Assessment of Tumor Growth in Pancreatic Neuroendocrine Tumors in von Hippel Lindau Syndrome

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BACKGROUND: The incidence of pancreatic neuroendocrine tumors (PNETs) is increasing, but only a subset of these heterogeneous tumors will progress to malignant disease, which is associated with a poor prognosis. Currently, there are limited data on the natural history of these tumors and it is difficult to determine which patients require surgical intervention because the risk of metastatic disease cannot be accurately determined.

STUDY DESIGN: We conducted a prospective study of 87 patients with von Hippel Lindau syndrome-associated solid pancreatic lesions to determine the natural history of these tumors with biochemical testing, follow-up anatomic and functional imaging, and advanced imaging analysis, with a median follow-up of 4 years.

RESULTS: Approximately 20% of consecutive tumor measurements during follow-up were decreased in size and 20% showed no change. This included 2 of 4 surgically proven malignant tumors, which had a net decrease in tumor size over time. Tumor volume, as derived from greatest diameter and volumetric measurements, showed good correlation to pathology tumor measurement of surgically resected tumors (Spearman rank correlation $\rho = 0.72$, $p = 0.0011$, and $\rho = 0.83$, $p < 0.0001$, respectively). Tumor density measurement had an inverse relationship with tumor size (Spearman rank correlation -0.22, $p = 0.0047$). A tumor density cutoff of 200 was 75% specific for malignant tumors.

CONCLUSIONS: Pancreatic neuroendocrine tumors demonstrate a nonlinear growth pattern, which includes periods of no growth and apparent decrease in size by imaging. These growth patterns are variable and are not associated with tumor grade and malignancy. Tumor density, as measured in this cohort, may offer a specific diagnostic tool for malignant disease. (J Am Coll Surg 2014;218:163–169. © 2014 by the American College of Surgeons)

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of rare tumors with a low but increasing incidence, accounting for 1.3% of all pancreatic tumors.[1-5] They may be functional, manifesting in one of several characteristic clinical syndromes, or nonfunctional.[2-5] They may be sporadic or can occur within the context of multiple endocrine neoplasia type 1, von Hippel Lindau (VHL) syndrome, neurofibromatosis type I, or carcinoid syndrome.[2-5] Pancreatic neuroendocrine tumors display a variety of histologic characteristics, presenting as a spectrum of well-differentiated to poorly differentiated neuroendocrine cells, with only a subset progressing to malignant disease.[2-5]

There are limited prospective data on the optimal management of localized PNETs. Benign tumors, excluding insulinomas, do not threaten patient survival and may

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Abbreviations and Acronyms

CgA = chromogranin A
PNET = pancreatic neuroendocrine tumor
PPP = pancreatic polypeptide
VHL = von Hippel Lindau syndrome

not require surgical resection if symptoms associated with hormonal hypersecretion are medically controlled.[6,7] Malignant tumors, on the other hand, exhibit a poor prognosis.[6-8] Survival rates average 1 to 3 years once metastases are identified.[1] Early surgical intervention offers the best potential for curative therapy or the prevention of metastatic disease but is not without morbidity.[6,7,9]

Unfortunately, it is difficult to distinguish benign tumors from those that are potentially malignant without histopathologic analysis, with a significant number of tumors still of undetermined malignant potential based on the World Health Organization (WHO) classification.[10] Chromogranin A (CgA) and pancreatic polypeptide (PPP) are often used as serum tumor markers for PNETs once disease has been surgically confirmed; however, they provide little preoperative prognostic information.[5,8] Radiographic evidence of advanced disease, such as local tumor invasion or evidence of metastasis, are currently the only reliable clinical predictors of malignancy. However, these findings provide little benefit to the patient because curative resection may not be possible at that point. Previous studies have suggested tumor size and/or growth rate as useful indicators of malignancy.[11] However, recent studies have shown that even small tumors ($\leq$2 cm) may have aggressive behavior.[5,12,13]

Patients with VHL syndrome have an approximate 20% risk of developing 1 or more PNETs over their lifetime. As such, they undergo routine lifetime screening and surveillance to allow for early intervention for PNETs, which have malignant potential.[14] Computed tomography is the most commonly used imaging modality for screening and surveillance, due to its high sensitivity (about 94%) for identifying PNETs.[15-18] Fortunately, PNETs are easily identifiable, with characteristic radiographic features, appearing as an early enhancing well-circumscribed solid mass with rounded or lobulated borders and a rich vascular supply, and characteristic hyperintensity on the arterial phase of CT scan.[17,19] The aim of this study was to review a prospectively maintained database and identify PNETs that develop in patients within the context of VHL and follow their natural course of disease progression in hopes of identifying a means to distinguish patients who are more appropriate for active surveillance compared with those who may benefit from early surgical intervention for tumors with high malignant potential.

METHODS

As part of a prospective clinical protocol approved by the National Cancer Institute's Institutional Review Board, 134 patients with pancreatic manifestations of VHL were enrolled and underwent comprehensive biochemical testing and anatomic and functional imaging studies annually at the National Institutes of Health (NIH) Clinical Center.

Radiographic imaging and volume and density assessment

As part of our clinical research protocol, we performed a routine pancreatic protocol (2-mm slices) abdominal CT and magnetic resonance imaging, both with contrast (both protocols inject contrast at 3 mL/second, with arterial phase typically 10 to 20 seconds after injection). These are performed annually in patients with solid pancreatic lesions and every 2 years in those with complex or cystic pancreatic lesions. These defined intervals comprised the majority of all collected data points, and the measurements from CT scan were used to determine growth rate. If patients presented with concerning symptoms warranting further CT imaging between specified surveillance intervals, these studies were also included at 4- to 6-month intervals. Four of the 134 patients enrolled in the study had their CT scans repeated within 6 months.

Each imaging study was assessed by at least 2 independent reviewers (3 independent reviewers for the first 107 patients enrolled), who catalogued all solid radiographic lesions of the pancreas that displayed hyperintense signal during early arterial phase (Fig. 1). Size and location were recorded for each lesion. Key images were stored for each tumor to provide a reference baseline image for consistent analysis. For each lesion, the largest diameter of each tumor was recorded by each reviewer and then averaged to provide a consensus measurement. Volume measurements were derived using the equation: volume = diameter^3.

In addition, a software-based measurement for volume and density was calculated for each lesion identified on CT scan (Fig. 2). Using the stored key images provided by our independent reviewers, each tumor was centrally labeled within a computer workstation. Syngo.via for oncology (Siemens Health Care Corporation) was used to collect software-calculated measurements of volume and density for each identified pancreatic lesion.

Tumor measurements were used for comparison against different laboratory and radiographic data obtained within a 6-month time frame. Tumor greatest