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Original article

A comprehensive comparison of clinicopathologic and imaging features of incidental/symptomatic non-functioning pancreatic neuroendocrine tumors: A retrospective study of a single center

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ABSTRACT

Background: Incidentally discovered, nonfunctioning pancreatic endocrine tumors (NF-pNETs) are being increasingly diagnosed with the widespread use of imaging examination. The objective of this study was to analyze the different clinicopathologic and imaging features between incidentally discovered and symptomatic NF-pNETs.

Methods: From March 2010 to October 2014, we retrospectively analyzed 102 patients with pathologically confirmed sporadic NF-pNETs, among which 49 (48.0%) had lesions that were discovered incidentally. Differences in clinicopathologic features and various computerized tomography (CT) and endoscopic ultrasonography (EUS) findings were evaluated between incidental and symptomatic NF-pNETs.

Results: Among 102 patients with NF-pNETs, 49 (48.0%) had lesions that were discovered incidentally. Incidental NF-pNETs were more highly associated with low tumor grades, stages and lymphatic metastasis compared with symptomatic tumors ($p = 0.007$, 0.029 and 0.003, respectively). Moreover, incidental NF-pNETs had a lower rate of hypoenhancement ($p = 0.018$), main pancreatic duct dilatation ($p = 0.043$), and unclear border ($p = 0.022$). In addition, hypoechoic lesion was the most common and had a slightly higher rate in symptomatic tumors ($p = 0.032$).

Conclusions: Incidental NF-pNETs are associated with lower rates of aggressive behaviors of clinicopathologic and imaging features compared with symptomatic tumors.

Introduction

Pancreatic neuroendocrine tumors (pNETs) account for approximately 3% of pancreatic neoplasms and are extremely heterogeneous for various behaviors in comparison with pancreatic ductal adenocarcinoma [1,2]. In recent years, their incidence, particularly for incidentally discovered nonfunctioning pNETs (NF-pNETs), has rapidly increased due to the widespread use of endoscopic and cross-sectional imaging [1,3].

Our knowledge of the natural history of incidentally discovered NF-pNET is limited. Some institutes have demonstrated that incidental NF-pNETs are usually smaller than their counterpart symptomatic tumors and are associated with earlier stages, so more curative resections could be performed [4–6]. In addition, several studies have focused on the prognostic impacts of incidentally discovered NF-pNET compared with symptomatic neoplasm [5,7,8], and they confirmed improved survival for incidentally discovered NF-pNET after pancreatic resection. However, in contrast with some studies on prognosis, little research has been

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done on imaging features, regardless of the widespread use and high accuracy of CT and EUS.

At present, it is unclear whether imaging features of CT and EUS are different between incidental and symptomatic NF-pNETs. Therefore, we aim to investigate the clinicopathologic and imaging features of incidentally detected pancreatic NETs compared with their symptomatic counterparts and to explore features that can predict biological and aggressive behavior.

Material and methods

Patients cohort

We retrospectively analyzed clinical and pathologic features of all consecutive patients with histological or cytological confirmed pNETs at Shanghai Cancer Center, Shanghai, China (single institution). From March 2010 to October 2014, of all 133 consecutive patients with pNETs, 102 patients were defined as NF-pNETs without distinct clinical syndrome or hormone alterations. Patients were defined as having symptomatic lesions if clinical manifestations related to the mass were present at the initial diagnosis. Patients with incidentally detected lesions were classified as tumors that were incidentally discovered in asymptomatic patients who underwent diagnostic evaluations for unrelated causes, or as patients with clinical symptoms not associated with the mass.

Evaluation of the clinical data and pathology work-up

Comprehensive clinical data that were collected included demographic characteristics, clinical presentation, preoperative work-up, and intraoperative information. Surgical resection with radical intent was performed whenever possible. Adjacent organs or liver metastases were routinely removed when involved with tumors. For patients with unresectable or widely metastatic lesions, fine-needle biopsy of the primary or metastatic lesions was performed in order to achieve pathological confirmation. This study was approved by the Ethics Board, Shanghai Cancer Center, Fudan University.

Pathologic diagnosis of pNET was determined on the basis of conventional histological and immunohistochemical examinations. All immunohistochemical evaluations were performed including chromogranin A, synaptophysin, neuron specific enolase and Ki-67 proliferation index. The TNM staging of PNETs was classified according to the newest edition of the AJCC Cancer Staging Handbook [9]. Histopathologic grade was defined as low (G1), intermediate (G2), and high (G3), according to the 2010 WHO consensus [10]. Overall survival was determined from the time of diagnosis to death or the most recent follow-up. Survival information was obtained by electronic medical records or phone call follow-up.

Image acquisition and analysis

All CT images were reassessed via the Centricity PACS (picture archiving and communication system; General Electric, Fairfield, CT, USA). All images were reviewed in consensus by a blinded read of two radiologists with more than three years of experience in the imaging of pNETs. For each case, the following characteristics were assessed on the imaging: degree of tumor enhancement, presence of calcifications, dilatation of main pancreatic duct (MPD), tumor pattern and border. As a surrogate parameter for vascularization, the degree of lesions enhancement was defined compared with the normal pancreatic parenchyma during the arterial phase. The presence of calcifications was recorded by unenhanced CT scanning. The dilatation of the MPD was defined as 4 mm or greater.

To increase the sensitivity of diagnosis and provide a gold standard for preoperative tumor location, EUS examinations were performed under conscious sedation with fentanyl and midazolam. Fine-needle aspiration biopsy by EUS (EUS-FNA) was carried out for patients who were unable to undergo surgery [11]. EUS procedures were generally performed by two experienced endoscopists with more than 8 years of experience via curvilinear echoendoscope (GF-UCT 260; Olympus, Japan).

Statistical methods

Categorical variables are expressed as numbers (percentages) and were calculated using chi-square or Fisher's exact probability tests as appropriate. The distribution of continuous variables is presented as median (range) and was analyzed by a two-sample Student t-test or Mann–Whitney U test when possible. Univariate Kaplan–Meier analysis was calculated comparing by the log-rank test. Multivariate analysis was calculated by Cox's proportional hazards regression model for variables significant in univariate analysis. The statistical analysis was conducted by dedicated software (SPSS Inc., version 17.0, Chicago, IL, USA). A $p < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

Detailed clinicopathological characteristics of incidental and symptomatic patients are showed in Table 1. Of all 102 cases with histologically or cytologically confirmed NF-pNETs, 49 (48.0%) were incidentally detected. The entire group had a median age of 56 (16–77), and 47.1% were male (n = 48). Most patients had tumors located at the body and tail of the pancreas (n = 58, 56.9%), whereas 40 (39.2%) were located at the head, and only 4 (3.9%) had multifocal tumors. A total of 91 patients (89.2%) underwent surgical resection (80 curative and 11 palliative), compared with 11 cases without operation. The incidental tumors were more highly associated with small diameters ($p = 0.030$), early stage ($p = 0.029$), low grade ($p = 0.007$), curative operations ($p = 0.011$) and body or tail lesions ($p = 0.032$), but were less associated with lymphatic metastasis ($p = 0.003$), compared with their symptomatic counterparts. The incidental and symptomatic NF-pNETs groups were statistically similar in other clinicopathological characteristics, including gender, age-. For symptomatic patients, the most commonly presenting symptoms were abdominal pain (n = 23, 43.4%), postprandial fullness (n = 7, 13.2%), back pain (n = 6, 11.3%), vomit (n = 4, 7.5%), jaundice (n = 4, 7.5%), palpable mass (n = 3, 5.7%), diarrhea (n = 3, 5.7%) and weight loss (n = 3, 5.7%). To note, there were 9 symptomatic NF-pNETs with diameter less than 2 cm, including 5 abdominal pain patients, 3 postprandial fullness patients and one back pain patient.

Imaging characteristics

Among 102 patients, 88 received CT scan, while only 24 underwent further EUS detection. Tumors were not detected by CT scan in six cases (sensitivity, 93.0%). All patients were shown to have lesions by EUS examination (sensitivity, 100.0%). The indications of these examinations varied. Several cases suffered from gastrointestinal symptoms, while other common indications came from routine medical examination, including imaging procedures or follow-up of other diseases.

The CT characteristics of the entire cohort with positive CT findings are described in Table 2. Eleven (13.4%) cases presented with calcified changes, and a solid, cystic and cyst-solidary changed