

Original Article

Evaluation of the histologic grade of pancreatic neuroendocrine tumors using CT texture analysis and perfusion parameters

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Abstract: The aim of this study was to explore whether CT texture analysis and perfusion parameters can help differentiate between G1 and G2/3 pancreatic neuroendocrine tumors (PanNETs). In this retrospective study, preoperative unenhanced, contrast-enhanced, and volume perfusion computed tomography (CT) images for 37 patients (G1, n = 19; G2/3, n = 18) were compared with postoperative histological PanNET grades. CT texture analysis was carried out with TexRAD software on unenhanced and enhanced CT images representing the largest cross-sectional area of the tumor. Perfusion parameters were calculated on a post-processing workstation. Potential correlation of CT texture and perfusion parameters with histological grades was analyzed. Receiver operating characteristic (ROC) analysis was performed, along with the area under the ROC curve (AUC). Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using parameter cut-off values showing the highest AUC. Compared to G2/3 PanNETs, G1 PanNETs showed significantly lower skewness ($P = 0.031$) on unenhanced images. They also showed lower skewness ($P < 0.05$), higher mean gray-level intensities ($P = 0.047$), and mean of positive pixels ($P < 0.05$) on enhanced images. No perfusion parameters showed a significant ability to differentiate G1 from G2/3 PanNETs. Skewness < 0.23 at medium texture scale on enhanced images was able to differentiate G1 from G2/3 PanNETs with the highest AUC (0.724 ± 0.091) and with Se = 61.1%, Sp = 94.4%, PPV = 91.6%, NPV = 70.8%, and accuracy = 77.8%. CT texture analysis, but not volume perfusion CT, showed promise in differentiating G1 from G2/3 PanNETs. Skewness quantified at medium texture scale on enhanced images showed the best diagnostic performance in estimating histologic grade of PanNETs.

Keywords: Pancreatic neuroendocrine tumors, CT texture analysis, volume perfusion CT, histological grade

Introduction

Pancreatic neuroendocrine tumors (PanNETs) arise from the endocrine cells of the pancreas. Their incidence and prevalence have been steadily increasing over the past 30 years [1]. Although PanNETs account for only 1-3% of all pancreatic neoplasms, they are associated with 5-year survival rates of 42-71% [2-4]. Histologic grading is a crucial factor in guiding treatment of PanNETs and assessing patient prognosis [5]. Three grades are recognized by the WHO 2010 classification scheme: neuroendocrine tumor 1 (G1), neuroendocrine tumor 2 (G2), and neuroendocrine carcinoma (G3). These grades are differentiated based on mitotic counts, as determined through hema-

toxylin-eosin staining and the Ki-67 index. Higher tumor grades are associated with significantly worse survival than lower tumor grades [5]. G1 and G2, which exhibit different biological behaviors [6], are better differentiated and more malignant tumor types than G3. These differences indicate that pretreatment identification of PanNET histologic grades is important in determining the most appropriate treatment strategy [7].

Preoperative determination of PanNET histologic grades is difficult, thus the treatment strategy is usually decided based on imaging [8]. Computed tomography (CT), broadly available and convenient, has been widely used for this purpose. Conventional CT, however, pro-

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Table 1. General characteristics of patients and lesions

	All	Tumor grade	
		G1	G2/3
No. of patients	37	19	18
Gender			
Male	15	10	5
Female	22	9	13
Age (years) ^a	46±15	46±15	46±15
Location			
Head	11	6	5
Body	13	7	6
Tail	13	6	7
Size of lesions (mm) ^a	1.68±1.01	1.49±0.63	1.88±1.28
Arterial phase enhancement patterns			
Low	2	0	2
Iso	5	3	2
High	30	16	14
Duct dilation	3	2	1

^aData are mean ± SD.

vides data on relatively few parameters relevant to PanNET histological grade. As a result, CT on its own cannot reveal many biological features of PanNETs [9].

CT texture analysis, a novel imaging post-processing tool, can analyze the distribution of pixel intensities in CT images and identify relationships among those intensities. This may reveal subtle differences imperceptible to the naked eye, thereby compensating for the limitations of conventional CT [10-13]. CT texture analysis relies on objective computer-aided evaluation of gray-level patterns within lesions to assess tumor heterogeneity, quantitatively, in terms of numerous relevant parameters [14]. In locally advanced rectal cancer, CT texture features have been associated with better neoadjuvant chemoradiotherapy response and higher disease-free survival [15]. In pancreatic cancer, CT-derived texture features of dissimilarity and inverse normalized differences may be promising prognostic imaging biomarkers of overall survival in patients undergoing surgical resection with a curative intent [16].

Volume perfusion CT, a relatively new imaging technique, has been used in the field of oncologic imaging for a few years [17]. This type of CT involves repetitive scanning of a tissue volume after contrast injection. It can provide information about blood flow (BF), blood vol-

ume (BV), and capillary permeability (PM), which are functional parameters of tumor vascularity. Volume perfusion CT can evaluate tumor vascularization and monitor chemo- or radiotherapy, as well as the effects of novel functional drugs that affect the tumor microenvironment and tumor angiogenesis [18-22]. The technique can grade pancreatic adenocarcinomas in a preoperative and non-invasive manner [18]. It is unclear how well volume perfusion CT can support preoperative histologic grading of PanNETs and how its performance compares with that of CT texture analysis.

To address these questions, the present retrospective study aimed to assess the ability of CT texture analysis and perfusion features to discriminate G1 from G2/3 PanNETs.

Materials and methods

Patients

This retrospective study was approved by the Ethics Committee, which waived the requirement for informed consent. Medical records of patients with PanNETs treated from January 2016 to December 2016 were retrieved from the central electronic database. Inclusion criteria were a histological diagnosis of PanNETs confirmed by biopsy or surgical resection and availability of preoperative contrast-enhanced CT and volume perfusion CT results. Of the 105 patients initially enrolled in the study, 68 were excluded because no data were available on postoperative pathological characteristics (n = 36), they had received local or systemic treatment before surgery (n = 18), the diameter of their smallest tumor was < 5 mm, making it too small to contain a region of interest (n = 8), or artifacts in the CT images made the images unsuitable for post-processing (n = 6). In the end, 37 patients with a mean age of 46±15 years (range, 9-71 years) were included in the study. The histological grade of each tumor

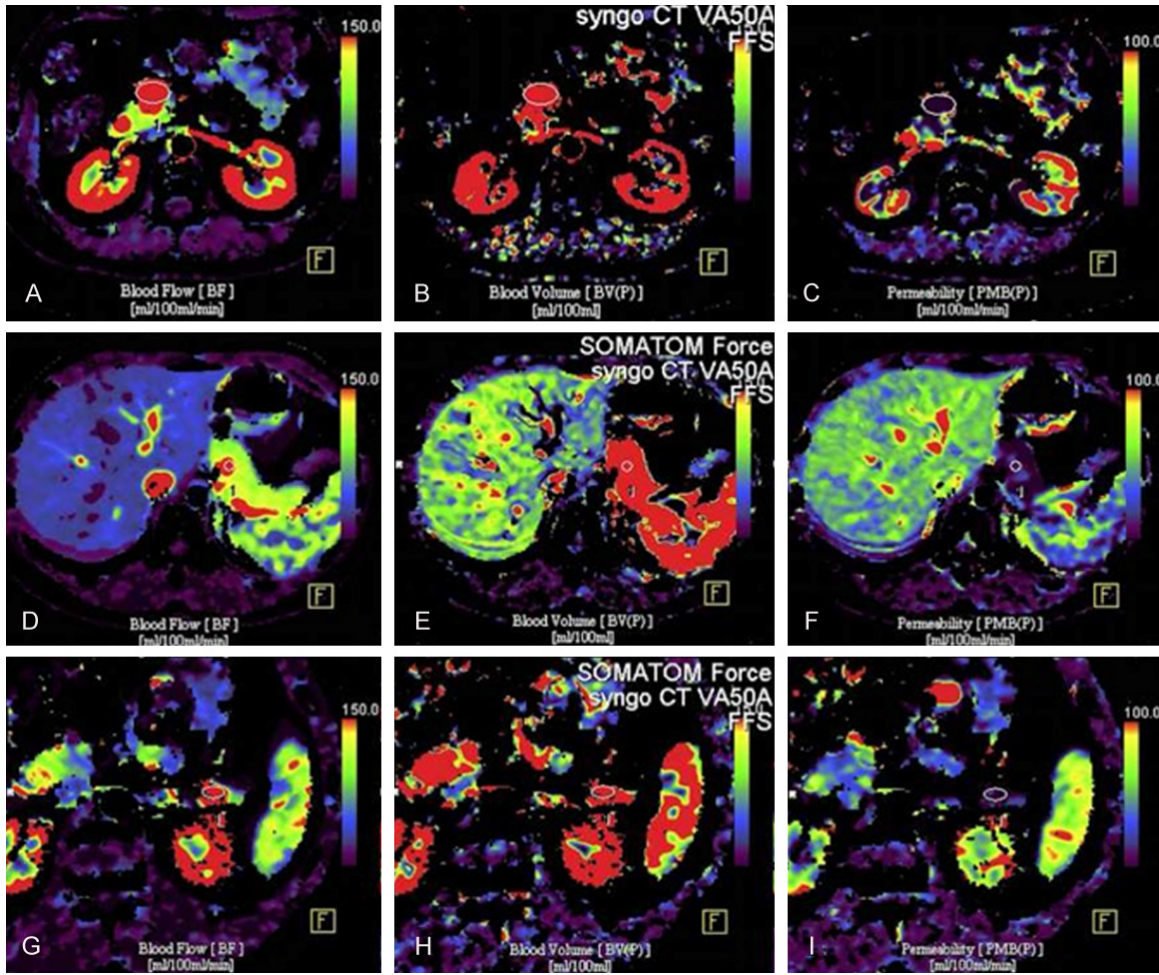


Figure 1. (color should be used) Examples of volume perfusion CT results and the corresponding perfusion images at different locations of the pancreas. (A-C) Perfusion images show an irregular lesion in the head of the pancreas of a 58-year-old woman, which was histologically diagnosed as G2 after surgery. (D-F) Perfusion lesions reveal a G2 PanNET in the body of the pancreas of a 22-year-old woman. (G-I) Images showed a 34-year-old man with G1 PanNET in the pancreatic tail. Regions of interest (ROIs) (white contours) were delineated slightly within the border of lesions. Corresponding color maps of functional parameters: BF (A, D, G), BV (B, E, H), and PM (C, F, I).

was extracted from pathology reports. Patient clinicopathological characteristics are presented in **Table 1**.

Volume perfusion CT

All patients signed informed consent for CT examinations. Scans were performed with patients in the supine position while freely breathing. To minimize artefacts, patients were asked to breathe quietly and shallowly throughout the examination. They were warned that they might feel a flushing sensation during contrast agent injection. In addition, a belt was placed over the abdomen. Scans covering the upper or entire abdomen were performed using a dual-source CT scanner (SOMATOM Definition Force, Sie-

mens Healthcare, Forchheim, Germany). First, a non-enhanced abdominal low-dose CT was performed to locate the pancreas. The tube current and voltage were set automatically, slice thickness was 5.0 mm, collimation was 192×0.6 mm, and pitch was 0.6. Next, volume perfusion CT of the tumor was performed using the DynMulti 4D scanning technique and the following perfusion parameters: tube voltage, 80 kV; tube current, 100 mA; time interval of data collection, 1.5 seconds (except for the last collection of 3 seconds); total scan time, 42 seconds; field of view, 176 mm. Dynamic data were collected 28 times. Contrast agent Ultravist 370 (45 mL; Bayer Vital, Leverkusen, Germany) was injected using a high-pressure

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Table 2. Influence of histologic grade on perfusion parameters ($n = 37$)

Grade	BF (ml/100 ml/min)	BV (ml/100 ml)	PM (ml/100 ml/min)
G1 ($n = 19$)	189.70±20.01	31.84±16.04	53.55±13.09
G2/3 ($n = 18$)	181.00±30.28	37.86±6.57	32.37±16.26
<i>P</i> value	0.478	0.602	0.076

Abbreviations: BF blood flow, BV blood volume, PM permeability, G1-3 tumor grading.

dual-head pump at a flow rate of 5 mL/s in an antecubital vein, followed by a saline flush of 40 mL NaCl at 5 mL/s and a fixed start delay of 6 seconds. All images were transferred to an external workstation (Multi-Modality Workplace, Siemens) for analysis.

Analysis of CT perfusion parameters

All data sets were transferred to a dedicated workstation (Syngo MMWP, VE 36A, Siemens Healthcare) and quantitative data evaluation was performed using commercial software (Syngo Volume Perfusion CT Body). Automated motion correction and noise reduction of all datasets were applied using an integrated motion correction algorithm with non-rigid deformable registration for anatomic alignment. A circular region of interest (ROI) was defined in the abdominal aorta, which provided the arterial input function for calculations. Volume of interest was defined in the pancreatic lesion to calculate tumor perfusion. This volume was drawn as large as possible and positioned to avoid vessels and artefacts in a slice-by-slice approach. Values for perfusion parameters (BF, BV, and PM) were obtained from parametric maps generated by the software package. Values of these parameters were compared for PanNETs of different histologic grades (**Figure 1**).

CT texture analysis

All unenhanced and enhanced axial images were evaluated using commercial image viewing software (Centricity, GE Medical Systems, Milwaukee, WI, USA) by one radiologist with 20 years of experience in abdominal imaging. This analyst was blinded to patient clinical and histological data. For each lesion in each phase, only the axial image with the largest cross-sectional tumor area was chosen for texture analysis and the maximal diameter of each lesion on

the chosen axial image was measured. All selected images were exported and loaded onto a workstation for texture analysis, which was performed using TexRAD software (www.texrad.com; Feedback, Cambridge, UK). A single trained operator carried out all analysis steps, as described below, and then repeated the process 6 weeks later. The two measurements of each texture parameter were averaged and recorded for later statistical analysis. A polygonal ROI was drawn manually along the tumor margin on the selected slice depicting the largest area of the lesion. To minimize the contribution of surrounding fat or normal tissue to the average volume, an approximate distance of 1-2 mm was left between the ROI outline and the lesion border. ROIs were drawn carefully to avoid artefacts, calcification, cystic areas, and vascularization.

The software automatically read the CT value of each pixel within the ROIs and generated a set of parameters through a two-step process. First, image filtration extracted image features of different sizes at different spatial scaling factors (SSFs) within the ROI. These SSFs ranged between object radii of 0, 2, 3, 4, 5, and 6 mm. SSF 0 indicated no filtration; SSF 2, fine texture scale; SSF 3-5, medium texture scale; and SSF 6, coarse texture scale. Second, the following texture parameters were generated at different SSFs: (1) Mean gray-level intensity (mean, brightness); (2) Standard deviation (SD), reflecting the spread of the distribution; (3) Entropy, referring to the distribution of grey levels over the ROI; (4) Mean of positive pixels (MPP); (5) Skewness, referring to the symmetry of the histogram distribution; and (6) Kurtosis, reflecting the sharpness or pointedness of the histogram distribution.

Statistical analysis

Patient characteristics were recorded. On the lesion level, a non-parametric Mann-Whitney U-test was used to compare the ability of the average value of each texture parameter or perfusion parameter to distinguish G1 and G2/3 PanNETs. The diagnostic performance of CT texture or perfusion parameters in differentiating these histological grades was evaluated by receiver operating characteristic (ROC) analysis, along with areas under the ROC

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Table 3. Texture analysis parameters for discriminating G1 from G2/3 on unenhanced and enhanced CT images

Parameter	Unenhanced images				Enhanced images			
	No filtration	Fine texture	Medium texture	Coarse texture	No filtration	Fine texture	Medium texture	Coarse texture
Mean	NS	NS	NS	NS	NS	NS	0.047	NS
SD	NS	NS	NS	NS	NS	NS	NS	NS
Entropy	NS	NS	NS	NS	NS	NS	NS	NS
MPP	NS	NS	NS	NS	NS	NS	0.047	NS
Skewness	NS	NS	0.031	NS	NS	NS	0.02	NS
Kurtosis	NS	NS	NS	NS	NS	NS	NS	NS

Data are *P* values of texture parameters showing significant differences between G1 and G2/3. Abbreviations: NS, no significant. *P* > 0.05.

curves (AUCs). Cut-off values of each parameter associated with the greatest AUC were determined by maximizing the Youden index. Data were dichotomized and diagnostic performance was assessed in terms of sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and accuracy. All analyses were performed using SPSS for Mac (version 20; SPSS, Chicago, IL, USA). Two-tailed *P*-values < 0.05 indicate statistical significance.

Results

Data were analyzed from 37 patients (15 men), with a mean age of 46±15 years (range, 9-71 years), with untreated Pan-NETs. Eleven of the 37 tumors were in the pancreatic head, 13 in the corpus, and 13 in the tail. Biopsy-proven pathologic tumor grades were available for all 37 patients: G1, 19 patients; G2, 17 patients; G3, 1 patient. Mean tumor size, measured in the largest diameter, was 1.68±1.01 cm (range, 0.80-5.22) (Table 1).

BF (mL/100 mL/min) showed no significant differences between G1 and G2/3 PanNETs. Mean values were 189.70±20.01 (range, 57.59-376.55) in G1 and 181.00±30.28 (range, 79.61-483.56) in G2/3 (*P* = 0.478). Similarly, BV (mL/100 mL) was similar between the two groups: 31.84±16.04 (range, 2.44-61.70) in G1 and 37.86±6.57 (range, 8.35-100.00) in G2/3 (*P* = 0.602). PM (mL/100 mL/min) was also similar between the groups: 53.55±13.09 (range, 4.16-244.89) in G1 and 32.37±16.26 (range: 2.97-150.66) in G2/3 (*P* = 0.076) (Table 2).

Table 3 summarizes the statistical results using CT texture analysis to differentiate G1 from G2/3 PanNETs. On unenhanced images, skewness quantified at SSF 3 differed significantly between G1 and G2/3. On enhanced images, skewness at SSF 4-5, the mean at SSF 5, and MPP at SSF 4-5 differed significantly between G1 and G2/3. Compared to G2/3 PanNETs, G1 PanNETs showed significantly lower skewness (*P* = 0.031) on unenhanced images as well as lower skewness (*P* < 0.05), higher mean (*P* = 0.047), and higher MPP (*P* < 0.05) on enhanced images (Figure 2). SD, Entropy, or Kurtosis did not differ significantly between G1 and G2/3 PanNETs at any texture scale on unenhanced or enhanced images.

Table 4 describes ROC curves of texture parameters differing significantly between G1 and G2/3 PanNETs. The highest AUC of 0.724±0.091 (95% CI 0.545-0.903) was obtained with skewness at SSF 4 on enhanced images. Based on a cut-off value of 0.23 for skewness (Youden index_{max} = 0.555), its diagnostic performance in differentiating G1 from G2/3 PanNETs was as follows: Se = 61.1%, Sp = 94.4%, PPV = 91.6%, NPV = 70.8%, and accuracy = 77.8%.

Discussion

In this cohort of 37 patients, none of the CT perfusion parameters tested were able to discriminate G1 from G2/3 PanNETs, effectively. In contrast, the texture parameters mean and MPP proved to be significantly higher for G1 PanNETs on enhanced images, while skewness was significantly lower for G1 PanNETs on unenhanced and enhanced images. Of these texture

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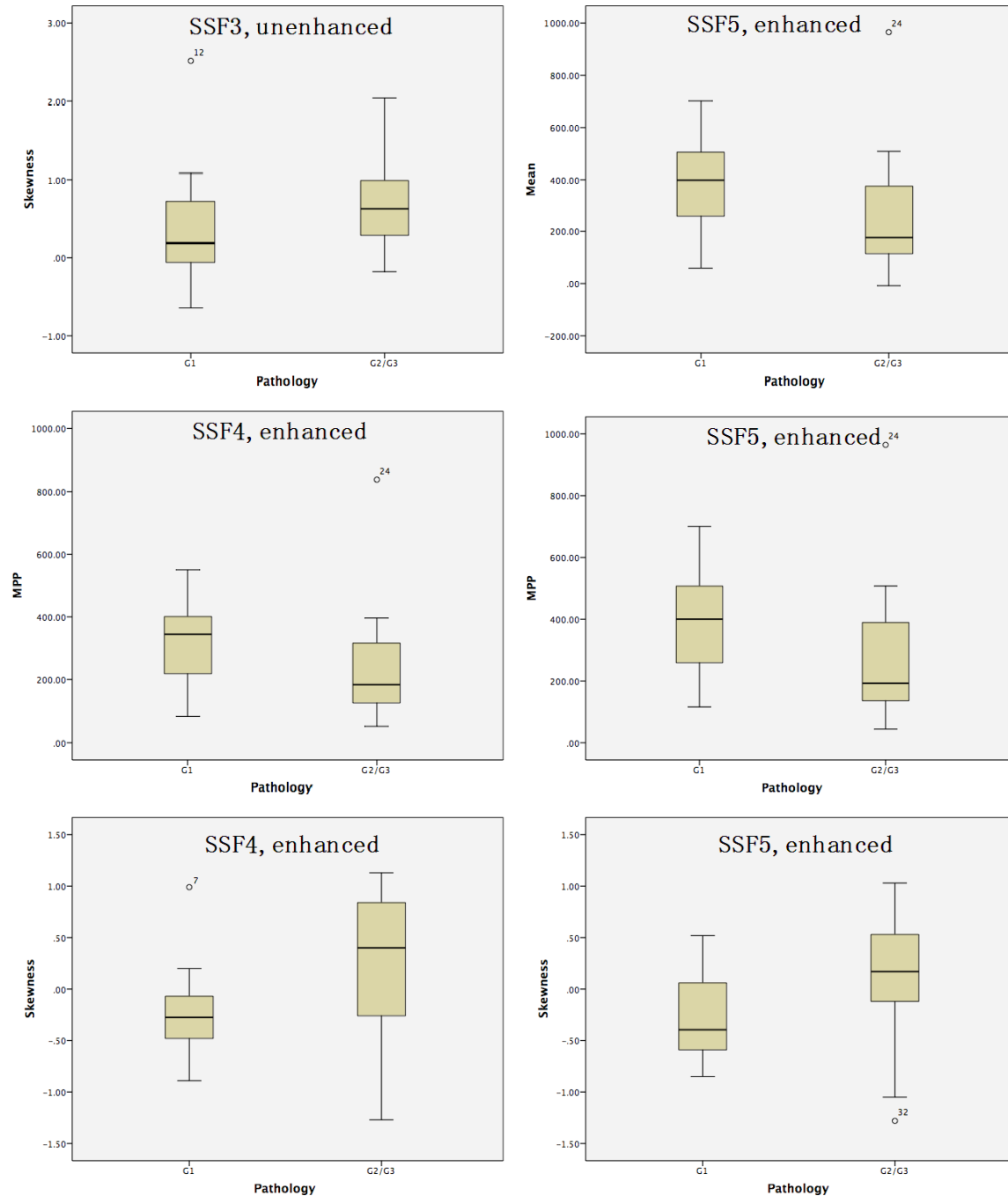


Figure 2. (color should be used) Boxplots demonstrating the differences between G1 and G2/3 based on CT textural analysis.

parameters, skewness at SSF 4 on enhanced images showed the best diagnostic performance for differentiating G1 from G2/3 PanNETs (AUC = 0.724 ± 0.091 , 95% CI 0.545-0.903). Present results suggest that CT texture analysis, in contrast to volume perfusion CT, can distinguish G1 from G2 PanNETs on both unenhanced and enhanced images.

Tumor grading is important in predicting prognosis for cancer. Several studies have investigated the use of CT perfusion parameters in assessing tumor grade non-invasively, such as in pancreatic adenocarcinoma [18]. In colorectal adenocarcinoma, BF and time to peak (TTP) differ between low- and high-grade tumors [23]. These findings may indicate that tumor grade is

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Table 4. ROC curves of texture parameters

Image type	Parameter	Spatial scaling factor	AUC ^a	95% CI	P
Unenhanced	Skewness	3	0.710±0.088	(0.538, 0.882)	0.031
Enhanced	Mean	5	0.694±0.090	(0.518, 0.871)	0.046
		4	0.694±0.090	(0.519, 0.870)	0.046
	MPP	5	0.694±0.090	(0.518, 0.871)	0.046
		4	0.724±0.091	(0.545, 0.903)	0.022
	Skewness	4	0.724±0.091	(0.545, 0.903)	0.022
		5	0.722±0.092	(0.543, 0.902)	0.023

^aData are mean ± SD.

associated with vessel maturation and functionalization in the tumor, such that the amount of blood passing through the tissue vessel per unit time changes as the disease progresses. Mean BF and mean BV have been found to be significantly higher in high-grade prostate cancer than in low- or medium-grade disease [24]. While these studies provide strong evidence that CT perfusion parameters can be useful indices of clinicopathological features of malignant tumors, the present study failed to identify perfusion parameters that could reliably differentiate between G1 and G2/3 PanNETs.

While this negative result is inconsistent with previous studies, it is consistent with a prospective study of 48 consecutive patients with pancreatic adenocarcinoma. In this study, volume perfusion CT imaging was not associated with histologic grade [25]. This discrepancy may reflect, in part, the fact that histologic grading is usually conducted on small biopsies or surgical samples that may be representative of the overall state of PanNETs, which are heterogeneous. In addition, perfusion values in PanNETs of all grades are generally quite high, thus CT may not be sensitive enough to detect slight differences between grades.

Recently, CT texture analysis has been demonstrated to be a useful tool for quantitatively assessing the heterogeneity of cell distribution and vascularization in tumors, reflecting their intrinsic biological aggressiveness. Assessment of intratumoral heterogeneity is critical, as tumors with low intratumoral heterogeneity have been associated with better prognosis or lower histopathologic grades than those with higher heterogeneity [26-28]. Miles et al. [29] examined the meaning of each texture parameter and how these parameters correlate with image heterogeneity. In the present study, G1

PanNETs had significantly higher mean and MPP on enhanced images and lower skewness on both unenhanced and enhanced images. No significant differences in SD, Entropy, or Kurtosis between G1 and G2/3 PanNETs were found at any texture scale on unenhanced or enhanced

images. This suggests that tumors that are more homogeneous (higher mean, higher MPP, and lower skewness) are potentially less aggressive in their biology (lower tumor grade), which is in line with conclusions of previous studies. It is also consistent with the fact that G1 PanNETs are less progressive and are associated with better prognosis than G2/3 PanNETs [30]. MPP reflects the average brightness of positive values of the image highlighted by filtration, while blood vessels appear as bright objects on CT images after contrast enhancement. In the present study, higher MPP correlated with lower tumor grade, which could be explained by irregularity in the distribution of tumor blood vessels. Ganeshan et al. [14] proved that MPP showed significant inverse association with tumor angiogenesis. In other words, increased brightness of highlighted objects (MPP) on filtered images was associated with reduced intensity of angiogenesis. In 2D and 3D arterial analysis, G2/3 tumors showed significantly higher skewness than G1 tumors [31], consistent with present results. Present findings are consistent with the idea that G1 PanNETs have lower skewness than G2/3 PanNETs because higher mean attenuation of the enhancing tumor portion, as well as the low attenuation voxels caused by cystic degeneration, can appear as a longer or fatter tail on the left side of the histogram, resulting in more negative skewness [31]. In fact, present results show that, even on unenhanced CT images, skewness was able to discriminate G1 from G2/3 PanNETs effectively. Skewness at SSF 4 on enhanced images showed higher AUC than other significant parameters, with a relatively high accuracy of 77.8%.

There were several limitations to the present study, however. First, this was a retrospective study, thus selection bias might be inevitable, lead-

ing to overestimation of the diagnostic performance of CT textural analysis. Second, this study involved a small sample. For example, only one patient had a G3 PanNET. Present results should be verified and extended in larger prospective studies. Third, the ROI was drawn only on the tumor slice that showed the largest lesion area, which might not reflect the overall characteristics of the entire tumor. Future work should develop 3D texture analysis software to depict tumor features more comprehensively. Fourth, although this study analyzed unenhanced CT images in case some useful information could be extracted, soft tissue on such images was poorly resolved. Margins between lesions and normal tissue were difficult to define accurately.

Conclusion

CT textural analysis, but not volume perfusion CT, shows promise in differentiating G1 from G2/3 PanNETs. Mean and MPP on enhanced images, as well as skewness on unenhanced and enhanced images, were found to be texture features useful in estimating histological grading of PanNETs. Skewness quantified at SSF 4 on enhanced images showed the best diagnostic performance for predicting histologic grade of PanNETs preoperatively and non-invasively.

Disclosure of conflict of interest

None.

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