

Arterial resection for pancreatic cancer: a modern surgeon should change its behavior according to the new therapeutic options

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Introduction

Pancreatic cancer (PC) is a frequent and lethal disease ranking fourth as a cause of cancer related death in Western country. It is estimated that almost 100.000 patients diagnosed with PC died annually in Europe and United States (1). Almost 80-90% of PC, at diagnosis, are locally advanced tumors or with distant metastases. Oncological surgical excision, whenever possible, remains the best treatment for patients affected by PC, providing a longer survival (2).

Pancreatectomy associated to vascular resection is still under discussion; venous resection demonstrated to be a feasible technique in experienced center, increasing survival. In contrast, arterial resection is still an issue of controversial debate, continuing to be a contraindication for resection in most of the center. However, in the last years, few authors are showing their results with pancreatic surgery associated to arterial resection with acceptable morbidity, mortality and long-term survival rates (3). These outcomes are achieved thanks to better technical procedures, in highly selected patients, in experienced HPB center in light of the last neoadjuvant treatment.

Because of its anatomical location, common hepatic artery (CHA), celiac trunk (CT) and superior mesenteric artery (SMA) are the arterial vessels most frequently involved. Less frequently, mainly because tumor location, right hepatic artery (RHA) might be involved as well (3).

Diagnosis

Preoperative stadition is essential in order to offer the best treatment to patients affected by PC. Its aim is to differentiate border line resectable (BLR) PC, which might be benefitted by neoadjuvant treatment, from the no resectable PC. BLR term has been used to describe a pancreatectomy in the setting of porto-mesenteric venous invasion (4). Posteriorly, various classifications have been used to define resectable PC (5-7); however, in all of them, arterial involvement when present, still define a PC as no resectable.

Currently, CT scan with vascular reconstruction, PET-CT scan, MRI and endoscopic ultrasound with fine-needle aspiration are the gold standard to establish a diagnosis and stadition of PC (7). In the context of arterial involvement, CT scan and endoscopic ultrasound allows define it better, showing the grade of arterial encasement inside the tumor, or its alteration of the vascular wall or its stenosis (7,8). However, these radiological findings are difficult to be detected in most of the time (9).

Studies from Sugiyama (10) suggest that endoscopic ultrasound shows higher sensibility than CT scan detecting arterial involvement. However the real advantages of endoscopic ultrasound over other radiological techniques have still to be rule out. Infact, some authors reports a lower sensibility and specificity of endoscopic ultrasound (50-100%; 58-100%, respectively) (11, 12).

The ability of pancreatic MRI to diagnose vascular involvement is similar to CT scan (13); therefore it is typically performed whenever a CT scan cannot be performed (renal insufficiency, contrast allergy, etc.).

In conclusion, it is necessary to explore the peripancreatic vascular structures in order to better define the type and grade of arterial involvement.

Operative management of tumor arterial involvement

Superior mesenteric artery

This type of vascular involvement is detected mainly during the surgical exploration. It is detected in a standard pancreatectomy along the pancreatic uncinate process and neck dissection. However, in literature, there are reports of “artery first” approaches to pancreateo-duodenectomy, in order to detect earlier the SMA involvement (14). The SMA is exposed at the point where the left renal vein crosses the aorta. The SMA is dissected along the plane of its adventitia to the junction of the third and fourth parts of the duodenum. At this point it is possible identify the tumor involvement of the SMA, before the pancreatic and gastric resection is performed. In literature there are further different technical procedures to dissect the SMA (15-18). If tumor invade the SMA, the surgeon may behave in different ways: the resection is abandoned or it can be carried out leaving part of tumor to do not divided the artery (R2 resection), logically, with poor patient survival (19). On other hands, for those whose the SMA involvement is not a contraindication for pancreatic resection, this step is useful to obtain an earlier vascular control before dissection.

This “artery first” approach is also useful to detect and safeguarded a replaced right hepatic artery, that occur in 9.8%-21% of cases (20). SMA involvement occurs mainly in uncinate process located PCs, especially at its distal part. Instead, proximal SMA involvement occurs most of the time for larger size tumors with concomitant vein involvement.

After the SMA resection, its reconstruction is usually performed with an end-to-end anastomosis (Figure 1). Fine dissection of the artery allows to achieve a tension free anastomosis. Prosthetic grafts are rarely used. In literature there are only few reports concerning SMA resection procedure for PC, performed only in high number pancreatic cancer centers (21-25).

Celiac trunk

Standard oncological procedure for neck and body PCs is the distal pancreatectomy with splenectomy (26). This procedure can be combined with CT resection, radical regional and perivascular lymph no-

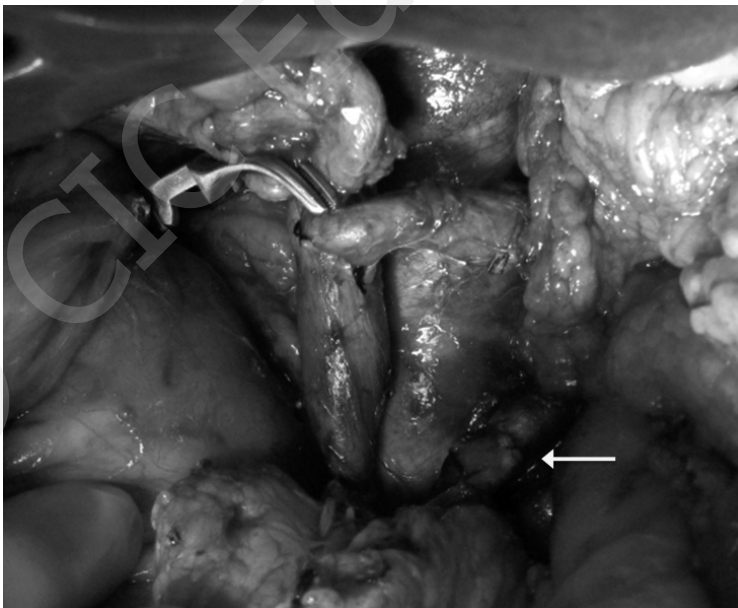


Fig. 1 - Total-pancreato-duodenectomy with Superior Mesenteric Artery resection and reconstruction (arrow).

des clearance and celiac plexus resection. In some cases, the resection is extended also to portal vein, left adrenal gland, middle colic vessels and adjacent organ involved by the PC (Figures 2-4).

Distal pancreatectomy with CT resection has gained an important interest in the last years. This technique was firstly reported by Appleby in 1953 in the setting of advanced gastric tumors to achieve an extended lymph nodes clearance along the celiac vessels (27). This procedure was modified later by Nimura for locally advanced pancreatic body tumors (28). Hishinuma (29) reported in 1991 a further modification of the Appleby procedure in order to safeguard the stomach in absence of tumor involvement. Up to 2003, less than 25 cases have been reported in the medical literature (28-34). Since then, a slightly increased number of cases are being described by a few groups of authors (35-41).

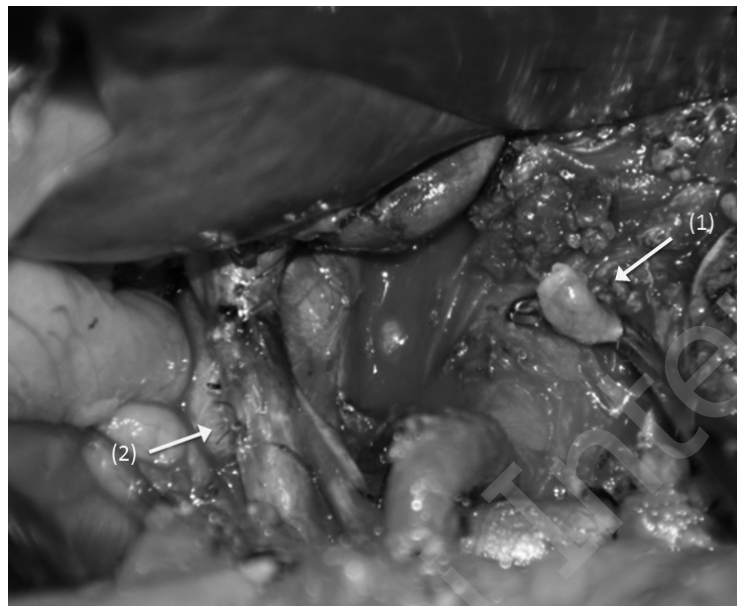


Fig. 2 - Pancreato-duodenectomy with celiac trunk (1) and superior mesenteric vein (2) resection.

The important technical issue of the Appleby procedure is to preserve the blood flow from the SMA via the pancreaticoduodenal arcades to the gastroduodenal artery (32,33). An adequate blood flow to the liver has to be well evaluated during the operation, clamping the CT and detect changes in color of

the liver and detect the pulsatile hepatic artery blood with the fingers or with a Doppler ultrasound ($<22\text{cm/sec}$ is related to liver ischaemia and failure) (42). Similarly, the right gastric artery as well as the gastroepiploic vessels has to be preserved in order to prevent a gastric ischaemia. If these previous signs are absent, as well as a total pancreatectomy is performed, an arterial vascular reconstruction must be performed between CT and CHA (43, 44). Most of the time, after an arterial dissection, it is possible perform an end-to-end anastomosis. If it is not possible, an arterial (middle colic artery-gastroepiplic artery bypass), vein (inferior mesenteric vein or saphenous vein) or prosthetic graft (45) may be used.

Main advantages after the Appleby procedure are: 1 an increased oncological resectability rates; 2 an increased quality of life thanks to a better pain control after the plexus resection; 3 a potentially increased survival.

Right hepatic artery

The replaced or accessory RHA is behind the head of the pancreas, along the right lateral cor-



Fig. 3 - Total-pancreato-duodenectomy with common hepatic artery resection and reconstruction (arrow).

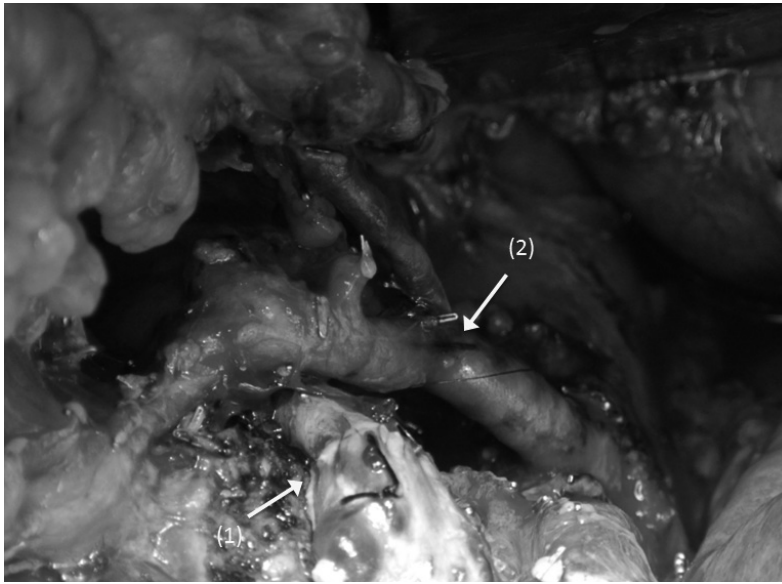


Fig. 4 - Total-pancreato-duodenectomy with celiac trunk resection. Superior mesenteric vein resection and reconstruction (1). Anastomosis between remaining celiac trunk and common hepatic artery (2).

ner of the portal vein (46). It is important recognize this variant preoperatively (47) as its integrity is of paramount importance to ensure a safe bilio-enteric-anastomosis in the immediate (biliary leakage) and late (biliary stenosis) post-operative course (48). This vascular anomaly may be a real challenge for surgeon performing pancreatectomy for PC. Because of its location, its preservation could be difficult as invasion by tumor is not infrequent. It can be ligated or resected only in type 6 (Michel classification)

(46, 49); otherwise, its injury may be associated to an important morbidity.

Various publications reports about the feasibility of replaced RHA resection and reconstruction (50). However, if there is a distal ligation of this artery, because of the small diameter, its reconstruction may be very difficult, and it should be performed with a microsurgery technique. For this reason, it is important that a surgeon who performs HPB surgery should also have training in microsurgery techniques (51, 52).

Preoperative vascular embolization

Preoperative coil embolization of the common hepatic artery is a technique used to stimulate the development of collateral pathway from the pancreaticoduodenal arcades when a potentially resection of CT is planned (53). It can be performed when there is a replaced RHA from SMA to stimulate the liver blood flow through the left hepatic artery. Ten days after this procedure the collateral pathway is completely developed.

In our opinion, this procedure should be used only when the planned vascular reconstruction may be difficult. On other hand, preoperative embolization for PC with CT involvement may be useful, avoiding the vascular reconstruction in difficult cases (54).

Minimally invasive surgery

Pancreatectomy with vascular resection for PC performed with minimally invasive surgery can be a real challenge for surgeons. The minimum experiences concerning venous resection by a laparoscopic approach suggest that it can be feasible (55). Arterial resection with this technique was reported only by Raut, performing a laparoscopic common hepatic artery ligation and staging followed by distal pancreatectomy with en bloc resection of celiac artery (56).

Robotic surgery represents a valid alternative to laparoscopy. Since its beginning in 1997 (57) its development has been constant and progressive, aimed to overcome some of the limitation of the laparoscopic approach. One of the surgical area where the robotic system raised a great interest in the last years is the HPB field (58,59). Major pancreatectomy has been possible by this approach with similar results of the conventional open technique (58,59). Successfully porto-mesenteric venous resections have been described with a robotic approach (59,60). A successfully Appleby procedure was also reported by Giulianotti in a similar matter of open surgery technique (60).

It is justified perform an arterial resection in patients affected by PC?

Technical justification

A ruptured pseudoaneurysm is the most serious and life-threatening cause after pancreatectomy, presenting with intraperitoneal or gastrointestinal massive hemorrhages (61-64). It is thought that in absence of postoperative arterial anastomosis it can be related to a disruption of the wall secondary to its surgical dissection. Another cause may be a local infection close to arterial wall.

Most of the time it is not easy recognize a vessel wall injury during surgery, if it is detected, a vascular resection should be always performed. However, a delayed pseudoaneurysm can develop even after an apparent not injured artery. The good prognosis of patients with arterial pseudoaneurysm depends on: delayed onset time, early diagnosis and fast interventionist radiological treatment (embolization) (64-66).

Oncological justification

A few of these are discussed below.

A. Significance of arterial infiltration

Currently, there are two different type of hypothesis:

1. arterial tumoral involvement is associated to a more aggressive tumor behavior. Micrometastatic spread is thought to limits the oncological benefit of a surgical excision (67, 68).
2. arterial tumoral involvement is not associated to a more aggressive tumor behavior. This hypothesis justifies, logically, pancreatectomy with arterial resection (69, 70).

Actually, with the exception of large tumors, it seems that arterial involvement does not represent a real poor prognostic factor, like lymph nodes metastases, perineural infiltration, tumor differentiation or R1 resection. Rehders (71) confirmed this hypothesis, thus arterial involvement should be considered as an "unfavorable topographic location" instead of a poor prognostic factor.

B. The importance of free tumor margins

The exact definition of specimen free margins after pancreatectomy for PC is not yet well established. According to the NCCN (7) the margins to be studied in pancreatoduodenectomy are: retroperitoneal tissue, pancreatic posterior tissue, peri-portal vein pancreatic tissue, neck pancreatic section tissue and biliary section tissue. Regardless the importance of these margins infiltration, the main objective of the surgery is achieve an R0 resection, even if some long-term survival have been described for R1 resections (72, 73). Anyway, R1 and R2 resection must be considered as palliative (74) and it should be avoided with a proper preoperative study and surgical technique.

Arterial resection seems to be justified in high selected patients in order to achieve an R0 resection.

C. Unknown future tumoral progression

Mean survival after pancreatectomy for PC increased slightly in the last years. Currently, mean survival at 5 and 10 years after surgery is 19% and 10%, respectively (75). Five years survival increased in 2% compared with that of 21 years ago (76, 77). There are also reported longer mean survivals in patients treated in multidisciplinary groups (78, 79). Patients with such longer survival are generally patients with small tumors, with no positive lymph nodes and free specimen margins. However, there are similar reports also with locally advanced tumors and with distant metastases (78). These reports show the heterogeneity of the biological tumoral behavior of PC that may be even more important than classical well known prognostic factors.

However, a longer survival is always related to free margins.

D. Neoadjuvant and adjuvant treatment for resectable pancreatic cancer

Multiagent chemotherapy maximizes survival duration and represents an important tool to achieve a potentially R0 resection for locally advanced pancreatic cancer. The basics of this treatment arise from:

1. PC seems to results from a cumulative succession of genetic mutations (80). Most of these patients carry out more genetical mutations (81).
2. PC presents a hard stromal matrix and cancer-associated fibroblasts play an important rule on

it (82). There is an emerging consensus that poor intratumoral drug levels may be related to this high stromal density within the tumor. This tissue is not only a barrier for chemotherapy, but it plays a role increasing tumoral progression and metastases (82). This stromal matrix shows a variety of proteins receptors, directly related to chemotherapy resistance. These protein receptors are the main target of new chemotherapies (83).

3. A target therapy aimed to disrupt this tumoral stromal tissue increase the drugs diffusion inside the tumor and so its effect (84).
4. It has been detected some multi-resistance drugs cells inside the tumor of PC that can represent up to 1-5% of all tumoral tissue (85). This may explain the inefficacy to a broad range of therapies and the need to disrupt these cells (85, 86).

In the last years, gemcitabine represents the standard first-line therapy for advanced PC (87). Concomitant therapies have been used but without important increase in survival (88), except for Erlotinib, a molecular inhibitor of the epidermal growing factor receptor (EGFR) (89).

More recently, gemcitabine plus nab-paclitaxel seems to produce a significant decrement in tumor stiffness, allowing increased drug diffusion inside the tumor (90).

New concepts that arise from studies of the tumoral micro-environment of PC allow use new prospective therapies (91, 92). One of these new concepts is the "hedgehog", a conserved developmental pathway, widely implicated in controlling various cellular responses such as cellular proliferation through external stimuli (84-86). Aberrant activation of this pathway may cause different types of cancers, as the PC. Therefore, targeting this pathway in cancer therapy in preclinical model has become indispensable in order to treat tumor progression (93). The genomic complexity of the PC explains the need for more individualized therapies in the future (94).

In the current practice, neoadjuvancy allows also to select those patients which are potentially going to benefit from surgical resection. Patients with PC and suspicious arterial involvement with a good response to neoadjuvancy should undergo surgery.

Conclusions

During a long period of time, most of the surgeon maintained a conservative attitude about extended pancreatectomy for PC. This attitude was justified for the limited therapeutic option available at that time. This approach should change in light of the therapeutic improvements that are taking place in the last decade. The current outcome concerning pancreatectomy with concomitant arterial resection is not brilliant; however, there is a new therapeutic effort focused on the better understanding of the biological behavior of the cancer that may keep on improving this outcome.

The surgeon involved in this process should not be taken apart from this new research.

Main objective of the surgery must be achieving an oncological resection with free margins (R0), fundamental condition with which future therapeutic options may improve survival. In high selected patients, as stated before, arterial involvement should not be considered as contraindication for surgery. An adequate knowledge of the exact tumor location and an high experience with vascular and digestive surgery are fundamental to achieve good results.

Nevertheless, arterial resection for patients affected by PC should be performed only in well-established pancreatic oncological centers, with a multidisciplinary team. On the contrary, this aggressive approach is arguable.

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