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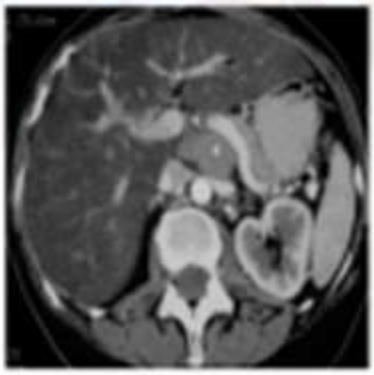
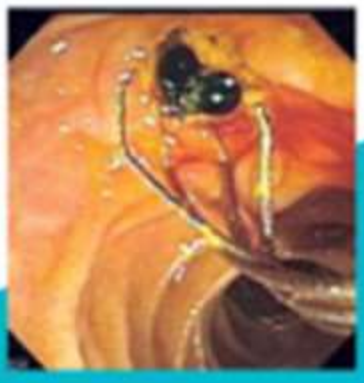
Total Pancreatectomy in Management of Pancreatic Tumors

First Edition





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Introduction

The pancreas is an elongated organ, light tan or pinkish in color that lies in close proximity to the duodenum. It is covered with a very thin connective tissue capsule which extends inward as septa, partitioning the gland into lobules ***(Cuschieri, 2002)*.**

Pancreatic cancer is the eighth most common malignancy and the fifth leading cause of the adult cancer death in the United States. Only 1-4% of all patients diagnosed with pancreatic cancer can expect to survive 5 years. In the year 2000 about 28,300 new cases of adenocarcinoma of the pancreas were diagnosed in the United States, and about 28,200 patients died of this aggressive malignancy ***(Grau et al., 2004)***.

Depending on the extent of the tumor at the time of diagnosis, the prognosis is generally regarded as poor, with few victims still alive five years after diagnosis, and complete remission still extremely rare ***(Cuschieri, 2002)*.**

Risk factors for pancreatic cancer include age, male gender, African ethnicity and smoking. Cigarette smoking causes a 75% risk increase, and the risk persists for at least a decade after quitting. Diets high in red meat, obesity, diabetes mellitus and chronic pancreatitis have been linked, but are not

known to be causal. Helicobacter pylori infection, occupational exposure to certain pesticides, dyes, and chemicals related to gasoline are among the risk factors. 5-10% of pancreatic cancer patients have a family history of pancreatic cancer ***(Iodice et al., 2008)***.

Epithelial neoplasms of the pancreas include tumors that arise from ductal, acinar, or endocrine cells. The most common are adenocarcinomas of the ductal phenotype. Ductal adenocarcinoma is therefore the prototype of pancreatic cancer, and that is what is meant whenever epidemiological and clinical data on pancreatic cancer are discussed. All other epithelial tumors are uncommon, but they include a number of neoplasms with special biological features. Non-epithelial tumors of the pancreas are exceedingly rare ***(Kloppel, 1997).***

The recently published World Health Organization (WHO) classification of pancreatic exocrine tumors divides the tumors on the basis of their biological behavior into benign tumors, borderline tumors (uncertain malignant potential), and malignant tumors ***(Kloppel et al., 2011)***.

Early diagnosis of pancreatic cancer is difficult because the symptoms are so non-specific and varied, pancreatic cancer is sometimes called a "silent disease". Common symptoms include pain in the upper abdomen, loss of appetite, nausea,

vomiting significant weight loss and painless jaundice related to bile duct obstruction (carcinoma of the head of pancreas), diabetes mellitus ***(Bakkevold et al., 2002).***

Pancreatic cancer is usually discovered during the course of the evaluation of one of the forementioned symptoms. Liver function tests may show a combination of results indicative of bile duct obstruction (raised conjugated bilirubin, y-glutamyl transpeptidase and alkaline phosphatase levels). CA19-9 (carbohydrate antigen 19.9) is a tumor marker that is frequently elevated in pancreatic cancer, Imaging studies such as ultrasound or abdominal CT scan may be used to identify tumors. Endoscopic ultrasound (EUS) is another procedure that can help to visualize the tumor and obtain tissue biopsy to establish the diagnosis, ERCP (endoscopic retrograde cholangiopancreatography), PTC (percutaneous transhepatic cholangiography) and MRI (magnetic resonance imaging) are used for diagnosis and staging of pancreatic cancer ***(Ghaneh et al., 2007).***

People with pancreatic cancer may have several treatment options. Depending on the type and stage, pancreatic cancer may be treated with surgery, radiation therapy or chemotherapy. Some patients have a combination of therapies. The surgeon may remove all or part of the pancreas. The extent of surgery depends on the location and size of the tumor, the

stage of the disease and the patient's general health, the mortality rates for the pancreatic resection have fallen substantially over the last two decades. This is related to the better quality of peri-operative care, improvement in the skill and experience of the surgeons and the concentration of these patients in specialist centers ***(Evans et al., 2001)*.**

Total pancreatectomy (TP) for pancreatic cancer was first reported by Rockey in1943. Subsequently, it was considered that partial pancreatectomy (PP) would help to avoid pancreatic fistula. Because of high tumour recurrence rates after Kausch-Whipple procedures, any suggestion of possible tumour multicentricity supported a role for TP as a means of achieving R0 resection, Subsequent studies demonstrated no improvement in postoperative outcome and major metabolic problems were found to occur. These were difficult to address and the procedure fell out of favour. However, recent studies have demonstrated progress regarding postoperative outcomes of TP. In addition new pancreatic tumour entities have been identified in the past decade and these require total rather than partial pancreatectomy ***(Nathan et al., 2009).***

Total pancreatectomy has been used to treat both benign and malignant disease of the pancreas, but its use has been limited by concerns about management of the apancreatic state with its attendant total endocrine and exocrine insufficiency. It

also remains a viable option in the treatment of intractable pain associated with chronic pancreatitis, multicentric or extensive neuroendocrine tumors, patients with familial pancreatic cancer with premalignant lesions, and in patients with intraductal papillary mucinous neoplasia with diffuse ductal involvement or invasive disease ***(Sauve, 2007).***

Improvements in postoperative management include auto-islet cell transplantation and the use of glucagon rescue therapy which allow much tighter control of blood glucose than previously.

Laparoscopic approaches which are increasingly used in pancreatic surgery such as Laparoscopic enucleation of functioning neuroectodermal tumors like insulinomas ***(Kang et al., 2008)***.

Aim of the Essay

The aim of the essay is to highlight the role, advantages, disadvantages and operative procedures of total pancreatectomy in the management of pancreatic tumors.

Anatomy

Introduction

The name pancreas is derived from Greek (Pan) means all and (Krease) means flesh. The pancreas is perhaps the most unforgiving organ in the human body, leading most surgeons to avoid even palpating it unless necessary. Situated deep in the center of the abdomen, the pancreas is surrounded by numerous important structures and major blood vessels. Therefore seemingly minor trauma to the pancreas can result in the release of pancreatic enzymes and cause life-threatening pancreatitis. Surgeons that choose to undertake surgery on the pancreas require a thorough knowledge of its anatomy. However, knowledge of the relationships of the pancreas and surrounding structures is also critically important for all surgeons to ensure that pancreatic injury is avoided during surgery on other structures ***(Fisher et al., 2009).***

The pancreas is an elongated organ, light tan or pinkish in color that lies in close proximity to the duodenum. It is covered with a very thin connective tissue capsule which extends inward as septa, partitioning the gland into lobules ***(American Society Center, 2008).***

Duramen has summarized the anatomical relationship of the pancreas as follow: "the pancreas cuddles the left kidney,

tickles the spleen, hugs the duodenum, cradles the aorta, opposes the inferior vena cava, dallies with the right renal pedicle, hides behind the posterior parietal peritoneum of the lesser sac and wraps itself around the superior mesenteric vessels ***(Cuschieri, 2002)***.

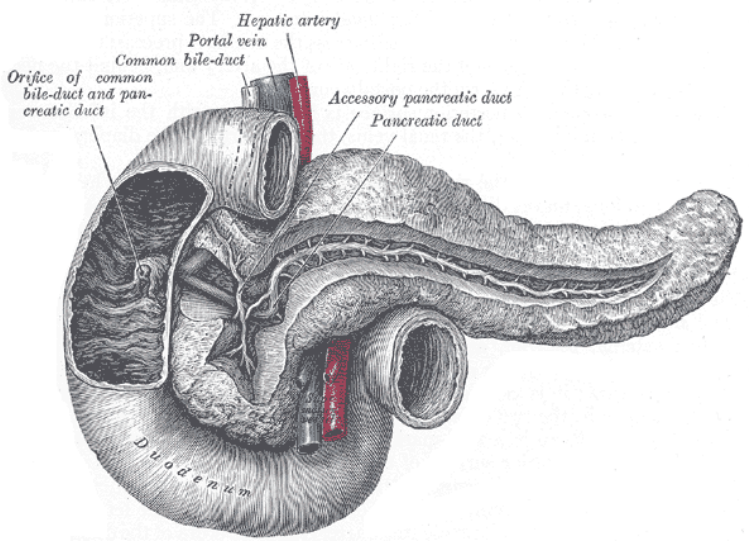


Fig. (1): Anatomy of the pancreas ***(Cuschieri, 2002).***

Embryology of the Pancreas

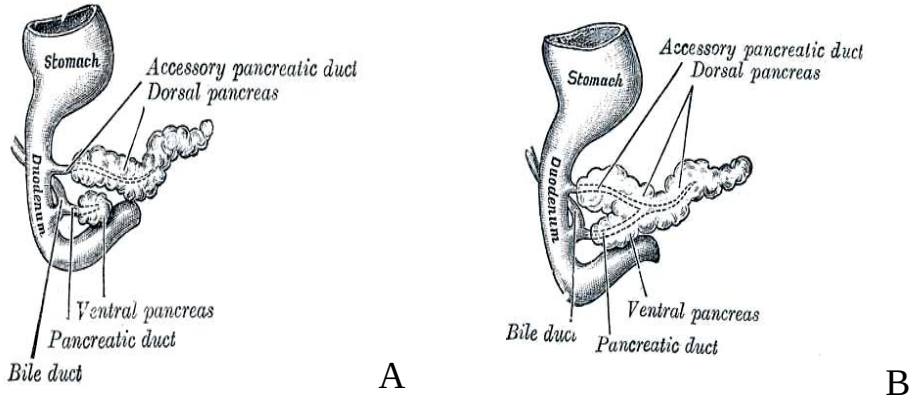


Fig. (2): Embryological development of the pancreas ***(Cuschieri, 2002).***

The pancreas develops as two separate dorsal and ventral buds, each as an outgrowth of endoderm at the junction of foregut and midgut ***(Skandalakis et al., 2007).***

The dorsal bud arises in the later half of the fourth week of gestation as a diverticulum from the dorsal wall of the duodenum short distance cranial to the hepatic diverticulum. It forms the whole of the neck, body, tail of the pancreas and part of the head. The ventral bud arises in the third week of gestation from the primitive bile duct near its opening into the duodenum.

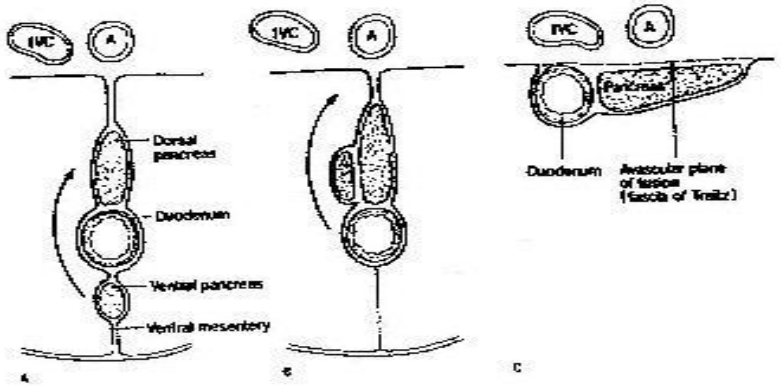


Fig. (3): Rotation of duodenum and pancreas during development ***(Cuschieri, 2002)***.

The duct of the dorsal part "The accessory pancreatic duct" therefore opens directly into the duodenum, while the duct of the ventral part. "The main pancreatic duct" opens with the bile duct. Early in the seventh week, the two parts of the pancreas meet and fuse as a continuation is established between

their ducts through postero-medial rotation of the ventral part associated with' the bile duct and the gall bladder. After this had occurred, the terminal part of the accessory duct undergoes little or no enlargement while the duct of the ventral part increases in size from the terminal part of the main pancreatic duct ***(Moore et al., 2011).***

The parenchyma of the pancreas is derived from the endoderm of the pancreatic buds which form a network of tubules early in the fetal period; acini begin to develop from cell clusters around the ends of these tubules "primordial ducts".

The pancreatic islets develop from groups of cells that separate from the tubules and soon come to lie between the acini ***(Moore et al., 2011)***. Insulin secretion begins during the early fetal period "10 weeks". The glucagon and somatostatin containing cells develop before differentiation of the insulin-secreting cells. Glucagon has been detected in fetal plasma at 15 weeks. With increasing fetal age, the total pancreatic insulin and glucagon content also increases ***(Moore et al., 2011).***

Parts of the Pancreas:

The pancreas may be arbitrarily divided into five parts head, uncinate process, neck, body and tail.

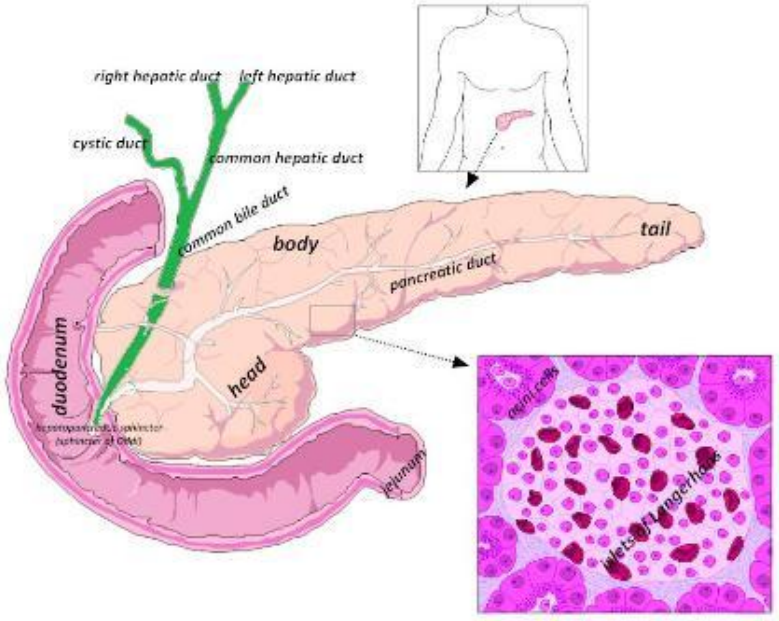


Fig. (4): Parts of the pancreas ***(Hartley et al., 2003)*.**

Head

It's that portion lying to the right of the superior mesenteric vessels and portal vein ***(Hartley et al., 2003)***.

Its junction with the neck is marked anteriorly by an imaginary line from the portal vein above to the superior mesenteric vein below ***(Skandalakis et al., 2007)***.

It is flattened from before backwards and is lodged within the curve of the duodenum. Its upper border is overlapped by the superior part of the duodenum and its lower border overlaps the horizontal part. It's right and left borders overlap in front and insinuate themselves behind the descending and ascending parts of the duodenum respectively.

On the anterior surface of the head and across the duodenum, the transverse mesocolon is very short so that the colon itself is attached to the underlying organ. The anterior pancreatico-duodenal arcade parallels the duodenal curvature on the anterior pancreatic surface. Posteriorly, the surface is related to the hilum and medial border of right kidney, the right renal vessels, the inferior vena cava with the entrance of the left renal vein into it, the right gonadal vein, the right crus of the diaphragm, the posterior pancreatico-duodenal arcade, and the distal portion of the common bile duct ***(Skandalakis et al., 2007)***.

The terminal common bile duct usually passes through the substance of the pancreatic head although in approximately 15% of people it remains externally in a groove on the posterior aspect just before entering the descending portion of the duodenum. Hepatic or middle colic artery can also lie behind the pancreatic head as a congenital anomalies ***(Skandalakis et al., 2007).***

Uncinate Process:

It is an inferior projection of the head of the pancreas that passes behind the superior mesenteric vessels and the portal vein and is anterior to the inferior vena cava and aorta. In sagittal section at the level of aorta, the uncinate process

lies between the aorta and the superior mesenteric artery having the left renal vein above and the duodenum below ***(Skandalakis et al., 2007)***.

Neck:

It is a constriction between the head and body 1.5 to 2 cm long. It is partly covered anteriorly by the pylorus and extends to the right as far as the origin of the anterior superior pancreatico-duodenal artery from the gastro-duodenal artery. The left boundary of the neck is arbitrary. Posterior to the neck, the portal vein is formed by the confluence of the superior mesenteric and splenic veins. One or two small veins may enter the portal vein and four or five may enter the superior mesenteric vein. Careful elevation of the neck and of these short vessels, if they are present, may be necessary to avoid bleeding that will make it difficult to evaluate the structures lying beneath the neck. Entering the portal vein from the right are a few small, short lateral veins; from the left are the left gastric and rarely, the inferior mesenteric vein ***(Skandalakis et al., 2007).***

Body:

It is the part of the gland that continues to the left of the neck or to the left of the superior mesenteric and portal veins. It forms a well-marked anterior convexity across the vertebral

column at approximately the first lumbar vertebra. Superiorly, it is related to the celiac axis and splenic artery and inferiorly, it lies adjacent to the fourth portion of the duodenum, ligament of Treitz and some jejunal loops. Posteriorly are the superior mesenteric artery, aorta, inferior mesenteric and splenic veins left adrenal gland and left kidney. The splenic vein, the most superficial of all of the vessels, accepts numerous small veins' from the pancreas. These must be ligated carefully in order to avoid injury to the splenic vein if the spleen is to be preserved ***(Skandalakis et al., 2007).***

Anteriorly, over the body of the pancreas, lies the peritoneal covering of the floor of the lesser sac. The transverse mesocolon is also related to the body with its peritoneum divided into two sheaths at the inferior margin of the pancreatic body. One of these sheaths covers the anterior aspect of the pancreatic body, while the other separates and covers the inferior surface of the gland. Between these two laminae lies the middle colic artery ***(Skandalakis et al., 2007).***

Tail:

The tail of the pancreas is relatively mobile. Its tip reaches the hilum of the spleen in 50 percent of cases (Fig. 3). Together with the splenic artery and the origin of the splenic vein, the tail is contained between two layers of the splenorenal

ligament. The outer layer of the splenorenal ligament is the posterior layer of the gastrosplenic ligament. Careless division of this ligament may injure the short gastric vessels. The splenorenal ligament is almost avascular, but digital manipulation should stop at the pedicle. Commonly a caudate branch arises from the left gastroepiploic or an inferior splenic polar branch and passes to the tip of the tail of the pancreas. Anticipate this branch in the pancreaticosplenic ligament ***(Skandalakis et al., 2007).***

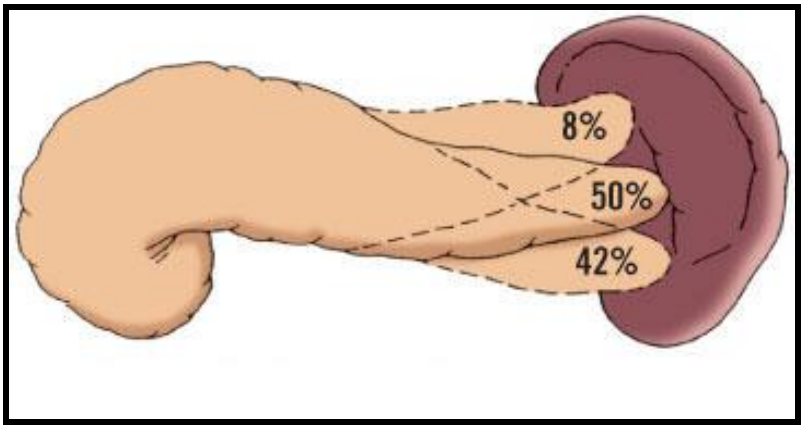


Fig. (5): Relations of tail of pancreas to splenic portas ***(Skandalakis, 2007).***

Pancreatic Ducts:

The pancreatic ducts consist of the main duct "Duct of Wirsung" and the accessory duct "Duct of Santorini".

The main pancreatic duct begins at the tail of the pancreas and runs towards the head of the organ passing nearer

to its posterior than to its anterior aspect and about midway between the superior and inferior borders. After passing the neck region of the gland, the duct turns downward, backward and to the right in the head and runs to the caudal side of the common bile duct with which it unites while running obliquely in the wall of the duodenum. In the tail and body of the pancreas, from 15 to 20 branches enter the duct at right angles with superior and inferior branches tend to alternate. In addition, the main duct may receive a branch draining the uncinate process and in some individuals the accessory pancreatic duct empties into the main duct. Small branches in the head may open directly into the intrapancreatic portion of the common bile duct ***(Sugiyama et al., 2008)***.

The main duct empties with the common bile duct into the duodenum through common channel "Ampulla of Vater" and the major papilla ***(Sugiyama et al., 2008)***.

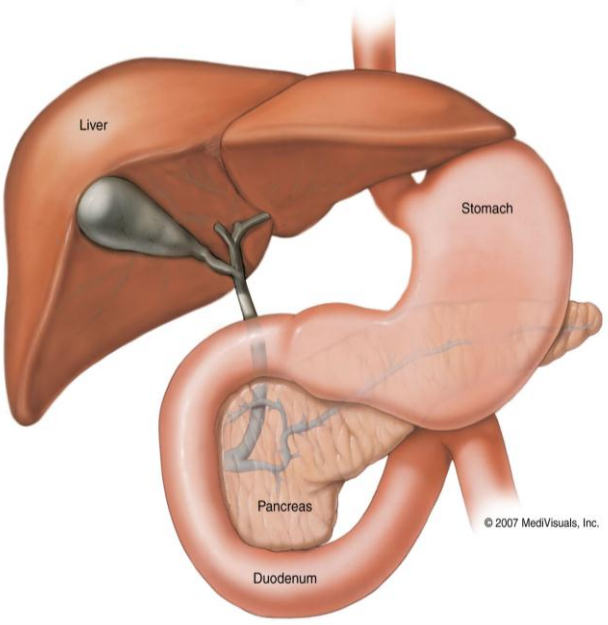


Fig. (6): Ductal anatomy of liver and pancreas ***(Skandalakis et al., 2007)***.

The dimensions of the main pancreatic ducts have been defined in ERCP studies by several authors. Its length varies from 175 to 275mm. The diameter is greatest in the pancreatic head at 3 to 4mm and decreases to 1 to 2 mm in the tail. A gradual increase in ductal diameter occurs with age. A natural narrowing may be present at the point of fusion of the main and accessory ducts ***(Hartley et al., 2003)*.**

The accessory pancreatic duct (of Santorini) may drain the anterosuperior portion of the head, either into the duodenum at the minor papilla or into the main pancreatic duct. Because of the developmental origin of the two pancreatic ducts, several variations are encountered; most can be considered normal. The usual configuration is seen in Figure 4a. The accessory duct

(Santorini) is smaller than the main pancreatic duct (of Wirsung) and opens into the duodenum on the minor papilla ***(Skandalakis et al., 2007).***

Fig. 4 b, c, d, and e, show examples of progressive diminution in size of the accessory duct, and its absence.

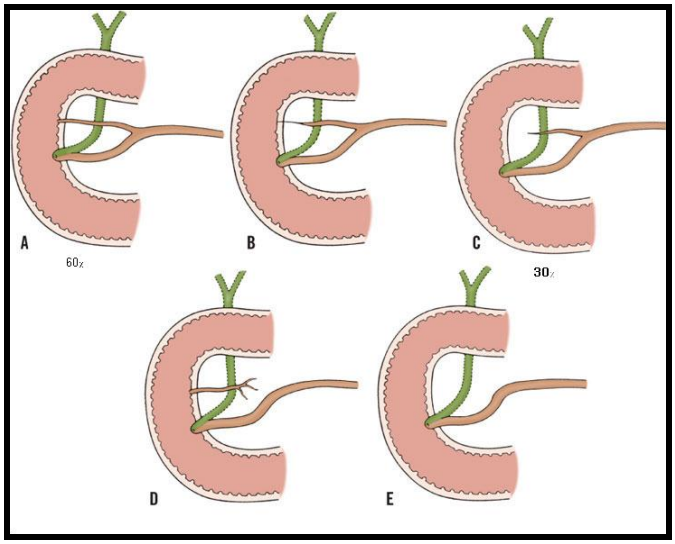


Fig. (7): Variations of pancreatic ducts. Degrees of suppression of accessory duct. ***A,*** Both ducts open into duodenum (60 percent). ***B,*** Accessory duct ends blindly in duodenal wall. ***C,*** Accessory duct ends blindly before reaching duodenum (30 percent). ***D,*** Accessory duct has no connection with main duct. ***E,*** Accessory duct absent ***(Skandalakis et al., 2007).***

The Major Duodenal Papilla

Viewed from the mucosal surface of the duodenum, the papilla is found where a longitudinal mucosal fold or frenulum meets a transverse mucosal fold to form a "T". The major duodenal papilla is most often situated on the postero-medial wall of the second portion of the duodenum but the position

varies. On endoscopy, the papilla is to the right of the spine at the level of second lumbar vertebra in approximately 85% of cases ***(Sugiyama et al., 2008).***

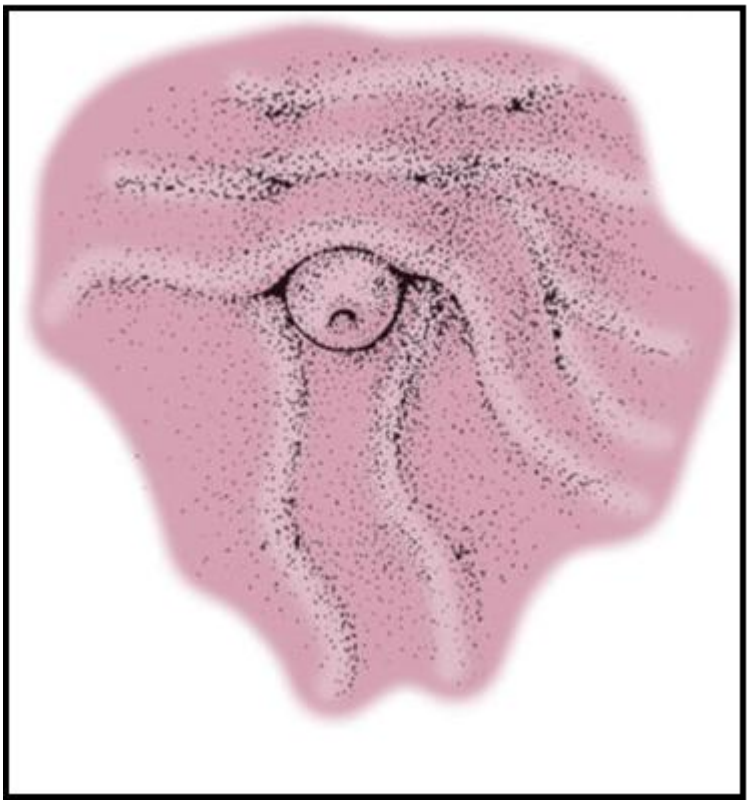


Fig. (8): Arrangement of duodenal mucosal folds indicates site of major duodenal papilla. Mucosal fold may cover orifice of papilla in some cases. Major papilla is rarely this obvious ***(Skandalakis et al., 2007).***

The Minor Duodenal Papilla

It is present in approximately 70% of cases and marks the site of drainage of the accessory duct of Santorini. It is usually

located about 2 cm cephalic and slightly anterior to the major papilla ***(Sugiyama et al., 2008)***.

The Ampulla of Vater

It is a dilatation of the common pancreatico-biliary channel adjacent to the papilla and below the junction of the two ducts. An ampulla was said to be present if the edge of the septum between the main pancreatic duct and the common bile duct did not reach the tip of the major papilla ***(Flati et al., 2004)***.

Michels classification for the relation between the common bile duct and the pancreatic duct openings through the duodenum and the presentation of ampulla of Vater is as follows:

Type 1:

The pancreatic duct opens into the common bile duct at a variable distance from the opening in the major duodenal papilla; the common channel may or may not be dilated (85%).

Type 2:

The pancreatic and bile ducts open close to one another but separately on the major duodenal papilla (5%).

Type 3:

The pancreatic and bile ducts open into the duodenum at separate points (9%) ***(Flati et al., 2004).***

The Sphincter of Oddi:

The present concept is that several sphincters of smooth muscle fibres surround the intramural part of the common bile duct, the main pancreatic duct and the ampulla if present. The sphincteric complex has a separate embryonic origin from that of the duodenal musculature and is functionally separate ***(Flati et al., 2004).***

Arterial Anatomy of the pancreas and duodenum:

The pancreas is supplied with blood from both the celiac trunk and the superior mesenteric artery. In general, it appears that the blood supply is greatest to the head of the pancreas, less to the body and tail and least to the neck ***(Skandalakis et al., 2007).***

Arterial supply to the head of the pancreas:

The head of the pancreas and the concave surface of the duodenum are supplied by two pancreatico-duodenal arterial arcades that are always present. These are formed by a pair of superior arteries (anterior and posterior) from the celiac trunk that join a second pair of inferior arteries from the superior mesenteric artery. These vascular arcades, lying within the

pancreas but also supplying the duodenal wall, are the chief obstacles to complete pancreatectomy without duodenectomy. Ligation of both vessels results in duodenal ischemia and necrosis ***(Skandalakis et al., 2007)***.

Anastomosis around the Head

The gastro-duodenal artery arises as the first major branch of the common hepatic branch of the celiac trunk. About 1 cm from its origin, it gives off the right gastro-epiploic artery and subsequently divides to form the anterior and posterior superior pancreaticoduodenal arteries **(*Skandalakis et al., 2007*)**.

The anterior superior pancreatico-duodenal artery, lies on the surface of the pancreas, gives 8 to 10 branches to the anterior surface of the duodenum, 1 to 3 branches to the proximal jejunum and numerous branches to the pancreas ***(Bertelli et al., 1998)***.

The posterior superior pancreatico-duodenal artery arises from the gastro-duodenal artery. Its course is visible only when the pancreas is turned upward to expose its posterior surface. Some of its branches may anastomose with branches of gastro-duodenal artery or with a right branch of the dorsal pancreatic artery. Other branches supply the anterior and posterior surfaces of the first part of the duodenum ***(Bertelli et al., 1998)***.

The anterior inferior pancreatico-duodenal artery arises from the superior mesenteric artery at or above the inferior margin of the pancreatic neck. It may form a common trunk with the posterior inferior artery. One or both vessels may arise from the first or second jejunal branches of the superior mesenteric artery. Ligation of the jejunal branches endangers the blood supply to the fourth part of the duodenum ***(Skandalakis et al., 2007).***

The most frequent arterial anatomical variant related to the head of the pancreas is a replaced or accessory right hepatic artery arising from the superior mesenteric artery (25% of the population). In 2-4.5% of cases, the main hepatic artery arises aberrantly from this position and its branches therefore arise behind the pancreas and pass to the liver posterior to the portal vein. Much more rarely, an aberrant left hepatic can arise from the superior mesenteric artery. The pulse of an accessory right hepatic artery can normally be palpated in the porta-hepatis posterior to the bile duct. Failure to identify such a vessel can result in ligation of part of the hepatic blood supply during pancreatico-duodenectomy ***(Hartley et al., 2003).***

The Arterial supply to the body and tail of the pancreas

The blood supply to the body and tail of the pancreas is through a number of collateral branches running posteriorly to the pancreas arising principally from the dorsal pancreatic artery. The origin of this artery is variable, arising from the splenic artery in 38%, directly from the celiac trunk in 22%, the common hepatic in 22%, the superior mesenteric artery in 12.7% and the gastro-duodenal artery in 5% ***(Hartley et al., 2003)***.

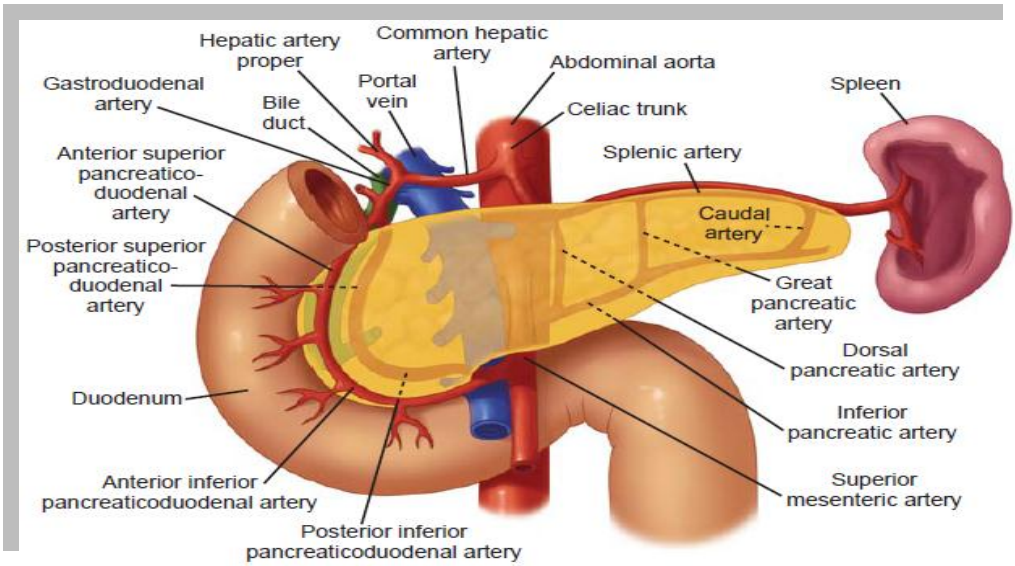


Fig. (9): Blood supply of the pancreas ***(Fisher et al., 2009).***

At the neck, the dorsal pancreatic artery gives a right branch that supplies the head and usually joins the posterior arcade. One or two left branches pass through the body and tail named the inferior or transverse pancreatic artery often making connections with branches of the splenic artery or the left

gastroepiploic artery at the tip of the tail. If there are no anastomosis thrombosis of the inferior pancreatic artery may produce infarction and necrosis. From 2 to 10 branches of the splenic artery anastomose with the inferior pancreatic artery. The largest of these, the great pancreatic artery or the artery of Von Haller, is the main blood supply to the tail of the pancreas ***(Skandalakis et al., 2007)*.**

Venous Anatomy of the pancreas and duodenum:

Attention to the portal venous system in and around the pancreas is the most important aspect in preventing blood loss during pancreatic surgery. These high flow vessels are situated in awkward positions and if they are torn, the application of proximal and distal vascular control is often neither advisable nor possible ***(Skandalakis et al., 2007)***.

The portal vein itself can be further defined as the hepatic portal vein and the pancreatic portal vein. The latter runs behind the neck of the pancreas and the former extends from the superior border of the pancreas to its bifurcation into the right and left portal vein branches. The pancreatic portal vein sits within a groove in the back of the gland. This groove may be further accentuated by the presence of a tumor within the head of the pancreas. It is formed from the confluence of

the splenic and superior mesenteric veins. The inferior mesenteric vein may also contribute to this junction, although it classically joins the splenic vein and occasionally joins the superior mesenteric vein directly. Ligation of the inferior mesenteric vein is often a necessary step in mobilization of the body and tail of the pancreas ***(Hartley et al., 2003)*.**

Venous drainage of the head of the pancreas

The venous drainage of the head of the pancreas and duodenum is via an anterior and a posterior arcade termed the anterior superior and inferior pancreatico-duodenal veins and the posterior superior and inferior pancreatico-duodenal veins. It is important to recognize the common sites at which these vessels join the portal vein when performing a resection of the pancreatic head. The posterior superior vein commonly drains directly into the portal vein near the superior border of the pancreas after crossing anterior to the bile duct. The anterior superior vein drains directly into the gastro-colic trunk. This vessel is both a common landmark and a source of trouble if not dealt with carefully. It is formed by the confluence of the right gastro-epiploic vein and middle colic vein. Ligation of the gastro-epiploic vein near this junction facilitates exposure of

the superior mesenteric vein and pancreatic portal vein ***(Hartley et al., 2003)***.

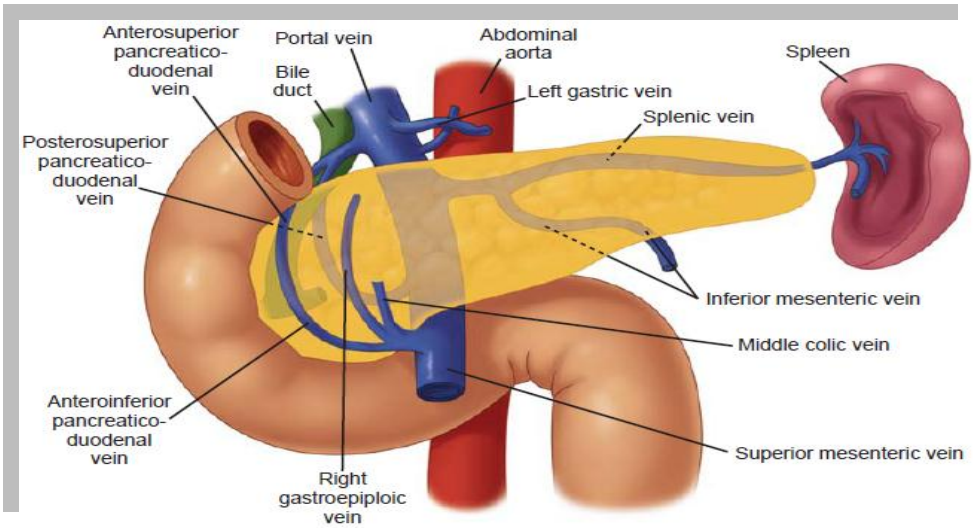


Fig. (10). Venous drainage from the pancreas. The venous drainage of the pancreas allows a pattern similar to the arterial supply, with the veins usually superficial to the arteries. Anterior traction on the transverse colon can tear fragile branches along the inferior border of the pancreas, which then retract into the parenchyma of the pancreas. Venous branches draining the pancreatic head and uncinate process enter along the right lateral and posterior sides of the portal vein. There are usually no anterior venous tributaries, and a plane can usually be developed between the neck of the pancreas and the portal and superior mesenteric veins. ***(Fisher et al., 2009)***

Venous drainage of body and tail of the pancreas

The splenic vein and the inferior pancreatic vein are the main drainage of the body and tail of pancreas. The splenic vein receives short pancreatic tributaries. The inferior mesenteric vein terminates in the splenic vein ***(Ooshima et al., 2010)***.

Lymphatic Drainage of the Pancreas:

Lymphatic drainage is centrifugal to the central groups of nodes. There is no standard terminology for these nodes. Pancreatico-duodenal, pyloric, left gastric, superior pancreatic, splenic hilus, inferior pancreatic, superior mesenteric, aortic and root of mesentery are the chief groups of lymph nodes receiving lymphatic drainage from the pancreas. Only in the body and tail is there a potential division between drainage toward superior or inferior nodal chains. There is evidence that valves in the lymphatics connecting the head of the pancreas and the wall of the duodenum are arranged so that normal flow is from pancreatic to duodenal vessels and not the reverse. There is no communication of lymphatics between pancreas and lesser or greater curvatures of the stomach ***(Skandalakis et al., 2007)***.

In view of the close relation of the pancreas with other organs, it is difficult to know how far to extend resection to remove lymph nodes. The lymphatic drainage is as frustrating a problem as is the arterial supply ***(Evans et al., 2012)***.

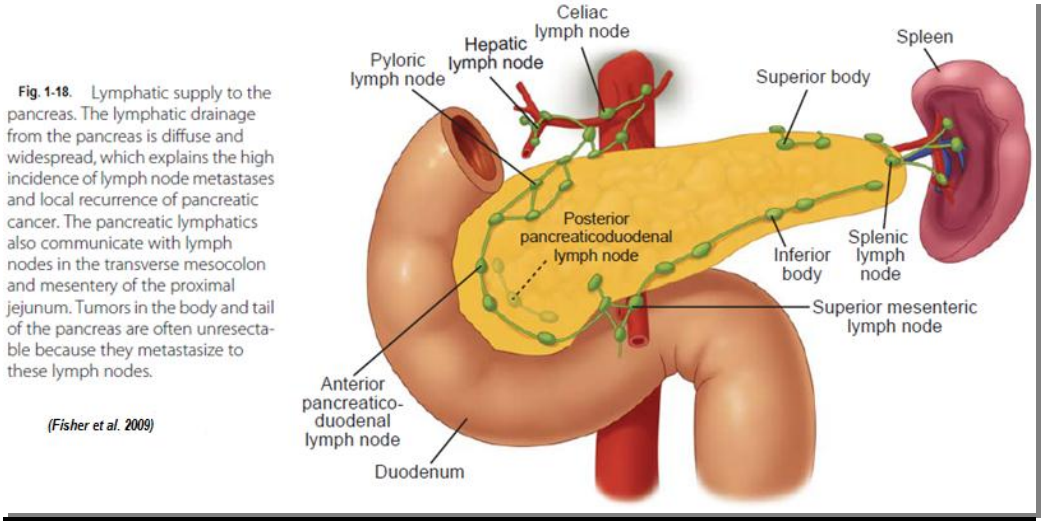


Fig. (11): Lymphatic drainage of the pancreas ***(Fisher et al., 2009).***

Lymph Node Groups

1- Superior nodes: Drain collecting trunks from anterior and posterior upper half of the gland. They are located on the superior border of the pancreas; they can be designated superior head and superior body for lymph nodes in the respective areas,

2- Inferior nodes: Collecting trunks from anterior and posterior lower half of the body and head.

3- Anterior nodes: Two collecting trunks run along the anterior surface of both superior and inferior portion of the head of the pancreas, and extend to the infra-pyloric and anterior pancreatico-duodenal group of lymph nodes.

4- Posterior nodes: Runs along the posterior surface of the superior and inferior portion of the head of the pancreas, they empty into the posterior pancreatico-duodenal lymph nodes as well as into the common bile duct lymph nodes, right lateral aortic lymph nodes and to some lymph nodes at the superior mesenteric artery.

5- Splenic nodes: These lymphatics lead from the tail of the pancreas and drain into the following lymph nodes; those at the hilum of the spleen, phrenolienal ligament and at the inferior and superior lymph node of the tail of the pancreas.

Nerve Supply of the Pancreas:

The pancreas receives both sympathetic and parasympathetic input. The parasympathetic input is by way of vagal fibres passing through the right and left celiac ganglia which are situated adjacent to the celiac axis. The sympathetic input is from the greater and lesser splanchnic nerves which are formed by branches from the T4 through T10 and T9 through L2 sympathetic ganglia, respectively. These then synapse in the celiac plexus and ganglia. Sympathetic and parasympathetic fibres then enter the pancreas by several routes ***(Hartley et al., 2003).***

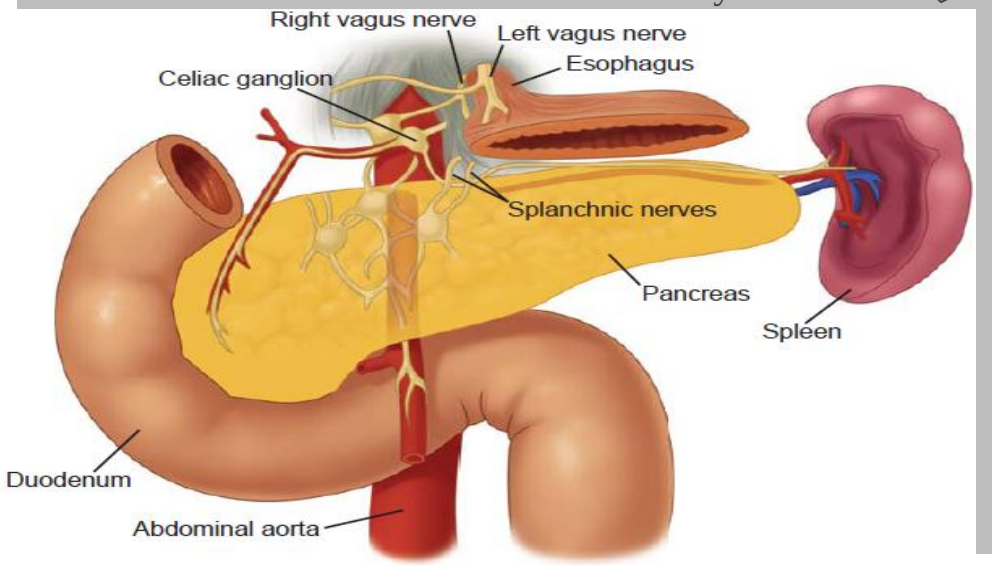


Fig. (12). Innervation of the pancreas. The pancreas has a rich supply of afferent sensory fibers that travel superiorly to the celiac ganglia. Interruption of these somatic fibers with a celiac plexus block can interfere with transmission of pancreatic pain ***(Hartley et al., 2003).***

The significance of the nerve supply clinically is in the relationship to the-control of endocrine and exocrine function, to the peri-neural spread of pancreatic malignancies and to strategies for the control of the pain of chronic pancreatitis and pancreatic malignancy. The parasympathetic nerves along the arteries enter the pancreatic parenchyma and end on intrinsic ganglia which lie near the parenchyma, in keeping with their role in stimulating secretion of pancreatic juice. Parasympathetic afferents provide feedback through the same routes. The sympathetic fibres also enter the pancreas with the arterial branches. They are distributed to the vascular plexus and the islets. With regard to pain control, the approach used

has been the destruction of the splanchnic nerves, either within the thorax where they are formed from the sympathetic chain or by way of ablation within the abdomen as they enter through the hiatus and the horn of the semi-lunar ganglia ***(Hartley et al., 2003).***

Pathology of Pancreatic Tumors

Neoplasms of the exocrine pancreas may be epithelial, mesenchymal or secondary. Confusion over terminology may arise because different names have been given to the same entity; the WHO classification of neoplasms of the exocrine pancreas is used in this contribution ***(Hamilton et al., 2000)*.**

Epithelial neoplasms of the exocrine pancreas in adults can be divided into:

1. Solid neoplasms (ductal adenocarcinoma, its variants, and acinar cell carcinoma), which have a poor prognosis.
2. Cystic neoplasms (serous, mucinous, intraductal papillary and solid pseudopapillary types), which are less common but have a much better prognosis.
3. Mesenchymal tumours and primary lymphoma are exceedingly rare.
4. Metastases may be found in the pancreas, usually renal cell carcinoma and malignant melanoma.
5. Pancreatoblastoma is the commonest malignant pancreatic neoplasm in childhood but is extremely rare.

(Hamilton et al., 2000)

Ductal adenocarcinoma:

Ductal adenocarcinoma accounts for 85-90% of pancreatic neoplasms and is usually diagnosed in the age range 60-80yrs ***(Wilentz, Hruban 2008)***.

Staging: the Japanese Pancreas Society and the UICC TNM classification systems can be used to stage ductal adenocarcinoma ***(Wilentz and Hruban 2008)***.

Prognosis: Extremely poor (mean survival of three months for untreated disease), Survival after radical resection is poor (median of 18 months and a five-year survival of <5%), only 10-15% of cases of ductal adenocarcinoma are potentially operable at the time of presentation ***(Wilentz and Hruban 2008)***.

Pancreatic intraepithelial neoplasia

It describes the microscopic precursors to infiltrating ductal adenocarcinoma that may be seen in resection specimens.

It is divided into four types:

- 1A: mucinous cell hypertrophy/hyperplasia (lesions are flat, tall columnar cells with basally located nuclei) ***(Hruban et al., 2009)*.**

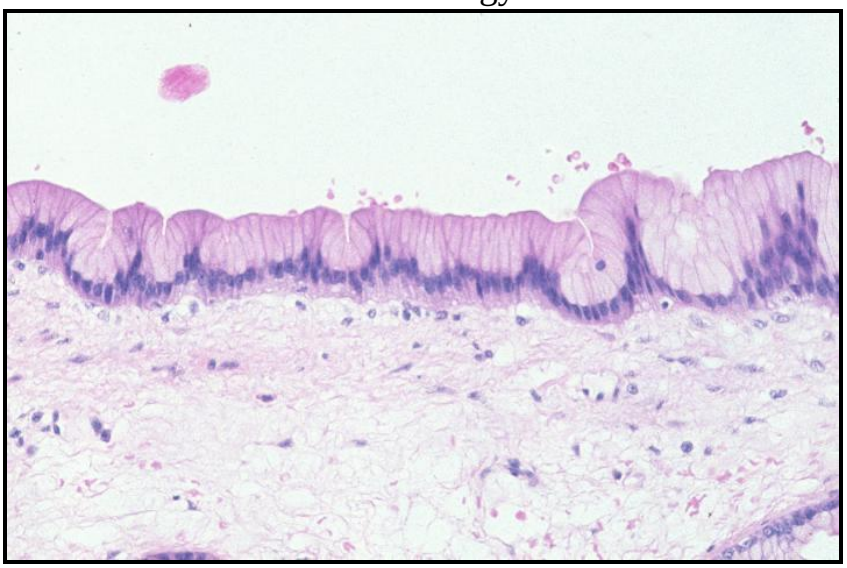


Fig. (13): Type 1A pancreatic intraepithelial neoplasia (Johns Hopkins Pancreas Cancer ***(Hruban et al., 2009)*.**

- 1B: Ductal papillary hyperplasia (lesions show papillary architecture) ***(Hruban et al., 2009)*.**

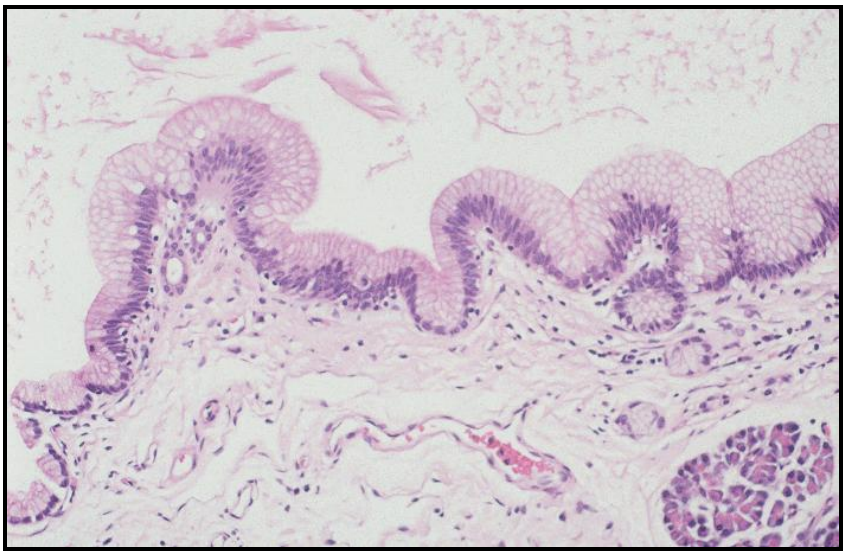


Fig. (14): Type 1B pancreatic intraepithelial neoplasia ***(Hruban et al., 2009)*.**

- Type 2: moderate dysplasia (lesions exhibit nuclear abnormalities, such as a loss of polarity or nuclear crowding) ***(Hruban et al., 2009)*.**

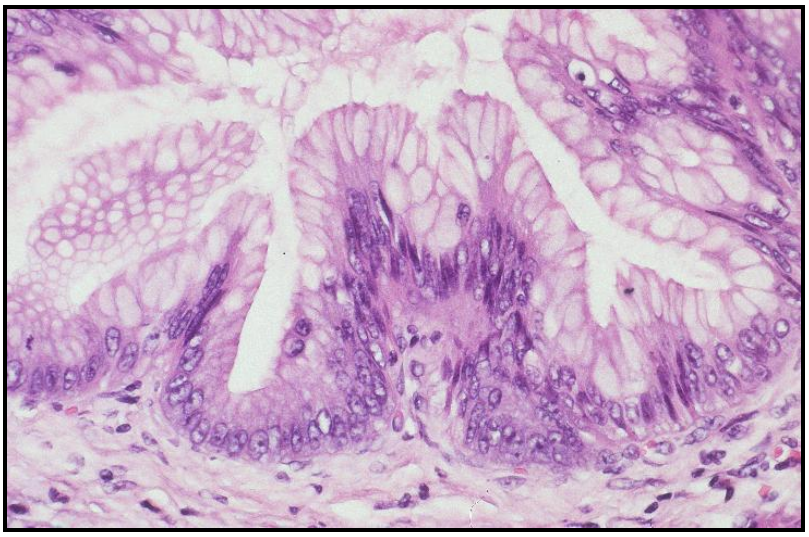


Fig. (15): Type 2 moderate dysplasia ***(Hruban et al., 2009)*.**

- Type 3: severe dysplasia, carcinoma *in situ.* (lesions have marked nuclear and cytologic abnormalities) ***(Hruban et al., 2009)*.**

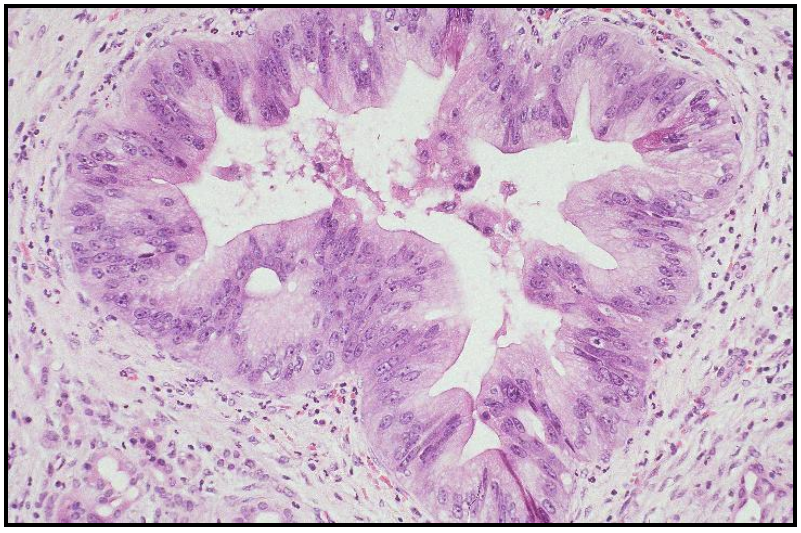


Fig. (16): Severe dysplasia (carcinoma in situ) ***(Hruban et al., 2009)*.**

Most ductal adenocarcinomas in surgical series are found in the head of the pancreas because they present with obstructive jaundice; at an earlier stage than those in the body or tail which may be large and widely invasive at the time of diagnosis, involving the spleen, stomach, adrenal gland and colon ***(Hruban et al., 2009)*.**

Macroscopically

Ductal adenocarcinomas are firm, ill-defined masses with a solid, yellow-white cut surface replacing the normal lobular architecture. They usually invade the common bile duct or the pancreatic duct, leading to chronic obstructive pancreatitis.

Distinguishing adenocarcinoma from chronic pancreatitis macroscopically may be difficult ***(Campbell et al., 2010)*.**

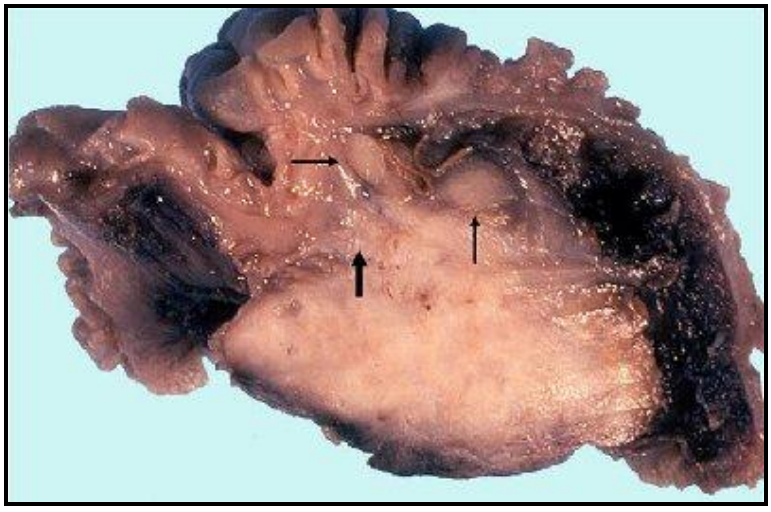


Fig. (17): Macroscopic picture of adenocarcinoma of pancreas ***(Hruban et al., 2009)*.**

Microscopically

Ductal adenocarcinomas are graded as well, moderately or poorly differentiated depending upon the worst (not the predominant) degree of differentiation ***(Campbell et al., 2010)*.**

- Well-differentiated ductal adenocarcinoma is characterized by large- to medium-sized glandular structures, resembling ducts, with mucin-containing columnar cells with eosinophilic or clear cytoplasm. The nuclei are round-ovoid with nucleoli, and may show loss of polarity; mitoses are scarce.
- Moderately-differentiated ductal adenocarcinomas show a mixture of medium-sized, duct-like and tubular structures with incomplete glands and variation in size and shape of the nucleus. There are mitoses but less production of mucin.
- Poorly-differentiated ductal adenocarcinomas comprise small irregular glands, small nests and individual tumour cells with marked nuclear pleomorphism, scant mucin and more mitoses. All grades of ductal adenocarcinoma are associated with abundant myxoid desmoplastic stroma.

Most have perineural invasion within the tumour and extending into the peripancreatic nerve plexus. Lymphovascular invasion is extremely common ***(Campbell et al., 2010)*.**

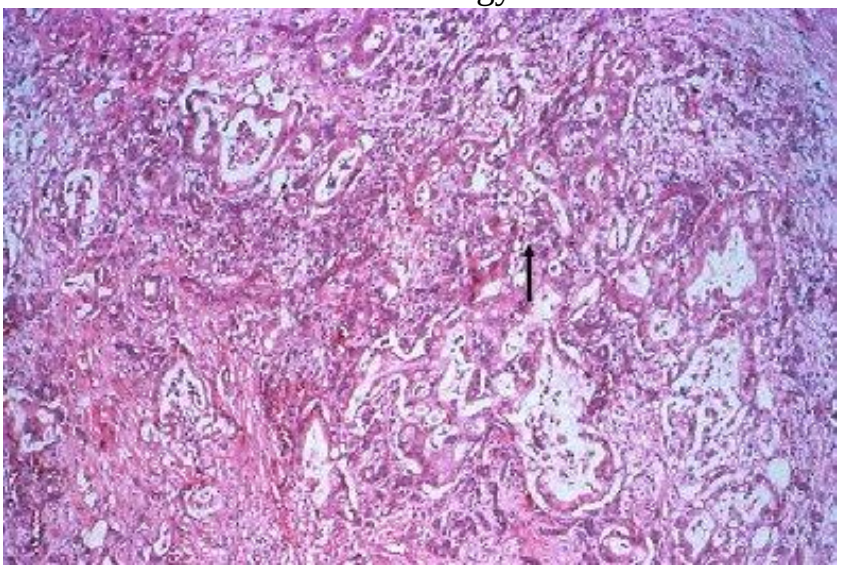


Fig. (18): Moderately differentiated adenocarcinoma. Irregularly shaped malignant glands are embedded in chronically inflamed fibrous tissue ***(Hruban et al., 2009)*.**

Histological variants of ductal adenocarcinoma

a. Mucinous non-cystic (colloid) carcinoma: is uncommon and consists of large pools of mucin (accounting for at least 80% of the tumour) partially lined by, or containing dissociated floating tumour cells (some of which may be signet-ring cell type, colloid carcinoma should not be confused with mucinous cystic neoplasms, which have a much better prognosis ***(Klöppel et al., 2006)*.**

b. Signet-ring cell carcinoma: is extremely rare and comprises predominantly (>50%) of signet-ring cells with intracellular mucin. Prognosis is very poor ***(Klöppel et al., 2006)*.**

c. Adenosquamous carcinoma: is rare; it is composed of a mixture of glandular and squamous components, with the latter comprising >30% of the tumour. Prognosis is poor with median survival of 12 months ***(Klöppel et al., 2006)*.**

d. Undifferentiated (anaplastic) carcinoma: is also called (giant cell carcinoma', 'pleomorphic large cell carcinoma' or 'sarcomatoid carcinoma). It comprises sheets of large pleomorphic and/or spindle cells with scant stroma. Some glandular differentiation is usually present. Perineural, lymphatic and vascular invasion are present in most cases. The mean survival is six months ***(Klöppel et al., 2006)*.**

e. Undifferentiated carcinoma with osteoclast-like giant cells: is rare, comprising pleomorphic and spindle neoplastic mononuclear cells with scattered non-neoplastic osteoclast-like giant cells.

These giant cells:

- May have >20 nuclei.
- Are often found around areas of haemorrhage
- May contain haemosiderin.

The atypical mononuclear cells express epithelial markers; the giant cells show histiocytic differentiation. Mean survival is 12 months ***(Klöppel et al., 2006)*.**

f. Hepatoid carcinoma: A very rare variant showing hepatocellular differentiation ***(Klöppel et al., 2006)*.**

g. Medullary carcinoma: is a poorly differentiated carcinoma with pushing margin, sheets of tumour cells, necrosis and microsatellite instability ***(Klöppel et al., 2006)*.**

h. Mixed ductal-endocrine carcinoma (also known as 'mixed exocrine- endocrine tumour') is rare and is characterized by ductal carcinoma cells and endocrine cells in the primary tumour and in the metastases. The endocrine cells should comprise at least one-third of the tumour by definition. Prognosis is identical to that for typical ductal adenocarcinoma ***(Klöppel et al., 2006)*.**

Serous cystic neoplasms

Serous microcystic adenoma

Serous microcystic adenoma (also known as 'glycogen-rich cystadenoma' and 'serous cystadenoma') is a benign neoplasm, accounting for 1-2% of exocrine pancreatic neoplasms, and occurring predominantly in females (mean age 65yrs). It occurs as a solitary lesion anywhere in the pancreas, ranging from 1-25 cm in diameter, but typically 5-10cm. Rare cases of multiple tumours have been reported ***(Solcia et al., 2007)*.**

Macroscopically:

There is a round, well-circumscribed mass with an irregular bosselated external aspect. On sectioning, there is a characteristic sponge-like or honeycomb appearance with multiple tightly-packed tiny cysts of varying sizes (typically <5mm) containing clear watery serous fluid with fibrous septa. Larger neoplasms may show a central or eccentric fibrous stellate scar with calcification ***(Solcia et al., 2007).***

Microscopically:

The cysts are thin-walled and lined by glycogen- rich cuboidal or flattened epithelial cells with clear cytoplasm, well-defined cytoplasmic borders and central small uniform nuclei. There may be papillary projections of epithelium into the cysts, but mitoses or nuclear pleomorphism are absent. A fibrous pseudocapsule may separate the neoplasm from the adjacent pancreatic parenchyma ***(Solcia et al., 2007).***

Prognosis: complete resection is curative but serous microcystic adenoma can be managed conservatively ***(Solcia et al., 2007).***

Variants

- ***Serous oligocystic adenoma:*** The oligocystic variant has few relatively large cysts or a single macroscopic cyst up to 8 cm in size and lacks a stellate scar ***(Solcia et al., 2007).***
- ***Serous cystadenocarcinoma***

(Solcia et al., 2007)

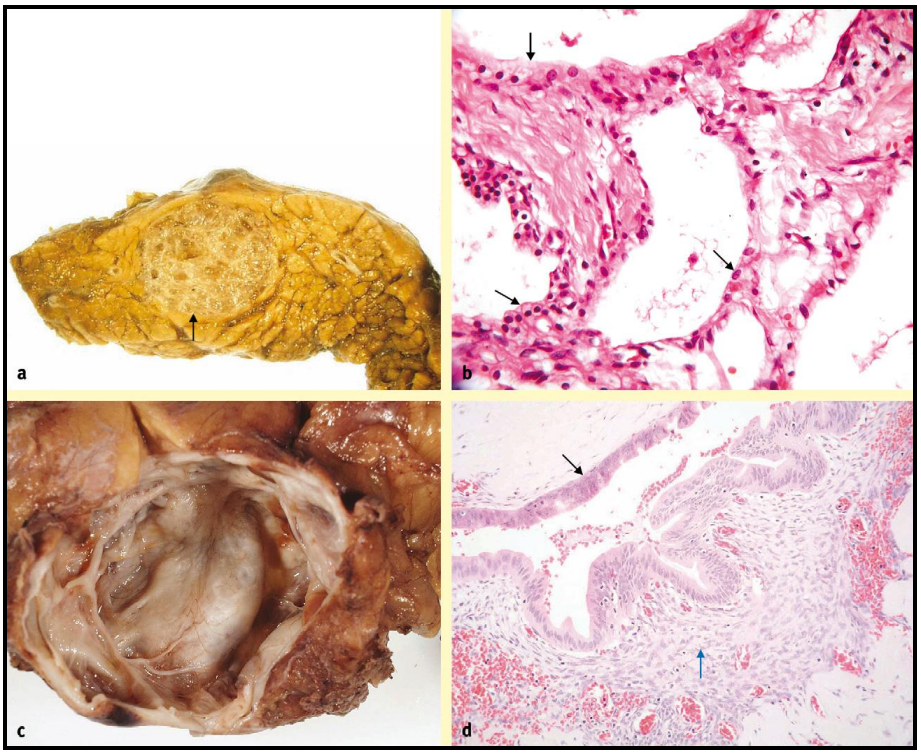


Fig. (19): Serous microcystic adenoma with **a** honeycomb cut-surface (arrow) and **b** a lining of clear, glycogen-rich, cuboidal cells (arrows). This **c** oligocystic lesion may be a mucinous cystic neoplasm, pseudocyst or serous oligocystic adenoma. Borderline mucinous cystic neoplasm showing **d** tall columnar mucin-producing epithelium with moderate dysplasia (black arrow) and typical ovarian stroma (blue arrow) ***(Solcia et al., 2007)*.**

Mucinous cystic neoplasms

Mucinous cystic neoplasms account for 2-5% of exocrine pancreatic neoplasms, occur almost exclusively in females (mean age 50yrs) and are found predominantly within the tail of the pancreas ***(Wilentz et al., 2008)*.**

Macroscopically

They are usually solitary and form a welldefined, smooth round mass, ranging from 1cm to 30cm in diameter (mean size 5-10cm). Opening reveals a multilocular mucin-filled cyst with a thick fibrous pseudocapsule that may show foci of calcification; cysts may contain haemorrhagic material. The inner lining of the cysts may be smooth, trabeculated or papillary; solid nodules may be present. The papillary and solid areas must be sampled because these are likely to show high-grade dysplasia or malignancy ***(Tanaka et al., 2006).***

Microscopically

The cysts are lined by columnar mucin-producing epithelium with associated pathognomonic ovarian-type stroma. The epithelium may show intestinal differen-tiation with scattered neuroendocrine cells ***(Klöppel et al., 2006).***

Classification: mucinous cystic neoplasms are classified in the WHO classification as:

- Benign (mucinous cystadenoma).
- Borderline/low-grade malignant (mucinous cystic neoplasm with moderate dysplasia).
- Malignant (mucinous cystadenocarcinoma, non-invasive or invasive).

(Hamilton et al., 2000)

Prognosis: the prognosis for non-invasive mucinous cystic neoplasms is excellent if excision is complete; there is a risk of recurrence if excision is incomplete. The prognosis for invasive mucinous cystadenocarcinoma depends upon the extent of invasion ***(Klöppel et al., 20066).***

Intraductal papillary mucinous neoplasms (IDPMNs)

IDPMN (also known as intraductal mucin hypersecretory neoplasm, 'mucinous ductal ectasia' and 'diffuse papillomatosis). Is characterized by cystic dilation of the main pancreatic duct or its major branches (branch-duct type), together with associated intraductal proliferation of mucin-producing cells. IDPMNs account for 1-5% of exocrine pancreatic tumours. More common in males (mean age of 60 years) and occur predominantly in the head of the pancreas. There is an association between IDPMNs and other neoplasms. Many patients are diagnosed with chronic pancreatitis before the diagnosis of IDPMN is made ***(Sohn et al., 2004).***

Macroscopically

IDPMN may be localized or diffuse within the main pancreatic duct or within the branch ducts. The cystically dilated ducts are distended with mucus that may extrude from the ampulla of Vater, a diagnostic endoscopic feature. The

lining of the ducts is usually papillary but may be smooth ***(Kloppel et al., 2006)*.**

One must identify:

- Communication with the duct system.
- Mucin extrusion from the ampulla.
- The distribution of the lesion to distinguish IDPMN from the mucinous cystic neoplasms.

Microscopically:

The cystic spaces or dilated ducts are lined by tall, columnar mucin-containing epithelial cells that usually form papillary projections. The papillae may show intestinal, pancreaticobiliary or gastric ('null')-type morphology ***(Kloppel et al., 2006)*.**

Classification:

IDPMNs are classified according to the grade of epithelial dysplasia into:

- Adenoma.
- Borderline malignant potential.
- Carcinoma *in situ*/non-invasive or invasive (papillary mucinous carcinoma).

IDPMNs must be sampled comprehensively because of the variability within a single tumor. About one-third of IDPMNs have associated invasive adenocarcinoma that may be a colloid/mucinous carcinoma (and behave in an indolent fashion) or may be a ductal adenocarcinoma (which is more aggressive) ***(Kloppel et al., 2006)***.

Prognosis:

The prognosis for IDPM adenomas and border-line tumours is excellent (five-year survival of 100%). Survival rates for non-invasive carcinomas are high. Survival for patients with invasive carcinoma may be higher than for patients with ductal adenocarcinoma. Incomplete excision can lead recurrence, and is a particular risk in multifocal disease ***(Kloppel et al., 2006)***.

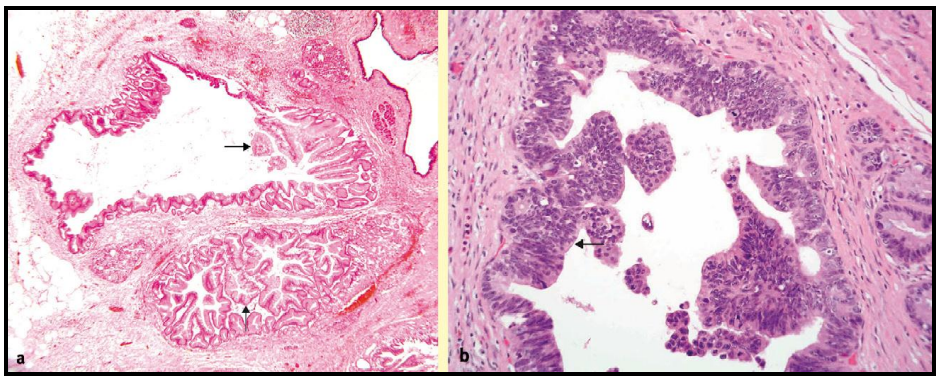


Fig. (20): Intraductal papillary neoplasm showing **a** typical papillary architecture (arrows) and **b** severe dysplasia (carcinoma *in situ*; arrow) ***(Solcia et al., 2007)***.

Solid pseudopapillary neoplasms

Solid pseudopapillary neoplasm (also known as 'solid and cystic tumour', 'papillary cystic tumour' and 'Frantz's tumour'). A clinically benign or low-grade malignant neoplasm that has cystic degeneration within a solid neoplasm, rather than true epithelial-lined cysts. Solid pseudopapillary neoplasm accounts for 1-5% of exocrine pancreatic tumours, predominantly affects adolescent and young females (mean age 25 years) and may be found anywhere within the pancreas(but usually in the tail) ***(Lack, 2003).***

Macroscopically

Solid pseudopapillary neoplasm is usually a solitary, sharply-demarcated, round mass (mean diameter of 10cm) with a fibrous pseudocapsule. The cut surface shows brown solid areas and cystic spaces. There may be extensive central necrosis with a rim of preserved tumour beneath the fibrous pseudocapsule. Calcification may be present ***(Lack, 2003).***

Microscopically

There are solid monomorphic areas of uniform polygonal cells resembling endocrine tumours, and pseudopapillary areas with intervening cystic spaces containing red blood cells, necrotic debris and foamy macrophages, The neoplastic cells have eosinophilic or clear cytoplasm and may contain periodic

acid Schiff-positive hyaline globules, Glycogen and mucin are absent; mitoses are rare. The nuclei are round/ oval with fine chromatin and are often grooved. The connective tissue between the neoplastic cells may be hyalinized, sclerotic and/or calcified ***(Lack, 2003).***

Prognosis is very good; complete resection is usually curative ***(Solcia et al., 2007)***.

Pancreatoblastoma

Pancreatoblastoma is a rare malignant epithelial tumour of young children (mean age four years) It can also occur in adults, It is found more commonly in the head and tail of the pancreas, and may range in size from 1 cm to 20cm, It is usually a well- circumscribed, soft, lobulated tumour with fibrous bands ***(Campbell et al., 2010).***

Staging

In the United States, the most widely used staging system for pancreatic cancer is that developed by the American Joint Committee on Cancer in cooperation with the TNM Committee of the International Union Against Cancer. This classification represents an expression of the anatomical extent of the disease, taking into account the size and invasiveness of the primary tumor (T), the presence or absence of regional nodal metastases (N), and the existence or nonexistence of distant metastatic disease (M).

Histologic grade, although shown to have prognostic significance in some studies, is not included in the current classification ***(Edge et al., 2010).***

Surgical resection is the only potentially curative treatment for pancreatic adenocarcinoma, although most of the patients are found with unresectable disease at the time of surgery. It should be limited to those patients without metastatic disease and in which the entire lesion can be resected with negative margins. In some patients the only obstacle for a radical resection is represented by the involvement of the portal or superior mesenteric vein. In the past, this was considered a contraindication for pancreaticoduodenectomy. This was due to technical difficulties and poor long term survival rate ***(Lall et al., 2007).***

Currently, venous resection and reconstruction can be performed with morbidity and mortality rates similar to surgery in patients without vascular invasion that showed survival advantage. Reflecting these management changes, isolated venous involvement is considered a locally invasive tumor, but potentially resectable (T3). However, the involvement of the celiac artery or superior mesenteric artery remains a T4 lesion, due to the concomitant presence of extensive celiac or mesenteric neural invasion. It is important to note that in carefully selected cases, early arterial invasion can be considered resectable ***(Varadhachary et al., 2006).***

TNM classification of pancreatic cancer

Primary tumor (T)

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

Tis: Carcinoma in situ.

T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension.

T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension.

T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery.

T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor).

(Devita, 2008)

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Regional lymph node metastasis.

Distant metastasis (M)

MX: Distant metastasis cannot be assessed.

M0: No distant metastasis.

M1: Distant metastasis.

(Devita, 2008)

Table (1): American Joint Committee on Cancer: Cancer Staging for Exocrine Pancreas

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (also PanIN 3)		
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
REGIONAL LYMPH NODES (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
DISTANT METASTASIS (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

(Devita, 2008)

Genetics of pancreatic cancer:

At the genetic level, cancer of the pancreas has been the focus of much recent study, making it among one of the better characterized cancers. A large number of resected pancreatic

adenocarcinomas have been investigated for genetic alterations in cancer causing genes. In general, these genes can be divided into 3 broad groups. First, tumor suppressor genes are genes that normally function as genetic barriers to control cellular proliferation. When these genes are inactivated by genetic events such as mutation, deletion, chromosome rearrangements, or mitotic recombination, their function as growth suppressors can be lost, resulting in abnormal growth regulation. The second type of cancer-causing gene is an oncogene. Oncogenes are derived from normal cellular genes called proto-oncogenes, and they encode for proteins that when over expressed or activated by mutation, possess transforming properties. The third broad class of cancer causing genes are the DNA mismatch repair genes. These genes normally function to insure the fidelity of DNA replication. When these DNA repair genes are dysfunctional, errors in DNA replication are not repaired ***(Yao et al., 2011)*.**

Oncogenes:

Activating point mutation in the K-ras oncogene are the most common genetic alteration identified in pancreatic cancer. Point mutations in codons 12, 13, or 61 of the K-ras oncogene impair the intrinsic GTPase activity of its gene product, resulting in a protein that is constitutively active in signal transduction. Mutations of K-ras possess transforming

properties. K-ras mutations have been found in 80% to 90% of pancreatic cancers, most of these being mutations in codon 12, and most being guanine to thiamine transversions, Importantly, these mutations are relatively easy to detect, making K-ras a potential candidate for the development of molecular-based screening tests for pancreatic cancer ***(Yaw et al., 2011)***.

DNA mismatch repair genes:

Six human genes responsible for DNA mismatch repair have been discovered. These include hMSH2, hMLHI, hPMSI, hMSH6, GTBP, and hMSH3. This mismatch repair enzymes function as heterodiamers to repair single based-pair changes and small insertion/deletions that occur during DNA replication. A recent report by *Goggins and colleagues* noted that 4% of pancreatic adenocarcinomas were characterized by disorder of DNA repair genes. Notably, these tumors were poorly differentiated and were marked histologically by expanding borders and a prominent syncytial growth pattern. This limited data available suggest that this subgroup of tumors may have a more favorable prognosis than the typical adenocarcinoma without mutation in DNA repair genes ***(Goggins et al., 2008)***.

Role of Growth Factors:

Accumulating data suggest an emerging role for various polypeptide growth factors and their receptors in the regulation of pancreatic cancer. These growth factors are produced by many cells, act at or near their sites of expression through autocrine and paracrine mechanisms, and may also exert their effects before release from the cell via a so-called "juxtacrine mechanism". Evidence suggests that the over expression of some specific growth factors and their receptors may play a role in the biologic aggressiveness of the pancreatic cancer ***(Korc, 2009)***.

Epidermal growth factor:

The epidermal growth factor receptor (EGFR) is a transmembrane protein which binds a family of peptides that includes epidermal growth factors (EGF),TGF-2, heparin-binding, EGF-Hke growth factor, amphiregulin, betacellulin, and epiregulin, All 6 of these growth factors are potent mitogenes toward a variety of cell types, and all may contribute to pancreatic cell growth: For example, the addition of these exogenous growth factors to cultured human pancreatic cell lines enhances their growth ***(Korc, 2009)***.

With the exception of epiregulin, the other 5 EGF-like ligands are expressed at high levels in pancreatic cancer cells,

suggesting that tumor cells may derive a growth advantage as the result of excessive EGFR activation. Although, some of these ligands have also been identified in chronic pancreatitis, over expression of EGFR and its ligands has been correlated with enhanced metastatic potential, and a short postoperative survival ***(Lemoine et al., 2009)***.

Transforming Growth Factor-B:

The TGF-B polypeptide family has been implicated in the regulation of many cellular processes including cellular growth and differentiation, regulation of cellular matrix, and the expression of cell adhesion molecules ***(Korc, 2009)***.

All 3 mammalian TGF-B isoforms are overexpressed in human pancreatic cancer and such overexpression has been associated with a significant decrease in patient survival ***(Friess et al., 2010)***.

Fibroblast Growth Factors:

The fibroblast growth factor (FGF) family consists of numerous polypeptide growth factors, which are mitogenic and angiogenic, that have an affinity for heparin with resultant alterations in cell differentiation and tissue repair. The actions of FGFs are mediated by 4 distinct high-affinity transmembrane tyrosine kinase FGF receptors. Human pancreatic cancer cell lines express various levels of FGFs, with apparently distinct

localization of FGF overexpression. For example, FGF-1 and FGF-2 are predominantly overexpressed within the tumour mass, whereas FGF-5 overexpression is seen in adjacent stromal element and infiltrating macrophages ***(Manson, 2011)***.

Cultured human pancreatic tumour cell lines express high-affinity FGF receptors, and the growth of these cell lines is enhanced by the exogenous addition of FGF. It is currently believed that FGFs participate in the enhancement of pancreatic cell growth and may contribute to abnormal epithelial-mesenchymal interactions within the growing neoplasm ***(Leung et al., 2009)***.

Insulin and Insulin like Growth factor:

The insulin -like growth factor (IGF) family consists of 3 members: IGF-1, IGF-2 and Insulin. IGF-1 is overexpressed in pancreatic cancer cells; the addition of exogenous IGF-1 enhances the growth of cultured pancreatic cancer cells. It also appears that IGF-1 may act through the autocrine and paracrine mechanisms to enhance pancreatic cancer cell growth in Vivo ***(Bergmann et al., 2008)***.

Diagnosis of Pancreatic Cancers

Epidemiology and Clinical Picture of Cancer Pancreas:

Incidence of pancreatic carcinoma:

The incidence of pancreatic cancer has tripled over the past 40 years throughout the West. It is highly fatal and has one of the lowest 5 year survival rates (1-2%) of all cancers. About 29.000 new pancreatic cancers are diagnosed each year in the USA and the disease now accounts for 10% of all the cancers of the digestive tract (second behind colorectal cancer). It is the fourth most common cancer of all sites as a cause of death (behind lung, colorectal, and breast) ***(Cuschieri et al., 2010)*.**

Risk factors of pancreatic cancer:

A. Geographic and Demographic patterns

In the United States, the incidence rates of pancreatic cancer were reported to have increased nearly 3 fold from 1920 to 1978. Since that time, they have remained constant or even declined, slightly. In nearly all European countries, the incidence rates of pancreatic cancer have continued to rise. Although worldwide geographic differences in the incidence rates of pancreatic cancer are not striking, it is generally true that the incidence rates of pancreatic carcinoma are highest in

Western and industrialized countries and lowest in underdeveloped nations. The demographic features of pancreatic cancer have been thoroughly investigated advancing age is a risk factor for pancreatic cancer. Incidence rates for pancreatic cancer increase steadily with age, with over 80% of cases occurring in individuals between the ages of 60 and 80 years. Cases in individuals younger than 40 years of age are uncommon, Pancreatic cancer still occur more frequently in men, the incidence and mortality rates have increased relatively in women since 1974 but have stabilized or decreased slightly in white men ***(Gold and Goblin, 2008).***

The incidence and mortality rates for pancreatic cancer in blacks in the United States of both sexes are higher than in whites ***(Gold and Goblin, 2008).***

Several studies in USA population have reported that pancreatic Cancer occurs more frequently among Jews than among Catholics or Protestant ***(Gold and Goblin, 2008).***

Pancreatic tumors in Egypt:

DIFFERING MOLECULAR PATHOLOGY OF PANCREATIC ADENOCARCINOMA IN EGYPTIAN AND UNITED STATES PATIENTS

Variations in genetic mutations in pancreatic carcinoma between different populations have not been studied

extensively, especially in developing countries where pancreatic cancer is rare. A study of the comparison between molecular pathology of 44 pancreatic carcinoma patients residing in a heavily polluted region in the Nile River Delta in Egypt and the findings with tumors from 44 United States patients was done. The study identifies that there are differences in the types of mutations found in tumors from pancreatic carcinoma patients in Egypt and the US, and suggests that environmental factors may explain these differences ***(Soliman et al., 2006).***

GEOGRAPHICAL CLUSTRING OF PANCREATIC CANCERS IN NORTHEAST NILE DELTA REGION OF EGYPT

The northeast Nile Delta, Egypt's most polluted region appears to have a high incidence of geographic clustering of pancreatic cancer which might be associated with environmental pollution. Using data from the medical records of the gastrointestinal surgical center of Mansoura University in the Dakahleia Province of Egypt and detailed geographical maps of the northeast Nile Delta region, the residences are plotted of all 373 patients who had pancreatic cancer diagnosed between 1995 and 2000. The study region has 15 administrative districts and the number of pancreatic cancer patients was determined for this study. Monte Carlo simulation identified

statistically significant clustering of pancreatic cancer in five subdivisions located near the Nile River and Delta plains. This clustering was independent of population size and formed two larger clusters. When data were analyzed by sex, clustering of pancreatic cancer was observed in the same five subdivisions for men but only two subdivisions showed clustering for women, Together, the data suggest that there is clustering of pancreatic cancer cases in the northeast Nile Delta Region and that this clustering may be related to water pollution. These data also warrant future studies of the association between water pollution and pancreatic cancer in the region ***(Soliman et al., 2006).***

METAL POLLUTION RECORDS IN CORE SEDIMENTS OF SOME RED SEA COASTAL AREAS, KINGDOM OF SAUDI ARABIA

In the last three decades, the industrial and human activities in the coastal area of Saudi Arabia have increased dramatically and resulted in the continuous invasion of different types of pollutants including heavy chemical metals in core sediments. Cadmium was one of those metals collected from three major industrialized areas; Jeddah, Rabigh and Yanbu, along the coast of Saudi Arabia to determine its spatio-temporal distribution and to assess the magnitude of pollution and its potential biological effects. The Cadmium concentrations

showed high fluctuations with depth which indicated land base sources of this element to the studied areas ***(Badr et al., 2008).***

B. Environmental risk factors:

1- Cigarette smoking:

Cigarette smoking is the only environmental risk factor that has been consistently associated with pancreatic cancer. The estimates of risk associated with current smoking are generally a 2- to 3- folds increase for both males and females. The risk increases with the number of cigarettes smoked and risk continues 10 to 15 years after smoking cessation. An elevated risk also has been associated with pipe and cigar smoking. The mechanism by which tobacco products cause pancreatic cancer appears to be related to tobacco-specific nitrosamines that reach the pancreas either through the blood or bile that is in contact with the pancreatic duct. Alternatively, smoking can elevate blood lipids, which also may increase the risk of pancreatic cancer. Pancreatic tumors can be induced experimentally in animals by the administration of tobacco-specific nitrosamines. either in the water or parenterally ***(Cameron et al., 2011)***.

2- Diet:

A second proposed risk factor associated with pancreatic cancer is diet. A high intake of animal fat or meat has been

linked to the development of pancreatic carcinoma. Japanese studies have shown that daily consumption of meat increased the risk of developing pancreatic cancer by 15 times, perhaps suggesting the adaptation to Western diet had contributed to the recent increase of pancreatic cancer in that country. It is felt that diets high in fat stimulate cholecystokinin (CCK) release, which may induce pancreatic ductal hyperplasia and hypertrophy of pancreatic acinar cells. Increased protein intake associated with meat consumption also may affect pancreatic enzyme output. Increased trypsin in the intestinal lumen leads to further increased CCK release, while excess protease secretion may damage ductal epithelium and promote carcinogenesis through the increased cell proliferation or the repair process. High intake of fresh fruits and vegetables and increased dietary fiber have been sighted as protective against pancreatic cancer ***(Cameron et al., 2011)*.**

The ability of vitamins C and E to inhibit nitrosation could help to explain the inverse association between pancreatic cancer and consumption of fresh fruits andvegetables***(Carter, 2010)*.**

3- Consumption of beverages and Alcohol:

Considerable controversy surrounds the possibility of a link between coffee drinking and pancreatic cancer. While the possibility of a link between coffee consumption and pancreatic

cancer can't be completely discounted, a causal association hasn't been established. As in case of coffee drinking, the available data show no consistent relationship between alcohol and the risk of developing cancer ***(Carter, 2011).***

Alcoholics have so many other problems that pancreatic cancer is one of their lesser worries. The main reason for considering an alcohol - pancreatic cancer association is that pancreatitis which can be induced by alcohol has been associated with pancreatic cancer ***(Cuschieri et al., 2010).***

C. Effect of diseases:

1- Diabetes Mellitus

An apparent association between diabetes and pancreatic cancer has been reported by many investigators. Although the data are somewhat inconsistent, the bulk of the data indicate no consistent association of diabetes with cancer of the pancreas except when cases are included where the diabetes was diagnosed within between 1 to 5 years-before the cancer diagnosis ***(Yao, 2011).***

Chow and Colleagues have suggested that the risk of the development of pancreatic carcinoma in a person with diabetes decreases with the duration of diabetes and that the elevated risk is limited to patients with non-insulin dependent diabetes or

with diabetes diagnosed at age 40 years or older ***(Chow et al., 2009)***.

These relationships suggest that diabetes is more commonly an early symptom of pancreatic cancer rather than a causative influence ***(Yao, 2011)***.

It is suggested that diabetes mellitus may be caused by either pancreatic duct obstruction with the development of chronic pancreatitis or release and action of tumoral islet amyloid polypeptide, which has a diabetogenic effect ***(Mulvihill, 2011)***.

The development of diabetes in a patient after 40 years of age should be considered a clue to the diagnosis of pancreatic cancer ***(Cameron et al., 2011)***.

2- Pancreatitis:

Chronic pancreatitis has been-suggested as a riskfactor for pancreatic cancer because of the frequent association between the two conditions ***(Cameron et al., 2011)***.

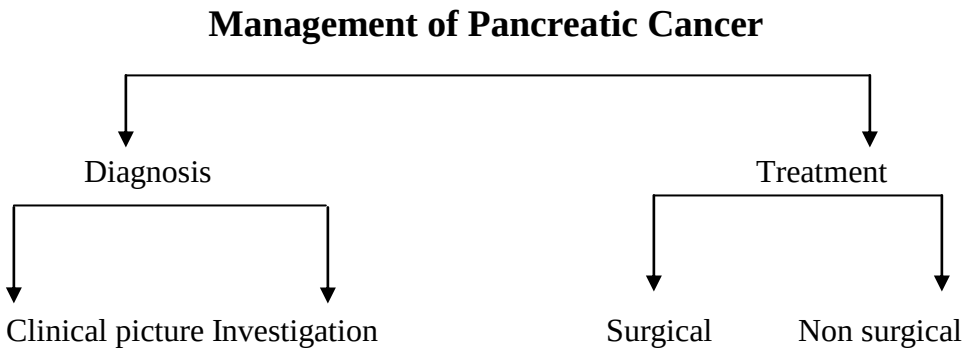
However it must be emphasized that pancreatitis may have three different meanings in pancreatic cancer patient:

1. Histologic pancreatitis invariably co-exists with pancreatic cancer, presumably due to ductal obstruction or direct destruction of parenchymatous tissues.

2. The acquired variety of chronic pancreatitis (clinical entity) doesn't seem to be related to pancreatic cancer.

The hereditary type of chronic pancreatitis seems to have a higher predisposition to pancreatic cancer than the general population ***(Cuschieri et al., 2010).***

Table (2): Management of pancreatic tumors



(Cuschieri et al., 2010)

I. Diagnosis

A. Clinical picture

1- Carcinomaof the head of the pancreas:

About 75% of patients with carcinoma of the head of the pancreas present with weight loss averages about 40 kg., obstructive jaundice, and deep seated abdominal pain, Back pain occurs in 25% of patients and is associated with a worse prognosis. In general, smaller tumors confined to the pancreas are associated with less pain, Hepatomegaly is present in half of patients but does not necessarily indicate spread to the liver.

A palpable mass, which is found in 20%, nearly always signifies surgical incapability, Jaundice is present in most patients but fluctuates in about 10%. Cholangitis occurs in only 10% of patients with bile duct obstruction. A palpable tender gallbladder in a jaundiced patient suggests neoplastic obstruction of the common bile duct **(Courvoisier's sign)** mostoften due to pancreatic cancer. This finding is present in about half of cases. Jaundice is often accompanied by pruritisespecially of the hands and feet. Weight loss is severe by the time the patient presents to the hospital. Haematemesis and melena may be late features due to mucosal invasion or portal hypertension ***(Cuschieri et al., 2010)*.**

2- Cancer of the body and tail of the pancreas:

Pain and weight loss are the two main consistent symptoms. The pain may initially be dull and vague, localized to the epigastrium or to the back, or it may move to either upper quadrant. It may be episodic and related to meals or it may become constant and severe. In late cases, the patient learns to obtain partial relief by flexing the trunk forward. Severe pain invariably indicates extension of tumor into the perineurallymphatics and the posterior parieties ***(Cuschieri et al., 2010)*.**

Migratory thrombophlebitis **(Trousseau's sign)** can be present in any patient with advanced cancer, It is not specifically indicative of pancreatic carcinoma and by itself does not merit diagnostic laparotomy or laparoscopy.Physical examination in the early stages may reveal surprisingly few abnormal physical signs. In late cases, abdominal masses or liver metastases may be palpable. A rectal shelf may be evident on rectal examination in the rectovesical or rectovaginal pouch **(Blumer's shelf)**, there may be evidence of ascites, and distant metastases may be present in the supraclavicular fossa **(Troisier's sign)** ***(Cuschieri et al., 2010)*****.**

Delay in diagnosis:

Over 90% of patients with pancreatic cancer present in the late stage of their disease at time when there is no chance of cure and often even meaningful palliation cannot be achieved. The factors responsible for late diagnosis are:

1) The tumor is asymptomatic in the early stages:

There is some evidence that pre-clinical phase of pancreatic cancer may be present for months or an even year before the tumor appears.

2) Patient delay:

The early symptoms are often vague and non-specific and the patient tolerates the discomfort.

3) Physician delay:

The physician often does not have a high index of suspicion and fails to properly evaluate the patient in the face of a vague history and normal physical examination. The patient may not have ready and easy access to competent diagnostic centers. Centralization or regionalization of the management of difficult pancreatic problems is long delayed because of the dependence on sophisticated diagnostic and therapeutic methods ***(Cuschieri et al., 2010).***

B. Investigations

Pancreatic cancer is an aggressive lesion. Fewer than 10% of patients have tumour confined to the pancreas at the time of diagnosis; over 40% have locally advanced disease, and more than 50% have distant spread ***(Singh et al., 2011).***

The most important factor determining outcome is whether the tumour is resectable. In general, larger tumors are less likely to be resectable. Thus, efforts have been focused toward early diagnosis when the tumour is still small. This has been difficult because pancreatic cancer remains asymptomatic or produces only vague symptoms at an early stage ***(Podolsky, 2010).***

To improve survival, diagnosis probably has to be made years before the patient is symptomatic. Screening tests for

pancreatic cancer are being investigated ***(Todd and Reber, 2011).***

A. Laboratory investigations

There are no specific lab tests for pancreatic cancer. For periampullary carcinoma, virtually all patients present with liver function tests abnormalities, including increased levels of total billirubin, alkaline phosphatase & transaminases. They reflect either common bile duct obstruction or hepatic metastasis. The billirubin level of neoplastic obstruction averages 18 mg/dL much less than that generally seen with benign disease of the bile ducts. Only rarely are serum aminotransferase levels markedly elevated. Serum amylase elevation is seen in only 5% of patients with pancreatic cancer ***(Todd andReber, 2011).***

Repeated examination of stool specimens for occult blood gives a positive reaction in many cases ***(Way and Dohertly, 2010).***

Role of tumour markers:

The results of CA19-9 have been the most encouraging; the test is easy to perform, inexpensive, non invasive and can be helpful in planning treatment and in early discussions with the patient ***(Connel, 2010)***.

However, the test is more likely to be positive when the tumour is large, so it is not likely to be able to diagnose early lesions ***(Malesci et al., 2007).***

As a result, CA19-9 should not be used as a screening test in asymptomatic individuals due to the fact that a significantly sized lesion needs to be present for the test to be positive. In addition, there are false positives with other tumors producing elevations such as upper gastrointestinal cancers, colon cancers, etc. Also, there are no studies to prove that CA19-9 is a worthwhile screening test that improves patient outcome.

However, in patients with jaundice, an elevated CAI9-9 is very helpful. Obviously, if the patient is jaundiced and has a significantly elevated CA19-9, then the assumption is that the patient has a malignancy as the cause, be it pancreatic, ampullary, or bile duct carcinoma. On the other hand, a negative test, especially a false-negative test, is of no help ***(Connel, 2010).***

B. Imaging Techniques

1- Pelvi-abdominal ultrasound:

It is used to confirm the mechanical nature of the obstruction and determine whether the site of obstruction is the intrahepatic or extrahepatic portion of the biliary tree ***(Evans et al., 2011)***.

Extrahepatic obstruction from a periampullary malignancy would be expected to show dilated intrahepatic and extrahepatic biliary radicals. Ultrasound (US) is a relatively inexpensive test with a sensitivity of 70% and a specificity of over 90% for the diagnosis of pancreatic cancer ***(Lawson, 2008)*.**

However, in 20% of patients the examination is unreliable due to body habitus or overlying bowel gas.

Although US provides some information about the relationship of the tumour to surrounding structures, CT is much better in this regard ***(Todd and Reber, 2011)*.**

Endoluminal ultrasonography (EUS) has similar accuracy to CT in the staging of pancreatic cancer but is undoubtedly better for the detection of early pancreatic tumours as small as 2–3 mm. The addition of fine needle aspiration (FNA) cytology to EUS is highly accurate for identifying malignancy in lesions identified on EUS and not seen on CT scan. The drawbacks of EUS are that distant metastases and nodal involvement cannot be accurately assessed. The sensitivity and specificity of endoscopic retrograde cholangiopancreatography (ERCP) alone are 70-82% and 88-94%, respectively, in symptomatic patients or those with suspected pancreatic cancer but should no longer be used as a pure imaging tool given the developments in

magnetic resonance cholangio- pancreatography and EUS. ERCP is used to insert biliary stents for relief of obstructive jaundice and to gain cytological diagnosis by sampling or brushings. These can also be obtained atpercutaneous transhepatic cholangiography (PTHC) ***(Lemke et al. 2007).***

2- Computerized tomography:

In patients with suspected or known pancreatic cancer, the main preoperative radiological staging study is the triphasic helical CT scan of the pancreas with 1 -2 mm sections through the head of the gland ***(Bold el al., 2009).***

CT has a sensitivity of at least 80% and a specificity of 95% for the diagnosis of pancreatic cancer ***(Freeny, 2005).***

These data were derived from experience with conventional imaging techniques; the newer helical (spiral) CT equipment provides images of even greater quality and precision. Lesions of 2 cm or greater should be detectable. CT is more reliable than US because it visualizes the entire pancreas and the presence of bowel gas does not interfere. It should be emphasized that helical computerized tomography is not used so much to make a definitive diagnosis of pancreatic cancer, but rather to determine resectability. The problem with using the CT to make a definitive diagnosis is the high rate of false negatives (approximately 20%). Often, the reason for the

false negative is a relatively small cancer in the head of the pancreas that cannot be adequately imaged on the CT scan. However, these small lesions are often the earliest and the most resectable. The presence of a mass in the head of the pancreas may be helpful but is not 100% diagnostic for carcinoma because CT scanning has a false-positive rate of less than 10%, which is usually attributed to focal pancreatitis, or variations in normal pancreatic anatomy***(Kloppel et al., 2011)***.

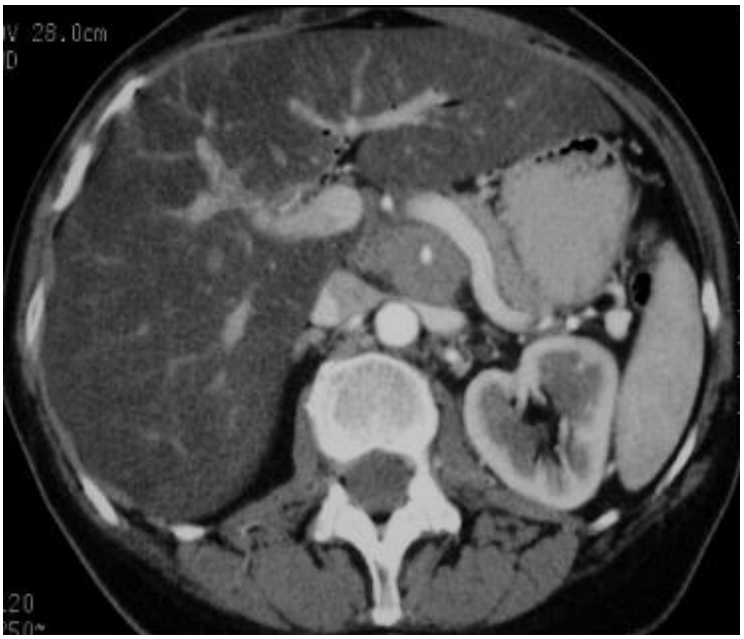


Fig. (21): The CT criteria used to define a potentially respectable pancreatic cancer ***(Kloppel et al., 2011).***

CT criteria for resectability:

The CT criteria used to define a potentially resectable pancreatic cancer are:

1- The absence of extra pancreatic disease.

2- A patent superior mesenteric-portal vein confluence.

3- No direct tumour extension to the celiac axis or superior mesenteric artery.

(Evans et al., 2011)

On the other hand, the ability of a CT scan to predict that a tumour will be 'unresectable' has been reported to be as high as 95%. It is suggested that the accuracy of such a prediction is related to the expertise of the radiologist, the nature of the CT finding on which the prediction is based, and the experience and philosophy of the surgeon. Thus, if the apparent presence of liver metastases is the basis for the prediction of unresectability, the level of reliability is high. If the radiologist finds evidence for tumour invasion of the superior mesenteric vein, with less than circumferential narrowing of the vessel, the implications of such a finding are less clear. For example, some surgeons will often resect such a tumor including a segment of the vein in an effort to treat a patient who seems to be a reasonable candidate. The pathologist eventually may determine that the adherence to the vein was only inflammatory, or that tumour had extended only to the adventitia of the vessel. Whereas it is not believed that many such patients are cured by the resection, some may be and some are undoubtedly palliated. In any case, the tumors clearly were resectable. A more accurate term to use

in these efforts to stage a tumour preoperatively might be 'resectable for cure' ***(Todd and Reber, 2011).***

For patients with locally advanced tumors by CT scan, portal vein invasion is a common finding on preoperative imaging. Tumors large enough or unfortunately placed to invoke the portal vein (PV) often involve the superior mesenteric artery (SMA), However, isolated PV involvement is not infrequently seen and can be resected safely ***(Way and Dohertly, 2010).***

Therefore, in the absence of distant metastatic disease and obvious arterial involvement, patients with suspected isolated portal vein involvement should still be considered candidates for resection ***(Hartley and Jones, 2003).***

Although no test is perfect in the investigation of unresectability, helical CT scans have a low incidence of false positives that would preclude the patient from potentially curable operation. Also the small incidence of false negatives (false resectable) can be accepted because the majority of patients who are found at operation to have additional disease not appreciated on CT scan can still have a palliative bypass and benefit from the operation. Again, perhaps in the future even better studies can be developed to determine resectability; however, helical CTs seem to be the best test at the present time ***(Connel, 2010).***

Usually, the CT scan will show intrahepatic and extrahepatic biliary duct dilatation that extends down to the pancreatic level. If it does, then one can assume that this is due either to pancreatic cancer or a periampullary lesion and proceed accordingly. Obviously, if there is no extrahepatic biliary dilatation or when the dilatation extends only partially down the duct, other diagnoses should be suspected and substantiated with either endoscopic retrograde cholangiopancreaticography (ERCP) or percutaneous trans-hepatic cholangiography (PTC) ***(Hartley and Jones, 2003).***

3- Angiography:

Once considered crucial in the assessment of operability, angiography is now virtually unnecessary. It was argued that the venous phase of the arteriogram was fundamental if invasion of the superior mesenteric and portal vein were to be excluded.

This has now been superseded by improvements in helical CT scanning, which is able to accurately determine venous involvement.

The issue of preoperative detection of vascular anomalies should not be an indication for routine angiography in the hands of experienced pancreatic surgeons ***(Shankar et al., 2011).***

4- Endoscopic retrograde cholangio-pancreatography (ERCP):

ERCP has a sensitivity of 95% and a specificity of 85%, in the diagnosis of pancreatic cancer ***(Frick, 2002)***.

The procedure can be performed successfully in more than 90% of patients and it detects some tumors not seen on CT. The classic finding that suggests pancreatic cancer is obstruction of both the bile and pancreatic ducts in the head of the pancreas, the so-called 'double-duct' sign. Endoscopic retrograde cholangiopancreatography (ERCP) is a technique that combines the use of endoscopy and fluoroscopy to diagnose and treat certain problems of the biliary or pancreatic ductal systems. Through the endoscope, the physician can see the inside of the stomach and duodenum, and inject dyes into the ducts in the biliary tree and pancreas so they can be seen on X-rays ***(Farrell et al., 2010)***.

ERCP is used primarily to diagnose and treat conditions of the bile ducts, including gallstones inflammatory strictures (scars), leaks (from trauma and surgery), and cancer. ERCP can be performed for diagnostic and therapeutic reasons, although the development of safer and relatively non-invasive investigations such as magnetic resonance cholangio-pancreatography (MRCP) and endoscopic ultrasound has meant

that ERCP is now rarely performed without therapeutic intent ***(McAlister et al., 2011)***.

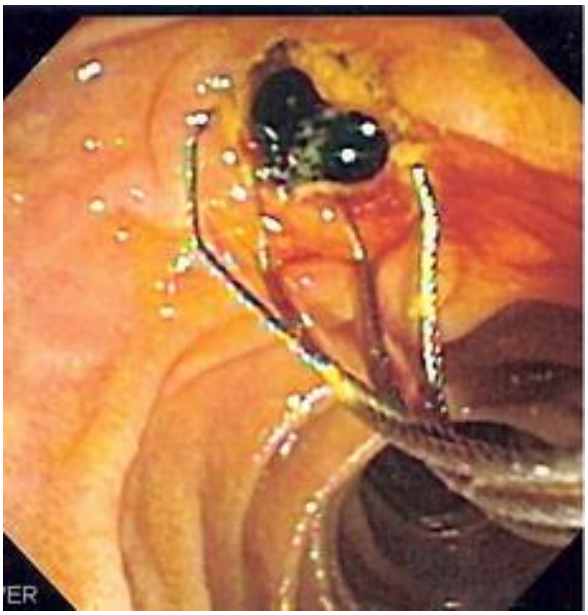


Fig. (22): Duodenoscopic image of two pigment stones extracted from common bile duct after sphincterotomy ***(McAlister et al., 2011)***.

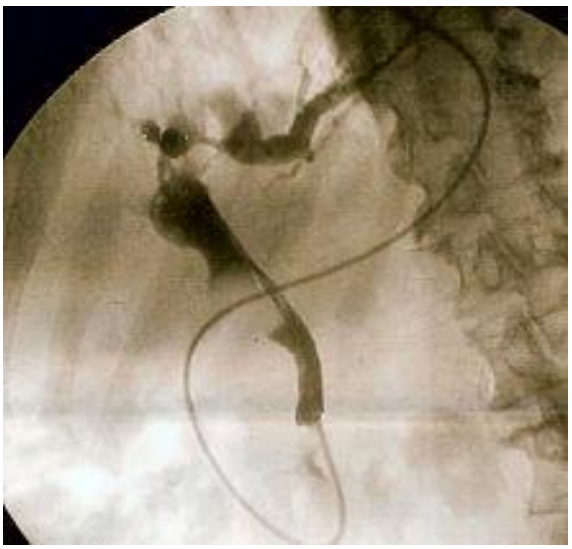


Fig. (23): Fluoroscopic image of common bile ductstone seen at the time of ERCP. The stone is impacted in the distal common bile duct. A nasobiliary tube has been inserted ***(McAlister et al., 2011)***.

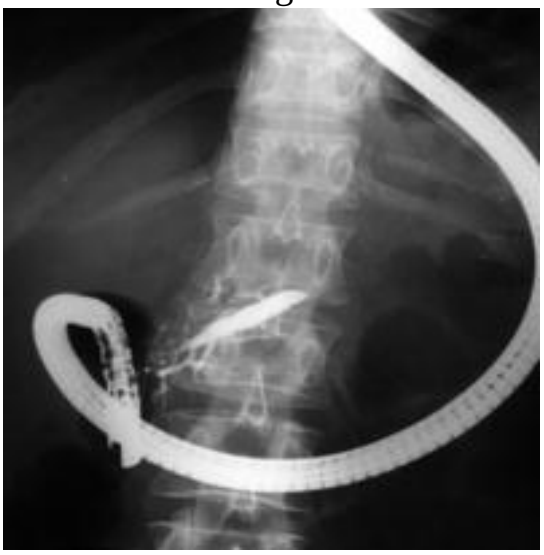


Fig. (24): Fluoroscopic image showing dilatation of the pancreatic duct during ERCP investigation. Endoscope is visible ***(McAlister et al., 2011)***.

At the time of ERCP, brushings for cytology may be obtained from the pancreatic duct, which has a sensitivity of about 60% in proving the diagnosis of malignancy ***(Hartley and Jones, 2003)*.**

Also, endoscopic ultrasound (EUS) can be done at the time of the ERCP or as a subsequent procedure. Although very much operator dependent, EUS does have the capability to accurately characterize changes in pancreatic gland substance as inflammatory or neoplastic. EUS can be particularly helpful in identifying small pancreatic lesion surrounded by chronic fibrosis or edema in the head of the gland. In addition, accurate Histologic characterization of mass lesions in the head of the pancreas is possible when multiple and deep needle biopsies

are carefully done. Aspiration of cystic fluid can also be accomplished readily and can help to differentiate a cystic neoplasm of the pancreas that may require a form of pancreatic resection from an inflammatory pseudocyst that may perhaps be treated with a surgical drainage procedure ***(Shankar et al., 2011).***

It is less useful at demonstrating malignant lymph node involvement due to confusing factors such as nodal reactivity and inability to differentiate nodal micrometastases ***(Shankar et al., 201l).***

ERCP can also be used for stent placement, which has an important role in the palliation of patients who do not require surgery. Some have argued that ERCP should be done routinely in these patients because it may be possible to determine the origin of the tumour (e.g., ampulla of Vater instead of the pancreas). Although this may be true in some cases, ERCP should not be done routinely. The reasons for this include:

1- The real purpose of preoperative testing is to determine resectability and this is not possible with an ERCP.

2- There are potential complications of ERCP, including cholangitis, perforations, etc.

3- The operation for ampullary, distal bile duct, or pancreatic cancers is exactly the same, that is, a pancreaticoduodenectomy. Knowledge of a specific diagnosis preoperatively usually will not change the operative plans.

(Connel, 2010)

If a patient has a history typical for pancreatic cancer (e.g., pain, jaundice, weight loss) with a mass in the head of the pancreas evident on CT scan, then an ERCP is unnecessary for the diagnosis and generally adds nothing to the work-up that is no value to either the patient or the surgeon ***(Todd and Reber, 2011).***

5- Magnetic resonance imaging (MRI):

Although a relatively new technique for assessing pancreatic lesions, MRI is particularly useful at differentiating inflammatory from neoplastic pancreatic lesions ***(Trede et al., 2011).***

In terms of vascular invasion, MRI was found to be the most sensitive, specific and accurate staging method. In addition to vascular evaluation, MRI is highly accurate in predicting liver metastasis, lymph node involvement and extrapancreatictumour extension ***(Harrison et al., 2012).***

Recent studies comparing new-generation MRI technology with helical CT suggest equivalence in terms of predicting resectability for pancreatic head carcinomas. MRI of the dilated biliary tract in a jaundice patient may also provide information comparable with ERCP, while sparing the patient an interventional procedure and exposure to allergic contrast media. Disadvantages of MR1 include its greater expense compared with CT, its inability to obtain tissue sampling, and its relative unfamiliarity to most surgeons, and gastroenterologists. None of these should necessarily preclude utilization of MRI, yet it remains to be determined whether MRI will ultimately replace CT or where in the management algorithm it should be employed ***(Talamonti et al., 2012)*.**

The use of magnetic resonance endoscopy may in the future improve the accuracy of MRI. At present, both MRI and CT scanning give additional information such that both techniques are of value in assessment ***(Shankar et al., 2011)*.**

6- Positron emission tomography (PET):

During the process of malignant transformation, the majority of cells become avid glucose scavengers, with increased glucose transport and utilization, several authors have reported overexpression of glucose transporter 1 (Glut-1) in human pancreatic adenocarcinoma ***(Higashi et al., 2009)*.**

In addition to increased transport, the metabolism of glucose has also been noted to be altered in malignancy. Hexokinase and other glycolytic enzyme have been shown to be overexpressed in multiple cancers, including pancreatic adenocarcinoma ***(Reske et al., 2012).***

These malignancy-associated alterations in glucose metabolism provide, the basis for the application of physiologic imaging using 18FDG.18FDG-PET takes advantage of this enhanced glucose uptake to functionally identify malignant tissue. 18FDG is a glucose analogue labeled by the positron-emitting radio-isotope fluorine-18 at the C2 position. This agent is actively taken up into the cell and phosphorylated by hexokinase during the first step in the glycolytic pathway. Unlike normal glucose, however, phosphorylated 18FDG cannot continue glycolysis and becomes trapped within the cell.18FDG-PET images are evaluated both visually and semi-quantitatively using an objective value based on local 18FDG concentration corrected for injected dosage per body weight (the standard uptake ratio" SUR") ***(Rose et al., 2009).***

By providing reliable preoperative distinction between benign and malignant pancreatic lesions, 18FDG-PET may facilitate selection of the optimal surgical approach. For example, for patients with no discrete mass on CT but a positive signal on 18FDG-PET (SUR>2.5), the surgeon may confidently

undertake resection with a minimal risk of inadvertently resecting benign disease. When 18FDG- PET imaging is entirely normal (SUR - 0.0), the likelihood of an occult adenocarcinoma appears to be negligible. The use of 18FDG-PET in the evaluation of suspected recurrent pancreatic adenocarcinoma has not yet been reported. This technique may be particularly useful when CT identifies an indistinct region of change in the bed of the resected pancreas that is difficult to differentiate from postoperative or postradiation fibrosis.As with any imaging modality, 18FDG-PET has identifiable limitations in the evaluation of pancreatic cancer. First, this functional imaging modality obviously cannot replace anatomic imaging in the assessment of local tumourresectability.Second, theoretical concerns have been raised regarding the limitations of this modality in a population of patients with a significant rate of glucose intolerance, false-negative 18FDG-PET scans have been noted in hyperglycemic patients and patients with diabetes, presumptively because of increased competition for glucose uptake. However, the true impact of serum glucose levels on the accuracy of 18FDG-PET in pancreatic cancer remains controversial ***(Rose et al., 2009)*.**

In addition, both glucose and 18FDG are avidly taken up by inflammatory cells. False-positive 18FDG-PET scans have been noted in the presence of acute and chronic inflammatory

reactions, including granulomatous disease, osteomyelitis, and abdominal abscesses especially, microabscesses in a locus of mass-forming pancreatitis .Inflammation as a source of false positive I8FDG-PET studies should therefore always be considered when interpreting these images. Overall, 18FDG-PET imaging appears to a sensitive and specific adjunct to CT when applied to the preoperative diagnosis of pancreatic adenocarcinoma. It is expected for this imaging modality to be of particular use in patients with suspected pancreatic cancer in whom CT fails to identify a discrete tumour mass. By providing preoperative documentation of pancreatic malignancy in these patients, laparotomy may be undertaken with purely therapeutic intent ***(Rose et al., 2009)*.**

18FDG-PET imaging would also appear to be useful in the clarification of CT-occult metastatic disease, allowing non therapeutic resection to be avoided altogether in this group of patients ***(Rose et al., 2009)*.**

Obtaining tissue diagnosis

Preoperative fine-needle aspiration (FNA) for cytology can be obtained percutaneously using a fine-gauge needle under CT or US guidance.

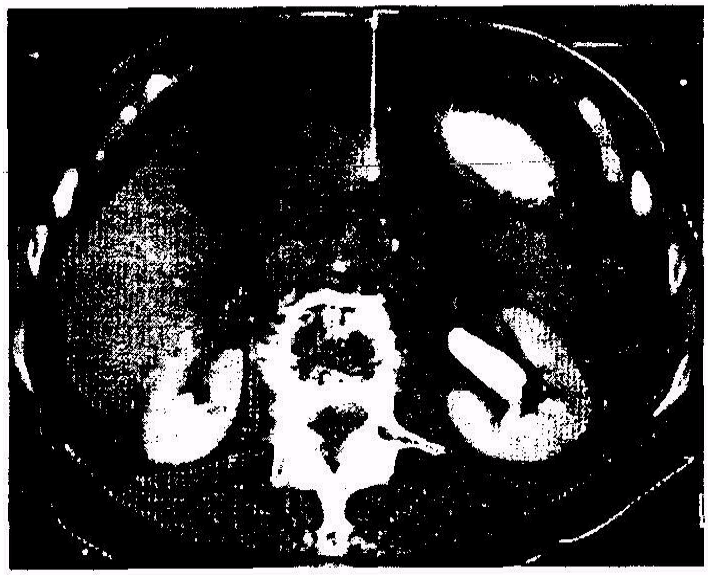


Fig. (25): Unresectable pancreatic carcinoma. CT guided fine-needle aspiration biopsy confirming the diagnosis of pancreatic carcinoma ***(Rose et al., 2009)*.**

The characteristic findings of malignancy are single or irregularly arranged clusters of cells exhibiting pleomorphism, large vesicular nuclei, and prominent nucleoli. The sensitivity is 85% and the specificity is almost 100%. It is important to stress that a negative FNA never rules out the possibility of malignancy. Complications include hemorrhage, pancreatitis, pancreatic fistula, and seeding of the needle tract with cancer cells, all of which are uncommon ***(Todd and Reber, 2011)*.**

It is not believed that this study should be done routinely in the work-up of these patients. It is uncomfortable for the patient, it is associated with considerable cost, and, in patients who are operative candidates, it does not change management ***(Todd and Reber, 2011)*.**

If the FNA is positive and the tumour is otherwise resectable, we proceed to operation. If the test is negative, we still must assume that this is a cancer that has been missed because of the false negatives (15%) and still proceed with operation ***(Connel, 2010)*.**

FNA is used in situations in which the cytological diagnosis of malignancy will have a clear impact on subsequent management. For example, in a patient with a tumour in the body of the pancreas who has no symptoms for which surgical palliation is required, FNA could confirm the diagnosis, and chemotherapy and/or radiation could be given. In a patient with obstructive jaundice and a mass in the head of the pancreas, who may not be a candidate for resection because of coexisting medical problems, FNA would be useful to confirm the diagnosis. Then a stent could be placed for palliation, and surgery simply to obtain tissue for diagnosis would have been avoided ***(Todd and Reber, 2011)*.**

Most pancreatic surgeons do not require histologic proof of malignancy before proceeding with resection. They decide to resect on the basis of the patient's history and the gross findings at operation. Of course, this issue is always discussed preoperatively with the patient. With this approach, experienced surgeons go wrong less than 10% of the time (i.e., a resection is performed for what turns out to be benign disease). This is

acceptable because the mortality rate of resection is quite low, and the majority of patients who undergo resection for benign disease have chronic pancreatitis, for which resection is also appropriate ***(Todd and Reber, 2011).***

C. Laparoscopy

Laparoscopy has been used to stage patients with pancreatic cancer. Some surgeons have favored its use in the majority of cases as a routine part of the work-up before laparotomy.

The use of laparoscopy has significantly reduced the percentage of patients undergoing an open exploration without resection. In some instances, laparoscopy was done as[1] a separate procedure in the outpatient setting, and the findings guided the subsequent work-up. More often, it was performed immediately before laparotomy under the same anesthetic; if evidence of unresectability was found, the operation was cancelled. There is some evidence that it was a cost-effective approach and that it spared many patients the discomfort of an unnecessary laparotomy ***(Todd and Reber, 2011).***

Laparoscopy has the advantage of being able to detect small (<10mm) hepatic deposits, assess degree of lymph node involvement and identify peritoneal disease over that detected by conventional imaging ***(Shankar et al., 2011).***

Laparoscopic ultrasound probes may assist in identifying deep parenchymal lesions and provide views of the tumour in relation to the superior mesenteric and portal veins. Importantly, those patients deemed unresectable by laparoscopy have a minimally' morbid procedure with a median length of hospital stay of 1 day, which is significantly less than an often exploration without resection (median 7 days) ***(Todd and Reber, 2011).***

Laparoscopy also may have a useful therapeutic role, Reported 15 patients who were treated palliatively with cholecystojejunostomy (7), gastro-enterostomy (5), or both procedures (3). The average hospital stay was 4 days and the patients appeared to recover more rapidly ***(Rhodes et al., 2010).***

However, routine staging laparoscopy is not recommended. Resection was possible in 75% of patients who were judged to have 'resectable' cancers of the head of the pancreas after CT scan. Of the remaining 25% of the total, who did not have resectable cancers, small liver or peritoneal metastases, which might have been seen laparoscopically, were the reason in only half. Thus, if all of the patients had undergone laparoscopy as a routine, at best, only 12.5% might have been spared subsequent laparotomy. This seems to be too low a yield to justify the additional operative time and expense of the procedure. The remaining patients who were falsely des-

ignated as resectable on the basis of CT evaluation had locally extensive tumour, which was discovered as unresectable only after mobilization of the pancreas from the superior mesenteric and portal veins at laparotomy. This would not have been safe to do laparoscopically***(Todd and Reber, 2011).***

In addition, while it may be true that even helical CT scans do not show the very small hepatic or peritoneal metastases (2-3 mm) that may be present, the newer technique shows vascular involvement much more reliably than the conventional scans did, and it has been found that most patients who have these small hepatic and peritoneal metastases also have been considered unresectable because of vascular involvement ***(Todd and Reber, 2011).***

It is recommended to use laparoscopy, selectively, in certain circumstances. Examples include some patients with body or tail cancers, and some patients with ascites who probably have peritoneal metastases, Advanced laparoscopic techniques and improved instrumentation (e.g., laparoscopic US) may allow the surgeon to perform a more complete and accurate assessment of respectability ***(Todd and Reber, 2011).***

In conclusion:

Helical CT scan may be the only test required. If it shows a mass in the head of the pancreas without evidence of

metastatic disease, laparotomy may be undertaken without further studies, If the CT suggests hepatic, peritoneal, or distant metastases, percutaneous FNA may be appropriate and a positive biopsy would obviate the need for resection, If the mass involves the body and tail of the gland, there is usually evidence of metastatic disease or advanced local spread. Because these patients seldom benefit from palliative operations, percutaneous FNA is often indicated to provide a tissue diagnosis before starting chemotherapy and/or radiation therapy. Occasionally, these tumors appear resectable, or the biopsy is negative or equivocal; then laparoscopy for further assessment may be reasonable. The patient should undergo laparotomy under the same anesthetic if the lesion appears respectable. If the CT is normal or the findings are equivocal in a patient with suspected pancreatic cancer, ERCP is indicated. If both the CT and ERCP are normal, pancreatic cancer is extremely unlikely ***(Todd and Reber, 2011)*.**

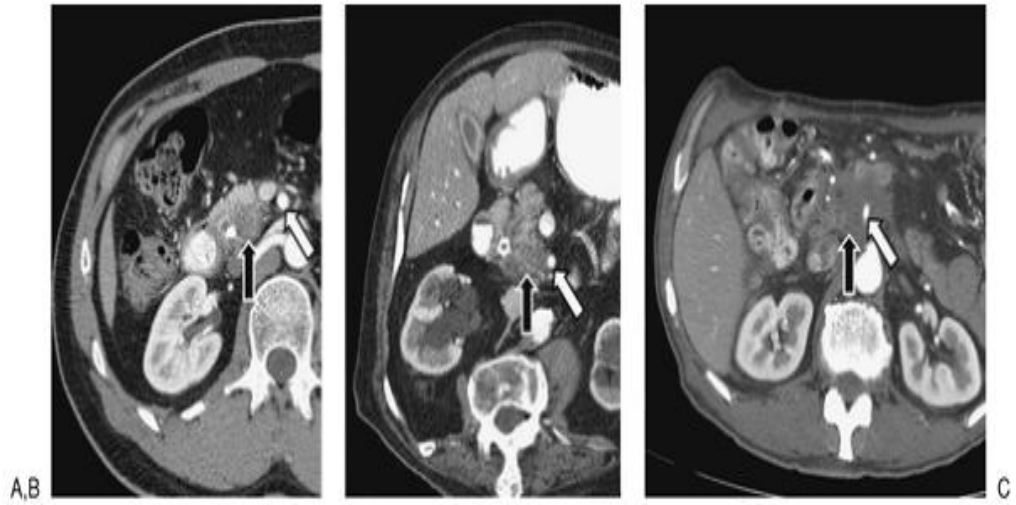


Fig. (26): Computed tomography images depicting spectrum of localized pancreatic cancer. Black arrows point to low density tumors; white arrows point to superior mesenteric artery (SMA) and show the relationship of tumor to vessel. A: Resectable tumor with clear fat plane around the SMA. B: Borderline respectable pancreatic cancer with tumor abutting about half of the SMA circumference. C: Locally advanced, unresectable disease with completed encasement of the SMA ***(Todd and Reber, 2011)*.**

Treatment of Pancreatic Tumors

1- Surgical management

A. Preoperative Management

As in all patients about to undergo major surgery, it is important to optimize cardiac, pulmonary, and renal function preoperatively. This can usually be done in the outpatient setting ***(Todd et al., 2011).***

Preoperative nutritional supplementation

The progressive and indolent nature of the wasting process makes correction of weight loss and malnutrition difficult and prolonged in pancreatic cancer patients who, in addition to weight loss, have muscle wasting and loss of fatty tissue i.e. cancer cachexia ***(De Blaauw et al., 2007).***

Although these patients have often lost weight, delay of the operation in order to restore nutrition with parenteral alimentation is rarely indicated ***(Todd et al., 2011).***

Preoperative biliary drainage

Several studies have shown that obstructive jaundice leads to alteration in glycogen metabolism, impaired mitochondrial and hepatic reticuloendothelial function, decreased cell-mediated immunity, high levels of circulating

endotoxins, and depressed synthesis of several hemostasis factors ***(Martignoni et al., 2010)*.**

Together, these alterations can renderthe patients more susceptible to infections, a well-known event in jaundiced patients undergoing surgery ***(Dixon et al., 2010).***

With the implementation of external transhepatic and thereafter, internal endoscopic biliary drainage, several authors have recommended relieving biliary obstruction pre-operatively in order to correct the alterations induced by jaundice and to reduce perioperative mortality and morbidity ***(Trede et al., 2008).***

Some studies demonstrated that patients who underwent preoperative endoscopic stenting had a reduced incidence of postoperative infective complications ***(Shankar et al., 2011).***

Other studies failed to show any benefit and suggested an increased postoperative risk ***(Povoski et al., 2011).***

B. Operative Management

Historical perspective

*Halsted*reported the first ampullary resection for tumour in 1899 and he successfully reimplanted the biliary and pancreatic ducts directly into the duodenum. This was done to

avoid the technical challenge of reconstruction when the duodenum was also removed ***(Todd et al., 2011).***

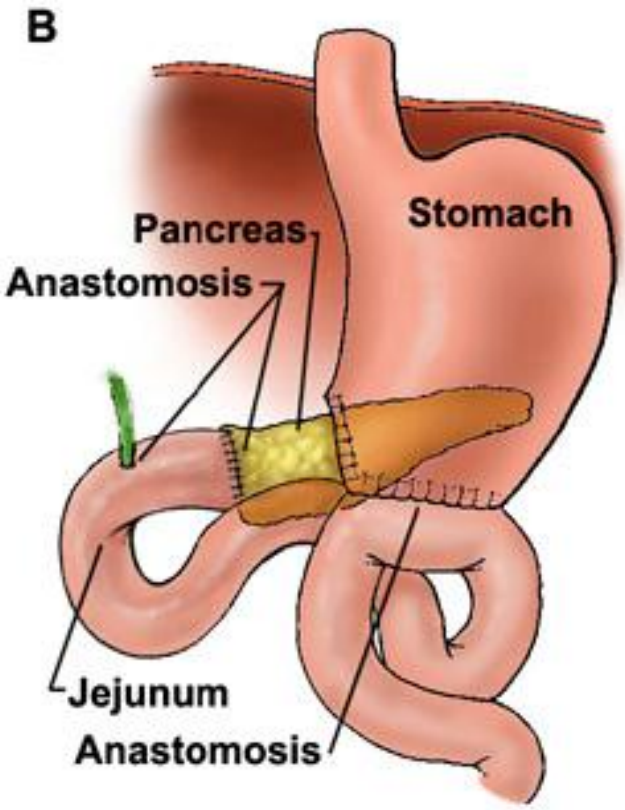


Fig. (27): Classical Whipple operation ***(Connel, 2011).***

In 1935, *Whipple*described a two-stage pancreatico-duodenectomy for a tumour of the ampullary region. In 1937 *Brunschwig*reported an extension of thisprocedure that included in resection of most of the head of the pancreas and duodenum. He performed an anastomosis between the cut end of the pancreas and jejunum ***(Todd et al., 2011).***

In 1945 *Whipple*revised his original operation, incorporating Brunschwig's modifications. The technique used today is quite similar. It involves a partial gastrectomy (antrectomy), cholecystectomy, and removal of the distal common bile duct, head of pancreas, duodenum, proximal jejunum, and regional lymph nodes. Reconstruction requires a pancreatico-jejunostomy, hepatico-jejunostomy, and gastro-jejunostomy ***(Todd et al., 2011).***

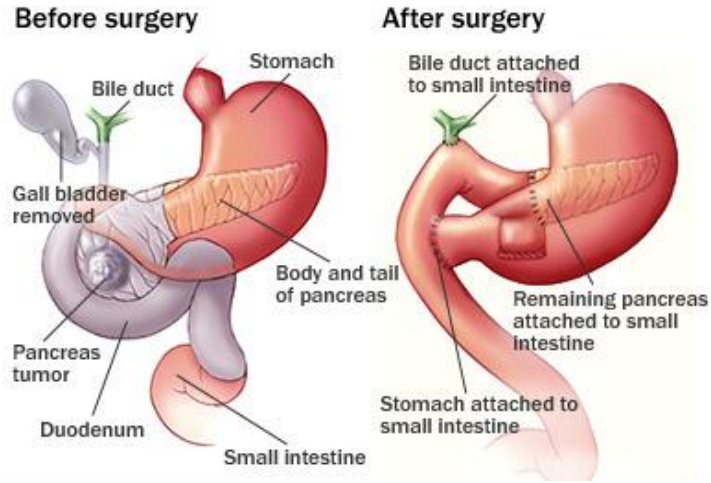


Fig. (28): The resected parts before surgery show after resection ***(Connel, 2010).***

A- Intraoperative determination of resectability&further management:

1- Liver & peritoneal metastasis

Pancreatico-duodenectomy is initiated by carefully exploring the abdomen to rule out extra-pancreatic metastatic

disease. The liver and peritoneal surfaces are examined intra-operative ultrasonography of the liver is used selectively when preoperative CT findings are indeterminate, suggesting possible hepatic metastasis, Progress with tumour resection in the presence of biopsy-proven liver or peritoneal metastases should be aborted ***(Evans el al., 2011)*.**

2- Effect of size:

Although it has been said that the size of the cancer is not a contraindication to surgical resection, it does have an impact on the surgical decision making and on outcome. A large tumour means that it has been present for a long time or is a very aggressively growing lesion. Although large size is not an absolute contraindication to resection, it is quite clear that patients with larger lesions have decreased survival rate, an increased rate of unresectability due to vascular invasion, and more difficult surgery with increased intra-operative and postoperative complications ***(Connel, 2001)*.**

3- Vascular invasion:

Intraoperative assessment of local tumor resectability was traditionally used to assess the relationship of the tumour to the SMA (Superior mesenteric artery) and SMPV (Superior mesenteric portal vein) confluence. While arterial resection still carries a high morbidity and mortality, extended pancreatic resections with venous reconstruction are feasible and may

render patients free of gross tumour ***(Takahashi and Tsazuki, 2009).***

The relation of the tumour to the superior mesenteric artery (SMA):

A Kocher maneuver was performed in an effort to palpate a plane of normal tissue between the firm tumour and the posterior pulsation of the SMA. The relationship of the tumor to the right lateral wall of the SMA is the most important aspect in this issue. It is strongly believed that this critical tumor-vessel relationship should be accurately evaluated before taking the patient to the operating room and that it cannot be assessed accurately intra-operatively after a Kocher maneuver, With larger tumors, those containing significant peritumoral fibrosis, or reoperative cases,(following a previous unsuccessful attempt at pancreatico-duodenectomy), palpation of the relationship of the primary tumour to the SMA (after mobilization of the duodenum) with any reasonable degree of accuracy is impossible ***(Evans et al., 2011).***

The relation of the tumor to the superior mesenteric-portal vein confluence (SMPV):

The relationship of the tumour to the SMPV confluence traditionally was assessed by attempting to develop a plane of dissection (beginning at the level of the infrapancreatic SMV)

between this venous confluence and the posterior surface of the neck of the pancreas. It was believed that if the surgeon could separate the SMV and portal vein (PV) from the neck of the pancreas, tumour involvement of the SMV or SMPV confluence was unlikely. In contrast, if such tumour involvement was present, the patient probably had locally advanced unresectable disease. There is no anatomic rationale for this maneuver early in the operation, because tumors of the pancreatic head or uncinate process do not invade the anterior wall of the SMV or PV as do locally advanced tumors of the pancreatic neck or body. Tumors of the pancreatic head or uncinate process are prone to invade the lateral or posterior wall of the SMPV confluence. This can be directly visualized only after gastric and pancreatic transection: by which point the surgeon has already committed to resection ***(Evans et al., 2011).***

High-quality CT should alert the surgeon to the possibility of tumour involvement of the posterior or lateral-wall of the SMV or SMPV confluence. Surgeons who perform pancreaticoduodenectomy should have a technical strategy to deal with such venous involvement because it is not an uncommon finding at the time of pancreatico-duodenectomy, While most pancreatic surgeons believe that arterial involvement remains a contraindication for resection based on

high operative morbidity and mortality and poor long-term outcome, on the other hand, PV resection for isolated PV involvement can be performed safely with a low perioperative mortality rate and overall survival is equal to those patients undergoing standard pancreatectomy. Therefore, suspected isolated portal vein involvement frequently does not preclude operability and, by itself, should not be a contraindication for pancreatic resection ***(Harrison et al., 2012)*.**

4- Extent of lymphadenectomy:

A wide variety of opinion exists regarding the extent of lymphatic dissection for both tumors on the right and left side of the pancreas. Although extended surgical procedures popularized in Japan may increase the resectability rate up to 50%, this does not necessarily translate into improved survival ***(Shankar et al., 2011).***

Not surprisingly, extensive node dissections have not proven to be of any benefit. The lymph node positivity, especially of lymph nodes distant from the pancreas, is an indicator of systemic disease but not a determinate. If the lymph nodes in the retroperitoneal, celiac, or para-aortic area are negative, then obviously the patient cannot benefitfrom having them removed. If they are positive, this is an indicator of distant

disease and the patient is not benefited by their removal ***(Connel, 2001)*.**

5- Pylorus Preservation (PPPD)

Proponents of pylorus preservation argue that preserving the antropyloric pump mechanism improves long-term upper gastrointestinal tract function and has associated nutritional benefits ***(Evans et al., 2011)*.**

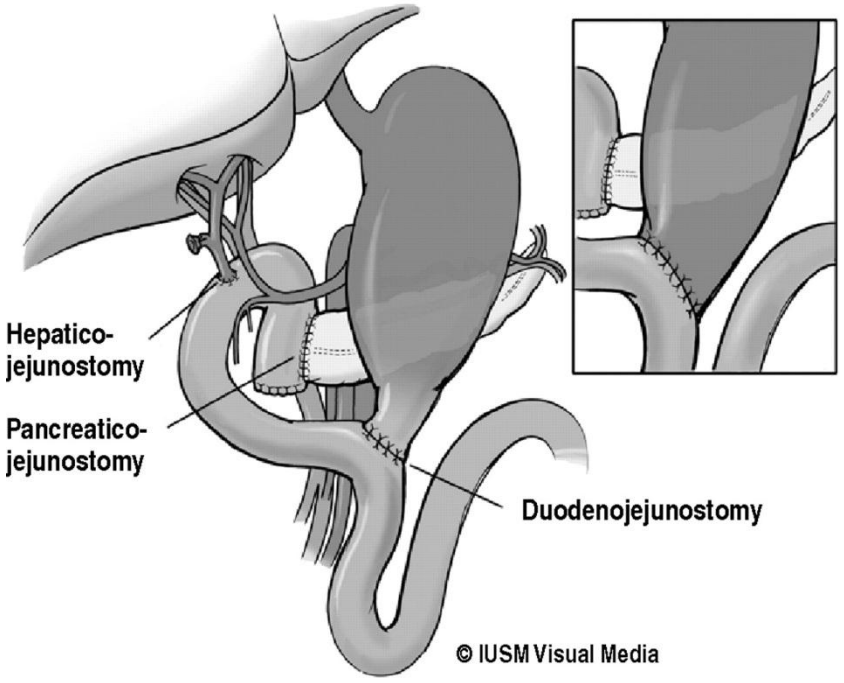


Fig. (29): Pylorus Preservation (PPPD) in whipple operation ***(Harrison et al., 2012).***

Physiologic studies suggest that pylorus preservation decreases intestinal transit time, lessens diarrhea (steatorrhea), normalizes glucose metabolism, and improves postoperative weight gain, In a recenttrial, 299 patients were randomized to standard (86%PPPD) or radical pancreaticoduodenectomy (standard resection plus distal gasterectomy& retroperitoneal lymphadenectomy).The standard group had a significantly shorter operating time & a significantly reduced complication rate (29% vs.43%) ***(Lorenzo et al., 2012)*.**

There was no difference in intraoperative blood loss or transfusion requirement. Patients in the radical group had a significantly higher rate of delayed gastric emptying, pancreatic fistula & increased mean postoperative stay. At a mean patient follow up of 24 months, there was no difference in overall survival ***(Lorenzo et al., 2012)*.**

B-Operative Technique:

An extensive Kocher maneuver is performed, elevating the duodenum out of the retro-peritoneum, assessing the superior mesenteric vein and its branches, and palpating the superior mesenteric artery pulse in its retro-pancreatic position. The portahepatis is carefully assessed by mobilizing the gallbladder out of the gallbladder fossa and following the cystic duct down to its junction with the common hepatic duct. In

some cases there may be the appearance of local tumour extension, giving an early impression that the tumour is unresectable. In these circumstances, one must be prepared to alter the normal sequence for performing a pancreatico-duodenectomy. With experience many tumors that initially appear unresectable, on the basis of local extension, can be resected successfully ***(Yao, 2011)*.**

Several maneuvers can speed the pancreatico-duodenectomy. Early division of the extra-hepatic biliary tree allows caudal retraction of the distal common bile duct and opens the plane to visualize the anterior portion of the portal vein. At this point, dissection is accomplished only on the anterior aspect of the portal vein as the pancreatic neck is elevated. Subsequently the gastro-duodenal artery can be identified, isolated, and triply ligated and divided. It is imperative that before ligation and division of the gastro-duodenal artery, a test clamping of the artery should be performed, to ensure that the hepatic artery is 'not being supplied retrograde through superior mesenteric artery collaterals. The superior mesenteric vein is most easily identified during the extensive Kocher maneuver. The, superior mesenteric vein is identified running anterior to the third portion of the duodenum, frequently surrounded by adipose

tissue, and receiving tributaries from both the uncinate and from the transverse mesocolon ***(Cameron, 2011)***.

The division of the proximal gastrointestinal tract is typically performed approximately 2cm distal to the pylorus with a linear stapling device. In similar fashion the jejunum just beyond the ligament of Treitz is cleared circumferentially and divided with a linear stapling device. Subsequently the proximal jejunum and distal duodenum can be delivered dorsal to the superior mesenteric vessels from the left to the right side, allowing easier dissection of the uncinate process off of the right lateral aspect of the superior mesenteric vein. Further steps in pancreaticoduodenal resection involve the division of the pancreatic neck with the electrocautery and the final dissection of the head and uncinate process from the superior mesenteric vein, portal vein and superior mesenteric artery ***(Lillemoe and Cameron, 2007)***.

The respected specimen

Methods of reconstruction in pancreatico-duodenectomy:

There are several options for reconstruction of the pancreas, bile ducts and gastrointestinal tract. Most commonly the reconstructive technique anastomosis the pancreas first followed by the bile duct then the duodenum.

The pancreatic- enteric reconstruction:

This is typically performed as a pancreatico-jejunostomy although a pancreatico-gasterostomy can also be done with equal rate of pancreatic fistula incidence, The method of reconstruction is debatable ie end - to-end versus end to side, Or invagination versus mucosa-to-mucosa. Some groups routinely stent the pancreatic duct others create separate Roux loops for patients at high risk for development of postoperative pancreatic fistula, If an end - to -side pancreatico-jejunostomy is performed, the outer layer is performed between the pancreatic capsule & parenchyma and the jejunum by interrupted silk sutures while the inner layer of absorbable sutures is placed between the pancreatic duct and a small opening in the anti-mesenteric border of the jejunum. The anastomosis may be stented with a small pediatric feeding catheter that can either be brought out through the jejunum and abdominal wall as an external stent or be left within the bowl lumen to be passed later through the alimentary tact ***(Lillemoe and Cameron, 2007)*.**

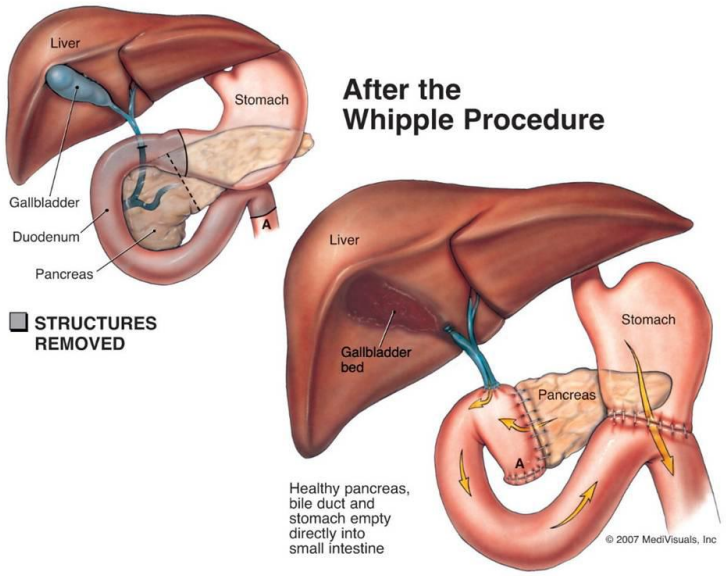


Fig. (30): Parts removed during Whipple operation ***(Carmon, 2011).***

The biliary - enteric reconstruction

The biliary - enteric reconstruction is performed 10 cm. distal to the pancreatic anastomosis in one layer with absorbable suture creating hepatico-jejunostomy. Stenting of the anastomosis withT-tube is usually used to decompressthe jeujenal loop during the postoperative period***(Lillemoe and Cameron., 2007).***

The enteric reconstruction:

The gastro (or duodeno) jejunal anastomosis is typically performed 10-15 cm distal to the biliary enteric anastomosis in two layers ***(Lillemoe and Cameron, 2007).***

Closed Suction drains can be placed adjacent to the hepatico-jejunostomy and pancreatico-jejunostomy. Feeding jejunostomy tubes may be placed to allow early postoperative enteral feeding however, this is rarely needed ***(Lillemoe and Cameron, 2007).***

C- The Postoperative Management:

The postoperative management consists of nothing by mouth, short term nasogastric and biliary decompression, parenteral analgesia and short course of peri-operative prophylactic antibiotics. On the fourth or fifth day, a cholangiogram and an upper gastrointestinal series with water soluble contrast material is performed. If no anastomotic leak is evident & gastric emptying is satisfactory, liquid diet can be initiated ***(Lillemoe and Cameron, 2007).***

Role of total pancreatectomy:

One of the proposed procedures is total pancreatectomy. The rationale for this procedure included the observation that in 30 to 40 percent of pancreatic cancer patients, the tumour was multicentric and would not be removed completely by a partial resection. However, most series of total pancreatectomy showed no evidence of increased survival, and recent studies have suggested that concerns regarding multifocal disease were unwarranted ***(Reber and Donahue, 2010).***

The controversy regarding the use of total pancreatectomy as treatment for patient with cancer of the head of the pancreas has diminished in recent years. Current practice avoids total pancreatectomy and favours partial resection. By avoiding total pancreatectomy, one avoids the obligate requirements for exogenous pancreatic enzyme supplements, avoids the inevitable generation of insulin dependent diabetes mellitus, reduces the intraoperative blood loss, and avoids the theoretic problem of loss of splenic function, Total pancreatectomy is reserved for cases in which the pancreatic cancer extends across the neck and body of the gland or when the pancreatic remnant is too soft and friable to allow a safe pancreatic enteric anastomosis. The latter is rarely the case when the resection is being performed for pancreatic adenocarcinoma ***(Reber, 2011).***

Complications of Pancreatic Resection

In specialist centres perioperative mortality should be less than 5% and in some are less than 1%, although the incidence, of postoperative complications is still 30%-40%.

The complications most commonly found are leakage of the pancreatic anastomosis, haemorrhage, abdominal abscess and delayed gastric emptying. Pancreatic fistulae occur with a reported frequency of 4%-24% and may progress to a full leak

with associated sepsis and haemorrhage. Such serious leaks occur in less than 5% in specialist units and may carry a mortality of up to 40% ***(Shankar et al., 2011).***

Octereotide does not appear to benefit patients with pancreatic cancer undergoing pancreaticodeodenectomy in terms of pancreatic fistula prevention, overall morbidity and mortality ***(Shankar et al., 2011).***

Prognostic Factors

The prognostic factor of greatest significance for survival duration is the presence or absence of local tumour extension on CT; this radiographic finding predicts the eventual resection margin status.

The margin of greatest importance is the retroperitoneal (or mesenteric) margin along the right lateral border of the SMA ***(Evans et al., 2011).***

Histologically positive margins at the sites of transection of the bile duct and pancreas are uncommon. Several investigators have examined pathologic characteristics of the resected tumour in an effort to establish reliable prognostic variables associated with decreased survival duration. Metastatic disease in regional lymph nodes, poorly differentiated tumour histology, and large size of the primary

tumour have been associated with decreased survival duration ***(Evans et al., 2011).***

2- Non Surgical

1) Adjuvant Therapy:

At present, the general consensus of most surgeons treating pancreatic and periampullary carcinoma is that any future improvement in the management of this disease will involve improved adjuvant therapy ***(Lillemoe and Cameron, 2007).***

The primary obstacle to the postresection cure of adenocarcinoma of the pancreas appears to be the burden of any remaining regional subclinical disease. The 2 classic approaches to the treatment and control of this persistent burden involve radiation therapy and chemotherapy. Ionizing radiation, as applied with external beam radiation therapy, intraoperative radiation therapy, or brachytherapy (the use of implanted radioactive materials) is destructive of both normal and malignant tissues ***(Abrams et al., 2011).***

Certainly, additional well - conceived trails of chemo radial ion therapy delivered in the adjuvant setting are needed ***(Yao, 2011).***

2) Neoadjuvant Therapy:

Neoadjuvant therapy involves the use of chemotherapy and radiation therapy before surgical exploration. The advantages of this approach include earlier administration of systemic therapy, decreased potential burden of locoregionaltumour at operation, and sterilization of tumour cells before intraoperative manipulation ***(Yao, 2011).***

Preliminary results suggest that neoadjuvant therapy can be completed without increasing subsequent morbidity and mortality of surgical resection. However limited available follow-up suggests that although improvement in local control of the disease is obtained, long term survival rates owing to distant failure is not improved from historical controls ***(Lillemoe and Cameron, 2007).***

It remains this policy to first attempt resection for patients with staging studies that appear favorable, reserving neoadjuvant therapy for patients with evidence of locally unresectabletumours (as determined by imaging studies or laparotorny) ***(Yao, 2011)***.

Role of intraoperativeradiotherapy:

Studies of intraoperative radiation therapy added to external beam irradiation have been reported and although suggesting the possibility of enhanced local control, long term

survival has not been improved ***(Lillemoe and Cameron, 2007).***

Radiation can be delivered to a pancreatic tumour in greater effective doses and with less injury to neighboring viscera if it is performed during surgery. This objective has been accomplished with conventional orthovoltage, electron beams and implantation of radioactive iodine. Only the electron beam therapy is said to prolong survival, and this treatment also appears to give substantial and lasting relief of pain in at least one half of treated patients. Late duodenal ulceration and stenosis may result from radiation injury, and for this reason all patients treated with intraopertive electron beam also must perform gastrojejunostomy ***(Lillemoe and Cameron, 2007).***

Management of Tumor of Body and Tail:

Approximately 25% to 30% of pancreatic cancers arise in the body and tail of the pancreas. If the diagnosis is made when the tumour is localized and not encasing the coeliac axis, the superior mesenteric vessels, or the portal vein, resection remains a surgical option. In addition to routine staging studies to include abdominal CT, there appears to be an important role for staging laparoscopy in patients with body and tail tumours. Should staging studies fail to reveal evidence of disseminated

tumour or unresectable local disease, then exploration is appropriate. The entire abdomen is explored to search for metastatic disease. A careful search of the liver for metastatic deposits and a thorough evaluation of all the peritoneal surfaces undertaken. The lesser omentum is opened to allow the assessment of the coeliac axis and periaortic region. The ligament of Trietz is evaluated carefully, because tumours in the body of the pancreas may invade the fourth portion of the duodenum at the ligament. Additionally, the gastrocolic ligament should be opened to allow full assessment of the body and tail of the pancreas and better assessment of the tumours proximity to the ligament of Trietz and to the superior mesenteric vessels. Although involvement of lymph nodes around the coeliac axis does not prevent resection, it does diminish the likelihood of long term survival. In the absence of finding of unresectability mobilization of the inferior surface of the body of the pancreas from the retroperitoneum may be helpful to assess retroperitoneal involvement. Involvement of the splenic vein does not indicate unresectability. Splenic preservation is not indicated when the resection is being performed for pancreatic adenocarcinoma. Therefore the spleen is mobilized out of the retroperitoneum, often with early ligation of the splenic artery. The short gastric vessels along the greater curvature and the vessels within the splenocolic

ligament require division. Mobilization of the spleen from the retroperitoneum facilitates dissection of the tail of the pancreas from the retroperitoneum. Once the spleen has been mobilised toward the midline, the pancreatic tail and body are elevated, typically exposing a thin avascular plane. Once the tumour has been elevated out the retroperitoneum, the splenic vein can be controlled at a variable distance from its junction with the portal vein. If necessary the inferior mesenteric vein can be sacrificed without any additional morbidity. The neck of the pancreas can then be divided, leaving a 1 to 2 cm gross margin away from the tumour. Closure of the pancreatic neck margin can be performed safely with mattress sutures or with a linear' stapler ***(Brennan et al., 2010)***.

A closed suction drain is left near the closed stump of the pancreas. In rare circumstances proximal obstruction of the pancreatic duct may be encountered or may have been visualized by preoperative ERCP. In this setting, a Roux en-Y pancreatico-jejunostomy should be performed to prevent pancreatic - fistula. At the conclusion of the resection, consideration should, be given to the placement of titanium clips to mark the borders of the resection bed, to serve as a target for postoperative external beam radiation therapy ***(Brennan et al., 2010)***.

The resectability rates for adenocarcinoma of the body and tail of the pancreas was approximately 10% in the era before routine staging laparoscopy. The routine use of staging laparoscopy to identify metastases not visualized by CT will improve the resectability rates overall, patients undergoing resection have median survival rates ranging from 7 to 13 months, with 5-years survival rates of approximately 10% or less***(Brennan et al., 2010)***.

Palliative Treatment

Goal of Palliation

Complete surgical resection is the only potentially curative treatment for pancreatic adenocarcinoma; however, patient outcome is dependent on tumour histology and stage. As a result of improved surgical and anesthetic techniques during the last two decades, the morbidity and mortality associated with pancreaticoduodenectomy have been greatly reduced. Because 80% to 90% of the pancreatic cancer patients are not candidates for surgical resection, improvements in resection technique have minimal impact on patient outcome; therefore, palliation remains a cornerstone of therapy for patients with pancreatic cancer. Palliative procedures should have a low-associated morbidity, provide symptomatic relief of

pain, obstructive jaundice, and potential and improve the quality of life for these patients ***(Connel, 2010)***.

As a result, it is not recommend an obviously purposeful palliative Whipple when patients have obvious distant disease in the liver, peritoneal metastasis, distant lymph nodes, etc. This is exposing patients to excessive morbidity to produce palliative results, which can easily be obtained by simple bypass procedures. Although some published series indicate that patients treated with palliative Whipples live longer than those not having Whipples, it must be emphasized that these are not randomized, prospective studies and probably those patients having a Whipple are younger, have comparatively less distant disease, and have lesions that the surgeon can more easily resect ***(Connel, 2001)*.**

Palliation of jaundice:

Relief of jaundice plays a key role in improving quality of life and survival in patients with advanced pancreatic and periampullary cancer. Palliative procedures for the treatment of obstructive jaundice can be divided into surgical, endoscopic and radiologic interventions. Surgical biliary decompression encompasses operative procedures that may include cholecystojejunostomy, choledochojejunostomv and Less

frequentlyhepaticojejunostomy. Endoscopic procedures include transampullary retrograde stenting. Radiologic interventions include percutaneous transhepatic (PTH) placement of internal-external biliary catheters, internal-only stents, or permanent expandable metallic wall stents ***(Farrel et al., 2010)***.

There are two types of stents that are commonly used the first one is made of plastic and looks like a small straw. A plastic stent can be pushed through the ERCP scope into the blocked duct to allow drainage by the major papilla or minor papilla in selected cases ***(McAlister et al., 2011)***.

The metal stent is flexible and springs open to a larger diameter than plastic stents and used for malignant biliary obstructions. Both plastic and metal stents tend to clog up after several months and you may require another ERCP to place a new stent. Metal stents are permanent while plastic stents are easily removed at a repeat ERCP ***(Andriulli et al., 2011)***.

ERCP balloon or plastic dilators can be placed into the bile or pancreatic ducts to dilate benign or malignant strictures. There are ERCP catheters fitted with dilating balloons that can be placed across a narrowed area or stricture. The balloon is then inflated to stretch out the stricture. Dilation can be done by plastic dilators with various sizes that can also be placed during the ERCP procedure ***(McAlister et al., 2011)***.

After the successful dilation, a temporary plastic stent may be placed for few months. These ERCP therapeutic procedures can be done as an outpatient basis. Some patients may be admitted to the hospital for few days but most of them go home from the recovery. You should not drive a car for the rest of the day and most patients can return to full activity the next day. The overall ERCP complication rate requiring hospitalization is 6-10% according to the US experience ***(Connel, 2010)***.

Although this rate is lower in personal experience during the last 34 years, depend on your age, your other medical problems, what therapy is performed, and the indication of your procedure, your complication rate may be higher or lower than the average will discuss your likelihood of complications before you undergo the test. It is important to read/understand the available pamphlets/write-ups regarding your procedure indication(s), limitations and complications. Then, sign the properly explained consent form ***(McAlister et al., 2011)***.

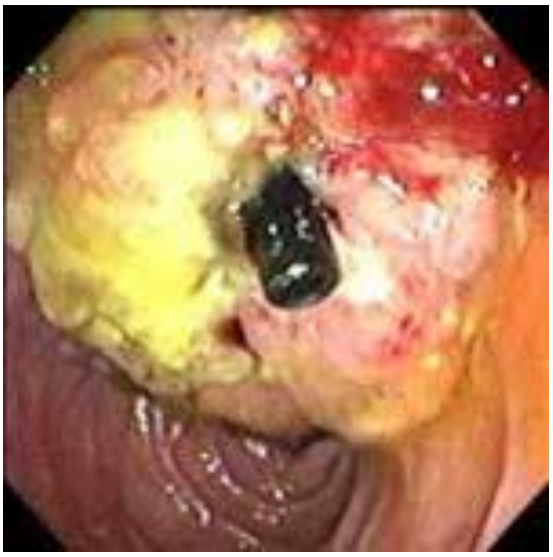


Fig. (31): Papillary malignancy with plastic stenting ***(McAlister et al., 2011)***.

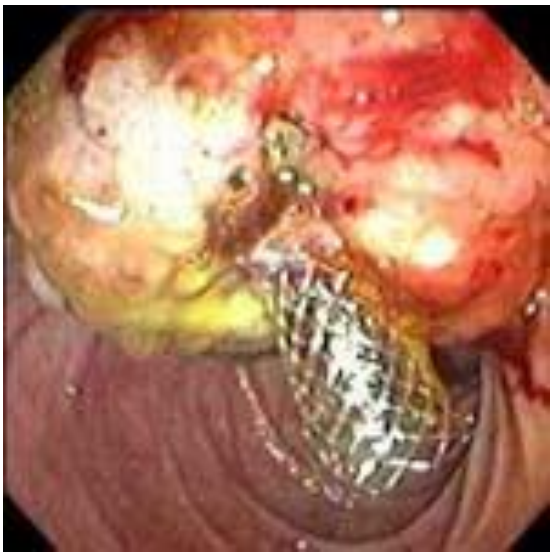


Fig. (32): Papillary malignancy with metal stenting ***(McAlister et al., 2011)***.

Procedure

The patient is sedated or anaesthetized. Then a flexible camera (endoscope) is inserted through the mouth, down the esophagus, into the stomach, through the pylorus into the duodenum where the ampulla of Vater (the opening of the common bile duct and pancreatic duct) exists. The sphincter of Oddi is a muscular valve that controls the opening of the ampulla. The region can be directly visualized with the endoscopic camera while various procedures are performed. A plastic catheter or *cannula* is inserted through the ampulla, and radiocontrast is injected into the bile ducts, and/or, pancreatic duct. Fluoroscopy is used to look for blockages, or other lesions such as stones ***(McAlister et al., 2011)***.

When needed, the opening of the ampulla can be enlarged with an electrified wire (sphincterotomy) and access into the bile duct obtained so that gallstones may be removed or other therapy performed.Other procedures associated with ERCP include the trawling of the common bile duct with a basket or balloon to remove gallstones and the insertion of a plastic stent to assist the drainage of bile. Also, the pancreatic duct can be cannulated and stents be inserted. The pancreatic duct requires visualisation in cases of pancreatitis.In specific cases, a second camera can be inserted through the channel of

the first endoscope. This is termed duodenoscope-assisted cholangio-pancreatoscopy (DACP) or mother-daughter ERCP. The daughter scope can be used to administer direct electrohydraulic lithotripsy to break up stones, or to help in diagnosis by directly visualizing the duct (as opposed to obtaining X-ray images) ***(Deziel et al., 2010)***.

Endoscopic drainage has a success rate of 85%-90% with a relatively low complication rate. Stent occlusion may be a problem and in an effort to overcome this metal stents are now commonly utilized for proven inoperable malignant tumours. Their greater patency rates compared to plastic stents have been demonstrated in randomized controlled trials. Even if occlusion does occur, Tumour in growth can be ablated using laser/thermal techniques. Percutaneous transhepatic stems can be used, although with a higher risk of complications ***(Speer et al., 2011)*.**

Centers performing laparotomy-based staging for pancreatic cancer patients advocate surgical biliary bypass at the time of laparotomy as a therapeutic biliary decompression procedure or as a prophylactic procedure. The common procedures performed are choledochojeunostomy or cholecystojejunostomy. However Choledochoduojenostomy has not been advocated in malignant disease, because of concerns regarding anastomotic leak and potential late

obstruction from local tumour growth. Traditionally, Roux-en-Y choledochojejunostomy has been the preferred technique for biliary bypass with a low rate of recurrent obstruction ***(Deziel et al., 2010)***.

In the past, cholecystojejunostomy was advocated because of its safety and technical ease of performance. For patients with early-staged unresectable disease, however, who have an extended expected survival, cholecystojejunostomy was associated with recurrent obstructive jaundice after cystic duct obstruction ***(Deziel et al., 2010)*.**

Centers that practice laparoscopy-based staging do not advocate prophylactic open biliary bypass. Instead, the use of endoscopic biliary decompression is favored in patients who have unreseclable disease ***(Espat et al., 2009)***.

Palliation of gastric outlet obstruction:

Distinguishing between gastroparesis as a motility phenomenon and mechanical obstruction of the gastric outlet remains the key issue. Like prophylactic biliary by pass, issues surround the role of prophylactic gastric bypass. There is no doubt that the patient with endoscopically or radiographically demonstrated obstruction of the gastric outlet requires decompression; however, the use of prophylactic gasterojejunostomy for the anticipated potential development of

Gastric outlet obstruction (GOO) is not as clearly defined ***(Molinari et al., 2011)*.**

Approximately 5% of patients with pancreatic cancer will have actual mechanical obstruction and 17% of patients undergoing biliary bypass alone will develop subsequent duodenal obstruction. A proportion of patients undergoing gastric bypass procedures will develop delayed gastric emptying, with significant morbidity attached to this procedure,Therefore, it seems sensible to reserve gastric bypass for those with definite obstruction or evidence ofimpending problems, especially given the availability of endoscopically placed metal duodenal stents ***(Shankar et al., 2011)*.**

Palliation of pain:

Pain is a major problem in the management of patients with pancreatic cancer and aside from standard analgesic regimens a variety of nerve ablative techniques are available. Coeliac plexus blockade, either at the time of surgery or percutaneously, has been reported as having significant success rates ***(Eisenberg et al., 2005)***.

More recently thoracoscopic division of the splanchnic nerves has reported variable success rates and the results of large randomized studies are underway. Initjal enthusiasm was tempered by high complication rates, which have now

drastically reduced. Unilateral versus bilateral approaches have been assessed and the left side appears to be the most important for its analgesic effect in pancreatic cancer ***(Shankar et al., 2011).***

Non-surgical management of advanced pancreatic cancer

1) Chemotherpy

Systemic chemotherapy is a generally unsuccessful treatment modality for advanced pancreatic cancer ***(Brennan et al., 2010).***

5-Fluorouracil (5-FU) has been the standard chemotherapy used in the UK over recent years, with evidence suggesting a small survival advantage and improvements in quality-of-life in a proportion of patients with pancreatic cancer. 5-FU is administered using a variety of doses and schedules; the response rate rarely exceeds 20% and no consistent effect on disease-related symptoms or survival has been demonstrated, Gemcitabine is a novel nucleoside analogue that exerts its action by inhibiting DNA synthesis with a wide spectrum of antitumour activity against a variety of solid tumours including pancreatic cancer ***(Carmichael, 2007)***.

Gemcitabine is licensed as a first line treatment of adult patients with locally advanced or metastatic adenocarcinoma of

the pancreas and as a second line treatment of patients with 5-FU refractory pancreatic cancer**,** As with all chemotherapy, gemcitabine is associated with potentially life-threatening side effects in an already debilitated group of patients ***(Hidalgo et al., 2009)***.

In the Bums trial, 26% of patients treated with gemcitabine had grade 3 or 4 neutropenia compared with 5% in the 5-FU The role of gemcitabine in the treatment of pancreatic cancer in comparison with other agents including combination regimens is being under investigation ***(Bums et al., 2011)***.

2) Radiotherapy

Pancreatic cancer is relatively radioresistant,Irradiation is made more difficult by the deep location of the pancreas and its proximity to areas that are sensitive to radiation (intestine, spinal cord, liver, kidneys), The trial failed to demonstrate prolongation of median survival for patients with localized pancreatic cancer treated with gemcitabine-based chemoradiation ***(Houry et al., 2011)*.**

3) Biologic Therapy

Detailed examination of the molecular make-up of pancreatic cancer has led scientists and clinicians to develop novel therapeutic approaches many of which have already entered clinical trials. The rapid development of knowledge of

pancreatic cancer tumour biology is narrowing the gap between science and clinical practice. These new modalities of treatment have been described as biological therapy:

Signal Transduction inhibitors

A number of agents are being developed that inhibit aberrant signal transduction in neoplastic cells.

BMS-2I4662, SCH 66336, and 5777 are oral benzodiazepine-based and quinolone inhibitors of Gluteryltransferase. These agents, therefore, inhibit the first step in post-translational modification of ras proteins (monomeric GTPases) resulting in arrest of the ras signal transduction cascade. Most pancreatic adenocarcinomas (> 70%) contain mutations in *k-ras*that effectively 'switch on' a continuous intracellular signal for cell cycle progression. This leads to uncontrolled cell division. It has been reported that patients treated with SCH 66336 have fewer incidences of haematological toxicity and GI side effects compared with gemcitabine. SCH 66336 is now being evaluated in combination with gemcitabine in patients with advanced pancreatic cancer ***(Lersch et al., 2012)***.

Metalloproteinases are a group of proteolytic enzymes, which degrade different substrates within the extracellular matrix. An imbalance between MMPs and tissue-specific inhibitors leads to matrix degradation and tumor invasion,

Several broad-spectrum synthetic MMP inhibitors have been developed. A recent study has reported evidence of a dose response for marimastat in patients with advanced pancreatic cancer. The 1-year survival rate for patients receiving "marimastat" (25 mg) was similar to that of patients receiving gemcitabine ***(Bramhall et al., 2012)***.

Selective non-hydroxamate MMP inhibitors are being developed that have potential for pancreatic carcinoma treatment. In a recent study, BMS-275291 was well tolerated with no dose-limiting arthritis with plasma concentrations sufficient to produce sustained MMP-2 and MMP-9 inhibition in cancer patients ***(Gupta et al., 2011)*.**

Neovastat targets two angiogenesis processes: the VEGF signaling pathway and MMPs. Neovastat, which also stimulates angiostatin expression in experimental glioblastoma has demonstrated antimetastatic properties in experimental tumour models and has no dose-limiting toxicity ***(Franqolsetal, 2011)*.**

COX-2 inhibition

The isoform of cyclo-oxygenase (COX), COX-2, is involved in the inflammatory response and is induced by several growth factors, cytokines and tumor promoters. Following activation of oncogenes such as Ras, COX-2

enhances proliferation, reduces apoptosis and increases angiogenesis ***(Kokawa et al., 2011)*.**

Selective COX-2 inhibitors, such as rofecoxib and celecoxib have been used in clinical trials to reduce neoplastic growth, most notably in familial adenomatous polyposis**.**

The expression of COX-2 in human pancreatic neoplasms and the effect of COX inhibitors on the growth of human pancreatic carcinoma cells was –investigated immunohistochemically in *42* human pancreatic duct cell carcinomas and in 29 intraductal papillary mucinous tumours (IPMT [adenomas, 19; carcinomas, 10]) of the pancreas. The growth of four human pancreatic carcinoma cell lines also was evaluated in the presence of COX inhibitors. Marker COX-2 expression was observed in 57% (24 of 42} of ductal adenocarcinomas, in 58% (11 of 19) of adenomas, and in 70% (7 of 10) of adenocarcinomas of IPMTs. *A* four pancreatic cancer cell lines expressed COX-2 protein weakly or strongly, and the inhibitory effect of aspirin on cell growth was correlated with the expression of COX-2. COX inhibitors may, therefore, be worthy of investigation as therapeutic and preventative agents for pancreatic carcinomas ***(Kokawa et al., 2011)*.**

4) Immunotherapy*:*

Immunotherapy involves active or passive stimulation of the immune system against cancer cells, their growth factors and growth factor receptors.

Antibodies and T-cells have the potential to recognize tumor antigens identified by modern genetic techniques ***(Jung et al., 2007)***.

It may be possible to use the host immune system to target activity against antigens such as ras protein or the MUC 1 tumour antigens found in virtually all pancreatic cancers,Pancreatic cancer escapes immune recognition by producing anti-inflammatory mediator; and by failure to express MHC-tumour antigen complexes (MHC majorhistocompitability complex). Clinically, effective immunotherapy, therefore, requires high tumour antigen specificity and good antigen delivery. Purified peptide and carbohydrate molecules, for example, can generate a potent antitumour response ***(Manges et al., 2009)***.

Mixed leukocyte cyloimplant (MLC) is a natural cytokine pump which reverses the anti-inflammatory activity of the tumour. It can be delivered by fine needle intratumoural injection using endoscopic ultrasound guidance ***(Chang et al., 2010)*.**

Passive immunotherapy with monoclonal antibodies

Both epidermal growth factor receptor (EGF-R) signaling mechanisms and VEGB-mediated angiogenesis have been used as targets for passive immunotherapy with monoclonal antibodies specifically for human pancreatic carcinoma treatment.

The anti-VEGF antibody HumV833 recently was found to be well-tolerated and tumour-specific on PET scanning ***(Jayson et al., 2011).***

In phase II studies of anti-epidermal growth factor receptor (EGFR) antibody Cetuximab (IMC-C225), promising activity was observed in *vivo* studies ***(Bruns et al., 2000)***

And in patients with advanced pancreatic carcinoma when used in combination with gemcitabine delay in disease progression was observed ***(Abbmzzese et al., 2011)***.

Chimeric monoclonal antibody Nd2 (c-Nd2), produced against protein derived from pancreatic cancer, has been used in clinical trials for pancreatic carcinoma immunotherapy. This treatment has been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC). Cytotoxicities to Nd2-positive tumour cells during culture with c-Nd2 were significantly higher than with no antibody. Reduced tumour marker levels in sera such as CA19-9 have been observed after intravenous

injection of c-Nd2 in some pancreatic cancer patients ***(Sawada et al., 2011)*.**

Cytokine immune modulation

Attempted stimulation of a patient's immune response against tumour cells using cytokine immune modulation is not new: however, il has been recently used to enhance the antitumour efficacy of monoclonal antibody therapy. IFN-y for example, is a lymphokine produced by T-lymphocytes in response to antigen exposure. Its immunomodulatory activity includes stimulation of natural killer cells, lymphokine-activated killer cells, Stimulation of ADCC and enhancement of HLA Class 11 expression. IFN-y treatment profoundly inhibited pancreatic cancer growth *in vitro* ***(Detjen et al., 2001)***.

Active specific immunothcrapy Active immunotherapy aims to activate a component of the immune system such as lymphocytes or antibodies against tumour-associated antigens presented by the tumour or tumour growth factors. B-HCG belongs to a superfamify of human growth factors, and may play a role in cancer progression by modifying angiogenesis, stimulating growth and invasion. Immunization of patients with pancreatic cancer with Avicine™, a vaccine composed of

synthetic peptides derived from B-HCG conjugated to diphthefia toxin (DT), is being investigated ***(Iversen et al., 2012)***.

5) Genetherapy:

Genetherapy is directed towards down regulation of oncogenes or restoration of tumour suppressor genes. Gene transfer by viral vectors is being investigated. Suicide genes are introduced into neoplastic cells that concert a non-toxic prodrug, to a highly toxic agent at the tumour site.

Anti-gastrin drugs exert some anti-tumour activity by eliminating the growth-promoting effects of gastrin on pancreatic epithelium.

Pancreatic Endocrine Tumors

Pancreatic endocrine tumors (PETs), which arise from pancreatic islet cells, account for 1.3% to 3% of pancreatic malignancies. PETs may be functional or nonfunctional, and the clinical manifestations are depen dent on the specific hormones produced. There is no gener ally accepted international staging system for PETs. The behavior of these tumors ranges from benign and indolent to malignant and aggressive. Recent series have suggested that metastatic disease, tumor size, neurovascular invasion* mitotic index, Ki-67 protein index,

nuclear atypia, tumor grade, and associated clinical syndromes may impact overall survival ***(Beckers and Daly, 2007)***.

1- Nonfunctioning Pancreatic Endocrine Tumors

Fifty-eight to eighty-five percent of PETs are nonfunctional, and they occur more commonly in the pancreatic head. PETs are often diagnosed late in the course of the disease because symptoms do not become evident until they grow large enough to compress adjacent structures. Patients with nonfunctioning PETs usually present with abdominal pain, weight loss, obstructive jaundice, or other obstructive symptoms. The median overall survival duration among all patients with nonfunctioning PETs is approximately 3.2 years; 7.1 years in patients with localized disease who have a potentially curative resection; 5.2 years in patients with locally advanced, unresectablenon- metastatic disease; and 2,1 years in patients with unresectable metastatic disease ***(Abood et al., 2009)***.

Diagnosis:

Nonfunctioning PETs are usually diagnosed with computed tomography (CT) or magnetic resonance imaging (MRI). They have a hypervascular appearance on radiographic images. CT, MRI, and ultrasonography detect: 20% of PETs <1 cm in size, 3O% to 40% of PETs 1 to 3 cm in size, and 75% of PETs >3 cm in size. The most sensitive technique for identi-fying small PETs is endoscopic ultrasound (EUS), which can

detect neoplasms as small as 0.3 cm in size. Because PETs and pancreatic ade have similar radiographic features, EUS may be needed obtain a pathologic diagnosis before treatment is initiated. EUS can helpful in defining the extent and distribution of multiple PETs n associated with patients who have inherited endocrine tumor romes (e.g., multiple endocrine neoplasia type 1 [MEN1]). Octreo-imaging may be useful when planning surgical intervention because this modality assists with tumor localization and occasionally identifies occult regional lymph node metastases ***(Clark et al., 2009)***.

Nonfunctioning PETs may secrete a variety of hormones whose effects are not clinically apparent. For instance, as many as 75% of patients with nonfunctioning PETs have elevated fasting pancreatic polypeptide levels. Chromogranin A levels are elevated in 60% to 100% of patients with PETs. However, chromogranin A levels may be falsely elevated in older patients, alcoholic patients, patients with inflammatory conditions, patients with renal failure, and patients consuming proton pump inhibitors (PPIs) ***(Doherty and Thompson, 2003)***.

Treatment

Surgical resection with regional lymph node dissection is the only potentially curative therapy for patients with localized nonfunctioning PETs. The anatomic considerations for

determining the respectability of and the surgical approaches for nonfunctioning PETs are the same as those for pancreatic adenocarcinomas. As patients with locally advanced nonfunctioning PETs often have favorable survival durations, incomplete resection or tumor debulking of nonfunctioning PETs is not recommended because of the potential considerable morbidity associated with palliative pancreatic resection. There is no standard adjuvant systemic therapy for patients who undergo potentially curative surgical resection. Careful follow-up after surgery is essential; up to 5O% of patients who undergo complete resection develop metachronous liver metastasis. Distant metastatic disease (e.g., solitary liver metastasis) should be resected if possible. Patients with unresectable hepatic metastases may benefit from radiofrequency ablation or Yttrium-90 radioembolization ***(Fendrich et al., 2010)***.

Since effective systemic treatment options for patients with unresectable locally advanced or metastatic PETs remain limited, and since PETs are often biologically indolent, initial observation without specific systemic therapy is an acceptable strategy for selected patients, particularly in the absence of symptoms. Patients with unresectable locally advanced or metastatic PETs who have symptoms or evidence of disease progression on serial imaging may be considered for systemic

therapy. Systemic treatment options include streptozocin-based chemotherapy octreotide (long-acting release form, LAR), and protocol-based therapies. At M.D. Anderson, streptozocin, doxorubicin, and 5-fluorouracil have elicited a tumor response in up to 39% of patients with nonfunctioning PETs. Alternatively (especially for patients with relatively indolent tumors), octreotide LAR has recently been demonstrated to lengthen time to progression in patients with metastatic neuroendo-crine tumors. Lanreotide, another somatostatin analogue, has been shown to have some antiproliferative effects on metastatic PETs when used alone or in combination with interferon-alpha. Other promising therapies for patients with metastatic PETs include mammalian target of Rapamycin (mTOR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, and hepatic chemoembolization or radionuclide embolization ***(Fendrich et al., 2010)***.

2- Functioning Pancreatic Endocrine Tumors:

Insulinoma

In 1935, Whipple and Frantz first described the clinical manifestations of insulinoma as a triad of hypoglycemic symptoms while fasting, blood glucose levels <50 mg/dL, and symptomatic relief after glucose administration (Whipple's triad). Insulinomas are the most common type of functioning

PET; approximately 10% exhibit malignant behavior, 10% are associated with MEN1, and 10% are multiple. Insulinomas over secrete insulin, and the resultant hypoglycemic episodes are exacerbated during periods of fasting or exercise. During an insulin surge, patients may develop a sympathetic overdrive characterized by sweating, weakness, tremors, hyperphasia, and palpitations. Neuroglycopenic symptoms including confusion, visual changes, altered consciousness, and convulsions have also been associated with insulinomas ***(Kindmark et al., 2007)***.

Diagnosis:

The most reliable test for diagnosing insulinomas is a monitored 72-hour fast, during which the patients plasma glucose, C-peptide, proinsulin, and insulin levels are measured every 4 to 6 hours. The test is continued until the plasma glucose level is <45 mg/dL and the patient develops hypoglycemic symptoms; 33% of patients become symptomatic within 12 hours, 80% within 24 hours, 90% within 48 hours, and 100% within 72 hours. The diagnosis of insulinoma is established by a serum insulin concentration ≥6 μ/mL, an insulin-to-glucose ratio >0.3, a C-peptide level >0.2 nmol/L, a proinsulin level ≥5 pmol/L, and a documented absence of plasma sulfonylurea. Patients who self-administer exogenous forms of insulin usually have low C-peptide and proinsulin levels because commercial insulin does not contain insulin

precursor or cleavage fragments. Patients who consume oral hypoglycemic agentsjnay have elevated C-peptide and proinsulin levels; however, these patients can be differentiated from insulinoma patients in that only insulinoma patients will have an absence of plasma sulfonylurea ***(Metz and Jensen, 2008)***.

Depending on the size of the tumors, insulinomas maybe visualized by CT, MRL or EUS. Octreotide imaging is of limited use because many insulinomas (especially smaller ones) do not express somatostatin receptor-2. Although rarely necessary nowadays because of improvements in cross-sectional abdominal imaging and EUS, selective intra-arterial calcium injection of major pancreatic arteries with hepatic venous sampling (calcium arterial stimulation test) has been reported to successfully regionalize tumors in more than 80% of patients with insulinomas. A twofold increase in insulin after intra-arterial calcium infiision (0.025 mEq/kg) identifies the arterial distribution supplying the tumor. Lesions in the head and neck of the pancreas are characterized by elevated insulin levels in the superior mesenteric artery or gastro-duodenal artery, whereas lesions in the pancreatic tail are characterized by elevated insulin levels in the splenic artery. Liver metastases demonstrate a response after calcium injection into the hepatic artery.

Treatment:

The primary treatment for sporadic insulinoma is surgical resection. The median disease-free survival after resection of-malignant insulinoma is approximately 5 years ***(Figueiredo et al., 2009)***.

Before surgery, glucose levels should be controlled with frequent small meals and diazoxide, a drug that inhibits insulin release and promotes glycogenolysis. The operation is directed by the results of preop-erative imaging; intraoperative ultrasound can be used to definitively localize small tumors deep in the pancreatic parenchyma as well as liver metastases. When possible, enucleation should be performed. Larger lesions require pancreatic resection (pancreaticoduodenectomy, distal pancreatectomy, or, in selected patients, central pancreatectqmy) depending on the location of the neoplasm. Pancreatic resection is also indicated if there are signs of malignancy (i.e., lymph node metastasis and/or local invasion). If no tumor can be localized at the time of operative intervention, the surgeon may perform a pancreatic biopsy to rule out beta cell hyperplasia or adult nesidioblastosis. Blind distal pancreatectomy is no longer recommended when a tumor cannot be localized. Instead, the surgeon should abandon attempts at resection and perform postoperative repeat biochemical testing, repeat imaging, and regionalization

studies, including consideration for selective arterial injection-hepatic vein sampling as described earlier ***(Ito et al., 2010)***.

Unresectable or metastatic disease may be treated using strategies similar to those recommended for patients with nonfunctioning PETs, for example, streptozocin in combination with doxorubicin or 5-fluorouracil. Hepatic metastases should be resected if possible ***(Kulke et al., 2008)***.

Gastrinoma

In 1955, Zollinger and Ellison first described a new clinical triad consisting of atypical peptic ulcerations, gastric hypersecretion with hyperacidity, and a noninsulin producing islet tumor of the pancreas. Later referred to as Zollinger-Ellison syndrome, gastrinomas secrete gastrin, a hormone that induces hyperchlorhydria and parietal cell hyperplasia. Patients with sporadic gastrinoma often present around 45 years of age with abdominal pain (75% to 100%), diarrhea (35% to 73%), heartburn (44% to 64%), duodenal and prepyloric ulcers (71% to 91%), and complications associated with ulcer disease. Gastrinomas account for <1% of all cases of peptic ulcer disease. Approximately 75% of gastrinomas are sporadic; the remaining 25% are associated with MEN1. Most gastrinomas are located in the duodenum and the pancreas (63% of pancreatic tumors are in the head) in a 3:1 ratio, but tumors

have been identified in other sites such as the stomach, jejunum, peripancreatic tissue, ovaries, and liver. The majority (60% to 90%) of gastrinomas are malignant, and the most important predictor of survival is the presence of hepatic metastasis ***(Clark et al., 2009)***.

Diagnosis:

Patients with a suspected gastrinoma should be evaluated with a fasting gastrin level and gastric pH 1 to 2 weeks after discontinuation of PPIs. Withdrawing PPIs among patients with gastrinoma should be done carefully because perforation can occur if not closely monitored. A fasting gastrin level >1000 pg/mL with a gastric pH of <2.5 is highly suggestive of gastrinoma ***(Clark et al., 2009)***.

Other causes of hypergastrinemia include PPI use, autoimmune pernicious anemia, vagotomy, fundectomy, gastric outlet obstruction, resection of the large bowel, chronic renal failure, and Helicobacterpylori gastritis with atrophy ***(La et al., 2009)***.

The majority of patients with gastrinomas have a basal acid output to maximal acid output ratio ≥0.6, or a 12-hour nocturnal gastric acid secretion >100 mEq of hydrochloric acid. To establish the diagnosis in the setting of occult (nonimageable) disease, a basal acid output >15 mEq/ hour and

a positive secretin stimulation test has traditionally been used; such testing is now rarely employed. The secretin stimulation test involves administering 2 units/kg of intravenous secretin after an overnight fast. Serum gastrin levels are obtained at 15 and 2 minutes prior to secretin injection and again at 0, 2, 5, 10, and 20 minutes after infusion. The test is positive for gastrinoma when there is a paradoxical increase in serum gastrin by more than 200 pg/mL over baseline levels ***(La et al., 2009)***.

Tumor localizing studies are usually deferred until the diagnosis of gastrinoma is established. CT and MRI are beneficial in localizing larger tumors; esophagogastroduodenoscopy (EGD) with EUS is necessary to identify smaller tumors (<1 cm). CT and MRI are the most sensitive imaging modalities for identifying liver metastasis from gastrinoma. Octreotide imaging may be helpful in localizing the tumor and determining the extent of the disease. Although 80% to 100% of gastrinomas may be detected by a combination of selective abdominal angiography mid selective arterial secretin injection, this invasive imaging strategy is rarely necessary in the current era ***(Ito et al., 2010)***.

Treatment:

Patients with gastrinoma should first be treated with a PPI or "a histamine (H2) antagonist to control acid

hypersecretion. Somatosta-tin may help decrease the secretion of gastrin and other hormones ***(Yao, 2011)***.

Because resection has been shown to increase overall survival in patients with sporadic gastrinomas, surgical treatment is recommended even if a tumor cannot be identified on preoperative localization studies. If a tumor is identified on imaging, then enucleation or resection along with regional lymph node dissection is recommended. Thirty to fifty percent of gastrinoma patients have regional lymph node metastasis at the time of operative intervention. If enucleation is not possible, distal pan-createctomy is appropriate for lesions in the pancreatic tail, and pancre-aticoduodenectomy with periduodenal lymphadenectomy is appropriate for lesions in the pancreatic head ***(Yao, 2011)***.

Surgical exploration should include the following: intraoperative ultrasound of the liver and pancreas; exploration of the lesser sac to evaluate the pancreatic body and tail; a Kocher maneuver to inspect the pancreatic head; duodenotomy with digital palpation to identify small duodenal wall tumors; periduodenal, peripancreatic head, portal, and hepatic arterial lymph node dissection; and exploration of extrapancreatic locations including the ovary, stomach wall, small bowel, omentum, and bowel mesentery. Intraoperative endoscopy with transillumination may help localize duodenal wall tumors; if

done, it should be performed prior to duodenotomy. Total gastrectomy may be considered for patients in whom medical therapy has failed, who are noncompliant, or who have recurrent complications from peptic ulcer disease. However, patients who undergo total gastrectomy must be followed up after surgery to monitor for disease progression ***(Beckers et al., 2007)***.

The strongest predictor of long-term survival in patients with gastrinomas is the presence of liver metastasis. Isolated liver metastases should be resected when possible, because there have been long-term survivors reported even when the primary tumor was not identified. When hepatic resection is not possible, hepatic artery embolization may be considered. Patients who have unresectable disease or diffuse metastasis may be treated with systemic chemotherapy or protocol-based therapies; streptozocin-based chemotherapy with doxorubicin or 5-fluorouracil has been shown to have some activity in these patients ***(Clark et al., 2009)***.

Vasoactive Intestinal Polypeptidoma:

Vasoactive intestinal polypeptide (VTP)-secreting tumors (VIPomas; also referred to as Verner-Morrison syndrome or watery diarrhea-hypokalemia-achlorhydria (WDHA) syndrome) are very rare tumors characterized by large-volume secretory

diarrhea that persists when fasting, electrolyte imbalances (hypokalemia and hypercalcemia), dehydration, hypochlorhydria or achlorhydria hyperglycemia, and flushing. Sixty to eighty percent of VIPomas are metastatic at presentation. The 5-year overall survival rate for patients with VIPomas (all stages) is 69%. The 5-year survival rate for patients with metastatic disease is 60%, and 94% for patients without metastasis. More than 80% of VIPomas are isolated to the pancreas; 75% involve the pancreatic body and tail. Extra-pancreatic primary tumors that secrete VIP have been identified in the chest and retroperitoneum and have included such tumors as ganglio-neuroblastomas, ganglioneuromas, and neuroblastomas ***(Doherty and Thompson, 2010)***.

Diagnosis:

Even if not visualized on imaging, fasting plasma vasoactive intestinal polypeptide levels >500 pg/mL along with high volume diarrhea is suggestive of a VIPoma. Concomitant elevation of serum pancreatic polypeptide helps to confirm the diagnosis. These tumors are usually identified on CT, MRI, EUS, or octreotide scans. Other options for tumor localization include mesenteric arteriography and portal venous sampling ***(Hausman et al., 2010)***.

Treatment:

VIPomas are usually treated with surgical resection. Before operative intervention, patients should be hydrated, their electrolytes should be normalized, and they should receive octreotide to control the diarrhea. Given the malignant potential of VIPomas, surgical resection should include regional lymph node dissection. As with other functioning PETs, streptozocin-based systemic chemotherapy is appropriate for unresectable tumors or metastatic disease that cannot be debulked. Somatostatin analogues may also be effective. The treatment of liver metastases is the same as previously described for other functioning metastatic PETs ***(Doherty and Thompson, 2010).***

Glucagonoma:

Glucagonomas, which arise from the alpha cells of the pancreas, are characterized by excess glucagon secretion that results in glucose intolerance (occurring in >90% of patients), weight loss, neuropsychiatric disturbances (usually depression or psychosis), and venous thrombosis. Approximately 70% of glucagonoma patients develop necrolytic migratory erythema, a rash that occurs on the lower abdomen, perineum, perioral area, and/or feet. The majority (70%) of glucagonomas are malignant; patients frequently present with metastasis ***(Hausman et al., 2010)***.

Diagnosis:

Inappropriately elevated fasting glucagon level >500 to 1000 pg/ mL is diagnostic of a glucagonoma. However, elevated glucagon levels may also be apparent in patients with cirrhosis, pancreatitis, diabetes mellitus, prolonged fasting, renal failure, burns, sepsis, familial glucagonemia, and acromegaly, A diagnosis of glucagonoma can be confirmed with a biopsy of the necrolytic migratory erythema. Glucagonomas are most often easily identified with CT and/or MRI because they are typically large (>5 cm in diameter) at diagnosis. Octreotide scanning is also helpful for localizing and staging glucagonomas. Although venous sampling has been used to localize glucagonomas, this modality is rarely necessary ***(La et al., 2009)***.

Treatment:

When possible, glucagonoma treatment should include surgical resection with regional lymph node dissection. Metastatic disease should be resected when possible to provide potential symptomatic relief. Like other functioning PETs, metastatic and unresectableglucagonomas have been treated with systemic streptozocin with doxorubi-cin or 5-fluorouracil, or dacarbazine based chemotherapy. Necrolytic migratory erythema secondary to glucagonoma can usually be effectively treated with somatostatin ***(Clark et al., 2009)***.

Somatostatinoma:

Somatostatinomas, which arise from the delta cells of the pancreas, are extremely rare and have an estimated incidence of 1 in 40 million. To date, only about 200 cases of Somatostatinomas have been reported. Ninety percent of Somatostatinomas are malignant. The majority (90%) of somatostatinomas are sporadic, and approximately 7% have been linked to familial disorders such as neurofibromatosis type 1 (NF1), MEN1, and Von Hippel-Lindau (VHL) disease ***(Clark et al., 2009)***.

Somatostatinomas are most frequently located in the pancreas or duodenum; however, there have been reports of somatostatinomas occurring in other locations such as the jejunum. Patients with duode nalsomatostatinomas commonly present with symptoms of obstruction, whereas patients with pancreatic somatostatinomas frequently present with diabetes mellitus, cholelithiasis, steatorrhea, weight loss, anemia, and/or diarrhea. In their literature review, Soga and Yakuwa found that the 5-year overall survival rate for patients with somatostatinomas (all stages) was 75%, 100% for patients with localized disease, and 60% for patients with distant metastatic disease ***(Metz and Jensen, 2008)***.

Diagnosis:

Patients with somatostatinomas are often diagnosed late in the course of the disease because the lesions are extremely

rare and the symptoms are often mild and nonspecific. A somatostatin level >100 no/ mL and a tumor identified on CT, MRI, octreotide scan, and/or EUS suggest a diagnosis of somatostatinoma. Pancreatic somatostatinotnas are typically solitary, large, and located in the head of the pancreas Duodenal somatostatinomas, which are generally smaller than pancreatic somatostatinomas, can usually be identified on EGD ***(Abood et al., 2009)***.

Treatment:

Somatostatinoma patients frequently present with metastatic disease; nevertheless, these patients should undergo surgical resection of the primary tumor and regional lymph node dissection when possible. Given the high incidence of cholelithiasis in somatostatinoma patients, cholecystectomy should be performed at the time of surgery. Tumor debulking may be performed for palliation ***(Abood et al., 2009).***

Total Pancreatectomy

Indications of Total Pancreatectomy

Total pancreatectomy has been used to treat both benign and malignant disease of the pancreas, but its use has been limited by concerns about management of the apancreatic state with its attendant total endocrine and exocrine insufficiency. Here, we review the indications for total pancreatectomy, operative technique, and improvements in the postoperative management of patients. Total pancreatectomy remains a viable option in the treatment of intractable pain associated with chronic pancreatitis, multicentric or extensive neuroendocrine tumors, patients with familial pancreatic cancer with premalignant lesions, and in patients with intraductal papillary mucinous neoplasia with diffuse ductal involvement or invasive disease. Improvements in postoperative management include auto-islet cell transplantation, advances in insulin formulations, and the use of glucagon rescue therapy which allow much tighter control of blood glucose than previously possible. This markedly lessens the risk of life-threatening hypoglycemia and decreases the risk of long-term complications, resulting in improved quality of life for these patients.

Billroth performed the first reported total pancreatectomy for pancreatic cancer in 1884 ***(Sauve, 1908)***.

This patient was said to have done well postoperatively, which would be questionable in the pre-insulin era. The first modern report of totalpancreatectomy for pancreatic adenocarcinoma was by Rockey in 1943, with early patient death in the perioperative period from a bile duct leak. Priestley performed the first successful total pancreatic resection in a hypoglycemic patient with a non-palpable 8×5 mm islet cell tumor in 1944 (Rockeycase report, 1943) ***(Sarr and Sakorafas, 2009).***

As reports of long-term metabolic complications of the apancreatic state have accumulated, total pancreatectomy for benign, premalignant, and malignant disease has generally been avoided because of the perceived difficulty of managing the associated brittle diabetes. However, new formulations of long-acting insulin and improvements in the use of autologous islet cell transplantation have made total pancreatectomy an increasingly viable option in the treatment of both benign and selected malignant pancreatic diseases. Here, we will review the indications for total pancreatectomy, technical considerations, and postoperative management strategy for the a pancreatic state ***(Sarr and Sakorafas, 2009)***.

Table (3): Possible indications of total pancreatectomy

Intractable pain of chronic pancreatitis
Neoplasm
Sporadic adenocarcinoma
Familial pancreatic cancer
Neuroendocrine tumors

(Sarr and Sakorafas, 2009)

Indications:

1-Chronic Pancreatitis

Warren first performed total pancreatectomy in patients with recurrent pancreatitis, proposing at that time that the procedure should be limited to patients with intractable pain and intraductal obstruction not amenable to a drainage procedure, He theorized that if the pain associated with end-stage chronic pancreatitis arose fromthe inflamed pancreatic parenchyma, then total pancreatectomy should result in complete relief of symptoms. Initialexperiences did not bear out this theory ***(Warren et al., 1966).***

Several large retrospective studies showed that only 30 to 60% of patients undergoing total pancreatectomy experienced significant pain relief, and a large percentage of

patients werereadmitted for diabetic complications ***(Sarr and Sakorafas, 2009).***

The Lahey Clinic's experience with total pancreatectomy, reported in 1978, showed that of the 25 patients studied, 12 had late deaths secondary to diabetic complications. Many of thesepatients who died suffered from substance abuse, highlighting that this subset of patients was poorly suited forthe intensive patient involvement required for the maintenance of normoglycemia following total pancreatectomyand were more likely to complain of continued pain postoperatively ***(Warshaw et al., 2008)***.

Advancements in the use of autologous islet cell transplantation have led to renewed interest in the use of total pancreatectomy for relief of the pain associated with chronic pancreatitis. The University of Minnesota has the largest experience with the use of total pancreatectomy and autologous islet transplantation in the current era, as described by Gruessner and colleagues ***(Gruessner et al., 2011).***

The records of 112 patients were reviewed, with follow-up ranging from 4 months to 26 years. Islets were isolated following pancreatectomy using the semiautomated technique originally described by Ricordi, followed by intraoperative infusion into the portal venous system. Of 112 patients, 70% experienced significant pain relief based on comparisonof pre-

and postoperative narcotic requirements. Importantly, 72% of patients who had not undergone previous pancreatic resection did not require insulin postoperatively. Those with previous pancreatic resection (and thus, with fewer islets available for autotransplantation) fared worse, with only about 20% of patients achieving insulin independence. Patients actively abusing alcohol were not enrolled in the study ***(Ricordi et al., 2007).***

Two additional reports from the University of Cincinnati and University of Leicester (with patient follow-up between 3 months–3 years and 7 months–6 years, respectively) show similarly excellent pain control in patients who were not actively abusing alcohol. The University of Cincinnati group reported that 82% of the 22 patients in their series were able to be weaned entirely from narcotics. At both centers, approximately 40–50% of patients became insulin independent following the procedure ***(Clayton et al., 2009).***

The need for insulin postoperatively following this procedure appears to be due to a number of factors, including number of islets transplanted, similar to that observed with non-autologoustransplantation used to treat type 1 diabetes ***(Ricordi et al., 2005).***

There is evidence that maintenance of normoglycemia in the immediate postoperative period is necessary to insure

recovery of transplanted islet cell function, which canoccuras late as 1 year following transplantation. Because higher islet recovery rates translate into better outcomes, proponents of this approach argue for early pancreatectomy in patients with chronic pancreatitis before they developglucose intolerance due to loss of β-cell mass ***(Clayton et al., 2009).***

Pancreatic allotransplantation has also been used as an alternative approach in patients with previous total pancreatectomy for chronic pancreatitis; long-term results in the small number of patientswho have undergone thisprocedure at the University of Minnesota show a 3-year graft survival of 77% in the tacrolimusera ***(Buchler et al., 2010).***

There were no transplant-related deaths in this group with total organ transplantation, these patients benefit from restoration of exocrine and endocrine function if enteric rather than bladder drainage is provided. The potential benefits of the procedure must be balanced with the need for lifelong immunosuppression and the resultant morbidity and mortality associated with rejection, infection, and malignancy ***(Gruessner et al., 2011).***

Table (4): Review of series of total pancreatectomy for chronic pancreatitis

Author	Year	Number of patients	Median follow-up	Percentage of pain improvement	Autotransplant	Percentage of nondiabetic
Gruessner, et al.[9]	2004	132	0.3–26 yr	72	Yes	33
Clayton, et al.[12]	2003	31	2–6 yr	50	Yes	0
Rodríguez-Rilo, et al.[11]	2003	19	19 mos (3 to 41)	94	Yes	40
Easter, et al.[66]	1991	8	29 mos (8 to 51)	75	No	0
Stone, et al.[4]	1988	15	9.1 yr (2.1 to 13.1)	67	No	0
Braasch, et al.[6]	1978	26	Unknown	78	No	0

(Sarr and Sakorafas, 2009)

2-Sporadic Pancreatic Adenocarcinoma

Historically, the rationale for total pancreatectomy for the treatment of pancreatic adenocarcinoma stems from: (1) thedesire to avoid the complications of pancreatic fistula; (2)the belief that the disease is frequently multicentric; and (3) the view that total pancreatectomy represents a more definitive oncologic resection than a partial pancreaticresection, with greater lymph node clearance and an increase in the percentage of R0 resections. Approachingthese arguments point by point:

1) Recent retrospective reviews of the complications of pancreatic resection show pancreatic fistula rates between 3 and 11% at high volume centers. More than 90% of those patients who develop pancreatic fistulas are now managed

successfully with percutaneous drainage.Without the relatively high mortality rate (up to 40%) previously reported with this complication ***(Munoz-Bongrand et al., 2012).***

2) Brooks et al. in the 1960s reported that up to 34% of patients with pancreatic adenocarcinoma undergoing resection had multicentric disease ***(Collins et al., 1966).***

This view was supported by data in two other reports. More recent studies using immunohistochemistry and PCR have found multicentricity to be much less prevalent, ranging between 0 and 6%. The prevalence of multicentric disease in earlier studies may have been due to sampling error, or operator bias, in the identification of truly discontinuous lesions. It could also be due to the inclusion of a disproportionate number of cases of familial pancreatic cancer ***(Motojima, 2012).***

Regarding the efficacy of total pancreatectomy as an oncologic operation, large retrospective series have shown no long-term survival benefit. In fact, several studies show that perioperative mortality is higher with total pancreatectomy than with subtotal pancreatectomy. Ihse, et al. reported an in-hospital mortality of 27% of their 89 patients undergoing total pancreatectomy for cancer ***(Ihse et al., 2008).***

In a more recent report from Memorial Sloan Kettering Hospital, 28 patients who underwent total pancreatectomy for adenocarcinoma had a 5-year survival rate of 9%, no better than that seen in patients undergoing partial pancreatectomy for adenocarcinoma. Given the fact that pancreatic fistulas are now better managed, most tumors are not multicentric and that total pancreatectomy results in higher perioperative morbidity and mortality with no increased long-term survival, there is no role for routine consideration of total pancreatectomy in the management of sporadic pancreatic adenocarcinoma ***(Karpoff et al., 2011).***

3-Familial Pancreatic Adenocarcinoma

In families affected by this condition, first degree relatives with three or more affected family members have up to a 57- fold increase in the risk of developing pancreatic cancer ***(Bartsch, 2010).***

The susceptibility to pancreatic cancer is inherited in anautosomal dominant fashion. Germline mutations in BRCA2 have been identified in up to 20% of affected families, and recently, a susceptibility locus has been mapped to chromosome 4q32–34***(Klein et al., 2004)***.

In patients with familial pancreatic cancer, there is often an early age of onset, and some question of anticipation (i.e.,

the disease presents earlier with a more aggressive clinical course in succeeding generations) ***(Greenhalf et al., 2006).***

Other familial cancer syndromes also predispose to pancreatic cancer, most notably Peutz–Jegher syndrome, familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal carcinoma (HNPCC), familial breast–ovarian cancer, and familial atypical multiple mole melanoma (FAMMM). Hereditary pancreatitis, a result of either a mutation in the cationic trypsinogen gene (PRSS1) or in the serine protease inhibitor (SPINK1), also results in increased susceptibility to pancreatic cancer. Screening with endoscopic ultrasound has been recommended in asymptomatic patients with two or more first-degree relatives with pancreatic cancer, one first-degree relative with cancer diagnosed before the age of 50, or with two or more second-degree relatives, one of whom was diagnosed before the age of 50.The exact timing for initiating surveillance is up to some debate, with experts agreeing that surveillance should begin somewhere between 5 to 10 years before the onset of pancreatic cancer in the youngest affected relative or by the age of 40 or 50, or at the onset of symptoms (including the development of diabetes or weight loss). In a study by Rulyak and colleagues of 35 family members undergoing surveillance,12 had positive findings of a mass lesion on endoscopic ultrasound (EUS) and/or endoscopic

retrograde cholangiopancreatography (ERCP). These patients underwent either total or partial pancreatectomy and all 12 had pancreatic dysplasia on histological examination without invasive adenocarcinoma. These patients were found to have extensive, multicentric lesions. A larger group of 50 kindreds has been followed at the University of Washington, of which 10 patients have undergone total pancreatectomy. All were found to have Pan IN-3 lesions (carcinoma in situ). One patient with postoperative hypoglycemic unawareness underwent solid organ pancreastransplantation and had normal glucose homeostasis 1-year post-transplant. Clearly, surveillance and total pancreatectomy have the potential to avert the development of invasive pancreatic adenocarcinoma in the setting of familial pancreatic cancer and should be considered as a prophylactic procedure in some patients ***(Tersmette et al., 2011).***

4-Neuroendocrine Tumors

In 1993, a large retrospective study from the Mayo Clinic showed completion pancreatectomy for recurrent insulinoma to be associated with 10 year decrease in mean survival when compared to patients undergoing repeat partial pancreatectomy. It should be noted that all of these patients underwent resection before 1977 ***(Thompson et al., 1993).***

More recent analysis suggests that endocrine tumors do not have as benign course as previously thought, and that aggressive resection might be warranted, including total pancreatectomy. Doherty et al. examined a group of 34 distinct kindreds of multiple endocrine neoplasia type I (MEN-I) syndrome with 1,838 members and found that 46% of MEN-I patients died as a result of their endocrine tumors at a median age of 47 years. These patients succumbed to metastatic islet cell or carcinoid tumors, ulcer disease, or complications of hypercalcemia. Aggressive screening of MEN-I patients using endoscopic ultrasound was therefore suggested ***(Doherty et al., 1998).***

In 2009, Norton et al. reported three patients who had undergone total pancreatectomy for locally advanced neuroendocrine tumors without postoperative complications**,** As our understanding of the natural history of pancreatic neuroendocrine tumors has evolved, it is clear that a place remains for completion pancreatectomy in the endocrine surgeon's armamentarium ***(Norton et al., 2003).***

Intraductal Papillary Mucinous Neoplasm (IPMN) Ohhashi et al. first described IPMN of the pancreas in 1982; initially, it was thought to be an indolent disease with a favorable prognosis ***(Ohhashi et al., 1982).***

It is now widely recognized to be a premalignant lesion with between 30 and 72% of patients having invasive or noninvasive carcinoma at the time of presentation. Those patients found to have invasive carcinoma after resection have a poor prognosis, with a 5-year survival ranging from 24–60%. The distribution of IPMN has been proposed as a predictor of progression: lesions involving the main pancreatic duct have a higher rate of malignancy discovered at the time of resection than lesions arising from a branch duct. Intraoperative frozen sections following planned partial resection for localized lesions are necessary to assure negative margins. If there is evidence of severe dysplasia or invasive cancer at the resection margin, the resection should be extended, up to and including total pancreatectomy. In patients with diffuse noninvasive disease, total pancreatectomy should be considered in select patients to minimize the chance of recurrent, invasive disease ***(Jang et al., 2010)***.

Operative Technique:

The operative technique utilized for total pancreatectomy depends upon whether the patient has undergone previouspancreatic resection. Distal pancreatectomy can be performed in patients who had a previous pancreatoduodenectomy. Patients with a previous distal pancreatectomy are candidates for either duodenum-preserving

pancreatectomy or completion pancreaticoduodenectomy. Preservation of the spleenshouldbe considered whenever possible if it is felt not to compromise the oncologic nature of the operation. In cases when accompanying splenectomy is planned, the patient should be vaccinated 2 weeks preoperatively against pneumococcus, Hemophilus influenza group B, and meningiococcus group C to minimize the likelihood of developing potentially lethal post-splenectomysepsis. The operative procedure begins with a thorough exploration to evaluate the presence of extra-pancreatic disease. The right colon and hepatic flexure of the colon are mobilized to provide access to the second part of the duodenum. A wide Kocher maneuver is performed, and the duodenum and pancreas are elevated off the inferior vena cava until the left border of the abdominal aorta can be palpated. The Kocher maneuver is extended by continuing mobilization of the third portion of the duodenum until the superior mesenteric vein is encountered. The gastrocolic ligament is widely divided to allow access to the body of the pancreas. The anterior surface of the superior mesenteric vein is identified and dissected under direct vision. Using a Cushing vein retractor, the neck of the pancreas is lifted, and entering this a vascular plane, the superiormesenteric vein is traced proximally to its confluence with the portal vein. Following cholecystectomy, the peritoneal

reflection over the hepatoduodenal ligament is carefully opened, and the common bile duct and common hepatic artery are carefully dissected, and vessel loops are placed around them. The gastroduodenalartery is identified and ligated in continuity to facilitate access to the portal vein at the superior aspect of the pancreas. The splenorenal ligament is divided, and the spleen is drawn medially together with the tail of the pancreas, thus, opening the retropancreatic plane. The splenic vein and artery are ligated. Next, the distal part of the stomach is mobilized and transected. The duodenojejunal flexure is located and dissected free from the retroperitoneum by dividing the ligament of Treitz. Approximately 10 to 15 cm distal to the duodenojejunal flexure, the vessels within the mesentery and subsequently the small bowel are divided. The pancreas, distal stomach, duodenum, and spleen are removed en bloc (Fig. 33). To restore gastrointestinal continuity, an end-to-side choledochojejunal anastomosis is performed. The stomach is then anastomosed to the jejunum in two layers ***(Raimondo et al., 2011).***

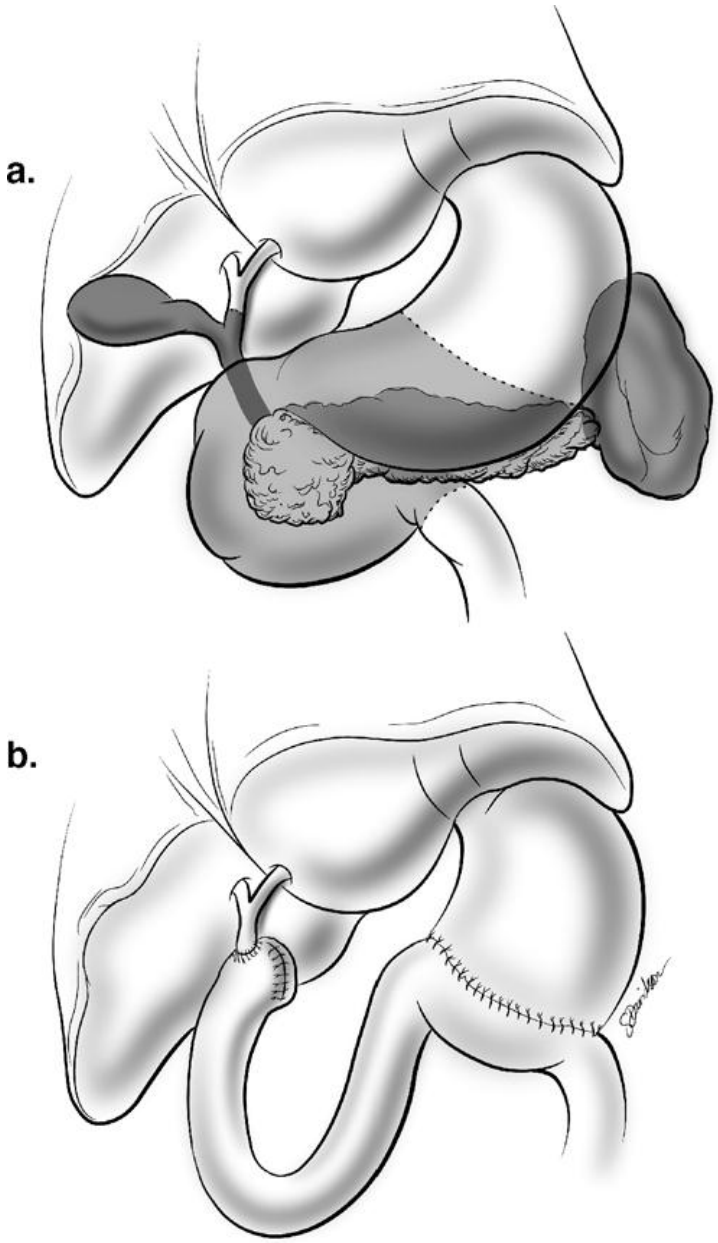


Figure (33): Total pancreatectomy with partial gastrectomy, duodenectomy, cholecystectomy, and splenectomy with choledochojejeunostomy and gastrojejeunostomy ***(Raimondo, 2011).***

Complications of Total Pancreatectomy

Endocrine Insufficiency

The diabetic state induced by total pancreatectomy is characterized by complete insulin deficiency (as confirmed by the absence of C-peptide in the serum), pancreatic polypeptide deficiency, and an absence of functionalGlucagon ***(Vigili de Kreutzenberg et al., 2010).***

Because the apancreatic state is characterized by a defect in gluconeogenesis secondary to hypoglucagonemia, daily insulin requirements in these patients are typically lower than in type I or type II diabetics.However, the therapeutic window is narrowed, resulting in frequent episodes of mild to severe postprandial hypoglycemia following insulin administration ***(Slezak and Andersen, 2011).***

Patients who are chronically hypoglycemic have been shown to up regulate cerebral endothelial glucose transporters which are responsible for the initiation of the autonomic response to hypoglycemia. This results in an attenuation of epinephrine secretion and may account for episodes of diabetic unawareness in pancreatectomized individuals ***(Boyle, 2007).***

Reductions in the adrenal secretion of epinephrine also decrease hepatic glucose production. The combination of insulin sensitivity and hypoglycemic unawareness was termed

"brittle" diabetes by R.T. Woodyatt in the 1930s ***(Tattersall, 2007).***

Insulin therapy for the apancreatic patient has been simplified by the availability of the long-acting insulin, glargine, a recombinant human insulin analogue which can be dosed once or twice daily. Because glargine is less soluble than native human insulin at physiological pH, there is a delayed absorption, resulting in a relatively 'peakless' insulin profile. The combined use of glargine with supplemental short-acting insulin such as insulin lispro or insulin aspart at mealtimes helps to prevent postprandial hypoglycemia after intestinal carbohydrate absorption has been completed. Most patients are able to achieve adequate glycemic control using these insulin preparations. However, continuous subcutaneous insulin infusion pumps have also been used to simplify dosing for patients. The use of insulin lispro or insulin aspart via continuous infusion has been shown in several open-label.

Randomized, crossover trials in type I and type II diabetic patients to provide better control of postprandial hyperglycemia and a significantly lower glycosylated hemoglobin level, with lower daily insulin requirements and less hypoglycemic episodes than with the use of regular insulin in the pump ***(Radermecker and Scheen, 2004).***

Current clinical work in patients with type I diabetes suggests that glucagon rescue injections can help prevent late postprandial hypoglycemia. Glucagon replacement therapy has been attempted in small numbers of apancreatic patients. Tankjoh et al. reported that when a physiological dose of glucagon is given proportional to the amount of insulin administered, the utilization of glycogenic amino acids and lipids increased along with a marked improvement in the utilization of carbohydrates ***(Tankjoh et al., 2009).***

Exocrine Insufficiency

Exocrine insufficiency also complicates postoperative management following total pancreatectomy. Even with aggressive pancreatic enzyme replacement (up to 120,000 IU of lipase per meal taken in conjunction with a proton pump inhibitor to prevent early inactivation of the enzymes by gastric acid), patients continue to have moderate steatorrhea which causes glucose malabsorption and further complicates diabetic management. Because of fat and glucose malabsorption, these patients can require an intake of up to 5,000 k/cal per day to maintain their body weight. High calorie/ complex carbohydrate diets with aggressive vitamin and calcium supplementation can help prevent weight loss, control postprandial glycemic shift, and prevent the osteoporosis associated with the apancreaticstate. Some simple sugars should be taken at the

beginning of a meal following the injection of short acting insulin because of its rapid onset of action. In some patients, it will be necessary to delay insulin injection until after the meal to reduce the risk of hypoglycemia. Maintenance of continuity of the upper gastrointestinaltract has been proposed as a mechanism to improve absorption following total pancreatectomy ***(Kahl and Malfertheiner, 2012).***

Buchler et al. have reported improved glucose tolerance following duodenum- preserving pancreatic head resection when compared to pylorous-preserving pancreaticoduodenectomy, leading some to speculate that patients undergoing total pancreatectomy might also benefit from more conservative resection ***(Buchler, 2009).***

Easter in 1991 reported that of eight patients undergoing duodenum-sparing total pancreatectomy for the pain of chronic pancreatitis, none experienced problems with the control of diabetes or any hypoglycemic attacks requiring medical treatment. Proposed mechanisms include improved intestinal transit, improved oral intake, and maintenance of sufficient insulin and pancreatic polypeptide secreting tissue to ameliorate the effects of pancreatic resection. However, more recent series of patients undergoing duodenum-sparing total pancreatectomy for chronic pancreatitis reported no statistically significant differences in diabetic complications ***(Easter and Cuschieri, 1991), (Alexakis et al., 2011).***

Table (5): Clinical difference between type 1 Diabetes Mellitus and apancreatic state

Conditions	Type I	Apancreatic diabetes
Glycemic instability	++	+++
Insulin requirement	+++	+
Hypoglycemia	++	+++
Ketoacidosis	+++	+
Vascular complications	+++	+

(Sarr and Sakorafas, 2009)

Steatohepatitis and Liver Failure

Another metabolic consequence of the apancreatic state is the development of steatohepatitis with progressive liver failure. Dressler, et al. noted that three of the patients in their series of 49 followed at Memorial Sloan-Ketteringdied of complications of hepatic failure, only one of whom had significant preoperative alcohol abuse. Centrilobularsteatosis was documented in two of these patients. All 49 patients demonstrated a durable elevation in levels of serum aspartate aminotransferase and alkaline phosphatase, but the degree of elevation did not correlate with an increased risk for the development of steatohepatitis. It has been hypothesized that decreased hepatic stimulation by glucagon results in progressive fatty deposition in the liver ***(Landoni et al., 2011).***

Periodic evaluation of hepatic aminotransferases, serum bilirubin, and prothrombin time are recommended to evaluate hepatic function in pancreatectomized patients. These patients are also at increased risk for the development of marginal ulcers or peptic ulcer disease secondary to lack of bicarbonate secretion, mandating proton pump inhibitor therapy ***(Kahl and Malfertheiner, 2012).***

Postoperative Rehabilitation after Total Pancreatectomy

Quality of Life Following Total Pancreatectomy:

A relative paucity of data exist on quality of life following total pancreatectomy in the current era. In 2004, 20 patients who had undergone total pancreatectomy at the University of Verona, a mean of 34 months earlier (range, 1.5–112 months), were surveyed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ). They were found to have a median insulin requirement of 30.5 IU/day with one patient requiring subcutaneous insulin infusion. Among the patients, 88% had a normal HbA1C level, while 72% of patients claimed to have hypoglycemic episodes at least weekly. The median Quality of life (QOL) score was 5.5 (range, 3–7) and the median health status score was 5 (range, 3–7), similar to age-

matched patients with type II diabetes. More recently, 34 patients who had undergone total pancreatectomy at the Mayo Clinic were surveyed with multiple quality-of-life instruments (SF-36, Audit of Diabetes Dependent Quality of Life, EORTC PAN26) and were found to have quality of life scores equivalent to age- and sex-matched diabetics. Three alcoholic patients died of late hypoglycemic episodes, emphasizing the importance of screening for substance abuse before performing total pancreatectomy. The authors concluded that in appropriately selected patients, total pancreatectomy can provide an acceptable quality of life ***(Billings et al., 2012).***

Diabetic control after total pancreatectomy

For many years, the use of total pancreatectomy was limited in surgical practice, but in the last 25 years, thanks to highly sensitive imaging techniques, the operability of many pancreatic diseases has increased and pancreatic resection has become more common as the operative mortality risk has fallen to less than 2%. Removal of the pancreas is often associated with a glucose intolerance called 'pancreatogenic diabetes'; most of the studies in this field have emphasised the difficulties in glucose control, considering the apancreatic patients as 'brittle diabetics' ***(Kiviluoto et al., 2011)***.

The metabolic control of apancreatic patients is rather complex because the pancreas secretes most of the hormones involved in glycemic homeostasis such as insulin, glucagon and pancreatic polypeptide (PP); furthermore, other gut hormones are involved in this control. The insulin secreting beta cells are distributed evenly throughout the pancreas, whereas glucagon cells and PP (pancreatic polypeptide) cells are localized selectively in the tail and the head of the pancreas, respectively. Insulin stimulates the transport of ions, glucose and amino acidsacross cell membranes, has anabolic effects such as protein synthesis and lipogenesis, and has growthpromoting effects secondary to the stimulation of RNA and DNA synthesis. Insulin is known to be a potent inhibitor of glucose production in the liver in humans and, under euglycaemic conditions, the intravenous infusion of insulin causes hepatic glucose production to decrease rapidly. The release of insulin into the portal vein after a glucose load causes suppression of net hepatic glucose production, stimulation of net hepatic glucose uptake and glycogen synthesis ***(Davis et al., 2009).***

Comparing the insulin action of patients with pancreatogenic diabetes to those with type I diabetics, enhanced extrahepatic tissue sensitivity to physiologic hyperinsulinaemia and higher insulin binding to red blood cell receptors have been observed in patients with pancreatogenic diabetes. Insulin decay

has also been analysed after discontinuing insulin infusion, and theplasma clearance rate of insulin is significantly higher in patients with pancreatogenic diabetes than in those withtype I diabetes. Thus, an up-regulation of peripheral insulin receptors in response to insulin deficiency occurs, renderingthese patients uniquely sensitive to horrnone replacement ***(Nosadini et al., 2010).***

Glucose intolerance after pancreatectomy may not be due to insulin deficiency alone; the reduction in beta-cell mass after an 80% proximal pancreatectomy in dogs resulted in lower peripheral insulin levels and altered glucose disappearance after glucose challenge. In the altered glucose metabolism of pancreatectomised subjects, animportant role is also played by glucagon deficiency ***(Barnes and Bloom, 2007).***

After total pancreatectomy in ducks, glucagon levels are reduced to 45% of the preoperative level immediately following the procedure. Controversy persists, however, over whether total pancreatectomy removes all sources of glucagon production. Some authors have reported no detectable circulating plasma immunoreactive glucagon after total pancreatectomy in humans, whereas others have detected varying amounts of the hormone in the plasma of pancreatectomised patients. Although there may be enteric sources of glucagon production in humans after total

pancreatectomy, there is a profound glucagon deficiency that in combination with insulin deficiency can produce a metabolic crisis. It has been reported that the metabolic response to glucagon was considerably more pronounced in total pancreatectomy patients than in type I diabetic patients. Therefore, a state of chronic glucagon deficiency may modify the effect of glucagon on the liver, presumably through up-regulation of glucagon receptors which results in enhanced hyperglycaemic responsiveness ***(Kannann et al., 2011).***

Despite an increase in peripheral insulin receptor availability, however, pancreatogenic diabetes is also accompanied by a decrease in hepatic insulin receptor availability. This paradoxical effect is probably due to a concurrent deficiency in PPs and renders the liver resistant to the suppressant effects of insulin on hepatic glucose production. In fact, a critical role for PP as a hormonal mediator of glucose metabolism has been suggested. This hormone is released in a biphasic manner in response to feeding and it has been shown to inhibit exocrine pancreatic secretion and gallbladder contraction. PP receptors have also been identified on rat hepatocyte plasma membranes. Studies on a canine model of chronic pancreatitis associated with PP deficiency demonstrated hepatic resistance to insulin with inappropriate hepatic glucose production despite physiologic levels of insulin. There is

evidence of a role for PP in the hepatic sensitivity to insulin, and it has been suggested that the maintenance of hepatic insulin receptor availability is PP-dependent. PP deficiency may therefore serve as a potentially reversible pathophysiologic factor which contributes to an altered glucose metabolism following proximal or total pancreatectomy due to diminished hepatic insulin receptor gene expression and insulin receptor availability ***(Seymour et al., 2007).***

Other gut hormones provide both stimulation and feedback inhibition of pancreatic endocrine and exocrine functions. Total pancreatectomy often involves resection of the distal stomach, duodenum, gallbladder, distal common bile duct and proximal jejunum. To study the effects of removing these sources of enteric hormones, Dammann et al. profiled guthormones in eight patients after total pancreatectomy and compared them with normal controls. The pancreatectomised patients exhibited impaired gastrin release after meal stimulation, which is consistent with the effects of antrectomy; but motilin and gastric inhibitory polypeptide (GlP) levels were no different from those in the controls. Enteroglucagonwhich is thought to slow intestinal transit time and promote mucosal growth, increased sharply in the pancreatectomised patients following meal stimulation. This may be due to the increased transit time through the stomach following gastrojejunostomy

or due to up-regulation of preproglucagon expression in the gut. Both GIP and glucagon-like peptide-I, which is a cleavage product of enteric preproglucagon, serve as enteric hormonal stimulants of insulin release. Changes in the secretion of these and other enteric hormones may therefore occur in a compensatory fashion after the loss of pancreatic mass. Thus, total pancreatectomy results not only in pancreatic hormone deficiency but in derangements of other gut hormones which are important for the metabolism ***(Dammann et al., 2008).***

To prevent this problem, Japanese authors claimed that a pylorus-preserving pancreatectomy is better than a standard total pancreatectomy in reducing the incidence of late complications of apancreatic patients including uncontrollable diabetes ***(Sugiyama and Atomi, 2010).***

Furthermore, Billings et al. have recently shown that the glycaemic control of pancreatectomised patients appears to be improved compared with earlier studies. The mean HbAlc level in their patients was equal to 7.4% and this figure reflects a glycemic control close to that which is capable of decreasing the risk of diabetic microvascular and renal complications and it is lower than what had previously been published ***(Billings et al., 2012).***

Likewise, the risk of hospitalization secondary to hypoglycemic complications is similar to hospitalization rates among patients with insulin-dependent diabetes from other causes. Although adequate glycemic control was achieved among the surviving respondents, there was a 3% overall risk of late death secondary to hypoglycemia in the sample studied, The results of the SF-36 questionnaire used for measuring the quality of life objectively quantify the fact that patients who undergo a total pancreatectomy experience a significant decrease in their perception of the quality of their health and their ability to live and work Similar to insulin-dependent diabetes mellitus from other causes, apancreatic diabetic patients expressed an almost universal negative impact of diabetes on their quality of life. The morbidity and mortality of the Mayo Clinic series show the relative safety of a total pancreatectcomy. Furthermore, in this study the average risk of hospitalization secondary to hypoglycemia, and the maintenance of a nearly appropriate HbAlc level in the long-term survivors suggests that apancreatic diabetes is tenable in selected patients. There remains, however, a late risk of death secondary to hypoglycemia: three patients in this series died from hypoglycemic attacks. Control of obligate diabetes mellitus remains difficult; 3 of 99 patients died from hypoglycemia and the specific effects of diabetes impact quality of life ***(MacLeod et al., 2012).***

In this issue of *Digestive and Liver Disease,* Jcthwa et al. followed 33 of the 47 patients who underwent a total pancreatectomy in their institution for a period of 50 months. In brief, this study adds the following to what was previously known: (a) the majority of patients reported good diabetic control and daily performance as excellent or good, even if the daily performance status was assessed without a validated questionnaire; (b) only two patients required in-patient treatment for diabetic complications and no deaths related to diabetes were observed. The main conclusion is the confirmation that glycemic control in apancreatic patients appears to be less problematic than in the past. We should take into account that these results could possibly be due to the fact that, in the last few years, careful monitoring, rapid referral to a diabetic centre, patient compliance and understanding their condition, irrespective of the social-economic class, have all contributed to rendering glycemic control less tenuous than in the past ***(Jcthwa et al., 2012).***

Management Protocol

A team approach to patient management was used with all patients followed by the same surgical and endocrine attending physicians (JG Fortner and DR Bajorunas)for the duration of the 11-year follow-up period. The team nurse clinician provided patient education on a daily basis during the

initial hospitalization and was present at every outpatient visit. Dietary guidelines. After operation all patients were managed for up to 3 days in the intensive care unit and after their transfer to the general surgical floor, total parenteral nutrition (TPN) was maintained until adequate oral feedings were clinically feasible. Thereafter the patients were placed on a high calorie (40 to 50 kcal/kg), three-meal, three-snack diet/day, limited in sucrose calories only if the patients were maintaining weight. Additional caloric intake was encouraged by the use of lactose-free lower osmolarity oral formula supplements and the liberal use of medium-chain triglyceride (MCT) oil. No specific dietary fat restriction was placed and the overall caloric distribution approximated 35% to 40% fat, 45% to 50% carbohydrate, and 15% to 20% protein calorie intake. In patients whose diarrhea was protracted, Anempiric lactose-free diet was instituted. Patients were discharged from the hospital only when a trend toward weight stabilization was demonstrated and calorie counts showed an intake of at least 2000 kcal/day.Following discharge all patients were maintained on the same dietary guidelines that focused on calorie-dense foods, except that a simple sugar restriction (less than 5% sucrose calories) was introduced to aid glycemic control when dietary intake had stabilized. A registered dietitian evaluated the patients every 3 months for the first postoperative year and yearly thereafter ***(Abraham et al., 2008).***

Diabetic management

The patients were instructed in the use ofa reflectance meter-assisted home glucose monitoring program before their discharge from the hospital. Comparable mean values to laboratory glucose determinations were achieved ($r = 0.85$, $p = 0.001$) whenthe patients were monitored as inpatients. Fingerstick glucose determinations were obtained before meals and at bedtime; in the immediate posthospital discharge period and periodically thereafter, patients were asked to check a 3 A.M. level. Compliance with this regimen on a longterm basis was readily achieved because both patients andtheir families thought that this technique provided them with increased security from hypoglycemia. At every subsequent hospital outpatient visit these glycemic records were reviewed with the patients and their families as well as insulin dosage adjustments were instituted. The patients were best managed on a regimen of 2:1 or 3:1 ratio of NPH/Lente:regular insulin administered subcutaneously in the morning, with an additional dose of regular insulin administered 30 minutes before dinner. Because ofthe frequency of nocturnal hypoglycemia, only the exceptional patient required a second (evening) injection of intermediate-acting insulin. All regular insulin was administered per a sliding scale regimen, depending on the result of the fingerstick glucose determination. A'salvage'

regular insulin sliding scale was prescribed to prevent excessive hyperglycemia before lunch and at bedtime. All patients were strongly encouraged to maintaina bedtime fingerstick glucose level of more than 11.2 mmol/L (200 mg/dL). Patients and family were well versed in the signs and symptoms of hypoglycemia, andglucagon (in 1 mg/mL vials) for parenteral administration by family members in the event of a serious hypoglycemic episode was routinely prescribed ***(Peterson et al., 2009).***

Management of Exocrine Insufficiency after total **Pancreatectomy**

Little information has been reported on the metabolic characteristics of the totally pancreatectomized patient or the efficacy of medical management after radical pancreatic surgery. The prospective evaluation of 49 such patients, with 31% followed for 48 or more months, forms the basis of this report. The major immediate postoperative challenge is control of diarrhea andweight stabilization. Chronically patients have an increased daily caloric requirement (mean ± SE, 56 ± 1 kcal/kg), not wholly explained by moderate steatorrhea (fecal fat excretion, 16% ± 2% of unrestricted fat intake). Despite persistent malabsorption, deficiencies in fat-soluble vitamin, magnesium, and trace element serum levels can be prevented in most patients, However adverse chronic sequelae of the

operation occur and include an unusual frequency of liver disease, characterized byaccelerated fatty infiltration, and osteopenia, with an 18% reduction in radial bone mineral content noted in pancreatectomized patients studied more than 5 years after surgery ***(Levin et al., 2008).***

The patients were instructed to take pancreatic enzyme replacement, consisting of variable amounts of lipase, amylase, and protease units depending on the commercial preparation used as soon as oral intake was instituted. Doseswere slowly increased to a usual maintenance dose of four to five capsules with meals and two to three capsules with snacks. The dosages of the enzymes were clinically adjustedon the basis of weight, serum magnesium levels and stool characteristics. Antacids or H-2 blockers were not routinely prescribed. Enteric-coated microsphere formulations appeared to offer no specific advantage in this patient population. It was not unusual for tachyphylaxis to develop to a specific enzyme preparation, requiring a product change. Patients were encouraged to take two multivitamins/day and were prescribed oral calcium (1g) and pharmacologic vitamin D (4000 to 12,000 IU) supplementation daily ***(Lowry et al., 2010).***

Laboratory Analysis

Routine hematology, chemistry screening profiles, and magnesium levels were obtained at every visit (bimonthly for

the first 6 months, then at 3- to 6-month intervals). Glycosylated hemoglobin levels were used to ascertain the degree of diabetic control. Vitamins A, E, 25-hydroxy, and 1,25-dihydroxy D and the trace elements copper and zinc were monitored every 6 months. Measurement of bone mineral content used direct photon absorptiometry technique at the distal third ofthe non-dominant radius. For the quantitative 72-hour fecal fat analyses, Patients were admitted to the metabolic unit and maintained on a defined diet that mimicked their outpatient dietary regimen. The usual pancreatic enzyme replacement was maintained. Nonabsorbable stool markers ensured adequacy of the 72-hour stool collection. Such inpatient testing validating outpatient management was supported by the close reproducibility of results in the four patients in whom such testing was repeated after at least 18 months ***(Van de Kamer et al., 2009).***

Carbohydrate absorption testing used an oral 25-g dose of D-xylose, with serum levels and urinary excretion measuredduring the subsequent 5 hours. In selected patients the completeness of the pancreatic resection was verified by stimulated C-peptide levels. Plasma immunoreactive glucagon (IRG) and IRG chromatographic profiles were assayed in the laboratory of using a doubleAntibody radioimmunoassay technique with 30K antiserum. In this assay cross-reactivity

with glucagon like immunoreactivity is minimal. Glucagon chromatographic profiles were obtained with a 1 X 50-cm BioGel P-30 column (Bio-Rad Laboratories, Richmond, CA), as previously described **(Finlay et al., 2011).**

In the present 'transplant era', there is the possibility of curing apancreatic state using transplant options, at least in patients operated on for chronic pancreatitis and in those with benign tumors of the pancreas. Finally, the recent evidence of the possibility of transdifferentiating stem cells to beta cells encourages further studies in order to determine the differentiation pathways of stem cells to insulin producing cells in order to ameliorate the glycaemic control in apancreatic patients ***(Kin et al., 2012), (Di Gioacchino, 2012).***

Summary

The pancreas is perhaps the most unforgiving organ in the human body, leading most surgeons to avoid even palpating it unless necessary. Situated deep in the center of the abdomen, the pancreas is surrounded by numerous important structures and major blood vessels. Therefore seemingly minor trauma to the pancreas can result in the release of pancreatic enzymes and cause life-threatening pancreatitis. Surgeons that choose to undertake surgery on the pancreas require a thorough knowledge of its anatomy.

Pancreatic carcinoma is one of the most aggressive human malignancies. It is the tenth most common malignancy and the fourth largest killer in adult. It has an overall cumulative 5 years survival rate below1%.

Approximately 90% of pancreatic exocrine tumors arise from pancreatic ductules and 80% of these tumors are adenocarcinoma, 60-70% arises in the head and the rest of the tumors located in the body, tail or diffusely throughout the gland.

The cause of pancreatic carcinoma remains unclear; there are many risk factors for developing pancreatic carcinoma as: tobacco smoking, high fatty meals, alcohol consumption,

diabetes mellitus, pernicious anemia, chronic pancreatitis, cholelithiasis, gastric surgery, radiation and genetic factors. Pancreatic carcinoma is uncommon before the age of 45 years old; more than 80% of Patients are aged 60-80 years.

Unfortunately, only 15-20% of patients diagnosed with pancreatic adenocarcinoma are candidates for resection, and even after complete (R0) resection the 5-year survival is only 15-20%.

This poor prognosis, attributable to delayed presentation, tumor biology, complexity of surgical intervention, and paucity of multimodality therapy, has engrained a pessimistic mindset in many clinicians, leading to an underutilization of surgery despite recent evidence challenging these long established beliefs.

Due to its poor prognosis there is a high unmet medical need to improve the treatment of pancreatic cancer and to extend patients' lives. Unfortunately, the majority of patients are deemed unresectable at the time of diagnosis and may die within one year, long term survivors are an exception, due to distant metastasis or a locally extensive disease.

The presenting symptoms of pancreatic cancer can include pain, unexplained weight loss, nausea, vomiting, steatorrhea, dyspepsia, depression and jaundice. There are no well known

warning signs of pancreatic cancer. However, new onset diabetes in an old patient has been associated with pancreatic cancer.

The main reason for the poor outlook for patients with pancreatic cancer is that very few of these cancers are found early, since the clinical features of pancreatic cancer initially are non-specific and vague, this contributes to delay in diagnosis of usually about 8 weeks, moreover the pancreas is located deep inside the body thus early stage tumors cannot be seen or felt by health care providers during routine physical exams. That's why diagnosis is more dependent on imaging studies and other methods of investigations.

Imaging Studies:

1. Transabdominal Ultrasound US (TUS).
2. Computed tomography scanning.
3. Spiral CT.
4. Endoscopic ultrasonography (EUS).
5. Magnetic resonance imaging.
6. Endoscopic retrograde cholangiopancreatography.
7. Positron emission tomography scanning (PET).

FDG-PET/CT may represent a useful add-on diagnostic tool in the evaluation of patients with suspected pancreatic cancer, especially when CT and biopsy results are inconclusive.

8. Percutaneous Biopsy.
9. Staging laparoscopy:

Patients who are suitable for resection, five-year survival rates of 25% are possible, which underlines that surgery offers the only chance of cure and long-term survival.

The operative management of pancreatic carcinoma involving head, neck and uncinate process consists of 2 phases, first assessing the tumor resectability and then if the tumor is resectable the Standard resections can be done which include pancreatico-duodenectomy with distal stomach resection or recently accepted as the preferable procedure preservation of the pylorus for tumors in the head of the pancreas, distal pancreatectomy for tumors of the body and tail as well as total pancreatectomy for more extended tumors or intraductal papillary mucinous neoplasias (IPMN) if necessary.

Adjuvant chemoradiotherapy like: 5-florouracil and gemcitabine improve the results of surgery, Surgical palliation of unresectable pancreatic tumors can improve the quality of life of these patients.

Surveillance and screening of high risk groups by effective and cost-effective methods will improve the detection of precancerous lesions thus improving the prognosis, However

Prognosis of pancreatic cancer is generally bad even with resected cancer.

Total pancreatectomy has been used to treat both benign and malignant disease of the pancreas, but its use has been limited by concerns about management of the apancreatic state with its attendant total endocrine and exocrine insufficiency.Total pancreatectomy remains a viable option in the treatment of intractable pain associated with chronic pancreatitis, multicentric or extensive neuroendocrine tumors, patients with familial pancreatic cancer with premalignant lesions, and in patients with intraductal papillary mucinous neoplasia with diffuse ductal involvement or invasive disease, Also it helps to avoid complications of other procedures like pancreatic fistula and recurrences. Improvements in postoperative management include auto-islet cell transplantation, advances in insulin formulations, and the use of glucagon rescue therapy which allow much tighter control of blood glucose than previously possible. This markedly lessens the risk of life-threatening hypoglycemia and decreases the risk of long-term complications, resulting in improved quality of life for these patients.

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