MR Imaging of Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Pancreatic neuroendocrine tumor • MR imaging • Tumor classification • Tumor grading and staging

KEY POINTS

- Pancreatic neuroendocrine tumors (PNETs) are uncommon pancreatic tumors that are potentially malignant neoplasms, with a World Health Organization classification system based on the proliferative rate to predict tumor aggressiveness.
- Tumor detection, localization, and staging with diagnostic imaging are crucial to determine treatment strategy. Although computed tomography (CT) is the mainstay for evaluation of PNETs, MR imaging continues to expand its role as an important tool in diagnostic imaging of these lesions.
- With superior soft tissue and contrast resolution, MR imaging offers improved detection of small tumors (<2 cm) and hepatic metastatic lesion detection over CT, particularly with the help of fat-saturated T2-weighted, diffusion-weighted, and arterial phase postcontrast imaging.
- MR imaging avoids radiation exposure in patients who will be undergoing repeated examinations for surveillance or screening, which often begins at a young age in patients with inherited familial syndromes.

INTRODUCTION

Neuroendocrine tumors are neoplasms that possess neuroendocrine differentiation. These tumors can be found throughout the body, including the lung, pancreas, and gastrointestinal tract; the focus of this review is on pancreatic neuroendocrine tumors (PNETs). PNETs have previously been called islet cell tumors, although this is a misnomer, because these tumors have since been shown to arise from ductal pluripotent cells rather than islets of Langerhans.[1,2] Imaging plays a crucial role in identifying and diagnosing PNETs as well as in treatment planning based on size, location, and extrapancreatic spread of the tumor. Imaging is also involved in tumor surveillance and evaluating treatment response to systemic therapies. Although computed tomography (CT) has been traditionally used for evaluation of neuroendocrine tumors, evolving techniques with MR imaging have broadened and strengthened its role as an important diagnostic tool in assessing PNETs.

EPIDEMIOLOGY

PNETs account for 1% to 5% of all pancreatic neoplasms, with a prevalence rate of less than 1 in 100,000.[1,3] PNETs do not have a significant age or gender predilection, although are most commonly encountered between the fourth and seventh decades of life.[3] PNETs that present earlier are often associated with a familial syndrome. The tumors are generally well-

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demarcated, round neoplasms, the majority ranging from 1 to 5 cm.[3] In rare cases, more than one tumor may be found within the pancreas; in these situations, the presence of an associated familial syndrome should be questioned.

Most PNETs are sporadic in nature, although the minority of PNETs are a part of inherited familial syndromes.[4] Common syndromes associated with PNETs include those with autosomal dominant inheritance, such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau (VHL) syndrome, neurofibromatosis type 1 (NF-1), and tuberous sclerosis complex (TSC). Patients with MEN-1 have the highest incidence of PNET, followed by VHL, NF-1, and then TSC.[5]

TUMOR CLASSIFICATION

PNETs can be classified as functioning or nonfunctioning tumors based on the presence or absence of associated clinical symptoms. Because of the associated clinical symptoms, functional tumors often present earlier when the tumors are small (often subcentimeter) in size, whereas nonfunctioning tumors often present when they are several centimeters in size, when they are exerting mass effect on surrounding structures, or when there is metastatic disease.[6] Specific hormone assays are required to establish the diagnosis of functioning PNETs.

Insulinomas are the most common type of functional PNET, accounting for 50% of functioning PNETs.[3,7–9] Diagnosis relies on supervised fasting with documentation of glucose and insulin levels at the time of symptoms.[10] Because of its dramatic clinical symptoms, insulinomas often present early when they are small, which may explain why insulinomas generally have the best prognosis of all PNETs, with only about 5% to 10% demonstrating malignant behavior.[9,11] There is an even distribution throughout the pancreas, and 90% of tumors are smaller than 2 cm in diameter and 40% are smaller than 1 cm.[12]

Gastrinomas are the second most common type of functioning PNET after insulinomas. More than 90% of patients with gastrinomas have peptic ulcer disease, and differentiation of gastrinomas from other PNETs is based solely on the presence of hypergastrinemia.[12] At the time of diagnosis, 50% to 60% of gastrinomas are malignant.[9] Gastrinomas are commonly found within the so-called gastrinoma triangle, which comprises the head of the pancreas, the duodenal sweep, and the porta hepatis.[3,13–15]

Other less common functioning PNETs include glucagonomas, VIPomas, and somatostatinomas. Glucagonomas and VIPomas are both usually large when discovered, in the distal part of the pancreas, and most often are malignant.[3,9] Somatostatinomas are also rather large when discovered, commonly in the pancreatic head, with 50% of them being malignant.[3,9] Rarely, functional PNETs can secrete other hormones, including adrenocorticotropic hormone, parathyroid hormone-related protein, calcitonin, luteinizing hormone, renin, or erythropoietin.[10]

The reported overall percentage of PNETs classified as nonfunctioning varies greatly in the literature, ranging from 10% to 70%.[9,10,12] This wide range can possibly be attributed to recent advances in imaging and the increased discovery of incidental nonfunctioning PNETs. Many of these nonfunctioning PNETs do also secrete hormones, although are not significant enough to cause a specific associated syndrome. Nonfunctioning PNETs are generally larger than functioning PNETs, and they are often large, solitary, and heterogeneous in appearance, with up to 60% to 80% with metastatic disease at the time of diagnosis.[3,9,12]

TUMOR GRADING AND STAGING

Management and prognostication of PNETs are based on both tumor grading and staging. All PNETs are potentially malignant neoplasms, although the rate of malignancy varies between tumor types. In general, these neoplasms are slow growing, with a survival period from the time of diagnosis ranging from 2 to 10 years.[3] The World Health Organization (WHO) classification system divides PNETs into well-differentiated and poorly differentiated categories related to their histologic grade, ranging from grade 1 to grade 3, with a higher grade correlating to increased biologic aggressiveness of the tumor.[16] Well-differentiated tumors are generally either low or intermediate grade and can be rather indolent, whereas poorly differentiated tumors are high-grade tumors that are highly aggressive[16] (**Figs. 1** and **2**). The proliferative rate, which is used to assign grade, has been shown to provide prognostic information about PNETs. The rate is assessed as the mitotic counts (number of mitoses per unit area of tumor, usually expressed as mitoses per 10 high-power microscopic fields or per 2 mm^2) or as the Ki67 labeling index (percentage of neoplastic cells immunolabeling for the proliferation marker Ki67).[16]

There are currently 2 staging systems available for PNETs proposed by the American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society (ENETS), which are both highly prognostic for relapse-free and overall survival.[17–19] Neither system is widely accepted, although the AJCC system is more widely used in