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Original Article

Texture analysis from CT in discrimination of pancreatic ductal adenocarcinoma and hypovascular pancreatic neuroendocrine neoplasm in the portal-venous phase

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Abstract

Aim: To evaluate the discrimination ability of computed tomography (CT) texture analysis between pancreatic ductal adenocarcinoma (PDAC) and hypovascular pancreatic neuroendocrine neoplasm (PNEN).

Materials and Methods: Preoperative CT examinations of 49 patients with pathologically proven PDAC (35) and hypovascular PNEN (14) were evaluated retrospectively. Images in the portal vein phase of each tumor were assessed by two radiologists. Differences in texture features between PDACs and PNENs were analyzed with Mann Whitney-U test and logistic regression analysis.

Results: Patients with PNEN (50.4 ± 11.7 y) were significantly younger than the patients with PDAC (62.0 ± 11.1y) (p = 0.002). Nine CT texture features were found statistically significant between groups. NGLDM and GLZLM texture features showed the best diagnostic performance on multivariate analysis. Between these parameters, NGLDM_ Busyness showed the best diagnostic performance with the AUC value of 0.865. Combination of NGLDM_ Busyness and GLZLM_LZLGE improved the diagnostic performance at a significant level (AUC = 0.906, 95% CI = 0.747-0.988, p < 0.05).

Conclusion: CT texture features of single portal venous phase images may help to discriminate hypovascular PNEN from PDAC.

Keywords: Computed tomography; pancreatic ductal adenocarcinoma; pancreatic neuroendocrine neoplasm;texture analysis

INTRODUCTION

Pancreatic neuroendocrine neoplasms (PNEN) account for less than 3% of pancreatic neoplasms (1) and has been known characteristic hyperenhancement pattern on the arterial phase of computed tomography (CT) or magnetic resonance imaging (MRI), that helps to differentiate them from other pancreatic lesions easily. On the other hand, some researchers revealed that a significant portion of PNENs (mostly grade 2 and 3 PNENs) exhibit hypoenhancement similar to pancreatic ductal adenocarcinomas (PDACs) (2-4). Treatment regimens and prognosis of these two types of tumors are so different, thus accurate differentiation at the initial step is essential. Surgery is often the first treatment option for PNENs. Although pancreatic neuroendocrine carcinomas are the most aggressive form of neuroendocrine tumors, the survival rate is better than PDAC (3).

Compared to PNEN, PDAC is a very aggressive tumor with poor prognosis (4). The chance of surgical cure is low due to adjacent tissue invasion. Adjuvant chemotherapy and/or radiation can be used as major treatments for locally invasive, unresectable PDACs (4). Preoperative noninvasive differentiation of PNENs from PDAC is very important in determining the treatment strategy.

In the literature, there are studies on conventional CT and MRI findings in distinguishing hypovascular PNEN from PDAC (5,6). However, in addition to overlapping imaging features, imaging findings are often based on qualitative data and are influenced by operators. Texture analysis (TA) is a new "radiomics" imaging evaluation method based on quantitative imaging features of tumor heterogeneity. It has shown effective results in tumor characterization of different organs (7,8). In addition, texture analysis methods are easy to perform and do not require highly specialized computer knowledge. To the best of our knowledge, there have been quite a limited number of preliminary CT TA studies in the discrimination of hypovascular PNEN from PDAC, and only a small number of textural features have been evaluated (9-11). In this study, we aimed to evaluate

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the diagnostic performance of TA values from portal phase CT images in distinguishing hypovascular PNENs from PDAC.

MATERIALS and METHODS

Patient Selection

This study was approved by the institutional review board, and written informed consent was waived due to the retrospective nature of the study. Between December 2012 and November 2019, pre-treatment CT images of 83 patients with pathologically proven PDAC and PNEN were identified from the institutional database. Among these patients, 22 patients with PNEN were excluded due to hypervascular pattern on arterial phase images. 9 patients with lesions smaller than 1 cm were excluded to avoid partial volume effect of surrounding tissue. 3 patients were excluded due to poor image quality. Consequently, 49 patients with 35 PDAC (16 female, 19 male) and 14 PNEN (9 female, 5 male) were included into this study. No one of the patients had prior treatment history of pancreatic lesions.

CT Imaging

Due to the study design, all patients in this study underwent pretreatment contrast-enhanced CT. Depend on patient history and complaints, some of the protocols contain dynamic scan or unenhanced images, but only portal vein phase images were evaluated. CT examinations were performed using 64-row multislice CT (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) after IV administration of non-ionic iodinated contrast material (Optiray 350/100 ml, Guerbet, Liebel-Flarsheim, Canada) at a rate of 3.0 mL/s with an automatic injector. Portal venous phase images were obtained at 60-70 seconds after the administration of contrast agent. Imaging parameters were as follows: automatic tube current = 200-440 mAs; tube voltage = 120 kV; rotation time = 0.8 s; slice thickness = 5 mm; reconstruction interval = 0.625 mm.

CT Texture Analysis

Two independent radiologists, unaware of the histopathological results, evaluated and measured the images individually. At the initial step, DICOM format images were downloaded to LIFEx freelance program (version v5.10, www.lifexsoft.org) (12). The segmentation technique of the tumor for single-slice 2D was applied using the axial image showing the maximum tumor diameter (Figure 1). Then, as the pixel pitch affects some texture features, it was resized to 1x1mm for comparison between images. Gray level discretization was applied to minimize the effect of CT device differences on texture parameters (13). The number of gray levels was set at 16. Minimum and maximum values for gray level normalization were determined and set as -50 and +200 Hounsfield units. A ROI was manually drawn along the margin of the lesion. Neighboring vascular structures, normal pancreatic tissue, necrotic and calcific areas were carefully excluded. A total of 40 parameters were automatically calculated, including gray-level histogram, gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRM), neighborhood gray-level different matrix (NGLDM), and gray-level zone-length matrix (GLZLM) features by the program. All measurements are noted.

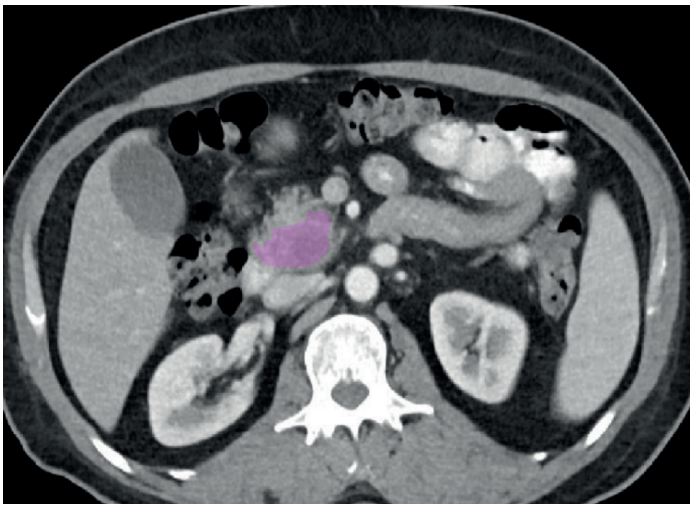

Figure 1. Two-dimensional segmentation of selected ROI excluding adjacent structures in Grade 2 ductal adenocarcinoma of head of pancreas

Statistical Analysis

The differences in TA parameters between PNENs and PDACs were evaluated using the Mann-Whitney U test. Due to a large number of texture features and the relatively small cohort size, unnecessary texture features must be removed. Therefore, the correlation between all texture features was evaluated. Correlation values higher than 0.9 were accepted as linear correlation and only one of the two textural properties was accepted to evaluate. The TA features which showed statistically significant differences between groups were then evaluated using logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed for diagnostic performances. Intraclass correlation coefficient (ICC) was used to assess inter-observer agreement. Statistical analyses were performed using SPSS, version 23 (IBM, Chicago,IL). P value less .05 was accepted as the significant level.

RESULTS

A total of 49 patients with 35 PDAC (16 female, 19 male) and 14 PNEN (9 female, 5 male) constituted the study population. In PDACs, 13 lesions were grade 1 (G1), 13 lesions were G2, and 9 lesions were G3. The PNENs were 6 lesions G1, 5 lesions G2, and 3 lesions G3 according to the WHO 2017 classification for neuroendocrine tumors. No significant differences were found for gender between PNENs and PDACs ($p > 0.05$). Patients with PNEN (mean age = 50.4 ± 11.7 y) were significantly younger than the patients with PDAC (mean age = 62.0 ± 11.1y) ($p = 0.002$). Mean tumor size did not show statistically significant difference between the same groups (3.76 cm for PNEN, 3.24 cm for PDAC; $p > 0.05$).

Table 1. Comparision of texture features between PDAC and hypovascular PNEN

	Texture Features	PDAC (mean ± SD)	PNET (mean ± SD)	P value*
Histogram	Skewness	**0.0730 ± 0.339**	**-0.1520 ± 0.387**	**0.138**
	Kurtosis	3.178 ± 0.550	3.165 ± 0.813	0.965
	Excess Kurtosis	0.178 ±0.550	0.165 ± 0.813	0.965
GLCM	Contrast	2.263 ±1.147	2.901 ± 1.297	0.036
	Correlation	0.358 ± 0.161	0.350 ± 0.179	0.774
GLRLM	SRE	0.796 ± 0.081	0.831 ± 0.034	0.330
	LRE	2.483 ± 0.853	1.988 ± 0.312	0.116
	LRHGE	173.041 ± 114.931	203.562 ±121.753	0.388
NGLDM	Coarseness	0.035 ±0.025	0.089 ±0.081	**0.001***
	Contrast	0.048 ±0.027	0.069 ±0.028	**0.007***
	Busyness	0.846 ±0.823	0.270 ±0.212	**<0.001***
GLZLM	SZE	0.508 ±0.114	0.520 ±0.156	0.319
	LGZE	0.021 ±0.010	0.033 ±0.067	0.080
	SZLGE	0.011 ± 0.005	0.009 ± 0.007	0.259
	SZHGE	37.205 ± 14.888	54.732 ±22.676	**0.003***
	LZLGE	12.362 ±29.975	5.556 ±20.068	**0.001***
	LZHGE	40278.190 ± 121551.476	2205.619± 1767.883	**0.012***
	GLNU	11.168 ± 6.951	6.740 ± 4.161	**0.016***
	ZLNU	1065.445 ± 6187.478	14.153 ± 11.023	0.341
	ZP	10.954 ±63.344	0.366 ± 0.114	**0.017***

PDAC: Pancreatic Ductal Adenocarcinoma; PNET: Pancreatic Neuroendocrine Tumor; SD: Standard Deviation, GLCM: Gray-Level Co-Occurrence Matrix; GLRM: Gray-Level Run-Length Matrix; NGLDM: Neighborhood Gray-Level Different Matrix; GLZLM: Gray-Level Zone-Length Matrix
*Mann Whitney U test. Significant at 0.05 level. Bolds are statistically significant

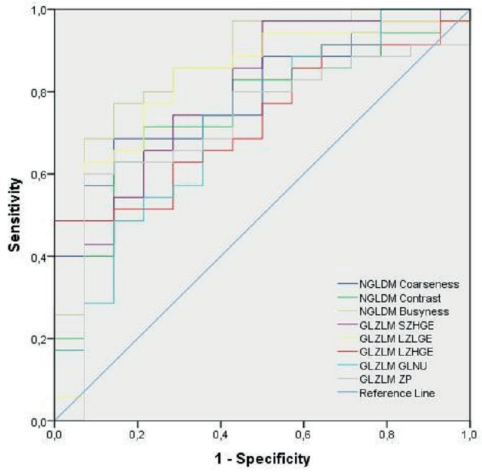

Figure 2. Receiver operating characteristic curve analysis for texture features in differentiation PDAC from hypovascular PNEN

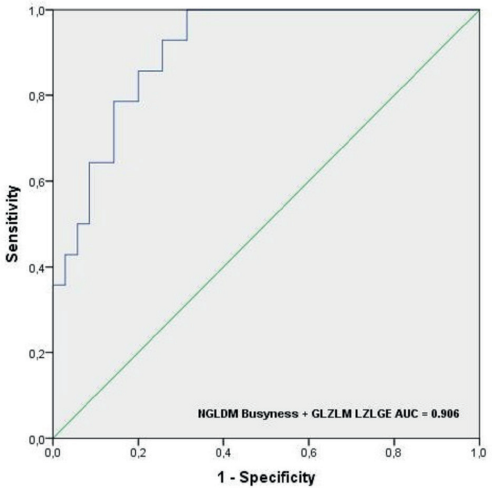

Figure 3. Receiver operating characteristic curve analysis for the combination of NGLDM Busyness and GLZLM LZLGE values, indicating higher diagnostic performance compared to each individual parameter

Texture Analysis

Forty texture features were assessed, and 20 texture features on univariate analysis were selected for logistic regression analysis. Among them, 9 texture features were independent predictor of differentiation hypovascular PNEN from PDAC. Compared to PNENs, PDACs had statistically significant higher NGLDM_busyness, GLZLM_LZLGE, GLZLM_LZHGE, GLZLM_GLNU, GLZLM_ZP values, and lower NGLDM_coarseness, NGLDM_contrast, and GLZLM_SZHGE values. The statistical data of CT TA between PNENs and PDACs was summarized in Table 1. ICC values of two measurements were in range of 0.923-0.992, which showed excellent agreement.

Diagnostic Performance

Figure 2 shows ROC analyses of texture properties. Between these parameters which showed statistically significant differences, NGLDM_ Busyness showed the best diagnostic performance with the AUC value of 0.865. GLZLM_LZLGE was the second one with the AUC of 0.814. Combination of NGLDM_ Busyness and GLZLM_LZLGE improved the diagnostic performance at a significant level (AUC = 0.906, 95% confidence interval = 0.747-0.988, $p < 0.001$) (Figure 3). Table 2 summaries the diagnostic performance of NGLDM and GLZLM texture features.

Table 2. Diagnostic performance of texture features with ROC curve analyses in differentiating PDAC from hypovascular PNEN

	Texture Features	AUC	Confidence Interval	P value
NGLDM	Coarseness	0.794	0.661-0.921	0.001
	Contrast	0.749	0.603-0.895	0.007
	Busyness	0.865	0.748-0.983	<0.001
GLZLM	SZHGE	0.771	0.611-0.932	0.003
	LZLGE	0.814	0.670-0.959	0.001
	LZHGE	0.731	0.590-0.872	0.012
	GLNU	0.722	0.563-0.882	0.016
	ZP	0.720	0.562-0.879	0.017

AUC: Area Under the Curve, NGLDM: Neighborhood Gray-Level Different Matrix; GLZLM: Gray-Level Zone-Length Matrix; ROC: Receiver Operating Characteristic Curve Analysis

DISCUSSION

It can be difficult to distinguish hypovascular PNENs from PDACs with routine CT or MR images, albeit dynamic imaging. However, these two types of tumors differ in biological behavior and prognostic features. Compared to PDACs, PNENs have a higher chance of total resectability, and a better prognosis (5,14). Therefore, differentiation between these two entities is so crucial for optimal treatment strategy.

Texture analysis is an evolving, non-invasive computational tool that measures the spatial relationships of gray-scale pixels and voxels in selected areas. TA enables quantitative data about tumor heterogeneity by assessing the distribution and relation of pixel based gray levels in 2D or 3D images (15). Recent studies showed that TA has the potential to distinguish benign from malignant lesions and to evaluate therapy response for different tumor types of other organs and pancreas (7,8,16,17).

In this study, texture features showed the ability to distinguish hypovascular PNEN from PDAC. NGLDM and GLZLM texture features have come to the front with higher diagnostic performances, compared to other TA features, such as histogram, GLCM, and GLRLM texture features. Among them, NGLDM_Busyness had the best discrimination ability (AUC = 0.865). Consistent with all these findings, a few studies revealed statistically significant results of different TA features between similar groups, but with different TA techniques (9-11). This may be explained by differences in tumor histopathological characteristics (cell density, amount of fibrous stroma) of tumor types. Vascularity features such as perfusion characteristics, microvessel density, capillary leakiness, may have also effect on the differences between groups. In PDAC, there is abundant fibrous stroma in the tumor tissue due to the desmoplastic reaction, and vascular density of PDAC is lower compared to PNEN (5,18). Notably, the skewness in PDAC was found higher compared to PNEN; but, this value did not reach statistical significance. Relatedly, Li et al. (11) studied on a similar patient group, and showed higher skewness values in PDAC than those in PNEN, which is compatible with the increased desmoplastic reaction in PDAC. On the other hand, a few studies also evaluated texture features between grades of PNEN, and they showed that as the tumor grade of PNENs increased, the skewness values increased at a statistically significant level (3,19). Guo et al. (20) studied on pancreas neuroendocrine carcinomas and PDACs, and did not found significant difference in kurtosis between these groups. However, they (20) suggested that the skewness and kurtosis in PDACs may be associated with mucin content or increased fibrosis. Basically, the kurtosis from TA reflects the shape of the voxel distribution (15). We could not find a statistically significant difference in kurtosis values between PNENs and PDACs, compatible with the studies mentioned above (11,20).

As mentioned before, NGLDM and GLZLM features showed the best diagnostic performance in the discrimination hypovascular PNENs from PDACs. NGLDM refers to the gray level difference in a pixel or voxel, and GLZLM provides information about the size of homogeneous regions for each gray level. None of the studies reporting texture analysis of tumor heterogeneity in the differentiation of hypovascular PNEN from PDAC used the NGLDM and GLZLM features to obtain results (9-11). Besides, the combination of NGLDM_Busyness and GLZLM_LZLGE from this study increased the diagnostic ability and also showed better diagnostic performance (AUC = 0.906) compared with the diagnostic performance results of other similar studies (9-11). Standardization of TA and its application in larger groups may provide more reliable results for the feasibility of the technique. This study may help as one of the reference studies for the development of CT TA.

LIMITATIONS

This study has some limitations, including selection bias caused by retrospective nature. Second, the number of hypovascular PNENs was comparatively lower than that of PDACs because hypovascular PNENs are rare pancreatic lesions and further studies with larger sample sizes are needed to confirm our results. Third, morphological imaging features were not evaluated in this study because we thought there was already sufficient evidence on this topic in the literature.

CONCLUSION

This study revealed that texture features of portal phase CT images may be helpfull in differentiating hypovascular PNEN from PDAC. Studies conducted by standardizing textural analysis and applying in larger groups of patients will enable us to obtain more accurate results on this subject.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study was approved by Gazi University ethics committee (24074710-604.01.01, 13 January 2020).

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