Review article

Is Arterial Infiltration Still a Criterion for Unresectability in Pancreatic Adenocarcinoma?☆

Emilio Vicente,* Yolanda Quijano, Benedetto Ielpo, Hipolito Duran, Eduardo Diaz, Isabel Fabra, Catalina Oliva, Sergio Olivares, Riccardo Caruso, Valentina Ferri, Ricardo Ceron, Almudena Moreno

Hospital Universitario Madrid Sanchinarro, Centro Integral Oncológico Clara Campal, Facultad de Medicina, Universidad CEU San Pablo, Madrid, Spain

ARTICLE INFO

Article history:
Received 30 October 2013
Accepted 4 November 2013
Available online 19 May 2014

Keywords:
Pancreatic cancer
Vascular invasion
Major pancreatic resection

ABSTRACT

As surgical resection remains the only hope for cure in pancreatic cancer (PC), more aggressive surgical approaches have been advocated to increase resection rates. Venous resection demonstrated to be a feasible technique in experienced centres, increasing survival. In contrast, arterial resection is still an issue of debate, continuing to be considered a general contraindication to resection. In the past few years there have been significant advances in surgical techniques and postoperative management which have dramatically reduced mortality and morbidity of major pancreatic resections. Furthermore, advances in multimodal neo-adjuvant and adjuvant treatments, as well as the better understanding of tumour biology and new diagnostic options have increased overall survival.

In this article we highlight some of the important points that a modern pancreatic surgeon should take into account in the management of PC with arterial involvement in light of the recent advances.

© 2013 AEC. Published by Elsevier España, S.L. All rights reserved.

¿Sigue representando la infiltración arterial un criterio de irresecabilidad en el carcinoma de páncreas?

RESUMEN

La resección quirúrgica representa en la actualidad la única posibilidad terapéutica para pacientes afectos de carcinoma de páncreas (CP). Procedimientos quirúrgicos agresivos han sido descritos en un intento de incrementar la resecabilidad. La resección venosa representa en la actualidad una técnica quirúrgica aceptada en centros con importante experiencia en cirugía pancreática. Por el contrario, la resección arterial en enfermos afectos de CP sigue siendo una técnica muy controvertida. La infiltración arterial en estos pacientes suele ser considerada un criterio de irresecabilidad. En los últimos años, importantes avances en la

☆ Please cite this article as: Vicente E, Quijano Y, Ielpo B, Duran H, Diaz E, Fabra I, et al. ¿Sigue representando la infiltración arterial un criterio de irresecabilidad en el carcinoma de páncreas? Cir Esp. 2014;92:305–315.

* Corresponding author.
E-mail address: emilvic@bitmailer.net (E. Vicente).

2173-5077/$ – see front matter © 2013 AEC. Published by Elsevier España, S.L. All rights reserved.
Introducción

En los países occidentales, el cáncer de páncreas (PC) es el cuarto y quinto cáncer que ocasiona la muerte en hombres y mujeres, respectivamente, con más de 100.000 muertes al año en Europa y Estados Unidos.1,2 Aproximadamente del 80–90% de los PC se clasifican como avanzados.3,4 Hasta ahora, es muy difícil establecer el grado de invasión de las arterias primeras en el páncreas. Sin embargo, la extensión de la enfermedad puede ser objetivada mediante técnicas diagnósticas como la tomografía computarizada (TC).5,6 El análisis del tumor y la arteria principal (first arterial) puede permitir la toma de decisiones terapéuticas.7,8

Diagnóstico

La estadificación preoperatoria es especialmente importante en los pacientes con PC. Su objetivo es establecer lesiones que requieren tratamiento neoadyuvante y que los tratamientos en tumores inoperables o incurables es de gran importancia.9,10 Para evaluar la inoperabilidad, se han propuesto diferentes criterios, como la TC y la ecografía a color con guía endoscópica (EU).11,12 Sin embargo, no existen criterios establecidos que permitan establecer el grado de invasión vascular.

Surgical Management of Vascular Involvement

Arterial Disease

La anastomosis de la arteria primera (A1) en el cuello del páncreas es una técnica quirúrgica que ha permitido reducir la morbilidad de las resecciones pancreáticas. Por otra parte, se han logrado importantes mejoras en el tratamiento neoadyuvante y adyuvante para mejorar la supervivencia de los pacientes.

En el presente artículo, se describen los siguientes aspectos importantes: el escenario clínico del tratamiento, el concepto de la resección quirúrgica, el diagnóstico de la enfermedad y, por último, las técnicas quirúrgicas que permiten tratar a los pacientes con PC. Se detallan los criterios diagnósticos que ayudan a determinar el grado de invasión de las arterias.

Superior Mesenteric Artery

La confirmación final de la infiltración vascular se realiza mediante la exploración quirúrgica. En el caso de la pancreatocitología, la arteria superior mesenterica (SMA) es normalmente la arteria que afecta el páncreas. Cuando esto ocurre, la arteria se diseca primero. La arteria se divide en el extremo posterior de la disección. Luego de la disección, la arteria se divide en el extremo final de la resección. En pacientes con PC, la resección de la arteria puede ser necesaria para tratar a los pacientes con PC.11 CT y EU son pruebas diagnósticas de la arteria.

The inclusion of arteries in the tumour mass or the combination of a greater than 50% involvement of the arterial circumference with irregularity or stenos of the blood vessel wall is radiological criteria for arterial involvement. However, tomography assessment of the condition of the arteries in some PC patients is difficult.12 Very often CT does not manage to identify arterial or venous involvement13 which is in fact relatively frequent (21–64%).13,14

Sugiyama et al. have reported that EU is more precise in identifying portal vascular involvement than CT, ultrasound and angiography.15 Other groups have reported similar conclusions.16,17 However there is no unanimity on this criterion. Vascular involvement is far more difficult to assess using EU,18,19 which has a reported sensitivity of 50%–100%20–22 and a specificity of 58%–100%.20,23

The diagnostic precision of magnetic resonance for vascular involvement is very similar to that of CT.24,25 Therefore this diagnostic technique is reserved for patients where CT is contraindicated; cocaine abuse, renal failure or pregnancy.
is always achieved from the start of surgery; this is advisable in patients with locally advanced tumours.

The most frequent anatomical anomaly of the hepatic artery is a replaced right branch arising from the SMA, which occurs in 9.8%–21% of the normal population. The artery-first approach also enables the early identification and preservation of this anomaly.

In PC, involvement of the SMA appears in localised lesions, principally in the uncinate process. This involvement is generally limited to the most distal part of the artery. Involvement of the proximal part of the SMA near where it stems from the aorta generally occurs in large lesions where the SMV has also usually been infiltrated.

When there is spread to the SMA, reconstruction is performed by end-to-end anastomosis (Fig. 1). Mobilising both ends enables tension-free arterial reconstruction. Vascular grafts are seldom used in these types of tumours.

There is little world experience with this situation and it is reduced to groups with a high volume of pancreatic surgery.43–44

Coeliac Trunk

Distal pancreatectomy associated with splenectomy is the standard oncological resection for tumours of the body and tail of the pancreas. Resection is combined with excision of the coeliac plexus, the lymph-nerve plexus which surrounds the superior mesenteric vessels and the regional lymph nodes around the pancreas. Occasionally vascular resection has to extend to a section of the portal vein, the left adrenal gland, the middle colic vessels and the infiltrated part of the adjacent organs.

Distal pancreatectomy with en bloc resection of the CT has been widely adopted in pancreatic surgery in recent years (Fig. 2). Reported for the first time by Appleby in 1953 to achieve a radical lymphadenectomy around the coeliac axis in advanced gastric tumours, it was adopted by Nimura for the treatment of pancreatic tumours of the pancreatic body. In 1991, Nagino et al. and Hishinuma et al. described modifications to the technique in order to preserve the stomach if it had not been invaded by the PC. Until 2003, fewer than 25 cases had been described in the medical literature.47–50,53,56,58–60 Since then, the number of patients has slightly increased, although experience is limited to a small number of groups.51,52,54,55,57,61,62

The challenge of the procedure lies in performing the resection of the coeliac trunk with its 3 visceral branches, preserving adequate arterial flow to the liver.56,63,64 In Appleby’s operation, hepatic vascularisation should be assessed and preserved during surgery (collateral blood supply from the SMA through the pancreaticoduodenal arteries and the gastroduodenal artery). If it is not possible to preserve vascularisation, the liver should be rearterialised in order to prevent ischaemic consequences in the liver.53,63,64 (Fig. 3).
Similarly, the right gastric and gastroepiploic arteries should be preserved to ensure blood supply to the stomach.

After clamping the CHA an arterial pulse should be detected in the hepatoduodenal ligament. After that it can be resected, and the gastroduodenal artery is always preserved to ensure adequate blood supply to the liver. The presence of an arterial pulse in the hepatic hilium is usually associated with the confirmation by intraoperative Doppler ultrasound of intrahepatic arterial flow. It is considered that there should be an arterial flow greater than 22 cm/s in order to prevent hepatic ischaemia and postoperative liver failure.

In certain cases where after clamping it is observed that there is: (1) no arterial flow at the hepatic hilium level, (2) a change of liver colour and consistency (3) no intrahepatic arterial flow (intraoperative Doppler ultrasound), it is recommended that the CHA should be reconstructed. Obviously the other reason for rearterialisation of the liver is when a total duodenopancreatectomy is performed due to technical or oncological circumstances.

After dividing the CT and the CHA, and after extensive mobilisation of the proximal and distal artery ends, a tension-free, end-to-end anastomosis is performed (Fig. 4). If this is not possible, an autogenous (splenic, middle colic or gastroepiploic artery) or synthetic vascular graft imposition can be performed.

The advantages of performing the Appleby procedure are: (1) resectability is increased, achieving a number of radical R0 resections which would not be possible without this procedure; (2) the patient’s quality of life is improved through suitable control of the disabling pain which is characteristic of the presence of cancer of the pancreatic body and (3) there is the possibility of prolonged survival.

**Right Hepatic Artery**

An RHA arising from the SMA is located in the area behind the pancreatic head, and runs through the right lateral area of the portal vein. Inadvertently injuring an anomalous RHA can cause major complications in the early postoperative period (biliary fistula, ischaemia or the formation of liver abscesses) or later (stenosis of the bilioenteric anastomosis).

This anatomical anomaly poses a surgical challenge for PC patients. Not resecting a replaced or accessory RHA during a duodenopancreatectomy can occasionally result in an incomplete resection. Furthermore, single arterial ligation might be associated with significant morbidity. It can only be performed on patients who have a type-six arterial anomaly according to Michel’s classification.

Several publications have reported that the resection and reconstruction of the RHA is possible and safe. If the section or lesion is in its most distal part, the diameter and characteristics of the artery make it difficult to perform vascular reconstruction. In this situation it is advisable to perform this using a microsurgical technique. In the area of digestive surgery, especially gastrointestinal and hepatobiliary pancreatic surgery, surgeons are occasionally faced with the need to reconstruct blood vessels of very small diameters; they very often require the help of plastic surgeons in order to do so. Therefore, it is a valuable asset for any surgical department if general surgeons have acquired experience in microsurgery techniques and this offers a solution to major vascular problems.

**Preoperative Vascular Embolisation**

Preoperative embolisation has been performed on patients with an RHA arising from the SMA, with the intention of increasing hepatic blood flow through the left hepatic artery. Collateral circulation develops ten days after embolisation. If possible, surgery should be postponed until this collaterality is sufficient to prevent liver complications secondary to ischaemia. In our opinion and that of other groups, this technique should be selectively indicated for patients for whom it is suspected, due to technical circumstances, that safe arterial reconstruction is not possible.

Another different aspect is preoperative embolisation in patients with PC which involves the coeliac trunk. With the intention of avoiding arterial reconstruction after radical resection, embolisation of the CHA can be performed preoperatively aimed at developing collaterality originating from the SMA. This is an excellent alternative for patients for whom, due to anatomical or technical circumstances, surgical reconstruction cannot provide adequate arterial flow to the liver. Without reconstruction, “natural hepatic arterialisation” after pancreatectomy with resection of the CT develops in very few days (Fig. 5).

**Minimally Invasive Surgery**

Vascular resection in patients with PC using minimally invasive surgical techniques poses a real surgical challenge.
Despite the little experience in this field with laparoscopic surgery, the results obtained with venous resections offer hope for the future. The only reference on arterial resection using this approach was performed in two stages.

Robotic-assisted surgery (RS) is an excellent alternative within minimally invasive surgery. Since it started in 1997, it has progressed constantly and progressively and has revolutionised the concept of modern surgery. RS offers a solution to many of the shortcomings of laparoscopic surgery.

Many of the greatest advances in RS have taken place in the area of pancreatic surgery. Using this innovative robotic system, it has been possible to undertake highly complex procedures with similar results to those obtained with open surgery.

It has been possible to undertake resection of the mesenteric-portal axis using the robotic-assisted system with satisfactory results. For Appleby’s operation using robotic assistance, Guillonetti performed a posterior approach towards the coeliac trunk described in open surgery. Although the 2 surgical procedures performed were undertaken for locally advanced tumours, the surgical time and intraoperative blood loss were appropriate to the characteristics of this complex surgical procedure.

### Oncological Justification

**Significance of Arterial Involvement**

There are two different theories which define the meaning of vascular involvement and justify which therapeutic approach to use:

1. Arterial involvement defines a more aggressive tumour. Micrometastatic spread not noticed at the time of presentation limits the oncological benefit of radical surgery, even when the resection was R0.

2. Vascular spread does not predict a more aggressive tumour, but reflects the location of the lesion. This theory would enable radical resection to be justified including the arterial axis.

With the exception of large tumours, it appears that the presence of arterial involvement is not connected with risk factors and traditional prognoses, such as metastatic lymph spread, perineural infiltration, tumour differentiation and the high rate of resections with positive margins. Rehders et al. have also confirmed that there is no correlation between vascular spread and the incidence of spread of tumour cells. These findings are consistent with the hypothesis that the presence of arterial involvement is an indicator of unfavourable tumour topography rather than an indicator of adverse tumour biology.

### Importance of Free Margins

The surgical margins of PC patients are not well defined. According to the NCCN clinical guidelines, the margins in pancreaticoduodenectomy are: SMA margin (retroperitoneal/uncinate), posterior margin, margin of the portal vein groove, the portal vein itself, margin of pancreatic neck transection and the margin of the bile duct.

Although there is some debate as to the significance of the involvement of the margins in terms of the patient’s prognosis, the objective of surgical treatment of PC must always be to achieve an R0 tumour resection. Although long-term survival after R1 resections has been described, any
incomplete resection (R1 or R2) should be considered palliative. \(^{124,125}\) R1 or R2 resection should be avoided by undertaking a suitable preoperative study and appropriate surgical technique.\(^{119,120}\)

Arterial resection appears to be justified in a select number of patients in whom otherwise it would not be possible to achieve an R0 resection.

**Lack of Knowledge of the Evolution of the Tumour**

The mean survival achieved for PC patients after radical surgical resection has slightly improved. Current total survival at 5 and 10 years is 19% and 10% respectively.\(^{126}\) The former is 2% greater than that described by the same group 21 years earlier.\(^{127}\) Other groups have achieved similar outcomes.\(^{128,129}\)

Prolonged survival has been described recently for PC patients after multidisciplinary treatments.\(^{128,130,131}\) In general these patients have small tumours which are well differentiated, with no lymph node involvement and with no involvement of the resection margins. But this is not always the case. Prolonged survival has been observed in patients with locally advanced and even metastatic tumours.\(^{130}\) These results demonstrate the heterogeneity of the biological behaviour of PC. In certain cases, it is the biology of the cancer rather than the traditional factors that determines the patients’ prognosis.

Performing radical surgery with free margins is an essential requirement in order to achieve prolonged survival.

**Current Status of Neoadjuvant and Adjuvant Treatments**

New and interesting concepts which have arisen in recent years have produced changes in the therapeutic strategy of patients with PC:

PC is the result of successive accumulation of genetic mutations.\(^{132}\) The majority of patients carry one or more genetic defects.\(^{133,134}\)

PC has a dense stroma.\(^{135,136}\) Pancreatic stellate cells (or myofibroblasts) play a major role in the formation and renewal of the stroma.\(^{135-138}\) Not simply a mechanical barrier, the stroma participates in the formation, progression and production of metastasis.\(^{135,136}\) Stroma cells express a variety of proteins which have been associated with resistance to treatment and as a consequence poor prognosis. These proteins constitute new therapeutic targets.\(^{139,140}\)

Therapy directed at modifying the stroma facilitates an increase in tumour vascularisation with the consequent increase in the diffusion of drugs into pancreatic tumours. This aspect improves the efficacy of these drugs.\(^{141}\)

Within the tumours, a subset of neoplastic cells has been identified with pluripotential properties.\(^{142,143}\) In PC these stem cells (1%–5% of the tumour population) are resistant to radiation and chemotherapy, which could explain the lack of efficacy of these treatments and the recent interest in directing treatment at these specific cells.\(^{143,144}\)

Gemcitabine has been the treatment of choice for PC\(^{145}\) in recent years. Several agents with mechanisms of action different from gemcitabine have been combined in a variety of clinical studies without improved results.\(^{146,147}\) The only agent which in combination with gemcitabine has demonstrated a slight improvement in the survival of PC patients is erlotinib (molecular epidermal growth factor inhibitor).\(^{148}\)

New concepts with regard to the characteristics of CP are opening up new and promising therapeutic perspectives. The new drugs include small signalling pathway inhibitor molecules and oncopgenes.\(^{149-156}\) The recognition of the fact that both the tumour microenvironment and the neoplastic stem cells are critical elements of PC has resulted in the development of agents such as hedgehog signalling pathway inhibitors which block these components.\(^{156,141,143,144}\) The possibility of there being preclinical models available to review the complexity of this disease helps to establish strategies and priorities for the development of new drugs and innovative therapies.\(^{157}\) The genomic complexity of PC demonstrates the heterogeneity of this type of cancer and makes it advisable to use individualised treatment methods.\(^{158}\)

**Conclusions**

A great many medical experts have long remained sceptical and non-discriminatory with regard to PC, especially in terms of the role played by radical surgery. This attitude was justified by the limited available therapies. It is clear that the situation has changed as a consequence of the advances achieved in the last 10 years. These advances which have repercussions on the medical and surgical specialities involved in the diagnosis and treatment of the tumour process enable the problem to be viewed differently.

Current results cannot be considered exceptional as yet. However, it is undeniable that a novel and promising therapeutic pathway has been established based on biological knowledge of the tumour process.

Surgeons involved in these morbid processes cannot remain on the sidelines of this new situation. The principal objective of the surgical treatment they provide should be to achieve resections with free margins. This can completely change the patients’ expectations. The vascular structures affected by the tumour should not be an impediment to undertaking radical treatment in a very select group of patients. Precise knowledge of the site of the tumour and suitable experience in digestive tract and vascular surgery will be decisive factors in achieving good outcomes from surgical treatment.

For selected patients with PC, arterial resection should be considered as a technical option in the current surgical arsenal. This technical possibility should be incorporated into modern multidisciplinary treatment. Its use outside this context is questionable.

**Conflict of Interests**

The authors have no conflict of interest to declare and have received no funding.

**Acknowledgements**

The authors would like to thank Isabel de Salas and Pablo Ruiz for their collaboration in this article.
REFERENCES

70. Vicente E, Quijano Y, Durán H, Esteban E, Marcello M, Conradi R, et al. Locally advanced malignancies of the
pancreatic body: celiac axis resection and subsequent liver rearterialization techniques. HPB. 2010;12 Suppl. 1:97.


