Pancreatic Disorders

85

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Pancreatic Tumors

Almost all types of neoplasms that commonly occur in the adults have been reported in children and must be included in the differential diagnosis of a pancreatic mass in a child. Pediatric pancreatic neoplasms are infrequent. According to the National Cancer Institute, between 1973 and 2007 only 73 cases of pancreatic malignant neoplasms in patients younger than 19 years were reported, which represents an incidence of 0.02 cases per 100,000 people per year, with a female to male ratio of 1.7/1. Because of their rarity, our understanding of the natural history of pancreatic neoplasms in children is limited, and the therapeutic regimens are not standardized.

In general, pancreatic neoplasms in children have an overall better prognosis than in adults, and the benign/malignant ratio is significantly higher. Nonetheless, some pancreatic tumors in children are very aggressive and have a poor survival rate. Complete surgical resection is the key in the treatment of all pancreatic neoplasms in children, but unfortunately is rarely achieved in cases of poorly differentiated infiltrative neoplasms.

The pancreas can develop primary neoplasms but can also contain secondary neoplasms (metastasis of distant primary neoplasms), non-neoplastic solid lesions (lymphangiomas and focal lesions of congenital hyperinsulinism), and non-neoplastic cysts (choledochal cysts, enteric duplication cysts, and pseudocysts).

Among all different types of pancreatic neoplasms in children, pancreatoblastoma (PBT) and solid pseudopapillary tumor (SPPT) are the most common ones in the first and second decade of life, respectively. The most common signs at presentation are abdominal pain or a palpable abdominal mass. Jaundice is rarely the presenting sign in children.

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Classification and Staging

The most recent classification developed by the World Health Organization in 2010 divides pancreatic neoplasms by cell line of origin, histological configuration, and degree of cellular dysplasia (Table 85.1). Pancreatic neoplasms are divided into *epithelial* and *non-epithelial* types. Epithelial tumors are those with a cell line that resembles the lining of the pancreatic ducts ("ductal" differentiation, typically mucin-producing cells), the lining of the pancreatic acini ("acinar" differentiation, typically enzyme-producing cells), or the cells that form the islets of Langerhans ("endocrine" differentiation, functional or non-functional). Non-epithelial tumors are those that arise from tissue of mesenchymal or ectodermal origin (liposarcomas, myosarcomas, and primitive neuroectodermal tumors) and they are extremely rare. The staging system for pancreatic neoplasms in children is based on the TNM classification and follows the criteria used in the adults (Table 85.2).

Pancreatoblastoma

Pancreatoblastoma (PBT) is the most common pancreatic neoplasm in the first decade of life, and it affects males four times more frequently than females. The mean age at presentation is 4–5 years, the vast majority of cases occurring before 10 years, and it very rarely occurs in adults. PBT belongs to a group of neoplasms called "embryonal" tumors, which occur mainly in children and appear to arise from multipotent stem cells. Nephroblastoma (Wilms tumor), hepatoblastoma, and neuroblastoma are also embryonal tumors. Embryonal tumors share a common genetic derangement: the loss of heterozygosity (LOH) of different regions of the short arm of chromosome 11, which affects the expression of imprinted genes that regulate cell proliferation. The 11p15.5 locus has two imprinted genes: Insulin-like Growth Factor 2 (IGF2) and H19, which have opposite roles in cell proliferation. The IGF2 gene is only expressed from the paternal allele (the maternal

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Table 85.1 Classification of pancreatic tumors

• Invasive ductal adenocarcinoma – Conventional – Atypical histologic variants	• Acinar cell neoplasms – Cystadenoma – Carcinoma – Cystadenocarcinoma
• Pancreatic intraepithelial neoplasia (PanIN) – 1A – 1B – 2 – 3	• Serous neoplasms – Cystadenoma – Cystadenocarcinoma – Solid serous adenoma
• Intraductal neoplasms • Intraductal papillary-mucinous neoplasms – *with low-, moderate-, or high-grade dysplasia* – *with invasive carcinoma* • Intraductal tubular neoplasms – *with low-, moderate-, or high-grade dysplasia* – *with invasive carcinoma*	• Pancreatic endocrine neoplasms • Well differentiated – *Functional* – *Non-functional* • Poorly differentiated
• Mucinous cystic neoplasms – *with low-, moderate-, or high-grade dysplasia* – *with invasive carcinoma*	• Solid pseudopapillary tumor
	• Pancreatoblastoma • Mesenchymal neoplasms • Secondary neoplasms

Source: Data from International Agency for Research on Cancer, World Health Organization, 2010

Table 85.2 TNM classification and staging system of pancreatic neoplasms

• T-Primary tumor – TX: Cannot be assessed – T0: No evidence of primary tumor – Tis: Carcinoma in situ—PanIN3 – T1: Limited to the pancreas ≤ 2 cm[a] – T2: Limited to the pancreas >2 cm[a] – T3: Tumor extends beyond the pancreas – T4: Tumor involves celiac trunk or SMA[b]			
• N-Regional lymph nodes – NX: Cannot be assessed – N0: No lymph node metastasis – N1: Lymph node metastasis			
• M-Distant metastasis – M0: No distant metastasis – M1: Distant metastasis			
• Staging	T	N	M
• Stage 0:	is	0	0
• Stage 1A:	1	0	0
• Stage 1B	2	0	0
• Stage 2A:	3	0	0
• Stage 2B:	1, 2, 3	1	0
• Stage 3:	4	Any	0
• Stage 4:	Any	Any	1

[a]Maximum diameter
[b]Superior mesenteric artery

allele is silent), whereas the H19 gene is only expressed from the maternal allele (the paternal allele is silent). IGF2 and H19 must be expressed in balance in order to maintain a normal cellular proliferation rate. LOH of the maternal region 11p15.5 with the subsequent imbalance towards cell proliferation in the IGF2/H19 expression has been demonstrated in nephroblastoma, hepatoblastoma, PBT, and interestingly in the focal form of congenital hyperinsulinism which is characterized by an abnormal proliferation of cells in the form of an adenomatous hyperplasia. Moreover, the LOH of the 11p15.5 region is one of the key features of Beckwith–Wiedemann syndrome, which is associated with disorders of cell proliferation (macroglossia, hemihypertrophy, and pancreatic islet cell hyperplasia) and a high incidence of embryonal tumors.

PBT is a solid epithelial tumor with cells that have usually some degree of differentiation towards acinar lineage and much less frequently towards ductal or endocrine lineages. Cells are divided into lobules separated by stromal bands. The pathognomonic feature of PBT is the squamoid corpuscle, which is a cluster of spindle-shaped cells of unknown origin (Fig. 85.1). Because of the acinar-type differentiation, PBT cells are usually positive for lipase and trypsin immunostaining. PBT develops more frequently in the head of the pancreas (60 %) than the body or tail (40 %), and extremely rarely it can occur in ectopic locations. The most common form of presentation is an incidentally found abdominal mass and less commonly abdominal pain.

Despite the usually large size at presentation, jaundice is rarely the initial sign of a PBT. Alpha-fetoprotein is elevated in approximately 30 % of PBT, and can be used as a long-term follow-up marker of disease status. On imaging studies PBT presents as a heterogeneous large mass. Some PBT are well-circumscribed and lobulated, and others are completely infiltrative (Fig. 85.2). Calcifications are frequent. Complete surgical resection, if possible, is the treatment of choice, even if an extensive surgical resection is required. Infiltrative tumors that are unresectable at presentation may respond to neoadjuvant therapy followed by surgical resection.

There is no standard chemotherapy protocol for the treatment of PBT, but the most significant responses have been observed after multiple cycles of cisplatin and doxorubicin (Fig. 85.2). Adjuvant therapy is also recommended for Stage III and IV tumors, and for recurrences. The role of radiotherapy remains unclear but there is evidence that it might be useful for local recurrences. Local recurrences are not uncommon even in cases with clean resection margins by pathology. The prognosis is generally good in cases that present without metastasis and can be resected completely, which occurs in 60–70 % of the cases. For the other 30–40 % of patients who present with stage IV disease, the overall survival rate is less than 50 % at 5 years. The most common sites of PBT metastasis are liver and lung.

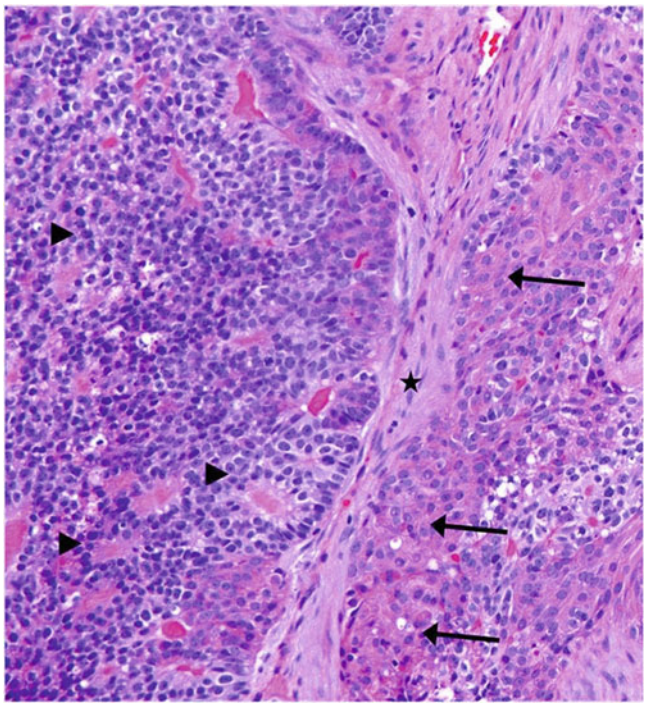

Fig. 85.1 Pancreatoblastoma. Hematoxylin and eosin, 40×. Acinar differentiation (*arrowheads*), squamoid corpuscles (*arrows*), and stromal band (*star*)

Solid Pseudopapillary Neoplasm

This neoplasm has had several different synonyms over the years: solid and papillary tumor, solid-cystic tumor, papillary-cystic tumor, and Frantz's tumor. They have all been replaced by the current term "solid pseudopapillary neoplasm" (SPPN). SPPN is the most common pancreatic neoplasm in the second decade of life and it affects females 10 times more frequently than males. The typical age at presentation is 20–30 years. SPPN is considered a malignant neoplasm due to its ability to form metastases, which are present at the time of diagnosis in 10–15 % of cases (Stage IV). However, SPPN usually has a remarkably benign behavior.

SPPN is an epithelial solid tumor that invariably develops cystic degeneration. The cellular lineage of origin is unknown. Cells are negative for mucin, enzymes, and hormones, which supports the theory that SPPN arises from an embryonal pancreatic pluripotent cell. Other histochemical markers such as neuron-specific enolase, beta-catenin, vimentin, and progesterone receptors are frequently positive but non-specific. A particular dot-like intracytoplasmatic expression of CD99 is highly specific for SPPN. Common serum tumor markers (CA 19-9, CEA, and CA 125) are consistently negative in patients with SPPN. Most SPPN are located in the body/tail of the pancreas, but they can also occur in the head, and very rarely in extrapancreatic locations. Histologically, SPPN has a very characteristic appearance of solid areas mixed with areas of poorly cohesive cells that form pseudopapillae around thin blood vessels (Fig. 85.3). Vascular or neural invasion are unusual findings in SPPN.

On imaging studies, SPPN are usually large and heterogeneous at presentation, but encapsulated and well demarcated from the surrounding structures. The most common forms of presentation are abdominal pain or an incidentally found abdominal mass, but jaundice is also common in tumors located in the pancreatic head (Fig. 85.4). Preoperative cytological diagnosis by percutaneous or endoscopic biopsy is feasible but has a sensitivity of only 50 %.

The mainstay treatment of SPPN is surgical resection, which should be as complete as possible even in Stage IV

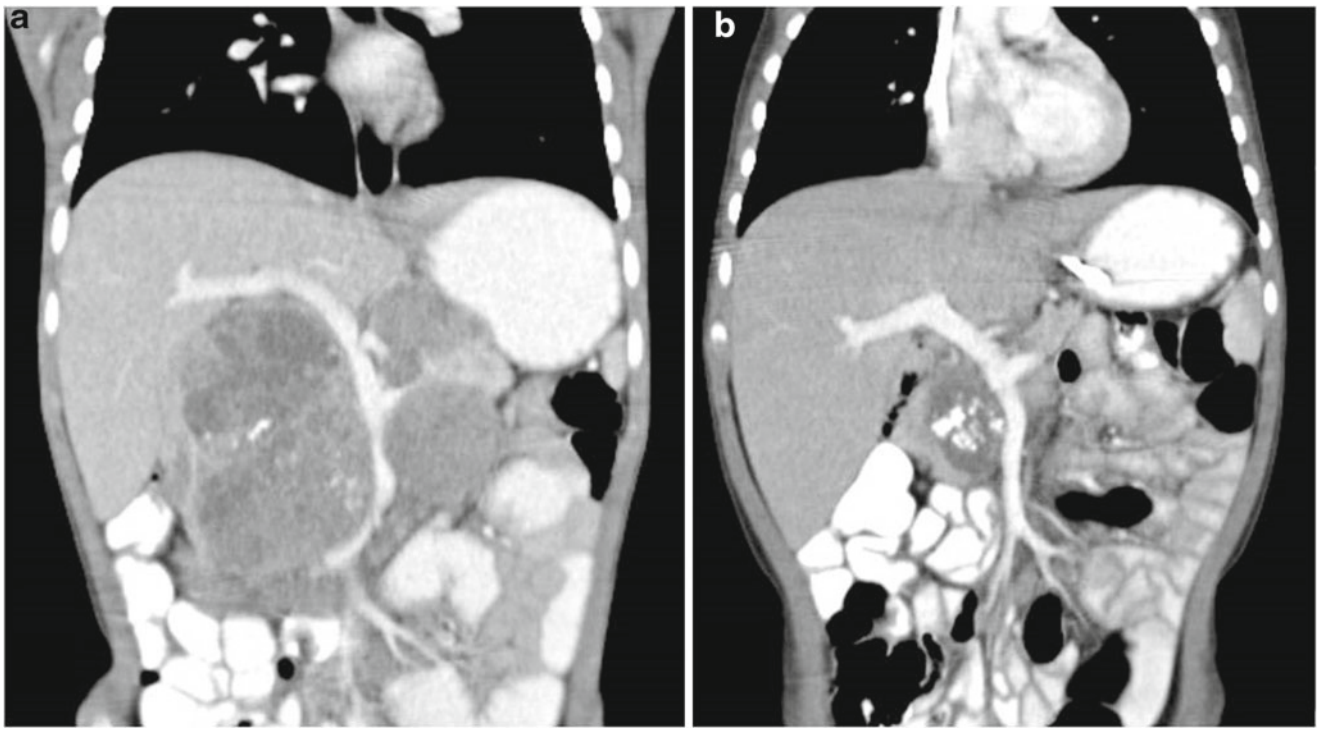

Fig. 85.2 (**A**) Large PBT at the head of the pancreas with calcifications in a 4-year-old male who presented with abdominal pain. Initially unresectable and stage IV (lung metastasis). (**B**) It shrank significantly after several cycles of cisplatin and doxorubicin after which he underwent a Whipple procedure

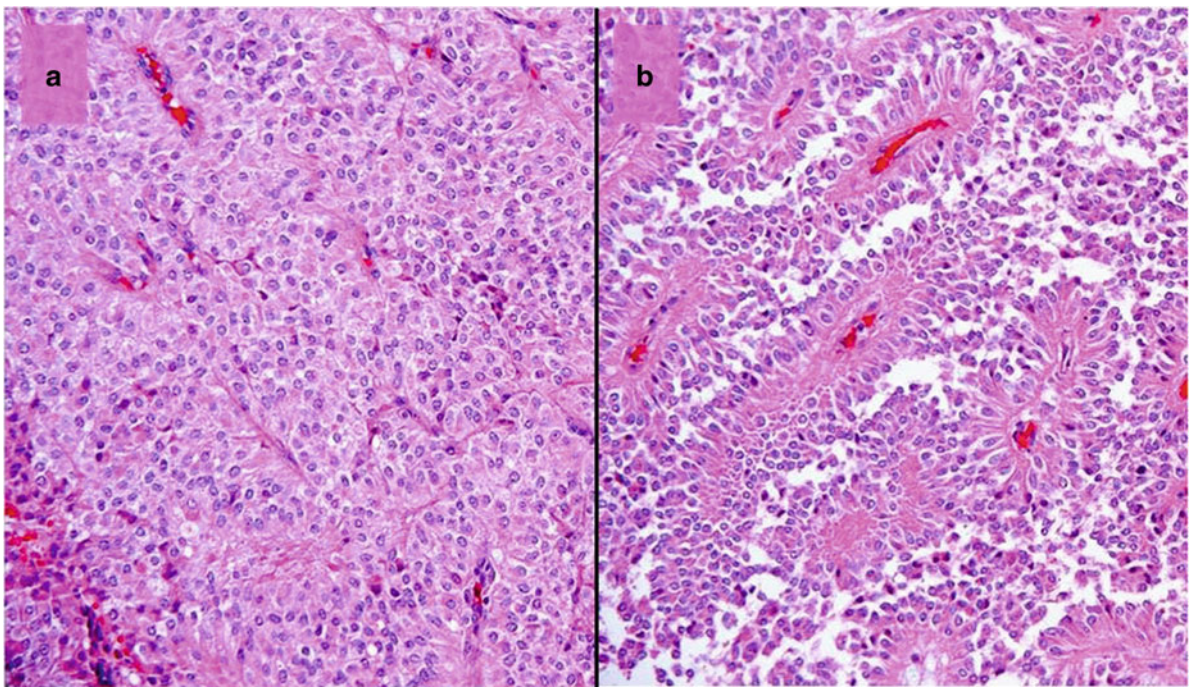

Fig. 85.3 Solid pseudopapillary neoplasm (SPPN). These heterogeneous neoplasms combine (**A**) solid regions of homogeneous cells and (**B**) pseudopapillary regions where poorly cohesive cells surround small and thin blood vessels

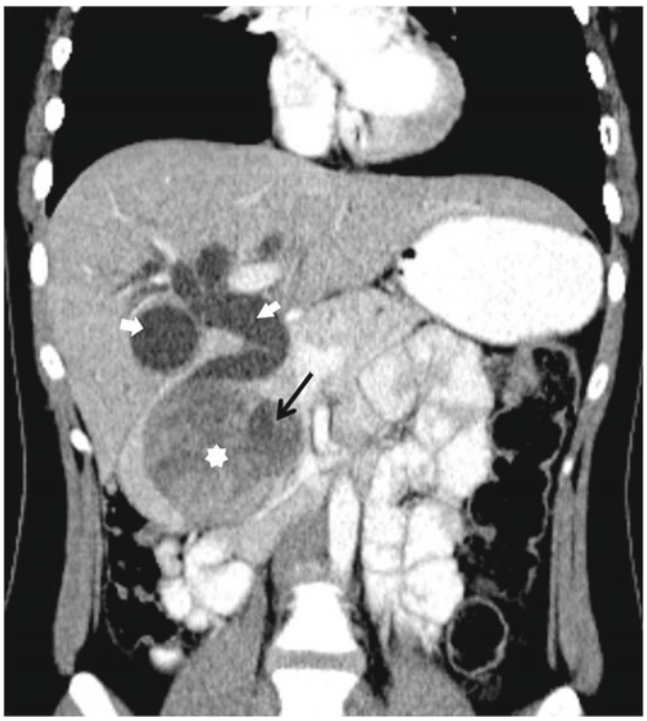

Fig. 85.4 Solid pseudopapillary neoplasm in the pancreatic head in a 16-year-old female. The tumor (*star*) is heterogeneous and well demarcated, and has an area of cystic degeneration (*black arrow*). It caused significant biliary obstruction (*white arrows*); jaundice was the sign at presentation

cases. Simple enucleation and incomplete resections are associated with more frequent local recurrences and a poorer prognosis. Distal pancreatectomy is the procedure of choice for pancreatic body/tail tumors, and pancreaticoduodenectomy is the procedure of choice for pancreatic head tumors. Lymph node involvement is very rare in SPPN and therefore lymphadenectomy is not required. The most common metastatic sites are the liver and the peritoneum. When feasible, metastases should be surgically resected, otherwise chemotherapy is the treatment of choice.

Chemotherapy has also been used as single or neoadjuvant therapy in cases that were deemed unresectable, and in cases of aggressive local recurrences, but its role in less aggressive tumors is not yet defined. Radiotherapy and hormonal therapies (anti-progesterone due to the frequent presence of progesterone receptors) have been used in the past without salutary effect and have been abandoned as therapeutic options in patients with SPPN. The prognosis of SPPN is generally very favorable, with an overall long-term survival rate greater than 90 %, even in Stage IV cases. There is a subset of SPPN, however, that is very aggressive and undergoes sarcomatous degeneration, with invasion of adjacent organs, neural and vascular elements. Factors that appear to be related to a more aggressive behavior are male gender, infiltrative growth pattern, nuclear pleomorphism, and vascular and extrapancreatic invasion.

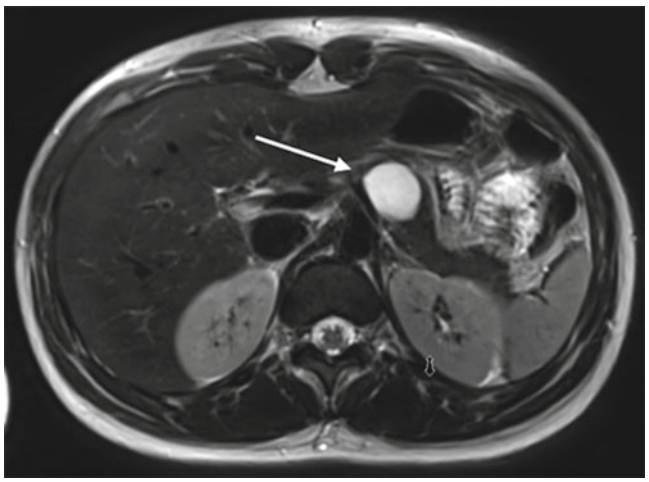

Fig. 85.5 Magnetic resonance of a cystadenoma located in the pancreatic body (*white arrow*)

Acinar Cell Neoplasms

Acinar cell neoplasms arise from cells that resemble normal acinar cells and produce pancreatic exocrine enzymes, testing positive for enzyme-like markers on immunohistochemical staining. This group of neoplasms includes cystic (cystadenoma and cystadenocarcinoma) and solid lesions (acinar cell carcinoma). *Acinar cell cystadenoma* is a rare, benign, and cystic pancreatic neoplasm. The cysts are lined by acinar cells and the fluid inside the cysts is rich in amylase and lipase. Cells have no atypia and do not cross the basal membrane. They can be unilocular or multilocular (Fig. 85.5). Surgical resection is the treatment of choice. *Acinar cell carcinoma* (ACC) is relatively common within the uncommon malignant pancreatic tumors in children, and it has been extensively reported in the literature. ACC is an aggressive neoplasm that affects males more frequently than females. Early metastases are common (>50 % at the time of diagnosis, mainly in the liver). The prognosis is relatively poor, compared to PBT and SPPN, but it appears to be better in children than in adults. Most ACC are located in the head of the pancreas and are large at diagnosis. Alpha-fetoprotein is frequently elevated. Histologically, the cells can have an acinar arrangement or, less frequently, a completely solid arrangement. Cells are almost always positive for trypsin, chymotrypsin, and lipase. ACC can be confused with PBT on histologic analysis due to the marked acinar differentiation of some PBT. The absence of squamoid corpuscles favors the diagnosis of ACC. A combination of surgery and chemotherapy offers the best outcome in ACC. Nevertheless, even patients with no metastases at presentation and a complete surgical resection have a high incidence of distant and local recurrence, and a poor survival rate.

Invasive Ductal Adenocarcinoma

The most common malignant pancreatic neoplasm in the adult population (>90 %), ductal adenocarcinoma (DAC) is very rare in children. Few pediatric cases have been reported in the literature, and almost all of them were diagnosed as Stage IV and had an eventual fatal outcome. Most DAC are solid and located in the pancreatic head. Rapid local invasion and early distant spreading are the rule, with 80 % of cases being unresectable at presentation. The most common sites of metastases are liver, lungs, lymph nodes, and bone. On imaging studies pancreatic DAC are irregular, heterogeneous, and infiltrative lesions. Macroscopically pancreatic DAC are firm and hard tumors. Histologically there is a *conventional* type (the most frequent) and several different variants (colloid, hepatoid, adenosquamous, and others). The neoplastic tissue consists of a tubular proliferation within a desmoplastic stroma that infiltrates the non-neoplastic ducts, islets of Langerhans, and acini. Immunohistochemical markers consistently positive in DAC are mucin, the glycoproteins CA19-9, CEA, and CA125, and the cytokeratins 7, 8, and 18. However, none of them is an unequivocal indicator of DAC. The treatment of choice is surgery, but a complete resection is rarely achieved. Chemotherapy is used in unresectable cases but there are no standardized protocols in children. The survival rate is very poor, with a median survival of less than 20 months from the time of diagnosis.

Pancreatic Endocrine Neoplasms

Pancreatic endocrine neoplasms (PEN) are relatively frequent in adults and, as expected, rare in children. The key feature of this group of neoplasm is the production of hormones or hormone-like bioamines. The group is divided into *well-differentiated* versus *poorly differentiated* lesions based on their histological features, and into *functional* versus *non-functional* lesions based on the clinical effects of hormone hypersecretion. The vast majority of PENs are well differentiated: uniform cells with normal-appearing nuclei and less than 20 mitoses per 10 high power fields (HPF). The minority of PEN is poorly differentiated: irregular cells with marked nuclear atypia and more than 20 mitoses per 10 HPF (these are also called "*neuroendocrine carcinomas*"). Despite the clear histological distinction between well- and poorly differentiated PEN, determining the benign or malignant character of an endocrine neoplasm is not always straightforward in the absence of obvious metastases. Factors associated with a more aggressive behavior are: size (>2 cm in diameter), the presence of necrosis, vascular or neural invasion, and local invasion. Some poorly differentiated PEN are very aggressive, metastasize early, and have an invariable fatal outcome.

Most PEN are functional (65 %). The nomenclature of these lesions is based on the clinical picture and not on the immunohistochemical (IHC) profile (a PEN that stains positive for insulin but does not produce symptoms is not an insulinoma). Non-functional PEN produce hormone precursors that can be detected by IHC, but tend to be diagnosed later in development due to the absence of early paraneoplastic signs.

In adults, approximately 90 % of PEN are sporadic and 10 % are syndromic. In children, on the other hand, the percentage of syndromic cases is higher. The syndromes that are most commonly associated with PEN are Von Hippel–Lindau, tuberous sclerosis, and multiple endocrine neoplasia type I (Wermer's syndrome, autosomal dominant, characterized by parathyroid, gastropancreatic, and pituitary tumors). Patients with syndromic PEN can develop multiple synchronous lesions that produce the same or different hormones, and are always at risk for metachronous neoplasms. The treatment of PEN is complete surgical resection. Functional tumors may need symptomatic treatment prior to surgery. PEN are generally small (particularly the functional ones) at the time of diagnosis, and preoperative imaging localization is only achieved in 50 % of the cases.

Insulinoma

Insulinomas are neoplasms that arise from the insulin-producing beta-cells of the islets of Langerhans. The vast majority are benign (>90 %), but malignant stage IV cases with aggressive behavior have been reported. Clinically, insulinomas manifest with "Whipple's triad": symptoms of hypoglycemia (syncope and seizures), hypoketonemic hypoglycemia (insulin inhibits the production of ketonic bodies), and rapid resolution of the symptoms with glucose intake. Most insulinomas in children are sporadic, and about 25 % are syndromic. Most insulinomas are small (<2 cm) at the time of diagnosis and their preoperative identification can be challenging. Larger lesions can be identified with standard techniques, but this does not occur often (Fig. 85.6). Sterile intraoperative ultrasound has the highest rate of success. Histologically, insulinomas consist of a proliferation of homogeneous cells that do not respect the limits and anatomy of the pancreatic lobules, displacing the normal elements towards the periphery. The treatment of insulinomas usually starts by counteracting the effects of the insulin hypersecretion by a high intravenous glucose infusion and hyperglycemic drugs like diazoxide or somatostatin analogs. Once the patient is euglycemic the next step in the treatment is the complete surgical excision of the insulinoma. If preoperative localization is not possible, all efforts should be made to identify the insulinoma intraoperatively by means of inspection, palpation, and sterile ultrasound. Complete resection of the insulinoma by enucleation or

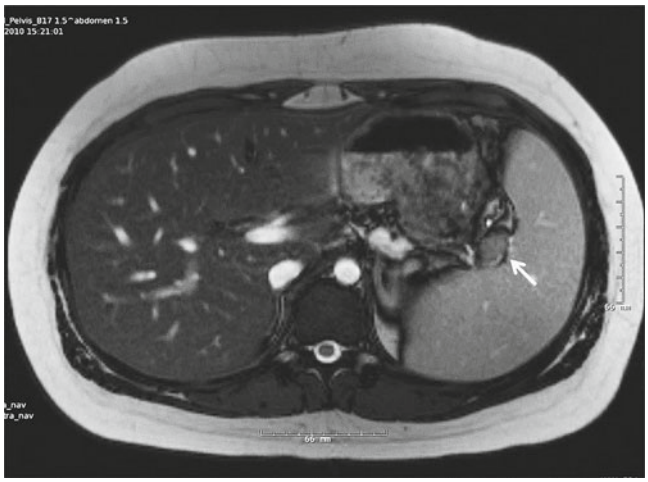

Fig. 85.6 Abdominal MRI of a 13-year-old male with MEN1 showing a relatively large insulinoma in the splenic helium. This patient had multiple synchronous smaller insulinomas and glucagonomas

segmental pancreatic resection is curative in non-syndromic cases. In syndromic cases, tiny undetectable synchronous insulinomas can be present, preventing a cure despite complete resection of the identified insulinoma. Obviously syndromic patients are at risk for metachronous tumors at any time later in life and require close clinical surveillance. In a series of eight patients we treated over a 5-year period at the Children's Hospital of Philadelphia, one patient had MEN1 and a previous insulinoma resection, no cases of malignancy were seen, and all patients were cured after surgery.

Gastrinoma

Gastrinomas in children have been reported numerous times. Only 25 % are syndromic. Gastrinoma is the most common pancreaticoduodenal endocrine neoplasia in patients with MEN1. Most of them are malignant (80 %) with metastasis to the liver and lymph nodes present at diagnosis. Clinically, gastrinomas manifest with Zollinger–Ellison syndrome, a severe form of peptic ulcer disease. The diagnosis is confirmed with an elevated serum gastrin level (>500 pg/mL). Nuclear studies are particularly helpful for the preoperative localization. The treatment starts with the administration of histamine H2-receptor blockers, proton-pump inhibitors, and octreotide, and is followed by surgical resection. Neoadjuvant or adjuvant chemotherapy is indicated in unresectable tumors and disseminated disease.

Glucagonoma

Glucagonomas are rare neoplasms that arise from the alpha cells of the islets of Langerhans. The overproduction of glucagon produces a constellation of metabolic effects that are similar to those of diabetes mellitus: hyperglycemia, lipolysis, and gluconeogenesis, resulting in pronounced weight loss. In the adult population, the majority of glucagonomas are malignant. Glucagonomas can be sporadic or associated with MEN1 syndrome. They can co-exist with insulinomas in patients with MEN1. The treatment of choice is the complete surgical resection. Sterile intraoperative ultrasound is helpful for the intraoperative localization of small, previously undetected lesions, as is the case with all other endocrine tumors (Fig. 85.7).

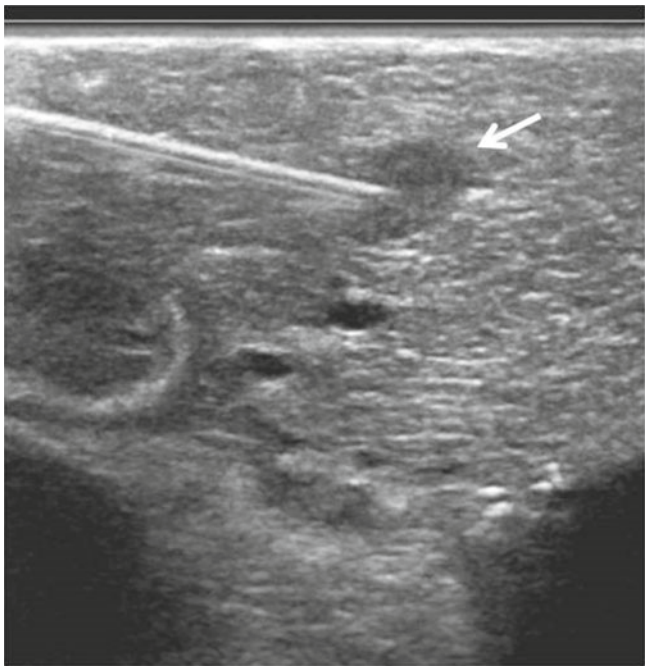

Fig. 85.7 Intraoperative ultrasound-guided needle localization of a 7×6×5 mm, 1 cm deep nonpalpable glucagonoma in the pancreatic head of an 11-year-old girl with MEN1. She had an insulinoma resected 4 years previously

Other Epithelial Pancreatic Tumors

Pancreatic Intraepithelial Neoplasia (PanIN) is a group of *microscopic* lesions confined to the epithelium of the pancreatic ducts that are precursors of invasive carcinomas. These lesions are classified by the degree of atypia in PanIN 1A, 1B, 2, and 3. PanIN are found incidentally in normal pancreatic specimens and in pancreatic specimens that contain neoplastic or non-neoplastic lesions. PanIN lesions are well-known to progress gradually from grade 1A to 3 and eventually turn into invasive ductal carcinomas. They can be found in children, particularly frequent in those with hereditary pancreatitis.

Pancreatic Intraductal Neoplasms are a group of *macroscopic* (>1 cm in diameter by definition) lesions that arise from the epithelium of the main pancreatic duct (rarely from branches) and are precursors of invasive carcinoma. These

are frequently found in men in their 7th and 8th decade, but have been reported in children.

Mucinous Cystic Neoplasms (MCN) are a group of cystic premalignant lesions characterized by a proliferation of mucin-producing ductal-like cells embedded in an "ovarian stroma" that do not involve the common bile duct. Most MCN occur in the distal pancreas of women in their 3rd and 4th decades of life, but several cases of non-invasive and invasive MCN have been reported in children.

Serous Neoplasms are cystic lesions that are relatively common in adults. The most common entity is the *serous cystadenoma*, which is benign in nature and has been reported in children. It is composed of multiple microcysts (<1 cm in diameter; rarely macrocysts) lined by cuboidal cells with acinar resemblance but without complete acinar differentiation. The fluid within the cysts does not contain enzymes or mucin. Macroscopically they are well-circumscribed lesions and the definitive treatment is surgical excision. The malignant version, *serous cystadenocarcinoma* has the potential to metastasize, and has not been reported in children.

Congenital Pancreatic Anomalies

The pancreas is prone to a number of well-defined developmental anomalies that are frequently associated with anomalies of the duodenum, bile ducts, and related anatomical structures.

Annular Pancreas

Annular pancreas is the result of an abnormal development of the pancreaticoduodenal unit, which occurs during the 5th and 6th weeks of gestation. The head of the pancreas surrounds the duodenum, as opposed to being located entirely within the duodenal c-loop. The portion of the duodenum that is encircled by pancreatic tissue is, in general, partially or completely obstructed. It is still unknown if the annular pancreas is what causes the duodenal obstruction, or if there is initially a duodenal stenosis/atresia that results in an abnormal pancreatic head development. From a surgical standpoint, the pancreas should be left untouched and the obstruction bypassed via a duodenoduodenostomy. Annular pancreas has an incidence of 1 in 20,000 live births and is twice as common in males.

Pancreas Divisum

Most of the exocrine pancreas drains into the duodenum via the major pancreatic duct, or duct of Wirsung, which merges with the common bile duct right before the ampulla of Vater and empties through the major papilla. A remaining minor portion of the pancreas drains into the duodenum via the accessory pancreatic duct, or duct of Santorini through the minor papilla. Commonly both pancreatic ducts have some degree of communication. In approximately 10 % of the population the normal anatomical arrangement is reversed, with most of the organ draining through the duct of Santorini, which has no communication with the otherwise rudimentary or absent duct of Wirsung (Fig. 85.8). Pancreas divisum is not a disease per se. However, in a subset of people with this anatomical variant, the minor papilla is functionally stenotic, which causes obstruction of the pancreatic outflow resulting in recurrent acute pancreatitis and chronic pancreatitis. The diagnosis is confirmed by ERCP or MRCP. There are a variety of options to treat this condition when it becomes symptomatic. The least invasive form is an endoscopic sphincterotomy of the minor papilla. This technique is well developed in adults, but is not always feasible in children due to size limitations. When the endoscopic approach is not available, a surgical sphincteroplasty of the minor and major papillae can be done via a transduodenal approach. In cases of pancreas divisum that have progressed to chronic pancre-

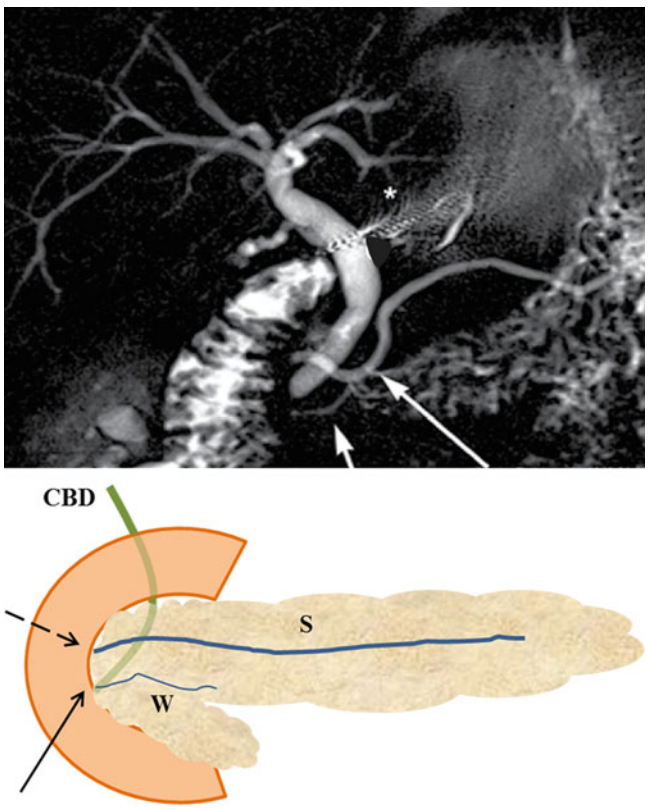

Fig. 85.8 MRCP of a patient with pancreas divisum (*above*) and schematic representation. The majority of the pancreas drains through the duct of Santorini (S, *long white arrow*). The duct of Wirsung (W, *short white arrow*) is rudimentary and drains a minor portion of the pancreas. CBD: common bile duct (*asterisk*). *Black arrow*: major papilla. *Dotted black arrow*: minor papilla

atitis with dilatation of the duct of Santorini, the Beger, Frey, or modified Puestow procedures become potential options for enteric drainage via Roux-en-Y jejunal reconstruction without the need to modify the anatomy of the minor papilla.

Pancreatic Pseudocysts

Pancreatic pseudocysts are localized collections of pancreatic fluid that has leaked out of the pancreas due to a disruption in the pancreatic ductal tree. These cysts, by definition, do not have an epithelial lining but are surrounded by a fibrous capsule that develops over the course of several weeks. The concentration of amylase in the fluid of the pseudocyst is typically very high.

The most common pancreatic problems that can result in a pseudocyst are severe inflammation (acute pancreatitis) and trauma, but a pancreatic pseudocyst can also occur when there is a blow out of the pancreatic duct secondary to a distal obstruction in the context of chronic pancreatitis (Fig. 85.9). The most common symptom is abdominal pain. Jaundice and vomiting are not infrequent, and develop when the biliary tree, the stomach, or the duodenum is extrinsically compressed by the pseudocyst. US, CT, and MRI are all helpful in the diagnosis. Serial US is generally used for evaluating the changes that occur with time. Without treatment pancreatic pseudocyst has an unpredictable behavior. Some pseudocysts continue to increase in size; some remain unchanged for long periods, and others regress and disappear spontaneously.

There is ongoing debate regarding the need to treat asymptomatic pseudocysts. The morbidity of any potential intervention must be balanced against the potential, although rare, risk of infection and hemorrhage. Symptomatic pseudocysts must be treated, but there is no standard treatment. There is a general consensus that no form of internal drainage should be attempted until the pseudocyst has formed the fibrous capsule that surrounds it, which takes at least 4 weeks. If a patient needs drainage prior to that time because of severe symptoms, an external percutaneous drainage is indicated. This approach is relatively easy, but carries a high risk of turning into a long-term pancreatic-cutaneous fistula. An alternative is endoscopic sphincterotomy with a temporary stent. The rationale behind this approach is that decreasing the pressure at the papilla may favor the outflow of pancreatic juice and turn the pancreatic duct into the path of least resistance. This approach is not always feasible in children.

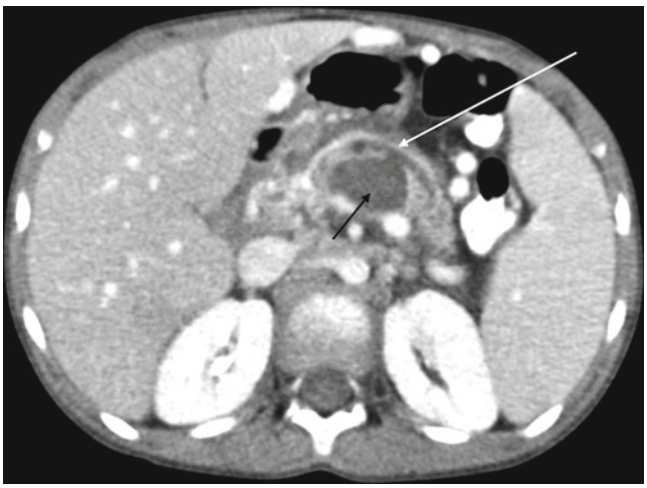

Fig. 85.9 Pancreatic pseudocyst (*black arrow*) in a patient with chronic pancreatitis and a severely dilated pancreatic duct. There is a communication between the pseudocyst and the duct (*white arrow*)

Once the pseudocyst has formed the fibrous capsule it becomes amenable to internal drainage. The current prevailing approach is an endoscopic drainage, which usually involves connecting the lumen of the pseudocyst with the lumen of the stomach or duodenum with double pigtail catheters. The most common surgical procedures used when endoscopy is not an option are cystogastrostomy and Roux-en-Y cystojejunostomy, both of which can be done open or laparoscopically. Very rarely a pancreatic resection, either proximal or distal, is required in the management of a pseudocyst.

Chronic Pancreatitis

There is no consensus regarding the exact definition of chronic pancreatitis, but in general it is diagnosed when a patient with any type of sustained pancreatic damage has anatomical changes in the pancreas on imaging studies (calcifications, atrophy, or ductal dilatation). US, CT, and MRI are all excellent studies for the diagnosis of CP. MRCP also provides very accurate images of the pancreatic ducts, the biliary tree, and the pancreaticobiliary junction. Furthermore, MRCP images can be processed to render three-dimensional reconstructions, which are very helpful when it comes to surgical planning. ERCP was in the past the most accurate diagnostic tool, but it has gradually been replaced by the non-invasive MRCP. ERCP still holds, however, an important role. If left untreated, chronic pancreatitis invariably progresses towards pancreatic endocrine and exocrine insufficiency. From a pathophysiologic perspective, the damage to the pancreas can occur due to persistent subtle inflammation and/or recurrent episodes of acute severe inflammation.

The causes of chronic pancreatitis are many, but are divided into four groups: *obstructive* (characterized by a ductal obstruction to the outflow of pancreatic secretions such as pancreas divisum with obstructive papillae, choledochal cyst, annular pancreas, or pancreaticobiliary malunion, and trauma-related obstructions), *toxic* (caused by certain drugs and, most frequently, ethanol), *systemic* (where pancreatitis is

part of a multi-organ disease, such as hypertriglyceridemia, lupus erythematosus, cystic fibrosis, or IgG4-related pancreatitis), and *hereditary* (a variety of genetic disorders characterized by an intrinsic process of pancreatic autodigestion based on mutations in a variety of genes that codify different components of pancreatic fluid). The toxic, systemic, and hereditary causes of chronic pancreatitis can provoke severe damage to the pancreatic duct, generating fibrosis, scarring, and obstruction to the outflow, which in turn results in an added mechanism of pancreatic damage.

Several genes have been implicated in the pathogenesis of hereditary pancreatitis, the *protease-serine-1* (PRSS1), the *serine protease inhibitor, Kazal type 1* (SPINK1), the *CTRC* (chymotrypsin C), and the *CFTR* (cystic fibrosis transmembrane conductance regulator). PRSS1 encodes the cationic trypsinogen, precursor of the proteolytic enzyme trypsin. A number of "disease-causing" mutations in the PRSS1 gene can lead to enhanced trypsinogen autoactivation and/or increased trypsin stability within the pancreas. SPINK1 encodes the pancreatic serine protease inhibitor which exerts a protective mechanism against prematurely activated trypsin. Therefore loss-of-function mutations in the SPINK1 gene can lead to pancreatic autodigestion. The diagnosis of hereditary pancreatitis is established when a patient with recurrent pancreatitis of unknown etiology has 1 or more first-degree relatives or 2 or more second-degree relatives, in 2 or more generations with recurrent acute pancreatitis and/or chronic pancreatitis of unknown etiology. Additionally, the diagnosis of hereditary pancreatitis is also established when a patient has recurrent/chronic pancreatitis and a known "disease-causing" mutation in the genes described above. Hereditary pancreatitis can occur in the setting of a familial pedigree or, less frequently, by de novo mutations. There are still patients with recurrent/chronic pancreatitis who do not have an identifiable cause. These cases are usually referred to as "idiopathic." Hopefully in the future advances in molecular genetics will allow finding the currently unknown genetic derangements that cause the disease.

The goal of all forms of therapy is to eliminate the pain and, if possible, to arrest the progression to pancreatic insufficiency. Patients are generally managed by gastroenterologists and pain specialists. From a surgical perspective, patients are divided into two groups: those with ductal dilatation and those without ductal dilatation. For patients with ductal dilatation, the treatment options are: (1) sphincteroplasty (endoscopic or surgical) and (2) a pancreatic drainage procedure. The optimal option depends on the exact anatomy of each case. Patients with a discrete obstruction in the proximity of the major papilla/ampulla of Vater are good candidates for an endoscopic sphincteroplasty with or without a temporary stent, as long as concomitant proximal obstructions have been ruled out. This approach is the least invasive but it requires great expertise, is not always feasible in children due to size limitations, and has a higher pain recurrence rate than the surgical options. Surgical transduodenal sphincteroplasty is rarely used, except in those with pancreas divisum.

Pancreatic drainage procedures have been used for many decades and are safe and effective. The most commonly performed procedure in children is the Puestow procedure modified by Partington and Rochelle. The abdomen is entered either using a transverse supraumbilical or a Chevron incision. The lesser sac is opened and the duodenum mobilized to expose the entire anterior aspect of the pancreas. The dilated main pancreatic duct is delineated by palpation or intraoperative ultrasound and needle aspiration is used to confirm its location. The anterior wall of the dilated pancreatic duct is filleted open with electrocautery along its entire dilated length. If intraductal stones are present, they are removed. A 20–30 cm-long Roux-en-Y jejunal limb is created, an end-to-side jejunojejunostomy is performed, and the Roux-limb is brought to the pancreatic area in a retrocolic manner. The Roux-limb is laid over the pancreas oriented with its free end on the pancreatic tail.

The pancreaticojejunostomy is built in two layers. First, a series of interrupted 3-0 silk sutures are placed between the seromuscular layer of the jejunum (just posterior to the antimesenteric edge) and the capsule of the pancreas, 2–3 mm away from the inferior edge of the opened duct. Next, the antimesenteric border of the jejunum is opened matching the length of the opened pancreatic duct and a running suture of 3-0 polydioxanone is placed between the full-thickness jejunal wall and the edge of the opened duct including the ductal mucosa in order to obtain a water-tight apposition between the jejunal and pancreatic ductal mucosa. The pancreaticojejunostomy is completed with interrupted 3-0 silk sutures placed between the seromuscular layer of the jejunum and the pancreatic capsule, cephalad to the superior half of the previous running suture. Lastly, an omental flap is used to cover the entire pancreaticojejunostomy. Drains are not necessary.

An alternative to the modified Puestow procedure are the Frey and the Beger procedures, which are designed for cases in which the fibrotic pancreatic head causes compression of the biliary tree, the duodenum, or the retropancreatic vessels. In the Frey procedure the majority of the pancreatic head is cored out, leaving a thin layer on the posterior aspect and a thin rim on to the duodenum, and the pancreatic duct on the body and tail is filleted open as in the modified Puestow procedure (Fig. 85.10). In the Beger procedure, the pancreatic head is cored out and the pancreas is transected at the neck, reconstructing the drainage with a lateral pancreaticojejunostomy to the remaining head and an end-to-end pancreaticojejunostomy to the pancreatic body (Fig. 85.10).

All surgical pancreatic drainage procedures are effective in providing a low-resistance outlet for the pancreatic secretions. However, the long-term outcomes in terms of pain control depend largely on the etiology and on whether or not the causative factor persists after the operation. Patients with *obstructive* disease are likely to have definitive pain relief

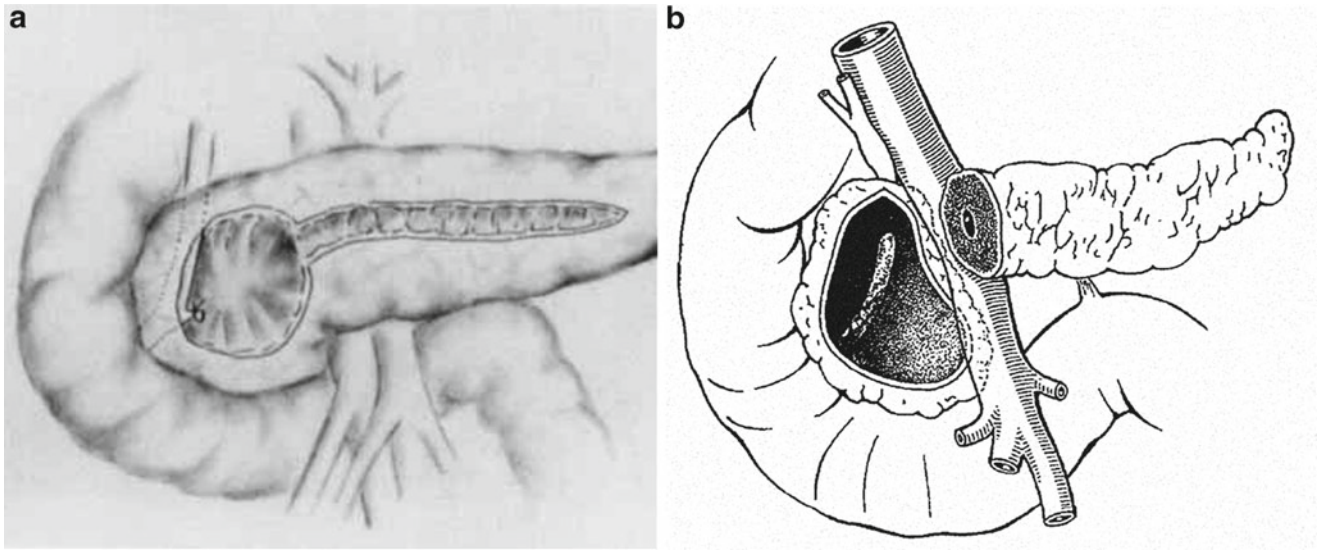

Fig. 85.10 (**A**) Frey procedure. The pancreatic head is cored out and the remaining pancreatic duct filleted open. The reconstruction is done with a lateral pancreaticojejunostomy. (Reprinted from Frey C, Smith G. Description and Rationale of a New Operation for Chronic Pancreatitis. Pancreas. 1987; 2(6): 701–7, with permission from Wolters Kluwer Health.) (**B**) Beger procedure. The pancreatic head is cored out and the pancreas transected at the neck, reconstructing the drainage with a lateral pancreaticojejunostomy to the remaining head and an end-to-end pancreaticojejunostomy to the pancreatic body. (From Buchler MW. Duodenum-preserving pancreatic head resection: long-term results. J Gastrointest Surg. 1997; 1(1): 13–9, reprinted with kind permission from Springer Science + Business Media.)

after the surgery, as long as the pancreatic duct remains appropriately decompressed. Similarly, patients with *toxic* chronic pancreatitis, particularly ethanol-induced, are likely to have definitive pain relief after the decompression of the pancreatic duct unless they continue to consume ethanol. In contrast, in patients with hereditary pancreatitis the intrinsic cause of the disease does not disappear after the operation, and while most patients improve their pain score after the surgery, the long-term results are variable. The same is true regarding the efficacy of the drainage procedures in arresting the progression to pancreatic insufficiency. For patients without ductal dilatation and intractable pain, the only surgical option is a pancreatectomy. In the right anatomical setting, partial pancreatectomy may be feasible, but in most patients the entire organ is affected and a total pancreatectomy is required.

From a technical perspective, a total pancreatectomy is straightforward to perform, but the operation turns the patient instantly diabetic. This can be prevented by total pancreatectomy and concomitant pancreatic islet autotransplantation (TPIAT). The principle of the technique is to harvest the islets contained in the pancreatectomy specimen and infuse them via the portal vein into the liver. The islets embolize into the liver capillaries and achieve long-term survival by inducing revascularization. The success of the procedure relies on the number of islets isolated from the pancreatectomy specimen. The islet yield is generally lower in patients with severe pancreatic fibrosis and in patients who underwent previous pancreatic surgical drainage procedures. TPIAT is a procedure that can only be done in centers with extensive pancreatic surgery experience and the appropriate expertise in pancreatic islet processing. Even though TPIAT was developed over 30 years ago, there is still an ongoing effort among experienced centers to optimize every aspect of the procedure. Appropriate patient selection is the first step. Among many other conditions, the eligibility for a TPIAT includes an adequate residual beta-cell function (measured by c-peptide levels), strong psychosocial support, and a thorough understanding of the potential risk of diabetes and the irreversibility of the operation. TPIAT is the only surgical option for small duct CP patients of any etiology that meets eligibility criteria, but because of the unavoidable progression of the disease, it has been suggested that TPIAT might be the procedure of choice in patients with hereditary pancreatitis and dilated pancreatic duct, instead of a surgical pancreatic drainage procedure. An additional benefit of this approach in patients with hereditary pancreatitis is the complete elimination of the risk of pancreatic cancer.

The optimal timing of TPIAT is still unknown. On one side, delaying the procedure delays the potential risk for failure and diabetes, but on the other side long-term narcotic dependence causes central sensitization of pain, among other effects, which makes pain very difficult to reverse even after the operation. From a technical perspective, attention to detail is critical to achieve the highest possible islet yield. Warm ischemia time must be minimized by isolating the entire duodenopancreatic block without compromising its perfusion, ligating the gastroduodenal and splenic arteries immediately before the harvest.

Heparinization after the transplant is critical to avoid portal vein thrombosis, which would affect the oxygenation of the engrafting islets that are only perfused by the already hypoxic portal blood. Tight glucose control in the immediate postoperative period after TPIAT is also critical, because hyperglycemia induces beta-cell apoptosis. Significant improvement in the severity of pain can apparently be achieved in the majority of cases and 40–50 % of patients can expect to achieve long-term insulin independence. Improvements and refinements in the islet isolation technique will hopefully result in much better TPIAT outcomes in the future.

Editor's Comment

Most of the pancreatic disorders commonly seen in adults are much less prevalent but much better tolerated in children. Annular pancreas is probably not an actual cause of duodenal obstruction but rather an anatomic variant that occurs in the setting of duodenal atresia. Although previous concerns about the risks of dividing the pancreas are probably exaggerated, there is no reason to disturb it, as a duodenoduodenostomy is therapeutic. Pancreas divisum is probably a normal anatomic variant and not a frequent cause of acute pancreatitis. Nevertheless, some patients with recurrent or chronic pancreatitis appear to benefit from endoscopic sphincterotomy.

Acute pancreatitis in children is usually idiopathic though the workup should include a search for gallstones, severe hyperlipidemia, toxins (L-asparaginase), anatomic abnormalities, cysts, and a positive family history. Treatment is supportive and individualized but the Ranson criteria are not very useful and imaging typically does not correlate with clinical severity. Pancreatic necrosis is uncommon and infected pancreatic necrosis requiring intervention is exceedingly rare. If the patient is stable, percutaneous drainage or laparoscopic debridement might be reasonable before embarking on a morbid and protracted course of serial surgical resections.

Pancreatic pseudocysts in children almost always eventually resolve spontaneously. Indications for intervention include persistent symptoms or a cyst that persists for more than 6 weeks. Radiology-guided percutaneous drainage and placement of internal stents is gaining popularity and seems to work in many cases. When indicated, surgical therapy should be performed using a minimally invasive approach.

Chronic pancreatitis with a dilated pancreatic duct responds well to Puestow procedure but the drainage should be extended to include the head of the pancreas (Frey procedure).

Pancreatic tumors include not only endocrine tumors such as insulinoma and gastrinoma but also pancreatoblastoma, solid pseudopapillary tumors, inflammatory myofibroblastic tumor, and sarcoma. The treatment is primarily surgical but should be coordinated with an experienced pediatric oncologist. The operations are the same as those used in adults, namely distal pancreatectomy for lesions in the body or tail and Whipple procedure for lesions in the head of the pancreas. Whipples are very rarely performed but very well tolerated in children. Aggressive attempts to balance negative margins and normal function of adjacent organs should be made.

Suggested Reading

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