Less Common Solid Tumors of Pancreas

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Introduction

Pancreatic adenocarcinoma arising from the ductal cells in the pancreas remains the most common pancreatic malignancy and accounts for 85–90 % of all pancreatic neoplasms. While pancreatic adenocarcinoma has a poor prognosis, nonductal solid pancreatic tumors may be associated with a considerably better prognosis and can be differentiated from the more common adenocarcinoma based on imaging and pathological characteristics. This chapter reviews these less common solid tumors, including pancreatic neuroendocrine tumors (PNETs), acinar cell carcinomas (ACCs), solid pseudopapillary tumors (SPTs), primary pancreatic lymphomas (PPLs), and isolated pancreatic metastases.

Pancreatic Neuroendocrine Tumors

Neuroendocrine neoplasms of the pancreas were traditionally referred to as pancreatic carcinoids or islet cell tumors, assumed to arise from the islet cells, and were thought to have an indolent course. As the heterogeneous nature of this lesion was recognized, the term "neuroendocrine tumor" was proposed in place of "carcinoid" as it conveys the potential malignant nature and histopathology of the tumor more accurately [1]. These tumors are now classified as pancreatic neuroendocrine tumors (PanNETs) and are believed to be a group of epithelial neoplasms that are derived from multipotential stem cells of endodermal origin with predominant neuroendocrine differentiation [2]. PanNETs account for approximately 3 % of all pancreatic neoplasms [3]. There is vast heterogeneity among these tumors; despite sharing a common histological appearance, they differ in biologic behavior, histologic differentiation, and functionality. PanNETs can be further categorized into functional and nonfunctional tumors based on the secretion of biologically active peptides and hormones, resulting in specific clinical syndromes [4, 5]. The WHO 2010 PanNET classification was revised to include mixed adenoneuroendocrine carcinomas, previously referred to as mixed-form carcinoid adenocarcinoma or mixed exocrine–endocrine carcinoma. This type of neoplasm is comprised of both adenocarcinoma and neuroendocrine carcinoma, with at least 30 % of each component [6].

Epidemiology

PanNETs are rare tumors with a reported incidence of 1–2 cases/10^6 population/year though a much higher rate ranging from 0.07 to 10 % has

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been reported in surgical and autopsy series [7, 8]. This variation underscores the limitation in determining the exact incidence and prevalence of PanNETs as the majority of these tumors are small and indolent and may remain asymptomatic. Registry data from Europe, the United States, and Japan showed a rising incidence of these tumors, which probably correlates with the increased use of cross-sectional imaging and more frequent detection of incidental and asymptomatic tumors [9]. Older European studies report an incidence rate (per 100,000) of approximately 0.1 while more recent studies report an incidence rate of 0.3. A similar increase is reflected in the SEER database, with a rise in incidence from 0.17 (1970s) to 0.43 (2003–2007) [9]. A stratified sample survey in Japan reported a much higher incidence rate of 1.01/100,000, with a prevalence rate of 2.23/100,000 [10]. 24 % of patients in this survey had an incidental diagnosis of their tumors.

The median age at diagnosis for PanNETs is 60 years, with a peak incidence rate occurring between the sixth and eighth decades. These tumors are slightly more common among men (53 %) than women (47 %) [11, 12]. Most PanNETs are nonfunctional and sporadic though they may be associated with hereditary endocrinopathies such as multiple endocrine neoplasia (MEN; Type 1), von Hippel–Lindau (VHL) disease, neurofibromatosis type 1 (NF1), and tuberous sclerosis [13]. Patients with these endocrinopathies have an increased risk of developing neuroendocrine tumors ranging from 35 to 75 % of MEN 1, 20 % for VHL disease, 10 % for NF1, and 1 % for tuberous sclerosis [5, 14]. In these patients, PanNETs tend to occur at a younger age, are multiple, and are likely to be diagnosed earlier because of surveillance in carriers of the mutations.

The incidence of functional PanNETs varies by tumor type with insulinoma being the most common (1–4 cases/10^6 population/year), followed by gastrinoma (0.5–2 cases/10^6 population/year), VIPoma (0.05–0.2 cases/10^6 population/year), and glucagonoma (0.01–0.1 cases/10^6 population/year), respectively [12]. The true incidence of rarer types of PanNETs such as somatostatinoma, GRHoma, ACTHoma, and PTHrPoma is difficult to estimate given their rarity.

Since the majority of PanNETs are nonfunctional, most patients present at an advanced stage with mass effect or metastatic disease, and the 5-year survival has been reported between 27 and 62 % [9]. The 5-year survival after surgical resection of noninsulinoma PanNETs has been reported as 65 %, with a 10-year survival of 45 % [15].

Classification

Functional PanNETs

Functionality of PanNETs depends on the clinical symptoms rather than the level or type of hormones secreted. Each type of functional PanNETs produces a distinct clinical hormonal hypersecretion syndrome, which will be described in detail later in this chapter.

Nonfunctional PanNETs

In contrast to functional PanNETs, nonfunctional PanNETs may not cause clinical syndromes; however, they may secrete hormones and other peptides such as chromogranins, neuron-specific endolase, pancreatic polypeptide (such as insulin, gastrin, glucagon, vasoactive intestinal polypeptide), or ghrelin. Usually these do not have clinical significance. However, the tumor itself or its metastatic lesions may manifest compressive symptoms from locoregional mass effect, resulting in abdominal pain, jaundice, pruritus, anorexia, nausea, weight loss, watery diarrhea, or peptic ulcer disease.

Patients with nonfunctional PanNETs are usually asymptomatic at presentation. In symptomatic patients, obstructive symptoms from mass effect are usually the main presentation [16, 17]. As nonfunctional PanNETs do not cause hypersecretory syndromes, they tend to be diagnosed incidentally late in the course of the disease.

The most common presenting symptom is abdominal pain (up to 78 %), which is usually caused by mass effect from the tumor itself. However, when the pain is more localized in the right upper quadrant, it should raise suspicion for a metastatic lesion to the liver causing capsule distension. Other common presenting symptoms include anorexia, nausea, and vomiting, which can be due to a compressive effect from the mass on the duodenum (45 %) [18, 19]. Rarely, PanNETs can present with upper gastrointestinal bleeding from ruptured gastric varices, caused by splenic vein thrombosis. Jaundice from bile duct compression is more commonly seen in PanNETs arising from the pancreatic head.

Functional PanNETs

1. *Insulinoma*
   Insulinomas are functional PanNETs that secrete proinsulin, causing a hypoglycemic hormonal syndrome, also known as Whipple's triad. Whipple et al. first described these features in 1938 of low plasma glucose together with hypoglycemic symptoms, reversible with normalization of the serum glucose level. The triad served as a clue to the diagnosis of insulinoma. The hypoglycemic symptoms include blurred vision, lightheadedness, dizziness, confusion, amnesia, abnormal behavior, loss of consciousness, seizure, and sympatoadrenal symptoms from catecholamine release in response to hypoglycemia such as palpitation, anxiety, diaphoresis, and tremor.

   Despite its rarity, with an incidence of 1–4 cases/10^6 population/year [12, 20], pancreatic insulinoma is still the most common functioning PanNET [21]. The tumor is more prevalent in women (57 %), with a median age of 50 years old. The majority are sporadic; however, up to 6 % may be associated with MEN-1 syndrome [22]. Insulinomas are usually indolent neoplasms. However, metastatic lesions can be found in up to 6 % upon initial diagnosis, and a more aggressive course may be seen in male patients [20, 22].

2. *Gastrinoma*
   The overall incidence of gastrinoma is 0.5–2 cases/10^6 population/year with a slight male predominance and a mean age of diagnosis at 41 years old [23, 24]. Approximately 20 % are associated with MEN-1 syndrome [25]. It is typically indolent; however, up to 33 % have been reported to have metastatic disease upon initial diagnosis. The most common site of metastasis is the liver, followed by the axial bones [26]. It usually arises in the pancreatic head and uncinate process [27].

   As its name implies, gastrinomas predominantly secrete gastrin, causing hypersecretion of gastric acid via stimulation of histamine-releasing enterochromaffin-like cells, in turn acting on the acid-secreting parietal cells. The syndromic features of gastrin hypersecretion are also known as the Zollinger–Ellison syndrome [28]. Presenting symptoms of gastrinomas include refractory peptic ulcer disease and associated complications (bleeding, stricture, perforation), steatorrhea (the overt acidic environment causing inactivation of pancreatic enzymes), chronic secretory diarrhea (disruption of sodium and water reabsorption in the small intestine secondary to high gastrin levels), gastroesophageal reflux, severe heartburn, abdominal pain, anorexia, and weight loss [24]. Approximately 0.1–1 % of patients with peptic ulcer disease have gastrinoma [20].

3. *VIPoma*
   Pancreatic VIPoma is a functional PanNET that predominantly secretes vasoactive intestinal peptide (VIP), which is a 28-amino-acid polypeptide which activates cellular adenylate cyclase and cAMP production in intestinal epithelial cells, leading to a net hypersecretion of free water, sodium, and chloride. It stimulates secretion and inhibits absorption in the bowel, inhibits gastric acid secretion, induces vasodilation, stimulates bone resorption, and promotes hepatic glycogenolysis [29, 30]. This malabsorption and secretory dysfunction lead to the VIPoma syndrome, which is also known as Verner–Morrison syndrome, watery diarrhea–hypokalemia–achlorhydria syndrome (WDHA), and pancreatic cholera

syndrome [31]. Patients typically present with large-volume secretory diarrhea that is not improved with fasting, leading to electrolyte imbalance (hypokalemia, hypochlorhydria, and hypercalcemia) and symptoms such as flushing, lethargy, nausea, vomiting, muscle weakness, and muscle cramps.

Compared to other PanNETS, VIPomas are much more aggressive, with 60–80 % of patients having metastatic lesions at the initial diagnosis. The primary tumor is usually large (>3 cm) and is commonly found in the pancreatic tail (75 %) [32, 33]. Fortunately, it is very rare, with an incidence of 0.05–0.2 cases/10^6 population/year [34]. Five percent of patients with VIPoma also have the MEN-1 syndrome [35].

4. *Glucagonoma*
Glucagonoma is a neoplasm arising from the alpha cells of the pancreas that secrete glucagon, an anabolic 29-amino-acid polypeptide that stimulates glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, amino acid oxidation, and catecholamine secretion. Thus, hypersecretion of glucagon causes hyperglycemia and hypoaminoacidemia. One of the unique manifestations, which can be seen in up to 70 % of patients with glucagonoma, is necrolytic migratory erythema (NME), a painful migratory erythematous plaque (or papules) involving the face, perineum, and extremities. The typical lesions coalesce with central clearing within 1–2 weeks, leaving indurated bronze-colored scars with crusted or blistering borders. Mucosal involvement such as angular cheilitis, glossitis, stomatitis, blepharitis, hair thinning, and dystrophic nails can be seen with NME. Skin biopsy is rarely needed and has a low yield; however, if done properly at the edge of the lesion, it may reveal the classic superficial necrolysis with lymphocytic and histiocytic perivascular infiltration and separation of the outer epidermal layers [36]. NME is believed to be a result of hypoaminoacidemia and a hypometabolic state caused by excessive glucagon.

Other manifestations of the glucagonoma syndrome include normocytic normochromic anemia from decreased erythropoietin, weight loss, venous thromboembolism, abdominal pain, anorexia, constipation, proximal muscle weakness, and neuropsychiatric symptoms such as ataxia, dementia, and optic atrophy [37, 38].

Similar to VIPoma, glucagonoma is a very rare tumor with an aggressive behavior. The common sites of metastasis are liver, bones, and lymph nodes [39]. The mean age of diagnosis is 50 years old, with a slight female preponderance [37, 38]. It almost exclusively arises from the pancreas, typically from the pancreatic tail.

5. *Somatostatinoma*
Somatostatinoma is a rare PanNET that arises from the D-cells of the pancreas, commonly in the pancreatic head. An extrapancreatic somatostatinoma is not uncommon (45 % of all tumors) and is usually found in the duodenum and periampullary areas. It secretes somatostatin, a 14-amino-acid polypeptide with widespread inhibitory effects on other hormones via paracrine signaling, especially acing on insulin, glucagon, gastrin, growth hormone, cholecystokinin-stimulated pancreatic enzymes, pancreatic bicarbonate, gallbladder contraction, intestinal contractility, intestinal amino acid absorption, and gastric acid secretion [40]. However, these inhibitory properties may not cause clinical symptoms. Only 10 % of somatostatinomas are associated with somatostatinoma syndrome [41, 42], which include diabetes mellitus, cholelithiasis, steatorrhea, and gastric hypochlorhydria, abdominal pain, anorexia, and obstructive jaundice [40].

6. *Corticotropinoma* (*ACTHoma*)
Corticotropinoma is a rare neuroendocrine tumor that is usually found in the adrenal gland or pituitary gland. Only 1–16 % of corticotropinomas are localized to the pancreas [43]. As its name implies, it secretes adrenocorticotropic hormone (corticotrophin), a polypeptide that stimulates production of glucocorticoids from the adrenal cortex, leading to a florid Cushing syndrome. The clinical presentation includes obesity, hypertension, glucose intolerance, osteoporosis, muscular atrophy, and hyperpigmentation [44].

7. *PTHrP-producing NET* (*PTHrPoma*)
   PTHrPoma is a very rare PanNET, with less than 50 cases reported worldwide [45]. It is usually found as a single large tumor in the pancreatic body (32 %) or pancreatic tail (53 %) [45]. It secretes parathyroid hormone–related peptide (PTHrP), which is a single monomeric peptide with multiple isoforms. Some of these isoforms have identical N-terminal domains as parathyroid hormone (PTH) and thus can stimulate PTH receptors [46]. Patients with PTHrPoma may present with hyperparathyroidism. These manifestations include malignant hypercalcemia, altered mental status, confusion, constipation, abdominal pain, nausea, vomiting, ureteric stones, osteolytic lesions, and renal failure.

Diagnostic Approach

The wide spectrum of clinical presentations and variability of the types can make the diagnosis and classification of PanNETs challenging. With widespread use of cross-sectional imaging techniques, the incidence of PanNETs has increased due to incidental detection. However, in order to accurately diagnose and classify the type of the tumor, a multimodality diagnostic approach is essential. Such an approach includes the use of serum biomarkers and radiologic studies and, in rare cases, arterial stimulation venous sampling (ASVS).

Role of Biomarkers

When a pancreatic neoplasm is detected and a clinical syndrome is present, the serum marker of the specific peptide can help confirm the diagnosis. These markers and their associated clinical presentations are summarized in Table 3.1. Caution should be exercised when interpreting the level of these peptides as they are all physiologic hormones and therefore can vary according to patients' physiologic changes.

For example, even though an insulin-to-glucose ratio of more than 32.2 (pmol/L)/(mmol/L) and C-peptide-to-glucose ratio of more than 0.24 (nmol/L)/(mmol/L) are highly suggestive of insulinoma [with new cutoff values of 53.6 (pmol/L)/(mmol/L) and 0.61 (nmol/L)/(mmol/L), respectively, being proposed to increase the specificity and positive predictive value], a sulfonylurea level should always be measured to exclude medication-induced hyperinsulinemia (insulin and C-peptide levels should be high while sulfonylurea should be undetectable in true hypoglycemia from insulinoma) [37, 47].

For gastrinoma, a serum gastrin level of greater than 1000 pg/mL (475 pmol/L) when gastric pH is less than 2 is virtually diagnostic. However, a falsely elevated serum gastrin level can be seen in patients with atrophic gastritis, pernicious anemia, *H. pylori* infection, proton-pump inhibitor (PPI) use, and status-post small bowel resection. Therefore, it is recommended to measure serum gastrin level while fasting and after stopping PPI for at least 7 days. A secretin or calcium stimulation test can be used to confirm the diagnosis in equivocal cases [23].

A glucagon level greater than 1000 pg/mL in patients with suggestive clinical symptoms (NME and/or hyperglycemia) is virtually diagnostic of glucagonoma. However, as glucagon secretion is a normal physiologic response for stress, it can be misleadingly elevated (usually less than 500 pg/mL) in patients with sepsis, burns, trauma, surgery, and fasting [48]. In the setting of diabetes, steatorrhea, and cholelithiasis, a somatostatin level higher than 160 pg/mL is highly suggestive of somatostatinoma [41].

It is more challenging when the PanNET is not functional or when the clinical presentation is vague and nonspecific. Among several biomarkers studied in the past, chromogranin A (CgA), neuron-specific enolase (NSE), and pancreatic polypeptide (PP) are the most promising [49–51].

CgA is elevated in both functional and nonfunctional PanNETs. Moreover, its level also correlates well with tumor burden and metastatic disease. Therefore, it is used to monitor response to therapy and progression-free survival [49, 52, 53]. However, CgA has some limitations and should not be used alone for diagnosis. False-negative results can be seen in insulinomas, MEN-1–associated PanNETs, and poorly

Table 3.1 Summary of characteristics of functional PanNETs

Functional PanNETs	Clinical syndrome	Laboratory diagnostics
Insulinoma	• Whipple's triad	• Elevated insulin and C-peptide during hypoglycemic episodes
	• Neuroglycopenic symptoms	• Insulin-to-glucose ratio < 0.3
	• Sympatoadrenal symptoms	• Undetectable sulfonylurea
Gastrinoma	• Zollinger–Ellison syndrome	• Serum gastrin >1000 pg/mL (475 pmol/L)
	• Diarrhea	• Gastric pH < 2
	• Hypergastrinemia	• Serum gastrin increases >200 pg/mL after secretin stimulation test
	• Gastric acid hypersecretion	• Serum gastrin increases >395 pg/mL after calcium stimulation test
	• Peptic ulcer diathesis	
VIPoma	• Verner–Morrison syndrome/WDHA syndrome	• Stool osmolal gap < 50 mOsm/kg
	• Watery diarrhea	• VIP > 75 ph/mL
	• Hypokalemia	
	• Achlorhydria	
Glucagonoma	• Glucagonoma syndrome (4D syndrome)	• Glucagon level >1000 pg/mL
	• Dermatitis (necrolytic migratory erythema) and mucositis	
	• Diabetes mellitus	
	• Deep vein thrombosis	
	• Depression (neuropsychiatric symptoms)	
Somatostatinoma	• Somatostatinoma syndrome	• Somatostatin level > 160 pg/mL
	• Diabetes mellitus	
	• Gastric hypochlorhydria	
	• Cholelithiasis	
	• Steatorrhea	
Corticotropinoma	• Cushing syndrome	• Plasma ACTH > 20 pg/mL
	• Diabetes mellitus	• Negative high-dose dexamethasone suppression test
	• Obesity	• Negative CRH stimulation test
	• Hypertension	
	• Hyperpigmentation	
PTHrPoma	• Hyperparathyroidism, hypercalcemic crisis	• Hypercalcemia
	• Altered mental status, confusion	• Hypophosphatemia
	• Abdominal pain	• Elevated PTHrP
	• Nausea, vomiting	
	• Ureteric stones	
	• Osteolytic lesion	

differentiated neoplasms, while a falsely elevated level may be seen in patients with renal failure, proton-pump inhibitor use, atrophic gastritis, and pernicious anemia [49].

NSE is a cytoplasmic dimer of the glycolytic enzyme enolase. It is used as a marker of secretory activity of the tumor. Even though it is not specific enough to be a diagnostic marker, it can be used for follow-up after treatment. Pancreatic polypeptide is less specific than CgA and NSE, but when its level is higher than three times the age-matched normal fasting basal level, its specificity increases and should raise suspicion for a PanNET [49–51].

Radiologic Studies

Helical multiphasic contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are the first-line diagnostic modalities for PanNETs. Most PanNETs are isodense with pancreatic parenchyma on precontrast images but demonstrate avid arterial enhancement; therefore, dual or multiphase contrast-enhanced CT has higher sensitivity than conventional CT scan [54]. Nonfunctional PanNETs are easier to detect on these cross-sectional studies because of their larger size (median diameter of 8.4 cm compared to 1.3 cm with functional PanNETs) and more frequent distinctive features (i.e., necrosis, cystic changes, and calcifications) [55]. Therefore, endoscopic ultrasound (EUS) plays an important role in these small CT-negative tumors. It detects 91 % of CT-negative lesions, which typically appear as round, homogeneous, and hypoechoic mass lesions. A sequential approach of CT followed by EUS is recommended, which has been shown to have 100 % sensitivity in diagnosing these tumors [54, 56]

On MRI, PanNETs have a low signal intensity on T_1-weighted images and a high signal intensity on T_2-weighted images. The tumors are most conspicuous on the fat-suppressed T_1-weighted sequence, where they appear of low intensity against the bright pancreas [55]. Compared to CT scan, MRI is superior for metastatic disease [57, 58]. The performance characteristics of various imaging modalities for assessing local spread, resectability, and metastasis are similar to those reported earlier for pancreatic adenocarcinomas.

Nuclear imaging studies using radiolabeled octreotide scanning, referred to as somatostatin-receptor scintigraphy (SRS) or Octreoscan, is another diagnostic modality to detect PanNETs with somatostatin-receptor-rich tissue. This study is particularly helpful in determining which patients would benefit from somatostatin-based therapies such as ^{90}Y-edotreotide or Tyr^3-octrotate. Even though its sensitivity and specificity are lower than CT and MRI, a new application with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) called SRS-SPECT has promising data with higher accuracy [59]. False negatives can occur in tumors with low expression of somatostatin receptors such as insulinoma and poorly differentiated PanNETs. Other nuclear imaging modalities such as glucagon-like peptide-1 (GLP-1) receptor scintigraphy and ^{18}F-fluorodeoxyglucose scintigraphy are under investigation to help detect such neoplasms [60]. Another useful modality is EUS, which has become a modality of choice in the evaluation and surveillance of PanNETs. It can detect lesions as small as 2 mm with a sensitivity of 82 % and a specificity of 92 %. The sensitivity of EUS is highest when the lesion is in the pancreatic head area. The biggest advantage is its ability to obtain a tissue diagnosis using fine-needle aspiration (FNA). EUS can also be used to tattoo the lesion preoperatively. However, the test may not be readily available in every center and its quality is operator-dependent [61].

Arterial Stimulation Venous Sampling (ASVS)

ASVS is an invasive test for tumor localization, which is rarely needed in the diagnosis of PanNET given the recent advancement of other modalities. The test is performed by directly stimulating the tumor via a selective arterial injection of a stimulant such as secretin for gastrinoma and calcium gluconate for insulinoma and subsequently measuring the hormonal response of the tumor by venous sampling of the hepatic venous effluent [62]. Other adjunct invasive modalities include intraoperative pancreatic ultrasound, which is sometimes required when other modalities fail [55].

Grading and Staging System

Classification of PNETs has evolved considerably over the past decade. Grading and staging systems proposed by the World Health Organization (WHO), European Neuroendocrine Tumour Society (ENETS), and American Joint Committee on Cancer (AJCC) share common schemes with minor differences (Table 3.2) [6, 63, 64].

Table 3.2 Histologic grading of pancreatic neuroendocrine tumors

Grade	Mitotic count (per 2 mm^2)	Ki-67 labeling index (%)
Low grade (G1)	<2	<3
Intermediate grade (G2)	2–20	3–20
High grade (G3)	>20	>20

Source: From [6, 63, 64]

Histologic features based on the proliferative rate determine the grading of PanNET, which reflects the biologic aggressiveness. The tumor staging systems reflect more on the extent of the disease based on vascular invasion, tumor size, and distant metastasis. Both systems are used independently to assess prognosis.

PanNETs are categorized into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinoma. Histologic features of well-differentiated neuroendocrine tumors include organized tumor cells in a trabecular or gyriform pattern with uniformly round or oval nuclei, coarsely stippled chromatin (salt-and-pepper chromatin), and finely granular cytoplasm with abundant neurosecretory granules [65]. They tend to have an indolent course with a much better prognosis, with an overall 5-year survival rate reaching up to 67 % [66]. However, it is not unusual for well-differentiated PNETs to present with metastatic disease [66].

Poorly differentiated neuroendocrine carcinomas have sheet-like or diffuse tumor cell arrangements with irregularly nonuniform nuclei, and less cytoplasmic granularity. These tumors have a more aggressive behavior with a rapid clinical course that resembles small or large cell neuroendocrine carcinoma of the lung [65].

Histologically, it is not possible to differentiate between benign and malignant tumors as morphology alone cannot predict the tumor behavior. Well-differentiated PNETs can have an aggressive clinical course while metastatic tumors may show little or no cellular pleomorphism, hyperchromasia, or increased mitotic activity [67]. Therefore, the terms "benign" and "malignant" are discouraged in histological grading of PNETs. WHO has updated its grading system to further subcategorize well-differentiated neuroendocrine tumors into low-grade (G1) and intermediate-grade (G2) subgroups based on their proliferative rate (mitotic count and Ki-67 index) [6]. This grading scheme, together with the staging system, is used for prognosis. The parameters used in this grading system as described in Table 3.2 are also endorsed by the AJCC and ENETS.

Based on this new grading system, poorly differentiated carcinomas are all high-grade neoplasms (G3) and are no longer defined by local vascular invasion or metastasis. The term "neuroendocrine tumor grade 3" is therefore a misnomer because, by definition, neuroendocrine tumors are well differentiated [6]. The Ki-67 protein is a large nuclear protein that is closely involved in cell cycle regulation and organization of the nucleolus. Ki-67 is expressed in G1, S, G2, and M phases, with a peak level during mitosis, hence its use as a surrogate marker of cellular proliferation [6, 63]. According to WHO and ENETS guidelines, 2000 cells in the area of highest proliferative rate (hot spots) should be counted to determine the Ki-67 labeling index [6, 63].

Mitotic count is the most direct marker of the proliferative activity of the tumor. It is recommended to perform an average count over 40–50 HPF, assuming that 10 HPF equals 2 mm^2. However, in contrast to Ki-67–labeled cells, the mitotic count is usually not as abundant and may not be able to be measured in a limited specimen such as with fine-needle aspiration [68].

If the mitotic count and Ki-67 labeling index yield different grades, the neoplasm should be regarded as the higher one. Other prognostic parameters such as tumor necrosis and lymphovascular and perineural invasion are not included in the grading criteria [6, 63].

Staging Systems

There are currently two widely accepted TNM staging systems by AJCC and ENETS, with only minor differences in primary tumor (T) staging

Table 3.3 Comparison between TNM staging systems of the AJCC and ENETS

		AJCC	ENETS
Primary tumor (T)	T_x	Primary tumor cannot be assessed.	Primary tumor cannot be assessed.
	T_0	No evidence of primary tumor.	No evidence of primary tumor.
	T_1	Tumor limited to pancreas, ≤2 cm.	Tumor limited to pancreas, ≤2 cm.
	T_2	Tumor limited to pancreas, >2 cm.	Tumor limited to pancreas, 2–4 cm.
	T_3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery.	Tumor limited to the pancreas and is larger than 4 cm or invading duodenum or bile duct.
	T_4	Tumor involves the celiac axis or the superior mesenteric artery.	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery).
Regional lymph node (N)	N_x	Regional lymph node cannot be assessed.	Regional lymph node cannot be assessed.
	N_0	No regional lymph node metastasis.	No regional lymph node metastasis.
	N_1	Regional lymph node metastasis.	Regional lymph node metastasis.
Distant metastasis (M)	M_x	No M_x categorized.	Distant metastasis cannot be assessed.
	M_0	No distant metastasis.	No distant metastasis.
	M_1	Distant metastasis.	Distant metastasis.

Staging systems for pancreatic neuroendocrine tumor [63, 64]

AJCC				ENETS			
Stage	T	N	M	Stage	T	N	M
IA	T_1	N_0	M_0	I	T_1	N_0	M_0
IB	T_2	N_0	M_0	IIA	T_2	N_0	M_0
IIA	T_3	N_0	M_0	IIB	T_3	N_0	M_0
IIB	T_1, T_2, T_3	N_1	M_0	IIIA	T_4	N_0	M_0
III	T_4	N_{ANY}	M_0	IIIB	T_{ANY}	N_1	M_0
IV	T_{ANY}	N_{ANY}	M_1	IV	T_{ANY}	N_{ANY}	M_1

Source: From [63, 64]

between the two, as shown in Table 3.3. The prognostic values of both systems have been extensively validated [69, 70]. Five-year overall survival rates for stages I, II, III, and IV disease of PNETs are 92 %, 84 %, 81 %, and 57 %, respectively, using AJCC staging and 100 %, 88 %, 85 %, and 57 %, respectively, using ENETS staging [70]. It is unclear which staging system has a better prognostic accuracy; therefore, applying the system that is widely used in a particular region is generally accepted.

The ENETS stages poorly differentiated neuroendocrine carcinoma in the same way as well-differentiated neuroendocrine tumors, while the AJCC stages poorly differentiated neuroendocrine carcinomas as adenocarcinomas. The functionality of the tumor plays no role in staging and grading systems.

Solid Pseudopapillary Tumor

Solid pseudopapillary tumors (SPTs) are rare pancreatic tumors characterized by unique clinicopathological features which were first reported by Franz in 1959. Historically, they have been classified by different names such as papillary cystic carcinoma, papillary-cystic epithelial neoplasm, and solid and papillary neoplasm. Most of these terms were descriptive and pertain to the cystic and papillary components of the tumors. In 1996, the WHO classification for exocrine pancreatic tumors classified them as "solid pseudopapillary tumors" of the pancreas and further defined malignant features associated with these tumors. This has led to a recent increase in the diagnosis of these tumors with a better characterization of their pathology.

Epidemiology

SPTs are rare tumors, accounting for only 0.13–2.7 % of pancreatic tumors. Though they have been reported across all age groups (range, 2–85 years), they characteristically affect young females (90 % females, mean age 22–27 years) [71, 72]. In one of the largest series, only 6 % of patients were more than 51 years of age, while 22 % of the patients were less than 19 years of age [71]. They are indolent, slow-growing tumors with a tumor-doubling time of 765 days; however, they have a malignant potential with metastases reported in 20 % of the patients [73]. The liver is the most common site of metastasis, followed by the portal vein and spleen. Local invasion into other organs such as the duodenum, omentum, colon, lung, peritoneum, and vasculature has been reported less frequently [71]. The prognosis, even with metastasis, local invasion, or recurrence, is good, with an overall 5-year survival greater than 95 % [71]. Long-term survival has also been reported in most patients with metastatic or locally advanced disease [74].

Molecular Genetics

The pathogenesis of SPTs has not been completely elucidated. The female preponderance led to the investigation of gender hormonal receptors; however, estrogen receptor (ER) expression in these tumors is variable and no gender-based differences in immunohistochemical staining for sex hormone receptor proteins have been demonstrated [75]. Furthermore, they exhibit a genetic profile distinct from pancreatic ductal adenocarcinoma in that they are not associated with mutations in K-ras, p-53, or DPC4 genes but, like colorectal and gastric cancer, demonstrate genetic abnormalities in the APC/B-catenin pathway [76]. Other hypotheses proposed for the pathogenesis of these tumors include chromosome abnormalities in the form of karyotype unbalance translocation and early incorporation of ovarian cells into the pancreatic tissue during the period of embryogenesis [77, 78].

Pathology

Typical SPTs are large, well-demarcated, soft tan to red masses with variable solid and cystic components demonstrating hemorrhagic changes surrounded by a fibrous capsule. Smaller tumors which are now commonly detected incidentally tend to be more solid and often lack the fibrous pseudocapsule which demarcates the larger tumors [71]. Microscopically, they are characterized by a solid growth pattern of discohesive polygonal cells arranged around fibrovascular septa which can undergo cystic degeneration and result in pseudopapillae formation [79]. Infiltration into surrounding tissues is common despite the well-circumscribed gross appearance and adjacent acini often appear separated from neoplastic cells by only a basement membrane [79]. Metastasizing tumors have a higher nuclear grade with more prominent necrobiotic nests characterized by cell aggregates with pyknotic nuclei and eosinophilic cytoplasm exhibiting high mitotic rates and true tumor necrosis [80]. Most SPTs stain for vimentin, CD10, neuron-specific enolase (NSE), CD56, progesterone receptors, and alpha-1 antitrypsin and can be differentiated from other pancreatic tumors by non-expression or only focal staining with keratin, chromogranin, synaptophysin, or endocrine and pancreatic enzymes [81].

Clinical Presentation and Diagnosis

Most patients present with nonspecific abdominal complaints likely caused by the bulky tumor compressing upon surrounding organs. The most common clinical presentation is abdominal pain (38–47 %), palpable mass (35–36 %), or abdominal discomfort (16–33 %) [71, 72]. Up to a third of patients are asymptomatic, and the tumor is diagnosed incidentally on abdominal imaging for another cause [72]. Other rare presentations include fever, jaundice secondary to bile duct obstruction, pancreatitis with pseudocyst formation, and hemoperitoneum due to tumor rupture [81]. The tumors are unifocal and are most

commonly found in the tail or the head of the pancreas though they can occur in all regions of the gland. Multifocal tumors may be present in 15 % of patients. The mean diameter of the tumor at the time of diagnosis is 6–8 cm (range, 0.5–34.5 cm) [71, 72]. Laboratory studies are not helpful in diagnosis as these tumors are not associated with elevation of known tumor-specific serum markers or pancreatic enzymes.

SPTs have characteristic imaging features though occasionally percutaneous or EUS-guided FNA may be required to differentiate them from necrotic neuroendocrine tumors. On US, they appear as a heterogeneous, encapsulated mass with solid echogenic and cystic hypoechoic components with peripheral calcifications [81]. The typical CT and MRI features of SPT are a large, well-encapsulated mass with varying solid and cystic components and early peripheral heterogeneous enhancement with progressive fill-in after contrast administration on dynamic examination [82]. Smaller SPTs have less typical imaging findings as they are predominantly solid, not well encapsulated, and less likely to demonstrate cystic degeneration. These may require preoperative tissue diagnosis using FNA. Local or extended resection, depending on the size of the tumor and involvement of adjacent organs or lymph nodes, is the mainstay of therapy and standard chemotherapeutic regimens are not established [71, 74].

Acinar Cell Carcinoma

Acinar cells secreting pancreatic enzymes account for 82 % of the pancreatic parenchyma and make up the bulk of the pancreas [83]. Malignant transformation of these cells is, however, exceedingly uncommon when compared to pancreatic ductal adenocarcinoma. ACCs are rare but biologically aggressive malignant tumors arising from the acinar cells in the pancreas.

Epidemiology

ACCs occur infrequently and account for 1–2 % of all adult malignant pancreatic neoplasms [84, 85]. They tend to present earlier than pancreatic adenocarcinoma, with a mean age of presentation of 58 years (range, 28–85 years) although they have also been reported in children [81, 83, 85]. In most series, there is a strong male predilection, and patients in the United States are more likely to be white (84.7 % white vs. 15.3 % others) [83]. ACCs are aggressive neoplasms; older, small, single-institution studies reported that approximately half of patients present with metastasis, most commonly to the liver, and most of the remaining patients develop metastasis on follow-up [84, 86]. A 2008 U.S. cancer database review of 333 patients reports nodal metastasis in 40 % and distant metastasis in 13 % of patients at presentation [87]. Based on a 2008 SEER database review of 672 patients, these tumors have a significantly better prognosis than ductal adenocarcinoma, with a median survival of 47 months (5-year survival, 42.8 %), which decreases to 25 months for unresectable tumors (5-year survival, 22 %) [83, 84]. The 5-year survival for resectable disease has also been encouragingly reported as 71.6–76.9 % (median, 123 months) [83, 85].

Molecular Genetics

Unlike pancreatic ductal adenocarcinomas, ACCs rarely contain mutations of K-ras, p-53, or p-16 or abnormalities of DPC4 protein expression [79]. Similar to pancreatoblastomas, loss of 11 p has been reported in 50 % of patients, and abnormalities in the APC/beta catenin pathway have been found in 24 % of patients [88, 89]. Other studies have demonstrated a loss of heterozygosity (LOH) at various chromosomes. In particular, chromosome 4q LOH was present in 75 % of ACCs compared to no patients with PanNETs and 17 % with pancreatic adenocarcinoma [90].

Pathology

Grossly, these tumors are well circumscribed, soft, and fleshy with scattered areas of hemorrhage and necrosis. On low-power microscopy, they have a high cellularity with a relative paucity of desmoplastic stroma. Histologically, several different architectural patterns may be present,

though the solid and acinar patterns are most common. Since these tumors arise from acinar cells, the cytoplasm contains abundant zymogen granules which appear intensely eosinophilic and granular [79]. Zymogen granules may be stained with periodic acid–Schiff (PAS) to confirm the diagnosis of ACC. In tumors with less abundant zymogen granules, the diagnosis may be confirmed with IHC staining for enzymes, especially trypsin and chymotrypsin, which is 95 % sensitive to detect acinar differentiation [91]. Some tumors may have more than one line of differentiation, which may cause diagnostic confusion when detected on IHC staining. If these elements exceed more than 25 % of the tumor, these tumors are classified as mixed carcinomas, of which acinar–endocrine carcinomas are best characterized, though mixed acinar–ductal or acinar–ductal–endocrine carcinomas have also been reported [79]. All these tumors are clinically aggressive and behave similarly to ACCs [79].

Clinical Presentation and Diagnosis

The clinical presentation is often nonspecific; most commonly patients may present with abdominal pain or bloating and a palpable abdominal mass on examination. Other reported symptoms include weight loss, nausea and vomiting, and, less commonly, a change in stool consistency or jaundice [84, 92]. Because this tumor arises from acinar cells, it is associated with the systemic release of pancreatic enzymes, including trypsin, chymotrypsin, amylase, and lipase, although the serum levels of these enzymes may not be elevated [81]. In 10 % of patients, this tumor can be functionally active and secrete lipase, resulting in signs related to excess lipase secretion which manifest with high serum lipase levels, diffuse subcutaneous nodules, and polyarthropathies and is referred to as the lipase hypersecretion syndrome [84]. Tumors tend to be focal, occur predominantly in the head or the tail, and tend to be larger than a pancreatic adenocarcinoma at presentation with a mean size of 4 cm (0.7–23.5 cm), but may be more than 10 cm at presentation in a third of the patients [84, 92]. Serum tumor markers such as CA 19-9, AFP, and CEA are variably expressed and are not specific to establish a diagnosis though they may be useful for evaluating recurrence if elevated [93]. On nonenhanced imaging, these tumors are well marginated, are exophytic, and appear homogeneous when small. When larger, they may be solid or heterogeneous with cystic components with occasional focal calcification due to necrosis and hemorrhage. With contrast, they enhance homogeneously though less than the pancreatic parenchyma, and hypervascular variants which may be confused with NETs have been reported [94]. Imaging studies are not always diagnostic for ACCs, and FNA or surgical pathology may be required to establish the diagnosis [94]. Aggressive surgical management with a goal of an R0 resection remains the mainstay of therapy. Anecdotally, neoadjuvant and adjuvant chemoradiotherapy regimens suggest some benefit; however, due to the low incidence of the tumor, large series to evaluate benefit are lacking [87, 92].

Primary Pancreatic Lymphoma

Around half of the patients with extranodal non-Hodgkin's lymphoma will have gastrointestinal involvement and secondary involvement of the pancreas is not infrequent [95]. Primary pancreatic lymphomas (PPLs), on the other hand, are a rare extranodal presentation of non-Hodgkin's lymphoma which may mimic pancreatic adenocarcinoma on presentation and pose a diagnostic dilemma.

Epidemiology

PPLs are extremely rare and compromise less than 0.5 % of all pancreatic tumors and less than 1 % of extranodal non-Hodgkin's lymphoma (NHL) [96, 97]. Most studies suggest a male predominance, with patients typically presenting in the sixth decade (range, 40–84 years) [98–100]. Survival in patients with PPLs is dependent on the stage of disease at the time of diagnosis and varies with treatment modalities used, with an

overall 3-year survival rate of 46 % using chemoradiation though newer chemotherapeutic agents were not included in these studies [101]. Some groups have reported dramatic response rates of 100 % with long-term survival rates of 94 % after surgery with early-stage, resectable pancreatic lymphomas [101].

Pathology

Histologically, most PPLs are intermediate or high-grade NHL with diffuse large cell lymphoma being the most common histotype (60 %). Rarer histotypes like anaplastic large cell (ALK) have also been reported [102]. Cytopathology is often employed to establish diagnosis and smears show a variable degree of cellularity. In most cases, the malignant lymphocytes appear as discohesive cells with large nuclei (greater than 3–4 times the size of a mature lymphocytic nucleus) with single to multiple prominent nucleoli in a background of abundant necrosis and karyorrhexis. Occasionally, a monotonous population of small mature lymphocytes may be seen and flow cytometry (FC) and immunophenotyping are often used to confirm diagnosis. By flow cytometry, most cases have Ig light chain restriction and CD20 expression, though expression of other cell surface markers has also been noted [99]. Immunophenotypically, most cases reported in the West have been B-cell lymphomas, while 21 % of cases reported in Japan are T-cell lymphomas and carry a worse prognosis [98].

Clinical Presentation and Diagnosis

The clinical presentation of PPL, like other uncommon solid pancreatic tumors, is nonspecific. Abdominal pain is the most common presenting symptom (83 %) followed by abdominal mass (58 %), weight loss (50 %), and jaundice (37 %). Less commonly, patients may present with pancreatitis, small bowel obstruction, and diarrhea. The classic B-type symptoms of nodal NHL such as fever, chills, and night sweats are uncommon [102]. They commonly present as large solitary masses varying in size from 2–15 cm with mean reported diameters across most series of greater than 8 cm [101]. The tumors frequently are confined to the head, though body or tail tumors and rarely diffuse involvement of the entire gland have also been reported [101]. On CT, the mass is hypodense and homogeneous and can extend into and infiltrate the peripancreatic vasculature and surrounding structures. Two patterns of CT appearance have been described: (1) a well-defined mass and (2) a large infiltrating lesion with poorly defined contours. On MRI, they appear as a low-signal-intensity homogeneous mass on T_1-weighted images with subtle postcontrast enhancement, and on T_2-weighted images, they show a more heterogeneous character with low- to intermediate-signal amplitude [103]. Due to their location, nonspecific clinical presentation, and imaging findings of a solitary pancreatic head mass, they may be mistaken for the more common pancreatic ductal adenocarcinoma. Imaging findings which may help differentiate a PPL from a pancreatic adenocarcinoma include a bulky localized tumor in the pancreatic head without significant dilatation of main pancreatic duct; enlargement of the lymph nodes below the level of the renal veins; invasive tumor growth not respecting anatomic boundaries and infiltrating the retroperitoneum or surrounding organs [103]. They can be differentiated from secondary involvement of the pancreas by lymphoma, which is much more frequent and can occur in up to a third of cases with non-Hodgkin's lymphoma by the following criteria: the absence of superficial or mediastinal lymphadenopathy; a normal peripheral leukocyte count; the main mass in the pancreas with lymph node involvement confined to the peripancreatic region; and no hepatic or splenic involvement [104]. A clinical suspicion of PPL should prompt percutaneous or EUS-guided FNA or core biopsy of the lesion with flow cytometry, which has been shown to reliably diagnose PPL and differentiate it from other pancreatic tumors. Once diagnosed, PPL is staged as other NHLs using the Ann Arbor staging system. Unlikely the pancreatic adenocarcinoma which it mimics, PPL is usually treated with a combination of chemotherapy and radiation therapy or stem cell transplantation and carries a much better prognosis [102].

Pancreatoblastoma

Pancreatoblastomas are rare pancreatic malignant neoplasms of presumed stem cell origin first reported in 1957 as "infantile pancreatic carcinoma." Due to the histological resemblance of this tumor to fetal pancreatic tissue, the name of "pancreatoblastoma" was first proposed in 1977 [105].

Epidemiology

Pancreatoblastoma is the most common pancreatic neoplasm of childhood, accounting for 25 % of all pancreatic tumors, with most patients being less than 10 years of age (mean age, 4 years) [106]. An association with Beckwith–Wiedemann syndrome has been reported [79]. These tumors have rarely been reported in adolescents and adults, and account for 0.5 % of all pancreatic exocrine neoplasms. In a recent review of published literature, the median age of adults was 37 years (range, 18–78 years) and no gender predilection was reported [105].

Pancreatoblastomas are aggressive tumors with more than half of patients presenting with locally advanced disease or metastases at initial diagnosis. The liver is the most common site for metastases followed by regional lymph nodes, lung, and peritoneum [105, 106]. The prognosis with a pancreatoblastoma is much better in children than in adults. In children, the 5-year event-free survival and overall survival were 58.8 % and 79.4 %, respectively, in a European registry, and the survival was not found to correlate with tumor site and size but was strongly influenced by the feasibility of complete resection [106]. The prognosis in adults is uniformly poor, with a median survival of 15 months (range, 1–108 months) [105].

Pathology

On gross examination, pancreatoblastomas are large, well circumscribed, lobulated, and soft and fleshy on cut section. Histologically, they are very cellular and are separated by broad fibrous bands into lobules, which have a geographic pattern of light and dark staining cells, reflecting the different cell types of pancreatoblastomas. A characteristic histological feature is the "squamoid nests" or "squamoid corpuscules" which are composed of spindle-shaped cells in whorled nests, giving a squamous appearance [79]. On IHC staining, pancreatoblastomas can have multiple lines of differentiation, including ductal, mesenchymal, acinar, and neuroendocrine. The molecular alterations in pancreatoblastomas are similar to ACC with LOH of the short arm of chromosome 11 p. Also, 50–80 % of tumors will manifest alteration in the beta catenin/APC pathway [79].

Clinical Presentation and Diagnosis

Abdominal pain (45 %), weight loss (29 %), jaundice (19 %), and a palpable abdominal mass (19 %) are the most frequent presenting symptoms and are typically related to mass effect from the tumor. Pancreatoblastomas are slow-growing tumors usually diagnosed when they are large, with a median size of 8 cm (range, 1.8–20 cm) [105]. They have most frequently been reported in the head (45 %) and tail of the pancreas (29 %). Elevation of alpha fetoprotein has been reported in up to 70 % of pediatric patients, but no tumor markers have been consistently shown to be elevated in adults [105, 106]. On imaging most of these tumors are well defined and at least partially circumscribed, seen as multilobulated masses with a mixed echotexture on US and enhancing septa on CT. On MR, the tumors appear heterogeneous with low to intermediate signal intensity on T_1-weighted sequences and high signal intensity on T_2-weighted images [107]. Complete tumor excision is associated with the best outcomes though chemoradiation may be beneficial to downstage tumors or in unresectable disease [106].

Isolated Pancreatic Metastasis

Pancreatic metastases occur most commonly from primary tumors in lung, kidney, or breast or with melanoma, though virtually any primary neoplasm can metastasize to the pancreas. The diagnosis is usually evident in the presence of the

primary tumor; however, occasionally isolated metastasis to the pancreas may occur years after resection of the primary tumor and may be mistaken for primary pancreatic neoplasm.

Epidemiology

Isolated pancreatic metastases can account for approximately 2 % of all pancreatic neoplasms in living patients [108]. Renal cell carcinoma (RCC) is the most common malignancy with isolated pancreatic metastasis (62.6 % of all tumors) followed by sarcoma (7.2 %), colorectal carcinoma (6.2 %), ovarian carcinoma (4.7 %), and melanoma (4 %) [109]. In a recent systematic review, the mean age of patients was 61.7 %, and these lesions were slightly more common in men (58 % men vs. 42 % women) [109]. The mean disease-free interval (DFI) for all tumors in this review was 66 months. This mean was probably skewed by a large proportion of RCC patients (62.6 %), which is characterized by a long disease-free interval (7–10 years) after nephrectomy for primary disease [81]. Resection of isolated pancreatic metastasis from RCC is associated with a good prognosis, with a 5-year survival of 68–75 %, whereas resection of pancreatic metastasis from other tumor sites carries a much worse prognosis, with a median survival of 2 years [81].

Pathology

Histologically, the metastatic tumor may resemble the primary tumor though it can mimic a pancreatic adenocarcinoma and IHC may be required for confirmation of the tissue of origin. RCC presents as sheets of tumor cells separated into solid acini, or variously into cystic, papillary, pseudopapillary, tubular, or sarcomatoid growth patterns, with polygonal or cuboidal tumor cells [81].

Clinical Presentation and Diagnosis

Lesions may be diagnosed during routine surveillance or by the presence of nonspecific symptoms and imaging findings may be similar to the primary tumor. On CT scan, metastatic RCC appears as a large hypervascular spherical mass with well-defined margins and central low attenuation that can mimic other hypervascular lesions of the pancreas such as PanNETs [110]. In patients with a history of resected RCC, this presentation is usually diagnostic and tissue biopsy is not required though percutaneous or EUS biopsy may be obtained for suspected metastasis from non-RCC malignancies or if diagnostic confusion exists. Once the diagnosis of pancreatic metastasis has been established, pancreatic resection may be considered after a careful search has excluded concurrent extrapancreatic metastatic lesions [109].

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