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Review Article

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Pancreatic ductal adenocarcinoma from a surgical perspective

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancers. Whilst most patients present with locally advanced or metastatic disease, a minority are candidates for curative-intent resection. This review covers the aspects of PDAC which are relevant to the surgeon. Firstly, an up-to-date overview of epidemiology, risk factors and pathogenesis are provided. Secondly, presentation, diagnosis and staging are covered, including a summary of the most recent staging guidelines. The review will then focus on the historical background of the pancreatico-duodenectomy (PD), the modern procedure and post-operative care. Finally, short sections provide the reader with an update on histological staging and adjuvant treatment.

Keywords: Pancreatic ductal adenocarcinoma, pancreatic cancer, pancreatico-duodenectomy, Whipple, resection

Introduction

Most cases of pancreatic ductal adenocarcinoma (PDAC) affect the head of the pancreas. Around 80% of patients present with locally advanced or metastatic disease. Unfortunately, there are no surgical treatment options available to this group of patients. About 20% present with resectable disease. In these patients, curative-intent surgical resection in the form of pancreatico-duodenectomy (PD) may be an option. This operation is high-risk and is associated with considerable morbidity. However, it remains the only treatment option which provides the possibility of long-term survival. This review covers the aspects of PDAC which are relevant to the surgeon.

Epidemiology

PDAC is the 11th most common cancer worldwide. The total number of cases is increasing [1]. Globally, 338,000 cases were diagnosed in 2012 and 458,000 cases were diagnosed in 2018 (an increase of 35.8%) [2,3]. During this time, the global population increased from 7.1 to 7.6 billion (an increase of 7.0%). Much of this rise is due to population aging which is set to continue [4]. Other contributory factors include increasing rates of type II diabetes mellitus and obesity [1]. Incidence rates are higher in the Western world (Figure 1) and are roughly equal between the sexes [2]. PDAC is very rare in those under fifty-five years and incidence is highest in those over seventy years [1].

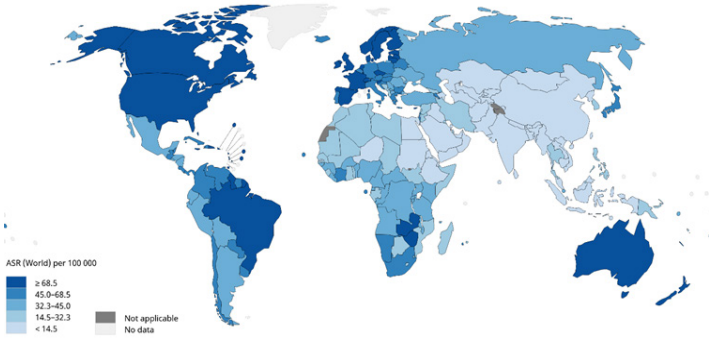

Figure 1: Estimated age-standardised incidence rates (ASR) for pancreatic cancer worldwide in 2018 (both sexes and all ages) (reproduced from: gco.iarc.fr [5]).

Since prognosis is so poor, mortality rates for PDAC are similar to incidence rates; PDAC has the lowest survival of all common cancers [2]. The main factor which influences outcome is tumour stage at time of diagnosis [6]. One-year survival has improved in recent decades, in the UK this has increased from 10% to 22% between 1971 and 2011. However, over the same time span, five- and ten-year survival rates remain relatively unchanged.

Risk factors

Non-modifiable risk factors include increasing age, male sex, black ethnicity, non-O blood group, family history, and type one diabetes mellitus [7]. The presence of allergies is protective [2]. Modifiable risk factors include smoking, high alcohol consumption, chronic pancreatitis, and obesity [7]. The International Agency for Research on Cancer has concluded that smoking is causally associated with PDAC [8]. Indeed, lifetime risk is nearly twice as high in smokers. Risk increases with number of cigarettes smoked per day and duration of smoking [9]. There is limited evidence to suggest that a diet high in red or processed meat may be associated with PDAC(10). Studies have also suggested an association with Helicobacter pylori and hepatitis C infection [11,12].

Pathogenesis

Most patients develop PDAC sporadically and are not known to have a genetic predisposition [13]. It is generally accepted that PDAC develops following a series of stepwise mutations; three precursor lesions have been identified [7]. Acinar-to-ductal metaplasia (ADM) is the process whereby acinar cells transition to epithelial cells when exposed to certain stimuli, such as cellular injury or chronic inflammation [14]. ADM results in acinar cells acquiring characteristics more typically associated with progenitor cells. As such, they are more prone to pro-oncogenic "hits" (the process whereby mutations in proto-oncogenes are activated) which results in the development of PDAC precursor tumours. The most common PDAC precursor tumours are pancreatic intra-epithelial neoplasms (PanINs) [15]. Other described malignant precursors include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). It is widely accepted that this is the initial phase of PDAC development. The lifetime risk of a single PanIN developing into a detectable PDAC is 1.3-1.5% [16].

Following the initial hit, further hits to tumour suppressor genes (TSGs) ultimately result in the development of malignancy [17]. Several genes have been identified which exhibit the most frequent alterations/mutations in PDAC. These include the proto-oncogene KRAS, as well as the TSGs TP53, CDKN2A, and SMAD4 [18]. Whilst KRAS has been found to exhibit a mutation in over 90% of PDAC tumours, mutations in numerous other genes have been identified in certain subsets of PDAC tumour [19]. The extensive heterogeneity of PDAC is one of the reasons traditional cancer therapies have such limited efficacy [20]. A key feature of PDAC is its early progression to metastatic disease [21]. The proponents of this behaviour are not well understood since the genetic composition of most metastases is comparable to that of the primary tumour [22].

Presentation

The signs and symptoms typically associated with PDAC are not clinically apparent in the early stages of disease so diagnosis is challenging. Jaundice and weight loss are the most common presenting complaints. Jaundice is more common with right sided lesions since they are more likely to cause biliary obstruction. In reality, despite what is taught in medical schools, less than 25% of patients present with Courvoisier's sign (a palpable gallbladder in the presence of painless jaundice) [23]. Unexplained weight loss can be the result of anorexia or malabsorption due to pancreatic exocrine insufficiency (PEI), or a combination of the two [23]. PEI can also result in steatorrhea [23].

Whilst not typically a symptom associated with PDAC, around two thirds of patients experience abdominal pain [23, 24]. This is often in the epigastrium and it is not uncommon for pain to radiate through to the back, as is typical with pancreatitis. This may indicate that disease has involved the coeliac plexus. Some patients will present with back pain alone [23]. Less common forms of presentation include new diabetes mellitus and venous thromboembolism [25]. Occasionally, peripancreatic oedema or a large tumour can result in gastric outlet obstruction [23].

Diagnosis

Almost half of PDAC patients present acutely and just 13% are diagnosed via the two-week wait (2WW) pathway. Most patients who present acutely will undergo routine blood tests (full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs), C-reactive protein (CRP), clotting screen, and serum amylase/lipase). If there is bile duct obstruction, the LFTs will reflect this. Otherwise, blood tests are likely to be largely normal unless disease is advanced. Transabdominal ultrasound scan (USS) may be requested at this point. This modality is readily available, inexpensive, non-invasive, and does not use ionizing radiation. However, it is operator-dependent and reliability may be reduced by over-lying bowel gas, or if the patient is overweight [26]. Whilst ultra-sound is useful for quickly identifying biliary obstruction, the retroperitoneal position of the pancreas means it is difficult to visualise with any level of detail. If PDAC is suspected, USS does not allow for accurate staging.

If PDAC is suspected, urgent pancreatic protocol computed tomography (CT) should be requested [27]. This includes arterial, late arterial, and venous phases [28]. Triphasic CT is advised as the difference in contrast enhancement between tumour and parenchyma is highest during the late arterial phase [28]. In addition to its diagnostic benefits, CT is the preferred modality for staging [28]. Future software developments may allow for the three-dimensional reconstruction of CT data so that even greater detail is provided on the anatomical relationship between the tumour and adjacent structures [29].

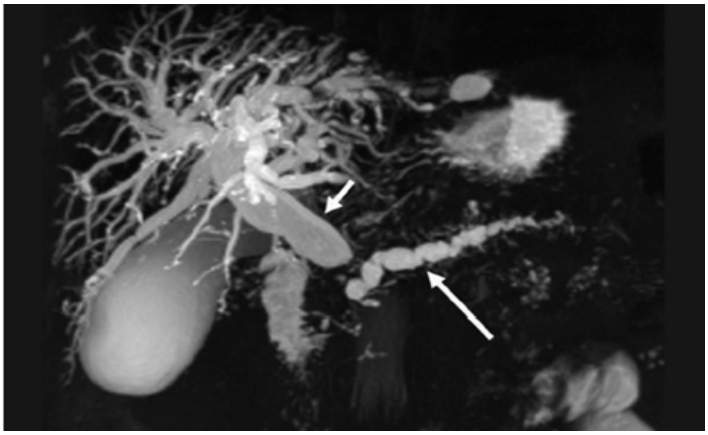

Figure 2: "Double duct sign" on magnetic resonance imaging. An obstructing pancreatic ductal adenocarcinoma within the pancreatic head has resulted in the dilatation of the bile duct (short arrow) and the pancreatic duct (long arrow) (reproduced from: qims.amegroups.com [30]).

Where CT is not possible due to contrast allergy, magnetic resonance imaging (MRI) with gadolinium infusion can be used for diagnostic and staging purposes [31]. MRI can also be a useful adjunct [32]. Adenocarcinomas are typically hypointense on T1-weighted images and hyperintense/isointense on T2-weighted images [33]. MRI has greater contrast resolution than CT and is superior when assessing small tumours or metastases [34]. MRI can also examine the biliary system without the need for additional invasive examinations (Figure 2). Drawbacks include cost and availability.

If there is diagnostic uncertainty following CT, UK guidelines recommend the use of positron emission tomography (PET/CT) [27]. This was originally used to differentiate pancreatic cancer and chronic pancreatitis [35]. Most malignant cells are hypermetabolic when compared with the normal pancreatic parenchyma [35]. Hence, the uptake of radiotracer, e.g. 18F-FDG, is greater in cancer cells. PET/CT takes advantage of this to provide a close depiction of the biologic behaviour of the tumour. Whilst PET/CT is limited in its ability to assess for locoregional lymphadenopathy and vascular invasion, it outperforms all other modalities in the detection of distant metastases (Figure 3) [35].

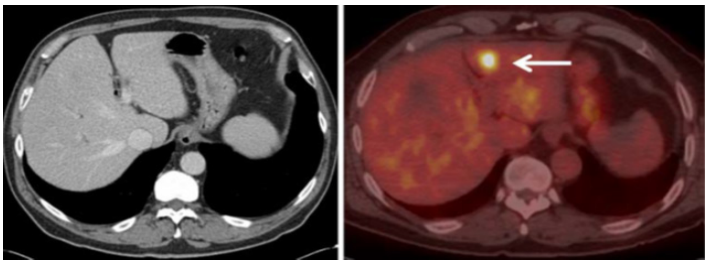

Figure 3: PET/CT image of an occult liver metastasis. In this case, the CT image (left) did not pick up the liver metastasis which is pointed out by the arrow on the PET/CT image (right) (reproduced from: citeseerx.ist.psu.edu [36]).

Endoscopic ultrasound (EUS) is a further important imaging modality which allows tissue sampling. In conventional mode, PDACs appear as an irregular heterogenous, hyperechoic mass, whereas on Doppler mode they are hypervascular [33]. EUS has better diagnostic yield for diagnosing early pancreatic tumours than both CT and MRI. EUS is able to identify pancreatic lesions as small as 2 mm in diameter [37]. Additional techniques such as elastography and contrast-enhancement further improve diagnostic accuracy [33]. However, EUS is expensive, operator-dependent, invasive, and cannot be used in isolation.

Screening

Screening for PDAC is not currently recommended for the general population. The reasons for this are multiple. Firstly, overall incidence is low; an individual's lifetime risk of PDAC is around 1% [38]. Secondly, there are no simple, safe, inexpensive, and non-invasive test with appropriate sensitivity [13]. Thirdly, no definite pre-malignant state has been defined which can be treated [13]. The International Cancer of the Pancreas Screening Consortium (ICPSC) group does recommend individuals with certain familial syndromes are screened. However, the details surrounding this are complex and remain a source of debate [39]. Whilst screening the general population is not-recommended, various campaigns have aimed to raise awareness and encourage patients to seek medical attention early [7].

Biomarkers

Extensive efforts have been made to identify biomarkers which aid in the diagnosis and treatment of PDAC [13]. Serum cancer (or carbohydrate) antigen 19-9 (CA 19-9) is currently the only biomarker which has been approved. CA 19-9 has a low positive predictive value so it is unsuitable for screening purposes, and its diagnostic performance in isolation is modest [13]. Furthermore, 10% of the population are non-secretors of CA 19-9 and it is unable to differentiate between benign and malignant disease in those with obstructive jaundice [40]. However, it is useful when considering a response to treatment and disease recurrence [41]. Although no other appropriate biomarkers are currently available, the situation is evolving. A recent study identified a biomarker signature of nine metabolites with an accuracy of 90% and a negative predictive value of 99% in differentiating chronic pancreatitis from PDAC [42]. Further exploratory studies have postulated that micro-ribonucleic acid (RNA) panels, circulating tumour cells, circulating tumour deoxyribonucleic acid (DNA) and/or exomes could be used as early diagnostic tools in the future [43].

Staging and resectability status

If a patient with PDAC has not undergone pancreatic protocol CT, a scan should be carried out which covers the chest, abdomen, and pelvis [27]. UK guidelines recommend that PET/CT is offered to patients with locally advanced disease who are considering treatment. If further information is required, MRI is the modality of choice for suspected liver metastases and EUS may provide further information regarding tumour and node staging [27]. If resectional surgery is being considered but small-volume peritoneal or liver metastases are suspected, diagnostic laparoscopy is indicated [44].

Primary tumour stage (T)	Tx	Cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma in situ
	T1	≤ 2cm*
	T2	> 2cm but ≤ 4cm*
	T3	> 4cm*
*greatest dimension	T4	Involvement of SMA or coeliac axis
Regional lymph nodes (N)	Nx	Cannot be assessed
	N0	No evidence of nodal involvement
	N1	1-3 regional lymph node metastases
	N2	> 3 regional lymph node metastases
Metastases (M)	Mx	Cannot be assessed
	M0	No evidence of metastases
	M1	Distal metastases present

Figure 4: Table summarising the 2017 (8th edition) IUCC/AJCC

TNM staging system for PDAC (adapted from Shin et al, 2020 [45].

The TNM staging system (officially known as the Tumour Node Metastasis classification system of malignant tumours) from the Union for International Cancer Control (UICC) is the most commonly used staging system for PDAC (Figure 4) [46]. The American Joint Committee on Cancer (AJCC) publishes its own cancer staging manual which is based upon this system. This standardised method is used to assess the extent of disease and guide treatment. It is important for determining whether a patient's disease is resectable or not (Figure 5) [47]. The resectability of a tumour is dependent of its location in the pancreas, involvement of local vessels and/or lymph nodes, and the presence of metastases [48]. It is important to note that exocrine and endocrine tumours of the pancreas are now staged using different systems.

Biliary drainage

Obstructive jaundice can result in coagulopathy which increases the risk of intra-operative haemorrhage. Jaundice is also thought to increase the risk of peri-operative infective complications [49]. As such, surgical candidates traditionally underwent biliary drainage prior to resectional surgery. Indeed, Whipple first described a 2-stage procedure for this very purpose [50]. UK guidelines now recommend against this unless there is a clear indication or the patient is enrolled in a trial [27]. This remains controversial. A recent Cochrane review found no strong evidence for or against pre-operative biliary drainage [51]. In contrast, a recent multi-centre randomised trial concluded that morbidity was higher in those who underwent biliary drainage [52].

Vessel	Primary resectable	Borderline resectable	Unresectable
PV/SMV	No contact < 180° without vein contour irregularity	Contact > 180° < with deformity of vein thrombosis but allowing safe and complete resection Contact with IVC	Unreconstructable obstruction Contact with most proximal draining jejunal branch
CHA	No arterial tumour contact	Contact without extension to CA or HA bifurcation	Contact with extension to CA or CHA bifurcation
CA	No arterial tumour contact	No contact (head) Contact < 180° (body and tail)	Contact > 180° Any contact with aorta
SMA	No arterial contact	Contact < 180°	Contact > 180°
			Contact with 1st jejunal SMA branch
			Contact with aorta

Figure 5: Table summarising the criteria which define resectability status of pancreatic ductal adenocarcinoma (adapted from: jnccn.org [53]. PV = portal vein, SMV = superior mesenteric vein, CA = coeliac axis, CHA = common hepatic artery, SMA = superior mesenteric artery, IVC = inferior vena cava, HA = hepatic artery.

In some patients, it may be necessary to relieve biliary obstruction prior to surgery. The preferred approach is endoscopic via endoscopic retrograde cholangiopancreatography (ERCP) [52]. This includes patients with severe pruritis, acute cholangitis, or renal dysfunction secondary to jaundice This may also be the case for patients whose resection is delayed to allow for neoadjuvant therapy or those who require optimisation. ERCP involves upper gastrointestinal endoscopy and intubation of the duodenum [54]. The endoscopist locates, and canulates, the ampulla. Contrast can then be injected, and fluoroscopy used to image the pancreaticobiliary tree. A stent can then be deployed to the area of obstruction to allow the passage of bile and pancreatic juice. For preoperative biliary drainage, metal stents are generally preferred to plastic stents since they are associated with a lower complication rate [55]. Aside from the management of obstructive jaundice, ERCP +/- sphincterotomy can also be used to manage choledocholithiasis, inflammatory structures, and surgical complications such as leaks. ERCP is an effective and safe tool but its potential complications must be considered. These include sepsis secondary to cholangitis, pancreatitis, duodenitis, haemorrhage (usually only following sphincterotomy), and perforation of the bile duct, pancreatic duct, or duodenum [56]. A serious complication following ERCP may prevent a patient from undergoing resection.

If ERCP fails, percutaneous transhepatic cholangiography (PTC) can be utilised. In this technique, a needle is passed via the skin, abdominal wall, and liver under ultrasound guidance. The biliary tree is catheterised and contrast is injected to allow fluoroscopic delineation of the anatomy. As with ERCP, an expanding metal stent can be deployed to relieve biliary obstruction. PTC is invasive and can be complicated by sepsis, haemorrhage, and pneumothorax (if the thoracic cavity is inadvertently breached) [55].

Neoadjuvant treatment

Neoadjuvant therapy (NAT) refers to any treatment, usually chemotherapy and/or radiotherapy, which is given prior to resection. NAT has been introduced with great success in the management of oesophageal, gastric and rectal cancers [57]. NAT aims to treat occult micrometastases and down stage primary tumours. Since morbidity is high following resection, NAT increases the chance a patient successfully completing a course of chemotherapy and can be used as a tool to select patients with a favourable tumour profile who are more appropriate surgical candidates. UK guidelines currently advise against the use of NAT in those with resectable disease unless the patient is enrolled in a clinical trail [27]. Whilst the guidelines are the same for those with borderline resectable disease, this is evolving and trials are ongoing [58].

Surgical treatment

Resectional surgery is the only treatment option which can pro-

vide long-term survival. Unfortunately, most patients present with unresectable disease. Surgical approach is dictated by tumour location. Surgical options include pancreatico-duodenectomy (PD, Whipple's procedure), distal pancreatectomy (+/- splenectomy), and total pancreatectomy (+/- splenectomy). PD is the most commonly performed, since PDAC most commonly affects the head of the pancreas.

The origin of the PD procedure remains controversial. Some reports claim that a version of the procedure was carried out by Codivilla in Italy as early as 1898 [59]. Codivilla's patient died on the eighteenth post-operative day and this led to the thinking that the duodenum was essential for human survival. It was Frenchmen, Desjardin, in 1907, and Sauve, in 1908, who first suggested that excision of the human duodenum was feasible. However, they only attempted this in cadavers [59]. In 1900, the Englishman, Sir Arthur Mayo-Robson, had attempted to excise a cylindrical segment of duodenum but his patient died on the operating table [60]. The German, William Koerte, attempted the same procedure four years later but his patient also died [60]. In 1912, also in Germany, Walter Kausch performed an incomplete duodenectomy with partial pancreatectomy [60]. He left part of the duodenum in situ and fashioned a pancreatico-duodenostomy as he believed the patient could not survive if the entire duodenum was excised. In 1918, the American, Lester Dragstedt, was able to demonstrate that duodenectomy was compatible with survival in dogs [61]. Almost twenty years later, in 1935, the Iran-born American, Allen Whipple, described a total duodenectomy as part of a two-stage operation [50]. Whilst the technique has been modified greatly, the pancreato-duodenectomy is often referred to as the Kausch-Whipple procedure to this day. Some historians argue that this is perhaps unfair since numerous individuals were instrumental in the development of the modern procedure. Although Whipple popularised the procedure in the 1930s, it wasn't until the 1980s that it was commonly performed.

Panceatico-duodenectomy is one of the most complex routine operations caried out by general surgeons. It is most commonly performed to treat cancers of the pancreatic head, duodenum, ampulla, of distal bile duct. Rarely, it may be performed in patients with severe chronic pancreatitis or severe pancreatic trauma. Whilst various modifications exist, the classic approach involves en-bloc removal of the antrum of the stomach, the first and second parts of the duodenum, the head of the pancreas, the distal bile duct, and the gallbladder [62]. In the pylorus-preserving PD, a cuff of duodenum and the antrum are left in situ to preserve the pyloric sphincter [62]. Regardless of the technique used, PD is a major operation and mortality remains around 1-3% [63]. General complications include chest infection, haemorrhage, myocardial infarction, arrythmias, stroke, venous thromboembolism, ileus, wound infection/dehiscence, and incisional hernias [64]. Procedure-specific complications include post-operative pancreatic fistula (POPF), biliary tree injury, bile leak, anastomotic leak, intra-abdominal sepsis, acute pancreatitis, delayed gastric emptying (DGE), and chyle leak[63,65]. Longer term complications specific to PD include anastomotic structure, malnutrition, pancreatic endocrine and/or exocrine insufficiency, and low mood/impaired quality of life [63]. Overall morbidity is in the region of 40%. It is possible that morbidity and mortality figures have been under-estimated due to publication bias.

A nasogastric (NG) tube and urinary catheter are placed once the patient is anaesthetised. The initial incision depends on the surgeon's preference. Modifications of a right subcostal (extended Kocher), bilateral subcostal (rooftop), or upper midline laparotomy are most-commonly used. After examining for extra-pancreatic disease, the surgeon will mobilise the hepatic flexure of the colon and "Kocherize" the duodenum to expose the retroperitoneum. The lesser sac is then opened before cholecystectomy is carried out. The common hepatic duct is divided before the lymph nodes adjacent to the porta are excised [66]. The gastroduodenal artery is divided and the surgeon proceeds to divide the distal stomach, or first part of the duodenum. The pancreas is divided in front of the portal vein and the specimen extracted and sent for histological examination [66].

The reconstructive phase of the operation can then take place; the surgeon proceeds to form a pancreatico-jejunostomy (PJ), or pancreatico-gastrostomy (PG), hepato-jejunostomy (HJ), and gastro-jejunostomy (GJ) (Figure 6). A drain is typically placed adjacent to the PJ/PG and HJ prior to closure. Providing there are no intra-operative complications, post-operative management is guided by the Enhanced Recovery after Surgery (ERAS) protocol [67]. The NG tube, urinary catheter, and surgical drains are removed as soon as is reasonable [67]. Early oral diet and mobilisation are encouraged [67]. In recent years, PD has been performed laparoscopically and with robotic assistance in some centres. Although some studies have suggested minimally invasive approaches may result in reduced length of hospital stay, reduced intra-operative blood loss, and more extensive lymph node dissection, uptake has been modest due the associated challenges and costs. Open PD remains the standard of care [68].

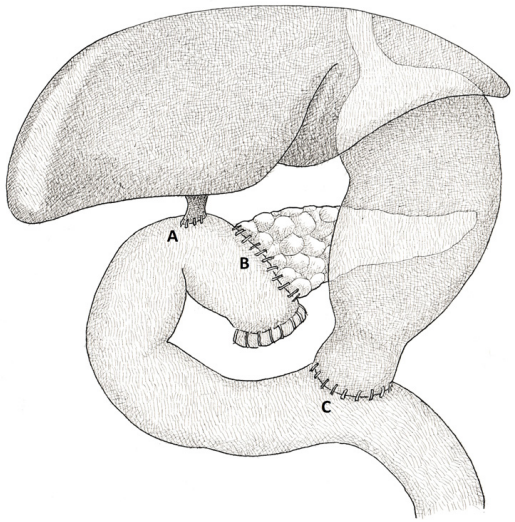

Figure 6: Anatomy following pancreatico-duodenectomy. A = hepato-jejunostomy, B = pancreatico-jejunostomy, C = gastro-jejunostomy (illustration provided by John Peter Ovens).

Histological examination and pathologic staging

A minimum of twelve lymph nodes must be sent with the specimen for staging to be considered accurate. PDAC is rarely diagnosed early and hence it is usual for a tumour to be 2-4cm (pT2) at time of examination, and invasion of adjacent structures is common.

PDAC tumours are typically a firm, poorly defined mass of off-white colour. PDAC is made up of abnormal tubular glands which mimic small pancreatic ducts, but a high level of heterogeneity is seen [69]. The circumferential resection margin (CRM) consists of the anterior, posterior, and medial pancreatic surfaces. A resection margin is considered clear is there is no evidence of metastatic disease within 1 mm of the cut surface [69].

Adjuvant treatment

Adjuvant chemotherapy has become the gold standard following resectional surgery whilst adjuvant chemoradiotherapy is not recommended [70]. Adjuvant chemotherapy improves survival rates by targeting early micro-metastatic disease [71]. UK guidelines recommend that patients be given sufficient time to recover following PD before adjuvant therapy is administered [27]. This is commenced once they are deemed fit enough to tolerate six cycles. First-line therapy is gemcitabine plus capecitabine, and gemcitabine alone can be considered in those not fit enough to tolerate combination chemotherapy [27]. The ESPAC-4 trial demonstrated that combination therapy significantly improves median overall survival [70]. Prognosis remains poor and some patients are unable to complete adjuvant treatment due to toxicity or disease recurrence.

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References

1. Rawla P, Sunkara T, Gaduputi V (2019) Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World journal of oncology 10:10-27.
2. Simoes PK, Olson SH, Saldia A, Kurtz RC (2017) Epidemiology of pancreatic adenocarcinoma. Chinese Clinical Oncology Chinese Clinical Oncology (Pancreas Adenocarcinoma-I-Guest Editors: Eileen M O'Reilly, Lei Zheng) 6: 2017.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68:394-424.
4. Klein AP (2019) Pancreatic cancer: a growing burden. The Lancet Gastroenterology & Hepatology. 4: 895-896.
5. Lam F, Colombet M, Mery L, Pineros M, Znaor A, et al. (2019) Global cancer observatory: Cancer today 2019.
6. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M, et al. (2011) Pancreatic cancer. Lancet (London, England) 378:607-620.
7. Mc Guigan A, Kelly P, Turkington RC, Jones C, Coleman HG, et al. (2018) Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World journal of gastroenterology 24:4846-4861.
8. Ezzati M, Henley SJ, Lopez AD, Thun MJ (2005) Role of smoking in global and regional cancer epidemiology: current patterns and data needs. Int J Cancer 116:963-971.
9. Kuzmickiene I, Everatt R, Virviciute D, Tamosiunas A, Radisauskas R, et al. (2003) Smoking and other risk factors for pancreatic cancer: a cohort study in men in Lithuania. Cancer Epidemiol 37:133-139.
10. Zhao Z, Yin Z, Pu Z, Zhao Q (2017) Association Between Consumption of Red and Processed Meat and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 15:486-493.
11. Guo Y, Liu W, Wu J (2016) Helicobacter pylori infection and pancreatic cancer risk: A meta-analysis. J Cancer Res Ther 12:229-232.
12. El Serag HB, Engels EA, Landgren O, Chiao E, Henderson L, et al. (2009) Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. Hepatology 49:116-123.
13. Bekkali NLH, Oppong KW (2017) Pancreatic ductal adenocarcinoma epidemiology and risk assessment: Could we prevent? Possibility for an early diagnosis. Endoscopic ultrasound 6:58-61.
14. Kopp JL, Von Figura G, Mayes E, Liu FF, Dubois CL, et al. (2012) Identification of Sox9-dependent acinar-to-ductal reprogramming as the principal mechanism for initiation of pancreatic ductal adenocarcinoma. Cancer Cell 22:737-750.
15. Orth M, Metzger P, Gerum S, Mayerle J, Schneider G, et al. (2019) pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiation Oncology 14:141.
16. Peters MLB, Eckel A, Mueller PP, Tramontano AC, Weaver DT, et al. (2018) Progression to pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia: Results of a simulation model. Pancreatology 18:928-34.
17. Kanda M, Matthaei H, Wu J, Hong SM, Yu J, et al. (2012) Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. Gastroenterology 142:730-790.
18. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, et al. (2015) Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 518:495-501.
19. Hu ZI, Shia J, Stadler ZK, Varghese AM, Capanu M, et al. (2018) Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. Clin Cancer Res 24:1326-1336.
20. Sarantis P, Koustas E, Papadimitropoulou A, Papavassiliou AG, Karamouzis MV, et al. (2020) Pancreatic ductal adenocarcinoma: Treatment hurdles, tumor microenvironment and immunotherapy. World journal of gastrointestinal oncology 12:173-181.
21. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, et al. (2016) Pancreatic cancer. Nat Rev Dis Primers 2:16022.
22. Yachida S, Jones S, Bozic I, Antal T, Leary R, et al. (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 467:1114-1117.
23. Bond Smith G, Banga N, Hammond TM, Imber CJ (2012) Pancreatic adenocarcinoma. Bmj 344:2476.
24. Porta M, Fabregat X, Malats N, Guarner L, Carrato A, et al. (2005) Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol. 7:189-197.
25. De Souza A, Khawaja KI, Masud F, Saif MW (2016) Metformin and pancreatic cancer: Is there a role? Cancer Chemother Pharmacol 77:235-242.
26. Ashida R, Tanaka S, Yamanaka H, Okagaki S, Nakao K, et al. (2018) The Role of Transabdominal Ultrasound in the Diagnosis of Early Stage Pancreatic Cancer: Review and Single-Center Experience. Diagnostics (Basel, Switzerland) 9:2.
27. OReilly D, Fou L, Hasler E, Hawkins J, OConnell S, et al. (2018) Diagnosis and management of pancreatic cancer in

adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology 18:962-970.
28. Tempero MA, Arnoletti JP, Behrman S, Ben-Josef E, Benson AB, et al. (2010) Pancreatic adenocarcinoma. Journal of the National Comprehensive Cancer Network: JNCCN 8:972-1017.
29. Klauss M, Schöbinger M, Wolf I, Werner J, Meinzer H P, et al. (2009) Value of three-dimensional reconstructions in pancreatic carcinoma using multidetector CT: initial results. World journal of gastroenterology 15:5827-5832.
30. Yang M J, Li S, Liu Y G, Jiao N, Gong J S, et al. (2013) Common and unusual CT and MRI manifestations of pancreatic adenocarcinoma: a pictorial review. Quantitative Imaging in Medicine and Surgery; Quantitative Imaging in Medicine and Surgery 3: 2013.
31. Horton KM, Fishman EK (2002) Adenocarcinoma of the pancreas: CT imaging. Radiol Clin North Am 40:1263-1272.
32. Schima W, Függer R, Schober E, Oettl C, Wamser P, et al. (2002) Diagnosis and staging of pancreatic cancer: comparison of mangafodipir trisodium-enhanced MR imaging and contrast-enhanced helical hydro-CT. AJR Am J Roentgenol 179:717-724.
33. Costache MI, Costache CA, Dumitrescu CI, Tica AA, Popescu M, et al. (2017) Which is the Best Imaging Method in Pancreatic Adenocarcinoma Diagnosis and Staging - CT, MRI or EUS? Current health sciences journal 43:132-136.
34. Hanbidge AE (2002) Cancer of the pancreas: the best image for early detection--CT, MRI, PET or US? Can J Gastroenterol 16:101-105.
35. Jha P, Bijan B (2015) PET/CT for Pancreatic Malignancy: Potential and Pitfalls. Journal of Nuclear Medicine Technology 43:92.
36. Farma J, Santillan A, Melis M, Walters J, Belinc D, et al. (2008) PET/CT Fusion Scan Enhances CT Staging in Patients with Pancreatic Neoplasms. Annals of surgical oncology 15:2465-2471.
37. Lami G, Biagini MR, Galli A (2014) Endoscopic ultrasonography for surveillance of individuals at high risk for pancreatic cancer. World journal of gastrointestinal endoscopy 6:272-285.
38. Del Chiaro M, Segersvärd R, Lohr M, Verbeke C (2014) Early detection and prevention of pancreatic cancer: is it really possible today? World J Gastroenterol 20:12118-12131.
39. Unger K, Mehta KY, Kaur P, Wang Y, Menon SS, et al. (2018) Metabolomics based predictive classifier for early detection of pancreatic ductal adenocarcinoma. Oncotarget 9:23078-23090.
40. Müller PC, Frey MC, Ruzza CM, Nickel F, Jost C, Gwerder C, et al. (2021) Neoadjuvant Chemotherapy in Pancreatic Cancer: An Appraisal of the Current High-Level Evidence. Pharmacology 106:143-153.
41. Mills K, Birt L, Emery JD, Hall N, Banks J, et al. (2017) Understanding symptom appraisal and help-seeking in people with symptoms suggestive of pancreatic cancer: a qualitative study. BMJ open 7:015682.
42. Mayerle J, Kalthoff H, Reszka R, Kamlage B, Peter E, et al. (2018) Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. Gut 67:128-137.
43. Schultz NA, Dehlendorff C, Jensen BV, Bjerregaard JK, Nielsen KR, et al. (2014) MicroRNA biomarkers in whole blood for detection of pancreatic cancer. Jama 311:392-404.
44. De Rosa A, Cameron IC, Gomez D (2016) Indications for staging laparoscopy in pancreatic cancer. HPB: the official journal of the International Hepato Pancreato Biliary Association 18:13-20.
45. Shin DW, Kim J (2020) The American Joint Committee on Cancer 8th edition staging system for the pancreatic ductal adenocarcinoma: is it better than the 7th edition? Hepatobiliary surgery and nutrition 9:98-100.
46. Zins M, Matos C, Cassinotto C (2018) Pancreatic Adenocarcinoma Staging in the Era of Preoperative Chemotherapy and Radiation Therapy. Radiology 287: 374-390.
47. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, et al. (2000) Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. Journal of Gastrointestinal Surgery 4:567-579.
48. Pietryga JA, Morgan DE (2015) Imaging preoperatively for pancreatic adenocarcinoma. Journal of gastrointestinal oncology 6:343-357.
49. Blamey SL, Fearon KC, Gilmour WH, Osborne DH, Carter DC, et al. (1983) Prediction of risk in biliary surgery. Br J Surg 70:535-538.
50. Whipple AO, Parsons WB, Mullins CR (1935) TREATMENT OF CARCINOMA OF THE AMPULLA OF VATER. Ann Surg 102:763-979.
51. Wang Q, Gurusamy KS, Lin H, Xie X, Wang C, et al. (2008) Preoperative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev. 2008:005444.
52. Van der Gaag NA, Rauws EA, Van Eijck CH, Bruno MJ, Van der Harst E, et al. (2010) Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 362:129-137.
53. Margaret AT, Mokenge PM, Mahmoud A H, Horacio A, Andrew B, et al. (2017) Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw 15:1028-1061.
54. Dominguez Muñoz JE, Larino Noia J, Iglesias Garcia J (2017) Biliary drainage in pancreatic cancer: The endoscopic retrograde cholangiopancreatography perspective. Endoscopic ultrasound 6:119-121.
55. Tol JA, Van Hooft JE, Timmer R, Kubben FJ, Van der Harst E, et al. (2016) Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut 65:1981-1987.
56. Szary NM, Al Kawas FH (2013) Complications of endoscopic retrograde cholangiopancreatography: how to avoid and manage them. Gastroenterology & herpetology. 9:496-504.
57. Labori KJ, Lassen K, Hoem D, Gronbech JE, Soreide JA, et al. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1) study protocol for a national multicentre randomized controlled trial. BMC surgery 17:94.
58. Ejaz A, He J (2017) Pancreaticoduodenectomy for pancreatic cancer: perspective from the United States. Chinese Clinical Oncology; Chinese Clinical Oncology.6: 2017.
59. Are C, Dhir M, Ravipati L (2011) History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. HPB: the official journal of the International Hepato Pancreato Biliary Association 13:377-384.

60. Whipple AO (1946) Observations on radical surgery for lesions of the pancreas. Surg Gynecol Obstet 82:623-631.
61. Dragstedt LR, Dragstedt CA, McClintock JT, Chase CS (1918) Extirpation of the duodenum. American Journal of Physiology-Legacy Content 46:584-590.
62. Johnson LB, Amin R (2009) Chapter 35 - Pancreaticoduodenectomy. In: Evans SRT, editor. Surgical Pitfalls. Philadelphia: W.B. Saunders 367-373.
63. Kapoor VK (2021) Complications of pancreato duodenectomy. Rozhl Chir 95:53-59.
64. Russell TB, Elberm H (2021) Emergency hernia surgery at a high-volume tertiary centre: a 3-year experience. ANZ Journal of Surgery 91:622-626.
65. Russell T, Tanase A, Bowles M, Briggs C, Kanwar A, et al. (2021) Chyle leak following pancreatico-duodenectomy: a tertiary hepatopancreaticobiliary unit's experience and a proposed management algorithm. ANZ Journal of Surgery 91:355-360.
66. Warshaw AL, Thayer SP (2004) Pancreaticoduodenectomy. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract 8:733-741.
67. Xu X, Zheng C, Zhao Y, Chen W, Huang Y, et al. (2018) Enhanced recovery after surgery for pancreaticoduodenectomy: Review of current evidence and trends. International Journal of Surgery 50:79-86.
68. Asbun HJ, Stauffer JA (2012) Laparoscopic vs open pancreaticoduodenectomy: overall outcomes and severity of complications using the Accordion Severity Grading System. J Am Coll Surg 215:810-819.
69. Haeberle L, Esposito I (2019) Pathology of pancreatic cancer. Translational gastroenterology and hepatology 4: 50.
70. Klaiber U, Hackert T, Neoptolemos JP (2019) Adjuvant treatment for pancreatic cancer. Translational gastroenterology and hepatology 4:27.
71. Tesfaye AA, Philip PA (2019) Adjuvant treatment of surgically resectable pancreatic ductal adenocarcinoma. Clin Adv Hematol Oncol 17:54-63.