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ORIGINAL ARTICLE

Solid non-functioning endocrine tumors of the pancreas: correlating computed tomography and pathology

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Abstract

Background: Since prognosis and treatment of pancreatic endocrine tumors (pNET) are based on tumor grade, contrast-enhanced multidetector computed tomography (MDCT) features of solid non-functioning pNETs were studied and correlated with pathology tumor grading.

Methods: MDCTs of diagnosed pNETs were reviewed retrospectively. Each tumor was analyzed for location, size, homogeneity, margins, arterial and venous phase enhancement, main pancreatic duct diameter, calcifications, vascular invasion, lymph-nodes enlargement, and liver metastases.

Results: Of 154 pNETs presenting between January 2000 and May 2016 with available histology from resected specimen or biopsy, there were 65 G1, 72 G2 and 17 G3 pNETs. Tumor diameter varied significantly between the three groups. Tumors >20 mm were more frequently malignant and non-homogeneous than smaller tumors. G1 tumors were more commonly hypervascular and G3 tumors more often non-hypervascular in the arterial phase. Arterial phase non-hyperdensity and tumor non-homogeneity had a higher rate of metastatic lesions. Vascular invasion correlated with presence of metastases and histological grade. G3 tumors were all >20 mm ($p = 0.007$), more often non-hypervascular in the arterial phase ($p = 0.0025$), and non-hyperdense in the venous phase ($p = 0.009$), and showed more often vascular invasion ($p = 0.0198$).

Conclusion: CT correlated with tumor grade; differentiating low-grade and high-grade pNETs through routine CT imaging might improve patient management.

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that may arise from pluripotent stem cells and demonstrate neuroendocrine differentiation.[1] Although often considered rare, the incidence of pancreatic endocrine tumors (pNETs) has shown a marked increase over the last two decades. With the widespread use of cross-sectional imaging, the current reported incidence for pNETs has risen to 0.32 per 100,000 per year, representing 6.9% of all NETs.[2,3]

A preliminary part of this work was presented at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America, in 2015.

The revised 2010 WHO classification primarily regards all gastroenteropancreatic (GEP) NETs as potentially malignant tumors and classifies them as G1 or G2 NETs or G3 NEC (neuroendocrine carcinoma) based on the Ki-67 proliferation index or mitotic index, with each grade associated with a progressively poorer prognosis.[4] The 2014 National Comprehensive Cancer Network guidelines define different therapeutic strategies for these tumors: all tumors should be resected if possible but G3 tumors should be treated with platinum-based chemotherapy with or without radiotherapy if resection is possible. In selected patients, incidentally discovered small NETS may be managed conservatively by follow-up.[5] The 2016 European Neuroendocrine Tumor Society (ENETS) guidelines on the management of

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non-functioning endocrine tumors suggest surveillance as an option for patients with G1 tumors and G2 tumors with low Ki-67, especially when the tumor is located in the head of the pancreas and there is no suggestion of malignancy. Accurate non-invasive determination of tumor grade would be useful for selecting patients that would benefit from surveillance.[6] Contrast-enhanced multidetector computed tomography (MDCT) is a widely used modality for the detection and staging of pancreatic tumors and its use in this context is recommended in several guidelines.[1,5–8]

The purpose of this study is to describe the MDCT features of solid non-functioning neuroendocrine tumors of the pancreas and to correlate these with tumor grading on histopathology.

Methods

This retrospective study was approved by the Institution Research Board, and informed consent was waived. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Radiological, surgical and oncological databases were reviewed to identify patients with non-functioning pNETs seen at the University Hospital GB Rossi in Verona between January 2000 and May 2016.

Patients were selected for inclusion if contrast-enhanced MDCT images were available for review along with histological grading and/or Ki-67 value. Patients with functioning pNETs, causing hormone-related symptoms and those cystic NETs were also excluded, since these latter tumors could not be evaluated with the same parameters as solid tumors.

Scans were performed most commonly on 64-row CT scanners, with multiphasic acquisitions that included a late arterial phase and a venous phase acquisition after administration of non-ionic iodinated contrast agents, and often included a non-contrast scan; the contrast-enhanced phases had been evaluated as diagnostic by the reviewers. One-hundred and one patients were studied on a 64-row CT scanner (Brilliance 64, Philips, The Netherlands), with 64 × 0.625 collimation and 0.5 s rotation time. Scan timing was determined with a bolus-tracking technique, positioning a 1-cm^2 region of interest (ROI) in the abdominal aorta at the origin of the celiac axis; this single level was scanned after 10 s from the contrast injection every 3 s at a low dose. Late arterial (pancreatic) and portal venous phase scanning were commenced, respectively, at 15 s and 60 s after the attenuation threshold of 150 HU was reached. All patients received 1.5 ml/kg of 370 mgI/ml contrast material (Ultravist, BayerScheringPharma) at a rate of 3–4 ml/s, followed by a 50 ml saline bolus administered by means of a dual-head power injector (Medrad Stellant, Indianola, PA).

Images were evaluated on a picture archiving and communication system (PACS) workstation in consensus by two radiologists with 7 and 12 years experience in abdominal imaging, respectively (MCA, GAZ), aware of the diagnosis of NET but blinded to the tumor grade, to the clinical data and follow-up of the patient and to other imaging studies performed, including nuclear medicine.

For each lesion, the two observers analyzed the following features: location, size, homogeneity, margins (sharp or ill-defined), degree of enhancement in the arterial and venous phases (evaluated qualitatively compared to the normal parenchyma), diameter of the main pancreatic duct, and presence of calcifications, vascular invasion, lymph nodes enlargement (short axis $\geq$10 mm) and liver metastases.

Pathological diagnosis and grading were obtained from the surgical specimen or from tumor biopsy. Tumors were divided into three different categories based on the proliferation index (WHO 2010 classification): well-differentiated neuroendocrine tumors (G1; ki-67 <3%), well-differentiated neuroendocrine tumors (G2; ki-67 3–20%) and poorly-differentiated neuroendocrine carcinomas (G3; ki-67 >20%).

Statistical analysis

Tumor diameters of the three groups were compared with an ANOVA test. The association between CT features and pathological findings was analyzed with Fisher's and Chi-square tests. Sensitivity, specificity, positive predictive value and negative predictive value in the differentiation between G1–G2 vs G3 tumors are reported for each CT feature and for the combination of the best two features. A difference with a p-value <0.05 was considered as significant. Statistical analysis was performed using GraphPad Prism version 6.01 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

Results

In the study period, 587 patients underwent resection for a pNET and 200 were diagnosed with a pNET but did not undergo surgery. For a large proportion of patients we did not have CT studies available for review: a search on our PACS system returned 154 solid non-functioning endocrine tumors in 148 patients who were equally distributed with respect to gender (74 males) with an age range of 18–83 years. Pathological diagnosis and grading were obtained from the surgical specimen in 95 resected tumors and from biopsy in 59 tumors. Median time interval between pathology and staging was 42 days and the mean interval was 94 days. The pathological features of the tumors are described in Table 1.

The median tumor diameter was 40 mm (range 5–145 mm) and liver metastases were observed in 51 patients (33.1%). There was a significant difference in tumor diameter between the three groups (G1 33 ± 27 mm; G2 55 ± 30 mm; G3 49 ± 18 mm; <0.0001) (Table 1). Tumors >2 cm were more frequently malignant (80/115; 69.6%) when compared with those $\leq$2 cm (9/39; 23.1%) ($p < 0.0001$), and showed more commonly a non-homogeneous enhancement pattern (55/115; 47.8%, vs 5/39, 12.8% for tumors $\leq$2 cm) ($p < 0.0001$). High-grade tumors had less defined margins as compared to lower grade tumors (Table 1).

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