European Journal of Radiology 110 (2019) 66–73

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Nonhypervascular pancreatic neuroendocrine tumors: Spectrum of MDCT imaging findings and differentiation from pancreatic ductal adenocarcinoma

Grigory Karmazanovsky[a,b], Elena Belousova[a,b,*], Wolfgang Schima[c], Andrei Glotov[d], Dmitry Kalinin[d], Andrei Kriger[e]

[a] Department of Radiology, A.V. Vishnevsky Institute of Surgery, Moscow, Russia
[b] Department of Radiology, Faculty of Postgraduate Professional Training of Physicians, I.M. Sechenov First Moscow State Medical University, Moscow, Russia
[c] Department of Diagnostic and Interventional Radiology, Goettlicher Heiland Krankenhaus, Barmherzige Schwestern Krankenhaus, and Sankt Josef Krankenhaus, Vinzenzgruppe, Vienna, Austria
[d] Department of Pathology, A.V. Vishnevsky Institute of Surgery, Moscow, Russia
[e] Department of Abdominal Surgery, A.V. Vishnevsky Institute of Surgery, Moscow, Russia

ARTICLE INFO

Keywords:
MDCT
Pancreas
Neuroendocrine tumor
Pancreatic cancer

ABSTRACT

Purpose: The purpose of our study was to determine contrast-enhanced MDCT features to differentiate non-hypervascular pancreatic neuroendocrine tumors (PNETs) from pancreatic ductal adenocarcinomas (PDACs).
Methods: and materials: We included 74 patients with PNETs and 80 patients with PDACs who underwent preoperative MDCT. Two radiologists evaluated the morphologic characteristic and enhancement patterns of the tumors. Quantitative and qualitative analysis was performed, including evaluation of tumor size, homogeneity, contrast enhancement pattern, presence of pancreatic duct dilatation and tumor invasion to the adjacent vessels and peripancreatic infiltration. Tumor-to-pancreas enhancement ratio was defined as the Hounsfield units (HU) value of the tumor divided by the HU value of the pancreas. the first group was hypervascular PNETs showing hyperenhancement on arterial phase images and nonhypervascular PNETs, showing iso- or hypoenhancement on arterial phase images. After that, two radiologists estimated the possibilities of PNET or PDAC were for non-hypervascular PNETs.
Results: On the basis of arterial enhancement, 43 PNETs were hypervascular and 31 were nonhypervascular. When compared to PDAC, nonhypervascular PNETs more frequently had well-defined tumor margins, intratumoral cystic components, calcifications and blood vessels and less frequently had main pancreatic duct dilatation, peripancreatic infiltration and vascular invasion ($p < 0.01$ for all). Nonhypervascular PNETs had higher tumor-to-pancreas enhancement ratio in venous phase (1.02 vs. 0.78, $p = 0.012$). Nonhypervascular PNETs more often had portal-venous hyperenhancement or persistent isoenhancement, while PDAC more often had persistent hypoenhancement or gradual delayed enhancement ($p < 0.001$). The absence of pancreatic duct dilatation and portal-venous hyperenhancement or persistent isoenhancement were the independent predictors for nonhypervascular PNETs.

(The most accurate MDCT-findings to predict nonhypervascular PNET were the absence of pancreatic duct dilatation and peripancreatic infiltration (79% and 92% accuracy), portal-venous phase hyperenhancement or persistent isoenhancement (77%), the presence of intratumoral blood vessels (77%) and relative enhancement intensity in venous phase > 0.9 (76%). Using these criteria, the area under curve for differentiation of PNET from PDAC was 0.906–0.846.
Conclusion: Combined assessment of the enhancement and morphologic characteristics can improve the differentiation between nonhypervascular PNETs and PDAC at contrast-enhanced MDCT.

Abbreviations: HU, hounsfield units; MVD, microvascular density; NPV, negative predictive value; PDAC, pancreatic ductal adenocarcinoma; PNEN, pancreatic neuroendocrine neoplasm; PNET, pancreatic neuroendocrine tumor; PPV, positive predictive value; ROC, receiver operating characteristic; ROI, region of interest; WHO, World Health Organization

* Corresponding author at: Department of Radiology, A.V. Vishnevsky Institute of Surgery, 27, Bolshaya Serpukhovskaya str., Moscow, 117997, Russia.
E-mail addresses: dr.elena.belousova@gmail.com, karmazanovsky@ixv.ru (E. Belousova).

https://doi.org/10.1016/j.ejrad.2018.04.006
Received 17 October 2017; Received in revised form 8 February 2018; Accepted 5 April 2018

1. Introduction

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors that arise from neuroendocrine cells of the pancreas. PNETs account for 2% of all pancreatic neoplasms and have an incidence of 1–2 per 100,000 persons per year [1,2]. Clinically, PNETs are divided into hyperfunctioning (functional) or non-hyperfunctioning (non-functional), depending on the presence of a specific clinical syndrome, caused by hormonal hypersecretion.

Among hyperfunctioning tumors, insulinomas and gastrinomas are the most common types. In most of the patients (up to 85%), however, the hormones are produced in small amounts or are functionally inactive, so these (non-hyperfunctioning) tumors are either discovered incidentally or due to local symptoms [3]. According to the recent World Health Organization (WHO) 2017 classification system, pancreatic neuroendocrine neoplasms (PNENs) are divided into Well-differentiated PNENs: PNETs (grade 1, grade 2 and grade 3) and poorly differentiated PNENs: pancreatic neuroendocrine carcinomas [4].

Contrast enhanced CT and/or MRI are the initial imaging techniques for patients with suspected pancreatic tumor. Typically, PNETS present as small, well-demarcated, homogeneously enhanced hypervascular lesions, yet up to 41% of PNETs are hypovascular [5]. Previous studies attributed tumor hypovascularity to lower microvessel count, extensive fibrosis or the presence of necrosis, that are more commonly encountered in less differentiated (grade 2 or 3) PNETs [6].

The differential diagnosis of PNETs and other hypervascular pancreatic lesions (solid-pseudopapillary tumor, pseudosolid serous cystadenoma, renal cancer metastases, intrapancreatic accessory spleen etc.) has been previously described in literature [7]. However, only few studies focused on the differentiation between PNET and pancreatic ductal adenocarcinoma (PDAC) [8–10]. Moreover, there has not been a direct comparison between MDCT imaging features of non-hypervascular PNETs and PDAC. Differential diagnosis of these two entities is of great importance, especially in the case of non-hyperfunctioning PNETs, since PNET and pancreatic adenocarcinoma have different prognosis and require different treatment strategies. The purpose of our study is to investigate the MDCT-features of hypovascular PNETs and to evaluate the MDCT performance for the differential diagnosis of PNET from PDAC.

2. Materials and methods

2.1. Study population

Institutional review board approval was obtained for this retrospective study, with informed consent being waived. A total of 89 patients with histologically proven PNETs were identified in our pathology database from the period between September 2011 and March 2017. Five patients who had a fine-needle aspiration biopsy and didn't undergo the surgery were excluded. 10 patients were excluded due to the lack of preoperative multiphasic MDCT-examination images. Finally, 74 patients with PNETs comprised our study population. For comparison, we reviewed the institutional database (in the period between March 2016 and March 2017) to select histologically proven cases of pancreatic adenocarcinoma (n = 105). Patients who didn't undergo a preoperative dynamic MDCT examination (n = 12) and a surgical resection of the tumor (n = 13) were excluded.

Therefore, we studied a total of 74 patients with PNETs and 80 patients with PADC. Table 1 summarizes the demographic characteristics of patients with PNET and PDAC.

2.2. Pathological analysis

All PNETs were diagnosed on the basis of the histologic findings and immunohistochemical expression of chromogranin A and synaptophysin. Pathological tumor grades of PNETs were determined according to the WHO 2010 classification by counting the number of mitoses and the Ki-67 index, with following definitions: grade 1: mitotic count, < 2 per 10 high power fields and/or ≤2% Ki67 index; grade 2: mitotic count, 2–20 per 10 high power fields and/or 3–20% Ki67 index; grade 3: mitotic count, > 20 per 10 high power fields and/or > 20% Ki67 index.

Table 1
Demographic characteristics of patients with PNET or PDAC.

Characteristic	Hypervascular PNETs (n = 43)	Nonhypervascular PNETs (n = 31)	PDAC (n = 80)	P-value
Age (y.o.)[a]	52 ± 9	54 ± 12	59 ± 13	0.547
Sex				
male	18 (42%)	14 (45%)	33 (41%)	0.278
female	25 (58%)	17 (55%)	47 (59%)	
Tumor location				
Head/ucinate	10 (23%)	7 (23%)	45 (76%)	0.089
Body	21 (49%)	9 (29%)	6 (10%)	
Tail	12 (28%)	15 (48%)	8 (14%)	

PNET – pancreatic neuroendocrine tumor.
PDAC – pancreatic ductal adenocarcinoma.
[a] mean ± standard deviation.

To identify tumor microvessels endothelial cell marker CD-34 (clone QBEnd/10, CellMarque) was used. Microvessels quantification was performed on the three microscopic fields at x200 magnification (~1.8 mm2). Microscopic field selection was carried out among the most vascularized areas («hot spots»). Using the colour threshold instrument, the total number of pixels belonging to the vessels was determined. This value was divided by the total number of pixels in the image to determine the tumor microvascular density (MVD).

2.3. MDCT imaging technique

MDCT was performed on one of two multidetector row helical scanners – Philips Brilliance CT 64-slice or Brilliance iCT 256-slice CT scanner (Philips Medical Systems Cleveland, OH, USA). The scanning parameters were as follows: slice thickness 1–2 mm, beam pitch 1, tube rotation speed 0.75 s, tube voltage 120 kVp, automatic tube current modulation (150–500 mAs). Following the precontrast imaging, the iodinated contrast media with the concentration of 370 and 400 mg iodine/mL was administered intravenously, in the amount of 1.6 and 1.5 mL per kilogram of body weight respectively, at a rate of 4–5 mL/sec, using a dual-head pump injector. The bolus of contrast agent was followed by saline chaser bolus (40–50 mL), injected at the same rate. The arterial, portal venous and delayed phase scans were obtained at 10, 35 and 180-s delays after the aortic attenuation reached 100 Hounsfield units (HU). The 4-phase examinations (unenhanced, arterial, portal venous phases) were performed for all patients.

2.4. Qualitative and quantitative image analysis

Two radiologists reviewed in consensus the MDCT images retrospectively. They were aware of a pancreatic tumor presence, but they were blinded to the detailed pathological findings. The radiologists evaluated the following MDCT imaging features: tumor location (head/neck, body, tail); size (maximal axial dimension); tumor margin (well-defined or ill-defined); tumor homogeneity (homogeneous or non-homogeneous); presence of intratumoral calcifications. The main pancreatic duct was considered dilated, if its diameter was 3 mm or larger. Cystic changes within the tumor were defined by non-enhancing, water-density areas with circular or ovoid shape and rather well-defined margins. Images were also evaluated for the presence of distant metastases and direct tumor invasion into adjacent vessels, peripancreatic infiltration.

The enhancement pattern of the tumor (hypoattenuating, isoattenuating or hyperattenuating) was evaluated in comparison to

Table 2
5-point scale to differentiate between nonhypervascular PNET and PDAC.

Grade	Description
1	Lesion is definitely PNET according to imaging findings: well-defined tumor margin, presence of calcifications, and/or cystic component, and/or intratumoral blood vessels, absence of pancreatic duct dilatation, vascular invasion and peripancreatic infiltration, relative enhancement intensity in venous phase > 0.9 and/or Type I or II contrast enhancement pattern
2	Lesion is probably PNETs, showing some of the above-mentioned findings, typical for PNET
3	Intermediate
5	Lesion is probably PDAC, showing some of the imaging features of PDAC
4	Lesion is definitely PDAC, according to the imaging findings, including: pancreatic duct dilatation, vascular invasion and peripancreatic infiltration; ill-defined margin; absence of calcifications, cystic component and intratumoral blood vessels; relative enhancement intensity in venous phase < 0.9 and/or Type III or IV contrast enhancement pattern

normal pancreas on arterial, portal venous and delayed phase MDCT – images. The Hounsfield units (HU) value was measured by placing the oval region of interest (ROI), 10 mm^2 large, within the tumor and adjacent pancreatic parenchyma on each phase image sets, carefully avoiding calcifications, areas of cystic or necrotic changes, vessels and pancreatic duct. Relative tumor enhancement ratio was defined as the HU value of the tumor divided by the HU value of the pancreas, measured on arterial and portal venous phases respectively.

After that, two radiologists divided all PNETs into one of two groups, based on the degree of arterial enhancement compared to the adjacent pancreatic parenchyma: the first group was hypervascular PNETs showing hyperenhancement on arterial phase images and nonhypervascular PNETs, showing iso- or hypoenhancement on arterial phase images. The tumor was considered hyperenhancing if its density in arterial phase was at least 10 HU higher than the density of the surrounding pancreatic parenchyma. Two weeks after completing the first interpretation session, two radiologists reviewed in consensus the MDCT – images and rated the possibilities of PNET or PDAC using 5-point scale (Table 2).

2.5. Statistical analysis

Descriptive statistics (mean, standard deviation, proportions) were calculated for all numeric data. MDCT-features were compared between the groups using Chi-square and Fisher exact test for categorical values and the Student T test for continuous variables. A p-value less than 0.05 was considered to indicate a statistical significance for all analysis. Az). Statistically significant MDCT-features associated with PDAC were further analyzed using multivariate logistic regression analysis. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy for differentiation between PNET tumor grades were measured for each parameter and their combinations. To assess the interobserver agreement, we performed Cohen's kappa analysis, a κ index above 0.8 was considered to be indicative of a very good agreement between the two readings. The individual performance of two independent reviewers for differentiating between PDAC and PNET was evaluated using receiver-operating-characteristic analysis (ROC). All statistical analyses were performed using Statistica, version 10.0 software package (StatSoft).

3. Results

A total of 74 PNETs were analyzed (Table 3). Thirty-one (42%) tumors were classified as hypervascular and 43 (58%) tumors were classified as nonhypervascular. The majority (n = 32/43, 74%) of hypervascular tumors were grade 1 (Fig. 1) and the majority of nonhypervascular tumors (n = 23/31, 74%) were grades 2 and 3 (Figs. 2 and 3), with a statistically significant difference between the two groups ($p < 0.001$). The mean MVD was significantly lower in nonhypervascular PNETs than in hypervascular PNETs (4.7% ± 2.1 vs. 8.4% ± 2.9, $p < 0.01$). The incidence of lymph node metastases, as well as Ki-67 index was significantly higher in hypovascular tumors ($p = 0.013$ and $p < 0.01$ respectively). There was no significant difference between the two groups with respect to the presence of liver metastases. Non-hyperfunctioning PNETs were also more often nonhypervascular than hypervascular (32% vs. 17%), however, the difference didn't reach statistical significance.

Qualitative and quantitative data on hypervascular, nonhypervascular PNETs and PDACs are summarized on Table 4.

The tumor size was significantly larger for hypervascular pNETs (24.8 ± 11.2 mm) than for nonhypervascular PNETs (20.5 ± 15.7 mm, $p < 0.05$). Hypervascular PNETs more often had well defined margins (38/43, 88% vs. 18/31, 58%, $p < 0.01$), and less often had peripancreatic infiltration (3/43, 7% vs. 9/31, 29%, $p = 0.011$) and vascular invasion (3/43, 7% vs. 8/31, 26%, $p = 0.02$). In terms of tumor homogeneity, presence of calcification or cystic component within the tumor, pancreatic duct dilatation – there were no significant differences between the two groups.

When compared to PDAC, nonhypervascular PNETs more frequently had smooth and well-defined tumor margins (18/31, 58% vs. 20/80, 25%; $p < 0.001$) and intratumoral cystic components (8/31, 26% vs. 2/80, 5%; $p < 0.001$). Intratumoral calcifications were observed only in nonhypervascular PNETs (4/31, 13%; $p < 0.01$). PDAC, on the other hand, more frequently had main pancreatic duct dilatation (77/80, 97% vs. 6/31, 19%; $p < 0.001$), peripancreatic infiltration (64/80, 81% vs. 9/31, 29%; $p < 0.0001$) and vascular invasion (42/80, 53% vs. 8/31, 26%; $p = 0.011$). There was no significant difference between nonhypervascular PNETs and PDAC with respect to the tumor location, tumor size and homogeneity.

Relative tumor-to-pancreas enhancement intensity in the venous phase was significantly higher in nonhypervascular PNETs than in PDACs (1.02 ± 0.14 vs. 0.78 ± 0.20, $p = 0.012$), however, in the arterial and delayed phases the difference was not statistically significant (Fig. 4). Using the ROC-curve analysis, we determined the cutoff value for tumor-to-pancreas enhancement in the venous phase as 0.9. The most prevalent enhancement pattern of nonhypervascular PNETs were portal-venous phase hyperenhancement (10/31, 35%) and persistent isoenhancement (12/31, 40%), while the most prevalent contrast enhancement type of PDAC was persistent hypoenhancement (45/80, 56%) and gradual delayed enhancement (18/80, 22%) (Table 5).

There were two independent MDCT-findings to predict nonhypervascular PNET on multivariate logistic regression analysis: the absence of pancreatic duct dilatation (Exp(B) = 106.9; 95% CI: 24.8, 459.3, $p < 0.0001$) and portal hyperenhancement or persistent isoenhancement (Exp(B) = 10.6; 95% CI: 4.0, 28.0, $p < 0.0001$). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for each significant MDCT- finding to predict nonhypervascular PNETs are represented in Table 6. The most accurate MDCT findings were the absence of pancreatic duct dilatation (92% accuracy), the absence of peripancreatic infiltration (79%), type I or II contrast enhancement pattern (77%), the presence of intratumoral blood vessels (77%) and relative enhancement intensity in venous phase > 0.9 (76%). The area under ROC-curve for differentiation of

Table 3
The relationship between the PNETs radiological appearance and pathological findings.

Patients characteristics	Nonhypervascular PNETs (n = 31/74, 42%)	Hypervascular PNETs (n = 43\74, 58%)	p-value
Grade 1 (n = 39/74, 53%)	7/31 (23%)	32/43 (74%)	0.0001
Grade 2 (n = 32/74, 43%)	22/31 (71%)	10/43 (23%)	
Grade 3 (n = 3/74, 4%)	2/31 (6%)	1/43 (3%)	
MVD[a]	4.7% ± 2.1	8.4% ± 2.9	< 0.01
Hyperfunctioning (n = 57/74)	21/31 (68%)	36/43 (83%)	0.106
Non-hyperfunctioning (n = 17/74)	10/31 (32%)	7/43 (17%)	
Lymph node metastases	7/31 (22%)	1/43 (< 1%)	0.013
ki−67 index[a]	6.0% ± 5%	2.2 ± 2%	< 0.01
Liver metastases	4/31 (13%)	1/43 (2%)	0.096

PNET – pancreatic neuroendocrine tumor.
PDAC – pancreatic ductal adenocarcinoma.
MVD – microvascular density.
[a] mean ± standard deviation.

PNET from PDAC using the 5-point scale was 0.906 for reader 1 and 0.846 for reader 2, with excellent agreement (k = 0.837).

4. Discussion

Our results showed that the enhancement pattern and additional imaging characteristics of the PNETs help to discriminate them from PDACs. Using specific MDCT findings, the area under curve for differentiation of PNET from PDAC was 0.906 for reader 1 and 0.846 for reader 2.

According to the old WHO 2010 classification system, PNETs were divided into three tumor grades, based on the mitotic count and Ki-67 index: well differentiated neuroendocrine tumors – grade 1 and grade 2, and poorly differentiated neuroendocrine carcinomas – grade 3 [11]. The new WHO 2017 classification is an improvement of the previous version [4,12]. Its main change is the introduction of a “pancreatic neuroendocrine tumor grade 3” category to recognize grade-discordant pancreatic neuroendocrine tumors and distinguish them from pancreatic neuroendocrine carcinomas. Another important issue in that Ki67 index of 3% was used as cutoff to discriminate between grade 1 and grade 2 PNETs instead of 2%. If pancreatic masses are incidentally identified, they are usually biopsied to confirm the presence of a PNET and to preliminarily grade the tumor [13].

PNETs are typically seen as hypervascular tumors in the arterial phase of dynamic contrast-enhanced MDCT, however, occasionally PNET can show either iso- or hypoenhancement. In the present study, 42% of PNETs showed iso- or hypoattenuation, and our results are similar to others. Rodallec et al. reported that 39% of PNETs showed iso- or hypoettenuation compared with normal pancreatic parenchyma [14]. Hyodo et. al reported that 43% of PNETs contained areas of iso- or hypoenhancement and up to 21% of PNETs showed iso- or hypoattenuation of the entire tumor [15]. These results point out the fact, that nonhypervascular PNETs are not rare, and require close attention in differential diagnosis of pancreatic neoplasms.

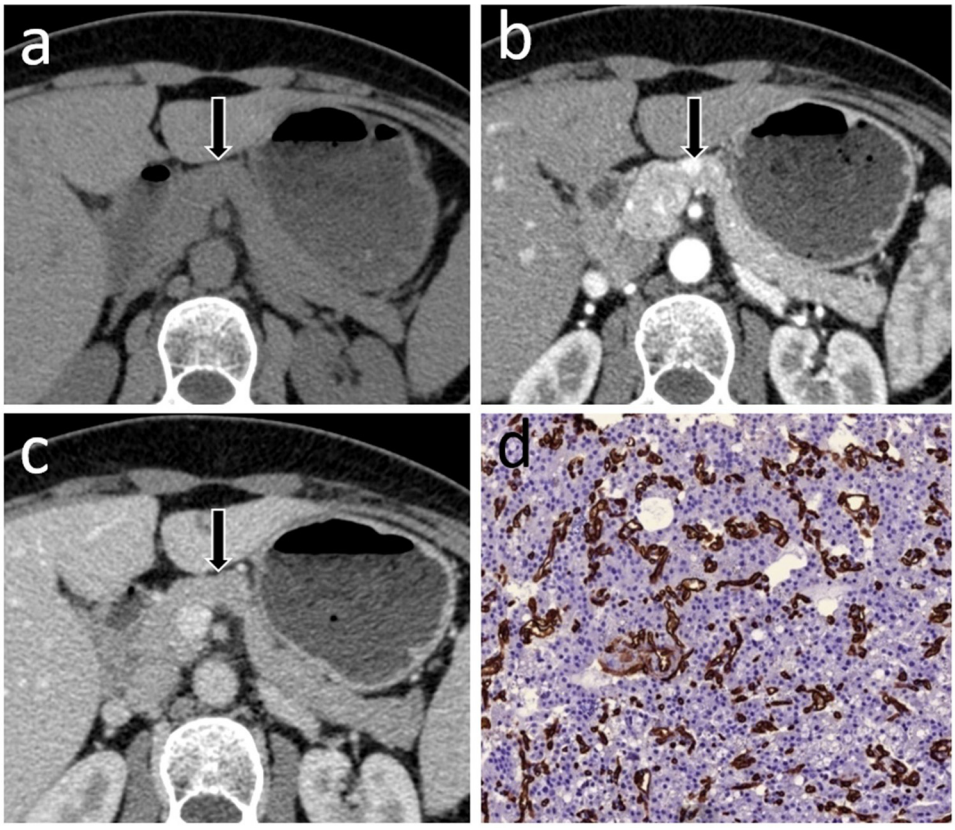

Fig 1. MDCT post-contrast appearance of a pancreatic neuroendocrine tumor grade 1: on native (a), arterial (b) and portal-venous (c) phases a small lesion in the pancreatic neck (arrow) is isodence in the native phase (a) and shows hyperenhancement in the arterial phase (b) with wash-out in the portal-venous phase (c). (d) Immunostaining with CD34 antibody (x200) highlights vessels (red), showing that the intratumoral microvascular density is high (8.8%).

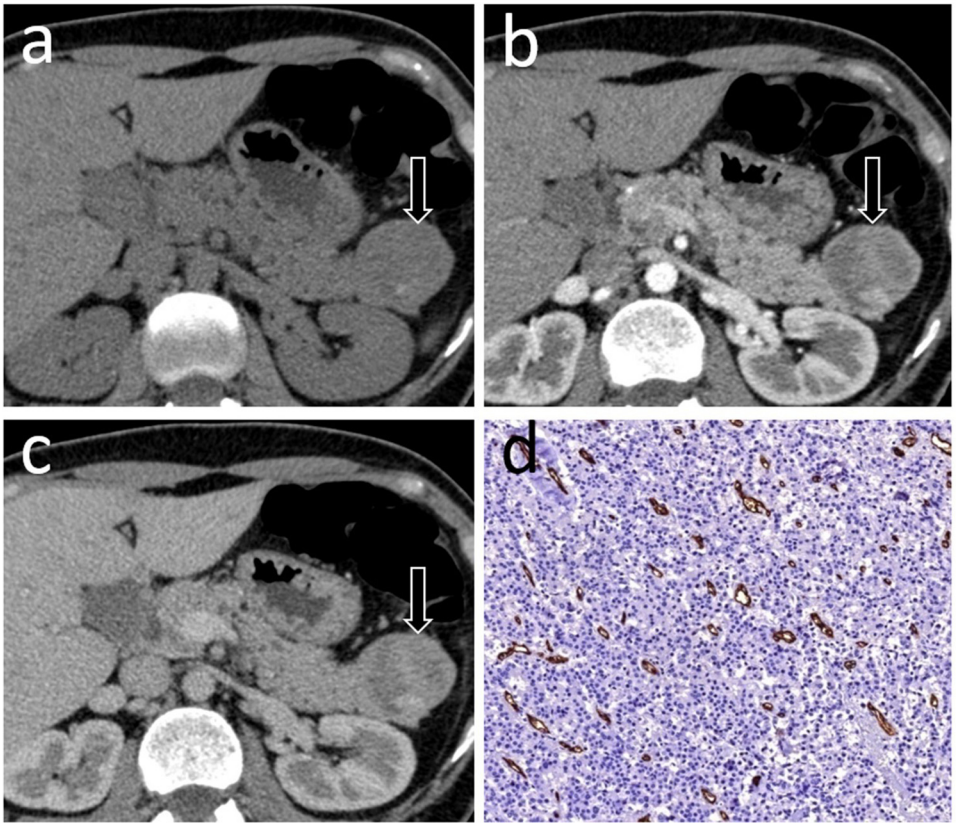

Fig. 2. MDCT post-contrast appearance of a pancreatic neuroendocrine tumor grade 2: on native (a), arterial (b) and portal-venous (c) phases a well-circumscribed mass is located in the pancreatic tail (arrow) and shows hypoattenuation in the arterial and portal-venous phases. (d) Immunostaining with CD34 antibody highlights vessels (red), showing that the intratumoral microvascular density is low (5.2%).

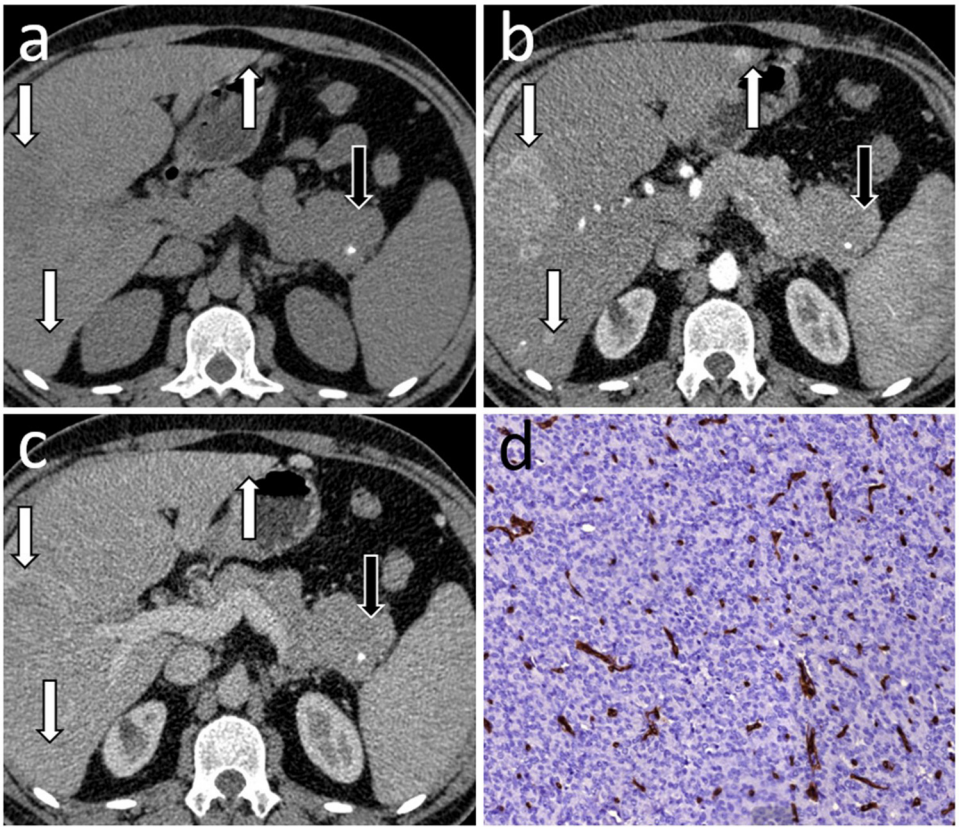

Fig. 3. MDCT post-contrast appearance of a pancreatic neuroendocrine tumor grade 3: on native (a), arterial (b) and portal-venous (c) phases an ill-defined mass is located in the pancreatic tail (black arrow) and shows hypoattenuation in the arterial and portal-venous phases. Note the metastatic lesions (white arrows) in the liver with peripheral rim enhancement. (d) Immunostaining with CD34 antibody highlights vessels (red), showing that the intratumoral microvascular density is low (2%).

Table 4
MDCT imaging findings of hypervascular PNETs, nonhypervascular PNETs and PDACs.

	Hypervascular PNETs (n = 43)		Nonhypervascular PNETs (n = 31)		PDAC (n = 80)		p**	p***
	n	%	n	%	n	%		
Size (mm)[a]	20,5 ± 15.7		24.8 ± 11.2		26,1 ± 8.8		0,2385	0,7947
Margin								
well-defined	38	88%	18	58%	20	25%	0.0027	0.001
ill defined	5	12%	13	42%	60	75%		
Calcification								
yes	3	7%	4	13%	0	0%	0.3901	0.0011
no	40	93%	27	87%	80	100%		
pancreatic duct dilatation (> 3 mm)								
no	40	93%	25	81%	3	3%	0.108	< 0.0001
yes	3	7%	6	19%	77	97%		
Cystic portion								
yes	9	21%	8	26%	2	5%	0.6227	0.0001
no	34	79%	23	74%	78	95%		
Homogeneity								
homogenous	30	70%	18	58%	54	68%	0.2981	0.3502
heterogenous	13	30%	13	42%	26	32%		
Intratumoral blood vessels								
yes	3	7%	5	16%	0	0%	0.2981	0.002
no	40	93%	26	84%	80	100%		
Peripancreatic infiltration								
no	40	93%	22	71%	15	19%	0.0111	< 0.0001
yes	3	7%	9	29%	65	81%		
Vascular invasion								
no	40	93%	23	74%	38	47%	0.0247	0.0112
yes	3	7%	8	26%	42	53%		
Relative enhancement intensity in arterial phase[a]	1,61 ± 0.36		0,87 ± 0.19		0,7 ± 0.23		< 0.0001	0.0651
Relative enhancement intensity in venous phase[a]	1,26 ± 0.30		1.02 ± 0.14		0.78 ± 0.20		0.002	0.012
Relative enhancement intensity in venous phase > 0.9	41	95%	23	74%	19	23%	0.008	< 0.0001
Relative enhancement intensity in venous phase < 0.9	2	5%	8	26%	61	77%		

PNET – pancreatic neuroendocrine tumor.
PDAC – pancreatic ductal adenocarcinoma.
p** – hypervascular PNETs vs. nonhypervascular PNETs.
p*** – nonhypervascular PNETs vs. PDACs.
[a] mean ± standard deviation.

Some of the previous studies showed that contrast PNET vascularity, assessed by contrast-enhanced MDCT, helps to predict PNET grade, however the results for grade 2 tumors remain controversial. Kim et al. showed that lower grade PNETs had common findings of PNETs, including a well-circumscribed margin, homogeneous enhancement, and hypervascularity in the arterial and venous phases [9]. On the contrary, higher grade tumors commonly had uncommon findings, including an ill-defined margin, heterogeneous enhancement, and hypovascularity in the arterial and venous phases, as well as the presence of duct dilation. D'Assignies et al. described that low blood flow in PNET

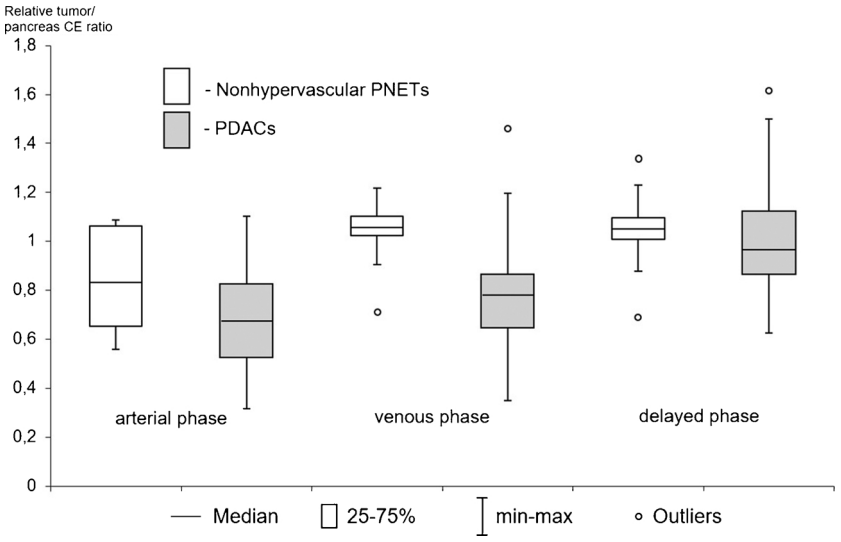

Fig. 4. Relative tumor-to-pancreas enhancement intensity in the arterial, venous and delayed phases. The enhancement ratios show a statistically significant difference between pancreatic neuroendocrine tumor (PNET) and pancreatic ductal adenocarcinoma (PDAC) in the venous phase (p = 0.012).

Table 5
Contrast enhancement patterns in nonhypervascular PNETs and PDACs.

Enhancement pattern	Nonhypervascular PNETs (n = 31)	PDAC (n = 80)	p-value
Portal venous hyperenhancement (Type I)	10/31 (35%)	7/80 (9%)	0.00001
Persistent isoenhancement (Type II)	12/31 (40%)	10/80 (13%)	
Persistent hypoenhancement (Type III)	6/31 (20%)	45/80 (56%)	
Gradual delayed enhancement (Type IV)	2/31 (5%)	18/80 (22%)	
Type I + II	23/31 (68%)	17/80 (21%)	< 0.00001
Type III + IV	8/31 (26%)	63/80 (79%)	

PNET – pancreatic neuroendocrine tumor.
PDAC – pancreatic ductal adenocarcinoma.

perfusion MDCT is associated with low microvessel density (the technique used to quantify angiogenesis in histologic studies by counting vessels on tissue specimens) and high Ki-67 proliferation index [16]. With PNET's progression towards malignancy, tumor vascularization is modified, resulting in lower MVD and lower degree of contrast enhancement [17,18]. Our study also showed that PNET arterial enhancement type (hypo- or hypervascular) significantly correlates with pathological findings and grading. Among 43 hypervascular PNETs, 32 (74%) were grade 1 and 11 (26%) were grade 2. In contrast to that, among 31 nonhypervascular tumors, only 7 (22%) were grade 1 and the majority of tumors were grade 2 (n = 21, 68%).

In our study, nonhypervascular PNETs were associated with the higher prevalence of peripancreatic infiltration and vascular invasion, when compared to hypervascular PNETs ($p < 0.0001$ and $p = 0.0112$ respectively). The higher incidence of lymph node metastasis and higher Ki-67 index were significantly more often present in nonhypervascular tumors according to the pathological study ($p <= 0.013$ and $p < 0.01$). Thus, in comparison to hypervascular PNETs, nonhypervascular PNETs are more likely to be associated with the worse overall survival. Indeed, in the study by Worshunsky et al. hypoenhancing PNET (22% of all PNET), had higher rates of lymph node and synchronous liver metastases and were also associated with significantly worse overall survival after a resection in comparison to isoenhancing and hyperenhancing tumors (5-year survival, 54% versus 89% versus 93%) [19]

Nonhypervascular PNETs may be difficult to differentiate from other solid pancreatic tumors, especially PDAC. Ductal adenocarcinoma is the most common malignant pancreatic neoplasm, accounting for over 90% of all solid pancreatic tumors. In up to 70% of cases the tumor involves the pancreatic head with atrophy of the distal pancreas [20,21].

The isolated upstream main pancreatic duct dilatation or main pancreatic duct dilatation with concomitant biliary dilation (“double” duct sign) are the typical signs of pancreatic adenocarcinoma. PNETs have a more favorable prognosis and higher resectability rate with less need for extensive radical excision in comparison with PDAC. The recent study by Clancy showed that aggressive types of surgery with extensive lymph node dissection didn't improve the overall survival of the patients with PNETs [22]. On the other hand, more aggressive surgical approaches, such as pancreaticoduodenectomy or distant pancreatectomy with extensive lymph node dissection are preferred in the case of PDAC. Combined interpretation of morphological and imaging findings of PNETs could reduce the rate of misdiagnoses of nonhypervascular PNETs as PDAC, which would contribute to better surgery planning and choice of treatment options [10].

In our study, the absence of pancreatic duct dilatation was one of the independent predictors for nonhypervascular PNET (Exp (B) = 106.9, $p < 0.0001$). PNETs do not arise from the pancreatic ductal epithelium, and therefore rarely cause ductal obstruction, except for the large tumors that cause obstruction secondary to the mass effect. However, even small and benign pNETs can cause pancreatic duct obstruction. Serotonin, produced by some PNETs, induces fibrotic stricturing and therefore causes upstream pancreatic duct dilatation and parenchymal atrophy [23]. Thus, additional imaging markers are needed to differentiate PDAC from nonhypervascular PNETs. According to our results, nonhypervascular pNETs more commonly had smooth and regular margins (58% vs. 25%, $p < 0.01$) and more often had areas of cystic degeneration (26% vs. 5%, $p < 0.01$). In comparison to PDAC, nonhypervascular PNETs were the only tumors to have intratumoral calcifications (4/31, 13%) and intratumoral blood vessels (5/31, 16%) ($p < 0.01$), which made these signs the most specific for diagnosing the nonhypervascular PNETs (100% specificity). Our results are similar with the results of previous studies. Kim et al., in a study on 31 PNETs with uncommon findings and 29 PDACs showed that pancreatic duct dilatation was an independent predictor for adenocarcinoma, and that cystic changes were also more commonly seen in PNETs ($p = 0.058$) [9]. However, their study did not show the significant correlation between the two groups with respect to the presence of calcifications and tumor delineation, and on the contrary, showed that PDAC more often had homogeneous enhancement ($p = 0.019$). Probably the reason for discrepancy between our results are different inclusion criteria: Kim’s study included PNETs with all uncommon findings (tumor hypovascularity, ill-defined margin, heterogeneous enhancement, pancreatic duct dilatation, etc.), while we included only hypovascular PNETs.

Hyodo et al. suggested that the presence of intratumoral blood

Table 6
Sensitivity and specificity of significant MDCT-findings in differentiation of nonhypervascular PNETs from PDACs.

MDCT-finding	Sensitivity	Specificity	PPV	NPV	Accuracy
Well-defined tumor margin	58,06%	74,58%	46,95%	82,11%	69,96%
Presence of calcifications	12,90%	100,00%	100,00%	74,77%	75,68%
Absence of pancreatic duct dilatation	80,65%	96,61%	90,21%	92,80%	92,15%
Absence of vascular invasion	74,19%	52,54%	37,73%	84,01%	58,59%
Absence of peripancreatic infiltration	71,88%	81,36%	60,66%	87,85%	79,36%
Presence of cystic component	25,81%	94,92%	66,29%	76,75%	75,61%
Intratumoral blood vessels	16,13%	100,00%	100,00%	75,47%	76,58%
Relative enhancement intensity venous phase > 0.9	75,00%	76,36%	48,00%	91,30%	76,06%
Type I or II contrast enhancement pattern	74,19%	78,75%	57,50%	88,73%	77,48%

NPV – negative predictive value.
PPV – positive predictive value.

vessels in early arterial phase could facilitate the discrimination between nonhypervascular PNETs and PDAC [12]. Indeed, in our study, intratumoral vessels were visible in arterial phase in up to 16% of nonhypervascular tumors, while no PDAC showed such a finding, though the prevalence was lower than in Hyodo's study (13/50, 26%). The discrepancy between our results can be explained by the absence of early arterial phase in our CT-examination protocol.

Our study also showed that the most prevalent enhancement patterns of nonhypervascular PNETs and PDACs were significantly different: Nonhypervascular PNETs commonly showed portal hyperenhancement (Type I) and persistent isoenhancement (Type II), whereas PDACs more often showed persistent hypoenhancement (Type III) gradual delayed enhancement (Type IV) ($p < 0.0001$). The enhancement degree of PNETs in the portal venous phase was significantly higher than that of PDACs (mean 1.02 ± 0.14 vs. 0.78 ± 0.20, $p = 0.012$). Recently, Jeon et al. reported that nonhypervascular pancreatic NET could be differentiated from PDAC at dynamic contrast-enhanced MRI by the presence of hyper- or isoenhancement in the portal venous phase [10]. Their results are analogous with ours in that in our study portal hyperenhancement or persistent isoenhancement of the tumor were one of the significant predictors of PNET ($Exp(B) = 10.6$; $p < 0.0001$). This finding may reflect the high vascularity and low rate of fibrosis of PNETs when compared with those of PDACs [24].

Our study has several limitations. First, our study was retrospective and the observers were aware of the pancreatic tumor present (either PNET or PDAC). Second, we included only patients with surgically resected tumors, so our study the had potential selection bias. Third, we analyzed PNETs that were non-hyperenhancing only in arterial phase.

In conclusion, a well-defined margin, hyper- or isoenhancement in the portal venous phase, the absence of peripancreatic infiltration, the presence of intratumoral blood vessels, calcifications and cystic changes, relative enhancement intensity in venous phase > 0.9 and type I or II contrast enhancement pattern were shown to be useful MDCT imaging features to discriminate nonhypervascular PNET from PDAC.

Conflicts of interest

None.

References

[1] T.R. Halfdanarson, K.G. Rabe, J. Rubin, G.M. Petersen, Pancreatic neuroendocrine tumors (pNETs): incidence, prognosis and recent trend toward improved survival, Ann. Oncol. 19 (2008) 1727–1733.

[2] J.C. Yao, M. Hassan, A. Phan, et al., One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35, 825 cases in the United States, J. Clin. Oncol. 26 (2008) 3063–3072.

[3] A.M. Rosenberg, P. Friedmann, J. Del Rivero, S.K. Libutti, A.M. Laird, Resection versus expectant management of small incidentally discovered nonfunctional pancreatic neuroendocrine tumors, Surgery 159 (January (1)) (2016) 302–309.

[4] G. Klöppel, D.S. Klimstra, R.H. Hruban, Pancreatic neuroendocrine tumors: update on the new World Health Organization classification, AJSP: Rev. Rep. 22 (September–October (5)) (2017) 233–239.

[5] T.R. Halfdanarson, K.G. Rabe, J. Rubin, et al., Pancreatic neuroendocrine tumours (pNETs): incidence, prognosis and recent trend toward improved survival, Ann. Oncol. 19 (2008) 1727 (e33).

[6] E. Belousova, G. Karmazanovsky, A. Kriger, et al., Contrast-enhanced MDCT in patients with pancreatic neuroendocrine tumours: correlation with histological findings and diagnostic performance in differentiation between tumour grades, Clin. Radiol. 72 (February (2)) (2017) 150–158.

[7] S.P. Raman, R.H. Hruban, J.L. Cameron, C.L. Wolfgang, E.K. Fishman, Pancreatic imaging mimics: part 2, pancreatic neuroendocrine tumors and their mimics, AJR Am. J. Roentgenol. 199 (August (2)) (2012) 309–318.

[8] S.K. Jang, J.H. Kim, I. Joo, J.H. Jeon, K.S. Shin, J.K. Han, B.I. Choi, Differential diagnosis of pancreatic cancer from other solid tumours arising from the periampullary area on MDCT, Eur. Radiol. 25 (October (10)) (2015) 2880–2888.

[9] J.H. Kim, H.W. Eun, Y.J. Kim, J.M. Lee, J.K. Han, B.I. Choi, Pancreatic neuroendocrine tumour (PNET): staging accuracy of MDCT and its diagnostic performance for the differentiation of PNET with uncommon CT findings from pancreatic adenocarcinoma, Eur. Radiol. 26 (May (5)) (2016) 1338–1347.

[10] S.K. Jeon, J.M. Lee, I. Joo, Nonhypervascular pancreatic neuroendocrine tumors: differential diagnosis from pancreatic ductal adenocarcinomas at MR imaging-Retrospective cross-sectional study, Radiology 284 (July (1)) (2017) 77–87.

[11] F.T. Bosman, F. Carneiro, R.H. Hruban, N.D. Theise, et al., WHO Classification of Tumors of the Digestive System, Lyon, IARC, 2010.

[12] J.Y. Scoazec, A. Couvelard, Réseau TENpath, Classification of pancreatic neuroendocrine tumours: changes made in the WHO classification of tumours of endocrine organs and perspectives for the future, Ann. Pathol. 37 (December (6)) (2017) 444–456.

[13] Cynthia Ro, Wanxing Chai, Victoria E. Yu, Run Yu, Pancreatic neuroendocrine tumors: biology, diagnosis, and treatment, Chin. J. Cancer 32 (June (6)) (2013) 312–324.

[14] M. Rodallec, V. Vilgrain, A. Couvelard, P. Rufat, D. O'Toole, V. Barrau, et al., Endocrine pancreatic tumours and helical CT: contrast enhancement iscorrelated with microvascular density, histoprognostic factors and survival, Pancreatology 6 (2006) 77–85.

[15] R. Hyodo, K. Suzuki, H. Ogawa, T. Komada, S. Naganawa, Pancreatic neuroendocrine tumors containing areas of iso- or hypoattenuation in dynamic contrast-enhanced computed tomography: spectrum of imaging findings and pathological grading, Eur. J. Radiol. 84 (November (11)) (2015) 2103–2109.

[16] G. d'Assignies, A. Couvelard, S. Bahrami, et al., Pancreatic endocrine tumours: tumour blood flow assessed with perfusion CT reflects angiogenesis and correlates with prognostic factors, Radiology 250 (2) (2009) 407–416.

[17] A.M. Marion-Audibert, C. Barel, G. Gouysse, et al., Low microvessel density is an unfavorable histoprognostic factor in pancreatic endocrine tumours, Gastroenterology 003 (125) (2018) 1094–1104.

[18] Y. Takahashi, Y. Akishima-Fukasawa, N. Kobayashi, et al., Prognostic value of tumour architecture, tumour-associated vascular characteristics, and expression of angiogenic molecules in pancreatic endocrine tumours, Clin. Cancer Res. 13 (1) (2007) 187–196.

[19] D.J. Worhunsky, G.W. Krampitz, P.D. Poullos, et al., Pancreatic neuroendocrine tumours: hypoenhancement on arterial phase computed tomography predicts biological aggressiveness, HPB (Oxford) 16 (April (6)) (2014) 304–311.

[20] P.J. Mergo, T.K. Helmberger, P.C. Buetow, R.C. Helmberger, P.R. Ros, Pancreatic neoplasms: MR imaging and pathologic correlation, Radiographics 17 (March-April (2)) (1997) 281–301.

[21] G. Karmazanovsky, V. Fedorov, V. Kubyshkin, A. Kotchatkov, Pancreatic head cancer: accuracy of CT in determination of resectability, Abdom. Imaging 30 (July–August (4)) (2005) 488–500.

[22] T.E. Clancy, Surgical management of pancreatic neuroendocrine tumors, Hematol. Oncol. Clin. North Am. 30 (February (1)) (2016) 103–118.

[23] S. Kawamoto, C. Shi, R.H. Hruban, M.A. Choiti, R.D. Schulick, E.K. Fishman, S.S. Siegelman, Small serotonin-producing neuroendocrine tumor of the pancreas associated with pancreatic duct obstruction, AJR 197 (Septmber (3)) (2011) W482–W488.

[24] M. Erkan, S. Hausmann, C.W. Michalski, A.M. Schlitter, A.A. Fingerle, M. Dobritz, H. Friess, J. Kleeff, How fibrosis influences imaging and surgical decisions in pancreatic cancer, Front. Physiol. 2 (October (3)) (2012) 389.