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Original article

Contrast-enhancement ratio on multiphase enhanced computed tomography predicts recurrence of pancreatic neuroendocrine tumor after curative resection

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ABSTRACT

Background/Objective: No previous study has quantitatively investigated the degree of enhancement of pancreatic neuroendocrine tumors (pNETs) using a routine preoperative modality. The aim of this study was to evaluate the contrast-enhancement ratio (CER) of pNETs using multiphase enhanced CT and to assess the impact of the CER on disease recurrence after surgery.

Methods: A retrospective study was performed using data from 47 consecutive patients with pNETs who had undergone curative surgery. The CER of the tumor was calculated by dividing the CT attenuation value obtained during the maximum-enhanced phase by that obtained during the pre-enhanced phase. A region of interest was placed in the largest tumor dimension plane so as to cover as much surface of the tumor as possible while avoiding adjacent normal structures, calcification, and necrotic areas of the tumor.

Results: During a median follow-up period of 51 months (range, 1–132 months), a total of 4 patients (8.5%) developed disease recurrence. The median CER value was significantly lower for the patients with recurrence than for the patients without recurrence (2.9 vs. 4.3, $P = 0.013$). Univariate analyses showed that a CER $\leq$3.2 was significantly associated with disease recurrence ($P < 0.001$). All the patients with disease recurrence had tumors that were both large (>20 mm) and weakly enhanced (CER $\leq$ 3.2), whereas no recurrences were observed even in patients with tumors >20 mm when the CER was greater than 3.2.

Conclusions: CER might be a useful predictor of disease recurrence in patients with pNETs.

Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare tumors of the neuroendocrine system originating in the pancreas and occur in 1 or less than 1 per 100,000 people per year [1,2]. Previous studies investigating survival after pNET resection have reported an advanced patient age [3–9], the Ki-67 index [3,4,7,10,11], the tumor differentiation status [9–12], the presence of metastasis [4,5], and the Tumor-Node-Metastases (TNM) stage [6,11] as significant predictors. However, some of these variables are not available before surgery, making it difficult to predict the biological behavior of pNETs preoperatively.

Angiogenesis has long been considered to play roles in both tumor growth and metastasis. Marion-Audibert and colleagues showed that the intratumoral microvascular density was significantly higher in well-differentiated benign endocrine tumors than in tumors of uncertain behavior or in carcinoma [13]. Interestingly, the microvessel density was significantly greater in hypervascular tumors than in hypovascular tumors, as assessed using contrast-enhanced computed tomography (CT) and/or arteriography.

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Because of the hypervascular appearance of pNETs, in general, imaging modalities have been traditionally used for the localization, diagnosis, and staging of pNETs [14–21], this study opened the way to predicting the biological behavior of pNETs using preoperative imaging modalities. So far, two studies have assessed radiologic–pathologic correlations in patients with pNETs. Rodallec et al. showed that for pNETs, the degree of enhancement on enhanced helical CT was associated with the tumor vascular density as well as the tumor differentiation status [22]. Less-enhanced tumors were correlated with a shorter survival period in a univariate analysis. D'Assignies and colleagues showed that tumor blood flow, as assessed with perfusion CT, reflected the intratumoral vascular density and was correlated with the proliferation index and the World Health Organization (WHO) classification [23]. These studies suggested that radiological findings obtained using CT could help to differentiate tumor grades and to predict patient outcome. However, some caveats must be considered when interpreting these studies: the former study assessed the degree of enhancement semiquantitatively, while the perfusion CT examinations performed in the latter study required a specific software for data analysis and carried a potential risk of artifacts.

The contrast-enhancement ratio (CER) of a tumor is a reproducible factor that can be determined independently of the type of CT scanner or software being used if the temporal enhancement of the tumor is acquired. The aim of this study was to evaluate the CER of pNETs in a quantitative manner. The CER values were calculated by dividing the CT attenuation value obtained during the maximum-enhanced phase by that obtained during the pre-enhanced phase using data from multiphase dynamic contrast-enhanced CT examinations performed as routine preoperative work-ups. The study also sought to clarify the impact of the CER on the long-term outcome after curative surgery for pNETs, since the preoperative prediction of long-term outcomes might be useful for explaining the disease course to both patients and their families.

Methods

Patients

Between January 2004 and June 2015, we performed pancreatic resections for 56 patients with pNETs. Among these patients, 47 patients who had undergone a preoperative multiphase (8–10 phases) dynamic contrast-enhanced CT examination were included in the final analyses. Nine patients were excluded for the following reasons: 7 patients had undergone a preoperative CT examination that did not follow our protocol, 1 patient had an undetectable mass when examined using CT, and data acquisition was not optimal in 1 patient because of chronic heart failure.

Surgical indications and procedures

The operative indications were discussed by a multidisciplinary pancreatic tumor board, including surgeons, radiologists, pathologists, and gastroenterologists. Surgical resection was primarily indicated irrespective of the tumor size [5,24]. The operative procedures were planned according to the location of the tumor on the preoperative images, and a final decision was made intraoperatively after confirming the position of the tumor in relation to its proximity to vascular structures around the pancreas as well as the main pancreatic duct.

Preoperative image analysis

All the CT examinations were performed using a 16- or 64-multirow detector helical CT (LightSpeed Ultra16 or LightSpeed VCT; GE Medical Systems, Milwaukee, WI, USA). Dynamic contrast-enhanced multiphasic CT was performed for patients who were suspected of having pancreatic tumors and were considered candidates for surgical resection; the examinations were performed using the following technical parameters: 0.625-mm collimation, 0.5 s/rotation, tube voltage of 120 kV, 300 mA, matrix size of 512×512, slice thickness of 2.5, and a table increment of 27.5 mm/s. The multiphasic CT protocol was comprised of 8 acquisitions at the following scan timings: before the injection of the contrast material (pre) and 15, 22, 29, 36, 43, 90, and 210 s after the injection of the contrast material at a rate of 3 mL/s into the median cubital vein. In 2009, the protocol was amended to a 10-phasic CT protocol (pre, 22, 29, 36, 43, 50, 57, 64, 90, and 210 s) to obtain more detailed information. Delayed phase images at 210 s after the injection of the contrast agent were acquired for use in a perfusion analysis, since prolonged delayed images are reportedly useful for estimating perfusion and permeability [25]. Nineteen patients were evaluated with 8-phasic CT scans, and the remaining 28 patients were evaluated with 10-phasic CT scans.

CT analyses were performed using a commercial software package (EV Insite; PSP Corp., Tokyo, Japan). For each phase of images, oval regions of interest (ROIs) were set on the pancreatic tumor, and the CER of the tumor was calculated by dividing the CT attenuation value obtained during the maximum-enhanced phase by that obtained during the pre-enhanced phase (Fig. 1). Each ROI was placed using a copy-and-paste method on the same axial slice. The size of the ROIs was maximized while avoiding adjacent normal structures, calcification, and necrotic areas of the tumor. The presence of calcification was evaluated using unenhanced CT. Macroscopic vascular invasion was defined on the images as infiltration of the main arterial (celiac, hepatic, splenic, or superior mesenteric artery) or venous (portal, splenic, or superior mesenteric vein) structures. Two readers (a surgeon and a radiologist, with 12 and 21 years of experience in the fields of abdominal surgery and abdominal imaging, respectively) reviewed the CT images and measured the CT values of the tumors independently, and the average value was used for the analysis. The parameters were assessed in a blinded manner.

Postoperative follow-up

After discharge, the patients were closely followed up at our outpatient clinic. All the patients underwent radiologic and laboratory assessments every 6 months for the first 5 years and annually thereafter. Recurrence was diagnosed when the imaging modalities showed a new lesion with radiologic features typical of pNETs on enhanced CT and/or magnetic resonance images.

Grading of pNETs

The histopathological tumor grade was defined according to the WHO classification [26]. The proliferative rate was assessed as the number of mitoses per unit area of tumor and as the percentage of neoplastic cells with immunolabeling for the proliferation marker Ki-67.

Factors analyzed

We evaluated the following variables as possible risk factors for recurrence: patient age (>50 years vs. $\leq$50 years); sex (male vs. female); multiple endocrine neoplasms-1 (MEN-1) (yes vs. no); functional status (functioning vs. non-functioning); location of the main tumor (head vs. body-tail); maximum tumor diameter (>20 mm vs. $\leq$20 mm); calcification of the tumor (present vs. absent); grading of the tumor (G1 vs. G2); CER of the tumor (>3.2 vs. $\leq$3.2); and lymph node metastasis (present vs. absent). For continuous valuables, the median

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