Local Experience of Laparoscopic Pancreatectomy

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Introduction

With the explosive development of laparoscopic surgery, there is increasing number of patients with different pancreatic pathologies who can now be managed by minimal access approach. Laparoscopy has been widely used to stage pancreatic tumours and to palliate obstructive symptoms in advanced malignancy.1-5 Laparoscopic pancreatectomy is a step further as a result of skill maturation and refinement of instruments. There are basically three main types of laparoscopic pancreatectomy, which include (1) enucleation, (2) distal pancreatectomy and (3) pancreaticoduodenectomy (Whipple).

Laparoscopic enucleation is commonly performed for those small neuroendocrine tumours located away from the main pancreatic duct but the danger of pancreatic fistula cannot be underestimated. In order to guarantee good postoperative outcome, special attention should be given to intraoperative localisation and preservation of the main pancreatic duct.6-8

Favourable results have also been obtained in cases of either chronic pancreatitis or benign neoplasms (cystic or small neuroendocrine tumours) undergoing laparoscopic distal pancreatectomy.9-12 This approach, rather than enucleation, is preferred for patients with multiple neuroendocrine tumours involving body and tail of pancreas. Therefore laparoscopic ultrasound is indispensable not just to accurately locate and delineate the tumour relationship with the main pancreatic duct but also to exclude multifocality.13 The favourable results of laparoscopic distal pancreatectomy can also be accounted by the relatively simple anatomy at the pancreatic tail and furthermore it does not require complicated reconstruction and extensive lymphatic dissection.9-12

Since Gagner et al described the first laparoscopic Whipple in 1994, it has not gained worldwide popularity because of the complexity of procedure, long operating time and higher complication rate.14-15 Experience of laparoscopic Whipple for malignant tumour at the head of pancreas is still very limited despite the explosive development in other laparoscopic abdominal surgery.14-18

In the following paragraphs, the different techniques of laparoscopic distal pancreatectomy and Whipple are described in details followed by sharing of our experience of laparoscopic pancreatectomy in Pamela Youde Nethersole Eastern Hospital (PYNEH).

Surgical Technique in Laparoscopic Distal Pancreatectomy

Indications for operation include mainly cystic neoplasms and small neuroendocrine tumours located at the body / tail of pancreas. All the patients are initially investigated with abdominal ultrasound (USG) and computed tomography (CT). If splenectomy is planned preoperatively, in addition to routine antibiotics prophylaxis, vaccination against pneumococcus and haemophilus should be given 2-4 weeks prior to surgery.

1. Position of patient and ports

The operation is performed under general anaesthesia with endotracheal intubation and the patient is placed in Lloyd-Davis position with legs apart. Since the spleen may have to be resected with the distal pancreas, a foam pad can be placed under the left chest to enhance exposure. Chief surgeon stands between the patient’s legs with the first assistant on the surgeon’s right side and the cameraman on the other side. The port positions are not fixed and usually 6 ports are used for total laparoscopic resection whereas 4 trocar ports and 1 hand-port for hand-assisted laparoscopic distal pancreatectomy. The layout of ports should be in such a way that both the surgeon and first assistant can work simultaneously during dissection. The length of the hand-port will depend on the hand size of the operating surgeon and it is usually situated on the right side of abdomen. (Figure 1)

2. Dissection into the lesser sac and laparoscopic examination

Diagnostic laparoscopy is performed following subumbilical cut-down and creation of pneumoperitoneum, the pressure is maintained at about 12mmHg. The lesser sac is then entered after division of the gastrocolic ligament using Harmonic Scalpel® (Ethicon Endo-Surgery Inc., Cincinnati, USA). Precaution should be taken not to jeopardise the gastro-epiploic arcade at this juncture. The dissection is continued towards the short gastric vessels and also close to the origin of right gastro-epiploic artery. A flexible retractor, inserted via the subxiphoid port, is used to retract up the greater curvature of the stomach for better exposure of the whole pancreas. The lesion is carefully assessed and the planned resection line is marked with cautery following laparoscopic ultrasound examination (UST-5536-7.5 MHz, linear array probe, Aloka, Tokyo, Japan)

3. Mobilisation of spleen in splenic-resecting laparoscopic pancreatectomy

The issue of splenic preservation is still controversial. In
general, it is recommended in obviously benign cases in view of the potential risk of fulminating sepsis following splenectomy. There is slight variation of procedure depending on whether there is any intention to preserve the spleen. Adequate exposure of both the spleen and pancreas is important to ensure a smooth operation, and we find the use of a foam pad under the left chest and a surgeon - controlled adjustable table very helpful. From our experience, we realise that it would be very tedious and technically demanding to preserve splenic artery and vein. In addition, the multiple tiny branches to supply the pancreas can only be appreciated after division of the pancreatic neck and therefore it is often approached first in contrary to the splenic-resecting approach in which the spleen is mobilised first and detached from tail of pancreas early on. Another possible approach is to sacrifice the splenic artery and vein but to preserve all the short gastric vessels. This approach has the theoretical risk of developing gastric varices and segmental splenic infarction but it does simplify the operation and cut down the risk of massive haemorrhage.

5. Pancreatic resection
With the pancreatic tail retracted and elevated, the gland is freed posteriorly towards the splenomesenteric vein junction. At this point it is necessary to consider if hand-assistance is required. Although successful total laparoscopic distal pancreatectomy has been previously reported, the additional tactile assistance from the hand can definitely increase the safety margin of the operation particularly if the dissection is very close to the splenomesenteric vein. If hand assistance is decided, we recommend insertion of the hand-port at the right side of abdomen. Usually a left hand is inserted through the hand-port for a right-handed surgeon. Once an adequate resection margin is ascertained, the pancreas is divided using endo-GIA (4.5 / 60, Autosuture, United States Surgical Corp., Norwalk, CT, USA). The final attachments of splenic artery and vein are also divided using vascular endo-GIA. The proximal pancreatic surface is carefully inspected for leakage. The cut end of pancreatic duct is controlled with titanium clip if it can be clearly identified. Haemostasis is secured and the transected surface is sprayed with tissue glue (Tisseel Kit, Tisseel, Immuno AG, Vienna, Austria).

If preservation of the splenic vessels is decided, dissection is then carried out exactly in reverse direction from the neck towards the splenic hilum. Similarly, the tail of pancreas is transected using endo-GIA when adequate margin is ascertained.

6. Drainage, specimen retrieval and postoperative care
A silicone drain is positioned close to the pancreatic stump. Specimen is delivered via a transverse incision at lower abdomen or via the hand-port using a protective bag depending on the approach. Perioperatively, subcutaneous octreotide (sandostatin, Novartis) injection is administered for a week to suppress pancreatic secretion and decrease the risk of pancreatic fistulation. Patient will resume diet when bowel activity returns and stitches are removed on day 7 after operation.

Surgical Technique of Laparoscopic Whipple

The preoperative work-up is essentially the same as laparoscopic distal pancreatectomy but those patients selected usually have already been extensively investigated with imagings like CT and endoscopic retrograde cholangiopancreatography (ERCP). Perioperative subcutaneous injection of octreotide (sandostatin, Novartis) is also routinely given but preoperative vaccination is not required. The indications of operation are mainly malignant tumours involving peripancreatic region and sometime chronic pancreatitis mimicking malignancy.

1. Position of patient and ports
The patient position and lay out of the operating team
is more or less the same as laparoscopic distal pancreatectomy. The chief surgeon is operating at the foot end of the table, between the legs of the patient. The camera operator is on the left side of the table and another assistant surgeon on the opposite side. A Gelport (Applied Gelport® XE, Applied Medical Resources Corp. California, USA) is inserted at the right upper quadrant via a 7 cm horizontal skin incision and the rest of trocar ports are again similar. However it is slightly different from hand-port assisted laparoscopic distal pancreatectomy by having the hand-port incision just below the right costal margin such that some of the anastomoses can be performed via the incision using open instruments if appropriate. (Figure 4)

2. Kocherisation of duodenum and dissection into lesser sac

Following diagnostic laparoscopy and laparoscopic ultrasonography in excluding tumour dissemination, duodenum is then extensively kocherised using both sharp and blunt dissection with the medial traction of laparoscopic hand until the anterior surface of inferior vena cava and part of the aorta is exposed. The lesser sac is then entered with the division of gastrocolic ligament using Harmonic Scalpel. Stomach is mobilised and divided at about the distal one-third using an endostapler (4.5 / 80, Autosuture, United States Surgical Corp., Norwalk, CT, USA) but care should be taken not to jeopardise the blood supply to the gastric remnant. The superior mesenteric vein is identified below the pancreatic lower border when the middle colic vein is joining to it. After gaining a better exposure by dividing the stomach, a tunnel is then created between the neck of pancreas and superior mesenteric vein using cherry swab stick (Cherry Dissector, Ethicon Endo-surgery, Tokyo, Japan). A vascular sling is passed around the neck and prepares it for subsequent transection using ultrasonic dissector.

3. Bile duct dissection & mobilisation of ligament of Trietz

The gallbladder is freed from liver bed using retrograde approach and it is then grasped with the laparoscopic hand to facilitate isolation of common bile duct. The bile duct was transected just proximal to the cystic duct insertion with an endostapler which prevents spillage of any contaminated bile. Lymph nodes along the porta hepatitis are cleared until both hepatic artery and portal vein are skeletonised.

When the ligament of Trietz is taken down with ultrasonic dissector, exposure can be enhanced by adjusting the table to left side up and head down position. Once the mesentery of duenojejunal flexure is clearly defined, it is then controlled and transected with endostapler (3.5 / 60, Autosuture, United States Surgical Corp., Norwalk, CT, USA). Using the laparoscopic hand to grasp the duodenal stump, the third and fourth parts of duodenum are freed towards the right side until a tunnel is created behind the pedicle of superior mesenteric artery and vein. Thereafter the duodenum is pushed to the right and ready for the final detachment from superior mesenteric pedicle.
4. Pancreatic transection

With the neck of pancreas elevated using a vascular sling, it is then transected with ultrasonic dissector and care should be taken not to injure the common hepatic artery which is situated just at the superior border of pancreas. Lymph nodes located at the superior border of pancreas and along the common hepatic artery are cleared carefully all the way back to coeliac trunk. The gastroduodenal area is identified, freed and divided between endoclips at the junction which it branches off from common hepatic artery. The pancreas is further mobilized from the superior mesenteric vein. Extreme care should be exercised to control all the branches from this area. The 5-12 mm anastomoses. Intact specimen is retrieved via the hand-port using a sterile specimen bag. All the 5-12 mm anastomoses. Intact specimen is retrieved via the hand-port incision using a sterile specimen bag. All the 5-12 mm anastomoses are performed together with the distal pancreatectomy including right adrenalectomy for Com’s syndrome (n=1) and marsupialisation for a huge (>10 cm) and symptomatic liver cyst at left lateral segment (n=1). There was also 1 wedge excision of a small gastrointestinal stromal tumour at anterior gastric surface and 1 patient with closure of perforated gastric ulcer, of which the perforated ulcer was thought to be the cause of a pseudotumour formation at the body of pancreas. (Table 1)

In terms of postoperative complications, pancreatic leak occurred in 2 patients (22.2 %) and 2 patients developed intraabdominal collection (22.2 %), all of which settled upon conservative treatment. No hospital mortality was reported in our series. Pathologically, clear resection margin was obtained for all neoplastic cases. Median hospital stay was 7 days (range 4 - 53). No other complication was noted upon a median follow-up of 37 months (range 7 -91). (Table 2)

The 6 laparoscopic Whipple were performed for carcinoma of Ampulla of vater (n=4), distal cholangiocarcinoma (n=1) and chronic pancreatitis mimicking malignancy (n=1). (Table 1) There were 3 male and 3 female of median age of 71 (range 51 - 75). Two patients had ASA grade 1, 3 patients had ASA grade 2 and 1 patient had ASA grade 3. All resections were performed using hand-assisting technique. Median operating time was 263 minutes (range 240 - 250) and median blood loss was 105 cc (range 100 - 150). The only open conversion was due to accidental injury of the superior mesenteric vein and ended up with significant intraoperative blood loss of more than 1 litre. The bleeding was temporarily aborted using the laparoscopic hand and finally controlled by open plication (Table 2)

Postoperative complications occurred in 4 patients (66.6 %) which included bile / pancreatic leak in 3 patients (50 %) and 3 patients developed intraabdominal collection (50 %), all of which settled upon conservative treatment. Two patients developed reactionary haemorrhage and 1 was successfully controlled by tranarterial embolisation and the other one developed significant haemotoma and required reoperation via the hand-port incision for clot evacuation. One patient discharged on postoperative day 8 and was readmitted a few days later for gastric

PYNEH Experience

A total 17 laparoscopic pancreatectomies were attempted in our institution since 1999. The were 11 laparoscopic distal pancreatectomy (1 enucleation) and 6 laparoscopic Whipple.

Of those 11 laparoscopic distal pancreatectomy, indications were cystic neoplasms (n=5), chronic pancreatitis with intrapancreatic pseudocyst (n=1), adenocarcinoma of pancreas (n=1), pseudotumour of pancreas secondary to perforated posterior gastric ulcer (n=1), pseudopapillary tumour (n=1) and neuroendocrine tumour (n=2). There were 7 female and 4 male with a median age of 55 (range 18 - 79). Three patients had ASA grade 1, 7 patients had ASA grade 2 and 1 patient had ASA grade 3. Total laparoscopic resection was performed in 8 cases and 3 resections were performed using the hand-assisting technique. Among the patients with total laparoscopic resection for cystic neoplasms, 1 patient had both splenic artery and vein successfully preserved. Median operating time was 180 minutes (range 105 - 250) and median blood loss was 100 cc (range 50 - 250). Open conversion was required in a patient with adenocarcinoma of tail of pancreas. The operation could not be safely performed in view of extensive tumour involvement. In addition to the 6 concomitant splenectomies, there were other additional procedures performed together with the distal pancreatectomy including right adrenalectomy for Conn’s syndrome (n=1) and marsupialisation for a huge (>10 cm) and symptomatic liver cyst at left lateral segment (n=1).
Outflow obstruction. The complication settled upon conservative measures. No hospital mortality was reported in our series. Pathologically, clear resection margin was obtained for all neoplastic cases. Median hospital stay was 36.5 days (range 8 - 68). No other complication was noted upon a median follow-up of 8 months (4 - 20). (Table 2)

Discussion
The initial development of laparoscopy in pancreatic surgery is focused mainly on diagnosis and staging purposes. The feasibility of palliation for gastric outflow obstruction by laparoscopy is later explored with promising results. This minimal access approach is also used to treat patients with pancreatic pseudocyst with impressive outcomes. Laparoscopic pancreatectomy can be considered as another breakthrough of therapeutic laparoscopy as a result of technological and skill refinements.

Reports from literature have already confirmed the feasibility of laparoscopic Whipple. However, it is not commonly performed as a result of technical complexity, long operating time and high incidence of postoperative complications. On the contrary, the results of laparoscopic distal pancreatectomy or enucleation seem to be much more favourable as reflected by faster recovery time. Majority of these are performed for chronic pancreatitis, cystic neoplasm and neuroendocrine tumour. More importantly, it is a simpler operation as tedious lymphatic dissection is not required unlike those frankly malignant cases. Similar to the reported series, retrospective comparative trial of our centre has also shown that this is a safe operation associated with less intraoperative blood loss and possesses the potential to replace the open approach provided that expertise and ancillary set-up are available.

The early results of laparoscopic Whipple did not draw too much attention probably due to the complexity of the operation even when performed in open approach. Important structures like stomach, duodenum, the inferior vena cava and the mesenteric vessels are all crowded together with the tumour. Subsequent meticulous reconstructions again have to be accomplished in such a small space and therefore the procedure would be particularly difficult when performed laparoscopically, and this would mean prolonged operation time and may sometimes produce major intraoperative complications like injuries to neighbouring structures or bleeding. However, with the improvement of instruments, like the stapling devices and ultrasonic dissectors, together with the maturation of skills, we do think the current apparently difficult laparoscopic Whipple could be accomplished much more easier when the "learning curve" problem is overcome.

Insertion of hand can probably increase the safety margin of the operation, but it demands a certain level of skill to co-ordinate the simultaneous movements of hand and laparoscopic instruments. The notable advantages of hand-assisted laparoscopic surgery over total laparoscopic approach are better exposure of anatomy and blunt dissection is possible with the assistance of the surgeon's hand. In addition, the "laparoscopic hand" can also provide immediate haemostasis and prevent air embolism even if branches of portal vein are severed. Last but not least, if extension of incision is required anyway for retrieval of intact specimen and it is quite reasonable to have it made earlier so as to facilitate dissection as well. Also the subsequent reconstruction of hepatico-jejunostomy, gastro-jejunostomy, and pancreato-enterostomy anastomoses would be much more easy with the surgeon's hand inside the abdomen. This Gelport device also allows surgeon to introduce instruments easily and quickly, like gauze or artery forceps, for better control and manipulation. However the main drawback of it is probably the increased risk of needle pick injury. The experience of the well-trained surgeon and the great awareness of the risk would be the only way to minimise it.

Another important concern would be oncological clearance. It is understandable that one may think complex anatomy, together with limited view through the laparoscope may make it difficult to assure the oncological clearance for frank malignancy. However, Ammori, Kimura & Dulucq were able to resect the tumours not just to achieve clear margins but also reasonable harvests of lymph nodes in laparoscopic Whipple. Again all the resection margins were clear of tumour in our series and indeed extensive lymphadenectomy has not been shown to improve patient survival but associated with increased postoperative complications in randomised controlled trial. Of course, the exact survival benefits could not be accurately assessed because of the limited number of cases and experience at the moment.

In the past, we might think that laparoscopic surgery of such magnitude is not worthwhile because the "access trauma" is comparatively less important when compared to the actual tumour ablation. We do agree that the benefit from minimal assess approach would be more pronounced in simpler procedures, such as bypass operations. However, learning from the experience of laparoscopic gastric and colorectal cancer surgery, we know that even for such major resectional procedures, wound-related complication, such as wound infection could be minimised with a smaller wound. This is also true for the pain-related complications, like atelectasis and subsequent chest infection. Postoperative ileus and deep vein thrombosis would also be less common due to earlier mobilisation. We are convinced that all these benefits can also be seen in laparoscopic Whipple once the learning curve is overcome.

Conclusion
Our results not only confirm the feasibility of laparoscopic pancreatectomy, but also demonstrated the promising results of this approach in selected patients. It should be considered as a favourable treatment option for cystic neoplasm located in body and tail of pancreas. The key to success would begin with careful case selection, proper staging of the disease and last but not least availability of expertise.
Table 1. Types of pathology in both laparoscopic distal pancreatectomy and Whipple

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Laparoscopic distal pancreatectomy (n = 11)</th>
<th>Laparoscopic Whipple (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic tumour</td>
<td>5 (1 concomitant splenic artery aneurysm, 1 marsupialization of huge liver cyst &amp; 1 wedge resection of gastric stromal tumour)</td>
<td>0</td>
</tr>
<tr>
<td>Benign neuroendocrine tumour</td>
<td>2 (1 simultaneous adenoma and 1 adenocarcinoma)</td>
<td>0</td>
</tr>
<tr>
<td>Pseudopapillary tumour</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pseudotumour of pancreas</td>
<td>1 (1 closure of perforated gastric ulcer)</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma of Ampulla of Water</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Distal cholangiocarcinoma</td>
<td>0</td>
<td>1 (open conversion)</td>
</tr>
<tr>
<td>Adenocarcinoma at tail of pancreas</td>
<td>1 (open conversion)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Summary of Patient Demographics undergoing laparoscopic pancreatectomy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Laparoscopic distal pancreatectomy (n = 11)</th>
<th>Laparoscopic Whipple (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 (18-79)</td>
<td>71 (51-75)</td>
</tr>
<tr>
<td>Sex</td>
<td>4 M : 7 F</td>
<td>3 M : 3 F</td>
</tr>
<tr>
<td>ASA grading</td>
<td>ASA 1 (n=3)</td>
<td>ASA 1 (n=2)</td>
</tr>
<tr>
<td>Complications</td>
<td>ASA 2 (n=7)</td>
<td>ASA 2 (n=3)</td>
</tr>
<tr>
<td>+ Blood/pancreatic leak</td>
<td>ASA 3 (n=1)</td>
<td>ASA 3 (n=1)</td>
</tr>
<tr>
<td>+ Collection</td>
<td>1 (9.0%)</td>
<td>1 (16.6%)</td>
</tr>
<tr>
<td>+ Bleeding</td>
<td>2 (32.3%)</td>
<td>4 (46.6%)</td>
</tr>
<tr>
<td>+ Gastric outlet obstruction</td>
<td>2 (22.2%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>7 (4-53)</td>
<td>36.5 (8-68)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>37 (7-91)</td>
<td>8 (4-20)</td>
</tr>
</tbody>
</table>

Values are presented as median and range
Some patients had more than 1 complications

References

1. Ishida H
   Peritoneoscopy and pancreas biopsy in the diagnosis of pancreatic disease

2. Cuschieri A
   Laparoscopic surgery of the pancreas

3. Tang CN, Siu WT, Ha JPY, Li MKW
   Endo-laparoscopic approach in the management of obstructive jaundice and malignant gastric outflow obstruction

4. Rhodes M, Nathanson L, Fielding G
   Laparoscopic biliary and gastric bypass: a useful adjunct in the treatment of carcinoma of pancreas

5. Mouiel J, Kothkonda N, White S, Dumas R
   Endo-laparoscopic palliation of pancreatic cancer

6. Gagner M, Pomp A, Herrera MF
   Early experience with laparoscopic resections of islet cell tumours

7. Desler SP, Martin IG, Leinieker L, Fowler R, McMahon MJ
   Laparoscopic enucleation of a solitary pancreatic insulinoma

8. Lo CY, Chan WF, Lo CM, Fan ST, Tam PK, Fan ST
   Surgical treatment of pancreatic insulomas in the era of laparoscopy

9. Cuschieri A, Jakimovics J, van Spreeuwel J
   Laparoscopic distal 70% pancreatectomy and splenectomy for chronic pancreatitis

10. Sussman LA, Christie R, Whittle DE
    Laparoscopic excision of distal pancreatic tumours including insulinoma

    Laparoscopic surgery combined with preservation of the spleen for distal pancreatic tumours

12. Tang CN, Siu WT, Chau CH, Ha JPY, Li MKW
    Laparoscopic pancreatectomy: an initial experience

13. Lo CY, Lo CM, Fan ST
    Role of laparoscopic ultrasonography in intraoperative localization of pancreatic insulinomas

14. Gagner M, Pomp A
    Laparoscopic pylorus-preserving pancreatectoduodenectomy

15. Jossart GH, Gagner M
    Pancreatectoduodenal resection

16. B.I. Aumorini
    Laparoscopic hand assisted pancreatectoduodenectomy, Initial UK experience

17. Yasutoshi Kimura
    Hand-assisted laparoscopic pylorus-preserving pancreatectoduodenectomy for pancreatic head disease.

18. Duhucu J, Wintringer P, Nabajia A
    Laparoscopic pancreatectoduodenectomy for benign and malignant diseases

19. Way LW, Legha P, Morii T
    Laparoscopic pancreatic cystogastrostomy: the first operation in the new field of intraluminal laparoscopic surgery

    Intraluminal stapled laparoscopic cystogastrostomy for the treatment of pancreatic pseudocyst

21. Tang CN, Tsai KK, Ha JPY, Wong DCT & Li MKW
    Laparoscopic distal pancreatectomy: a comparative study

    Pancreatectoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part2: randomized controlled trial evaluating survival, morbidity, and mortality.