hospital mortality was similar in the two groups.

The last randomized prospective study was published by Nimura *et al*[35] in 2012, who compared a group of 51 patients with SL and a group of 50 patients with standardized extended lymphadenectomy including the lymph nodes of the hepatoduodenal ligament, CHA and mesenteric artery (both circumferentially), celiac trunk, and periaortic nodes (from the celiac trunk to the inferior mesenteric artery). In this study neither neoadjuvant nor adjuvant therapy was administered. Recruitment of patients was suspended because no survival differences were observed with ELA. The only significant differences were a longer operative time (426 min *vs* 547 min, $P < 0.0001$), a higher number of lymph nodes removed (13.3 *vs* 40, $P < 0.005$), and increased intraoperative blood loss (1118 mL *vs* 1680 mL, $P < 0.0001$) in patients with ELA. There were no significant differences in the R0 resection rate or in hospital morbidity-mortality, although the

incidence of postoperative severe diarrhea was higher in the ELA group. Interestingly, tumor recurrence patterns were similar, including lymph node recurrence, although surprisingly the rate of local recurrence was higher in the group with ELA. The 1-year disease-free survival was similar, and the 5-year survival rate was 15.7% in the group with SL and 6% in the ELA group. Five-year survival in patients with negative lymph node involvement (N0) was 33.6% in SL and 15% in ELA. In patients with positive lymph node involvement (N1), survival was 6% and 0% respectively. None of these differences were significant.

CONCLUSION

In summary, randomized studies have not demonstrated a significant increase in survival with extended lymphadenectomy in patients with adenocarcinoma of the head of the pancreas. This is probably because the majority of patients have systemic disease on diagnosis, even in resectable cases, as demonstrated by the invasion of periaortic lymph nodes[6,7]. The randomized trials published do not recommend ELA as a standard approach for pancreatic ductal adenocarcinoma.

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