A Novel Observational Strategy for Nonfunctional Pancreatic Neuroendocrine Neoplasms With Texture Analysis: A Multicenter Retrospective Study

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Abstract. Background/Aim: Surgical resection is recommended for nonfunctional pancreatic neuroendocrine neoplasms (NF-pNENs). However, metastasis is rare in patients with small lesions with histological grade 1 (G1); thus, observation is an optional treatment approach for small NF-pNENs. Texture analysis (TA) is an imaging analysis mode for quantification of heterogeneity by extracting quantitative parameters from images. We retrospectively evaluated the utility of TA in predicting histological grade of resected NF-pNENs in a multicenter retrospective study. Patients and Methods: The utility of TA in preoperative prediction of grade were evaluated with 29 patients treated by pancreatectomy for NF-pNENs who underwent preoperative dynamic computed tomography scan between January 1, 2013 and December 31, 2020 at three hospitals affiliated with the Jikei University School of Medicine. TA was performed with dedicated software for medical imaging processing for determining histological tumor grade using dynamic computed tomography images. Results: Histological tumor grades based on the 2017 World Health Organization Classification for Pancreatic Neuroendocrine Neoplasms were grade 1, 2 and 3 in 18, 10 and one patient, respectively. Preoperative grades by TA were 1 and 2/3 in 15 and 14 patients, respectively. The sensitivity, specificity and area under the curve for TA-oriented grade 1 lesions were 1.00, 0.889 and 0.965 (95% confidence interval=0.901-1.000), respectively. Conclusion: TA is useful for predicting grade 2/3 NF-pNEN and can provide a safe option for observation for patients with small grade 1 lesions.

Neuroendocrine neoplasms (NENs) originate from neuroendocrine cells in many organs, including the gastrointestinal tract and pancreas (1). Gastroenteropancreatic NENs (GEP-NENs) account for 65-75% of all NENs (2) and include pancreatic NENs (pNENs), which comprise approximately half of all GEP-NENs. The data from the Surveillance, Epidemiology and End Results program in the USA show that the age-adjusted annual incidence of NENs has increased from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012, corresponding to an approximate seven-fold increase (3-5). According to the Surveillance, Epidemiology, and End Results 18 database encompassing the 2000-2012 period, the incidence of GEP-NEN was 3.56 per 100,000 persons (6). Advances in imaging modalities might have led to the incidental detection of even small pNENs.

Surgical resection has been recommended for all nonfunctional pNENs (NF-pNENs) regardless of their size and grade. However, recent studies indicate that pNENs with histological grade 1 (G1) and a small diameter have good prognosis and might be followed-up periodically for tendency to grow or malignant findings (7-9). The National Comprehensive Cancer Network (NCCN) (10) and European
Neuroendocrine Tumor Society (ENETS) (11) guidelines also support this conservative approach as a new strategy for pNEN. The observational approach for small (diameter ≤2 cm), low-grade, incidentally discovered and nonfunctional tumors suggested by Sadot et al. (12) is also recommended by the NCCN guidelines. The ENETS guidelines also recommend conservative management with annual high-quality imaging for incidentally discovered pNENs with a diameter of ≤2 cm in elderly patients (11). Importantly, conservative management, which is considered an alternative approach for pNENs, requires preoperative prediction of tumor grade. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA), which is currently the only modality available for preoperative prediction of tumor grade for pNENs, is challenging to perform for the evaluation of very small pNEN lesions (13) and the accuracy of EUS-FNA for histological grading remains low due to the small amount of biopsy sample (14). TA is an imaging analysis mode for quantification of heterogeneity by extracting quantitative parameters from images (15). We have previously reported the utility of TA in preoperative prediction of pNEN grade (16). TA was performed with dedicated software for medical imaging processing for determining histological tumor grade using dynamic computed tomography (CT) images. In the present study, we validated the reliability of TA in predicting the histological grade of small G1 pNENs, which might be managed by initial observation using the TA feature log-

sigma 1.0 joint-energy from the arterial phase of dynamic CT images.

### Patients and Methods

**Patient selection.** A retrospective review of the medical records of the Department of Surgery at three affiliated hospitals of the Jikei University School of Medicine was conducted to identify patients who were histologically diagnosed with pNEN between January 1, 2013 and December 31, 2020 and had available clinical and pathological information. The medical records were retrospectively reviewed to retrieve data on patient age, sex, tumor location, tumor size, histological tumor grade, and pathological findings. Histological tumor grade was defined based on the proliferative index (Ki-67 index or mitotic rate) that categorized the neoplasm into the higher grade. Histological tumor grade and pathological findings were based on the 2017 World Health Organization Classification for Pancreatic Neuroendocrine Neoplasms (17). The inclusion criteria were as follows: Preoperative dynamic CT according to routine protocols with a detectable tumor in which the region-of-interest (ROI) could be set on CT. The exclusion criteria were as follows: Functional pNEN or pancreatic neuroendocrine carcinomas, incomplete dynamic CT data due to another protocol or artifact, undetectable tumor on dynamic CT, patients included in previous studies from our group (Figure 1).

**CT scanning protocol.** In the present study, TA was performed using arterial-phase dynamic CT. All CT images were captured using a 64-channel (SOMATOM Perspective, Siemens, Munich, Germany; or Aquilion 64, Canon Medical Systems, Tochigi, Japan) or 128-
channel (SOMATOM Definition Flash or SOMATOM Definition AS+; Siemens) scanner. The scanning protocol comprised non-enhanced and biphasic contrast-enhanced scans. The non-enhanced phase was obtained to image the upper abdomen with the entire liver and pancreas and was followed by bolus injection of 600 ml/kg iodine contrast medium with an automatic power injector at a rate of 2.0-3.0 ml/s for 33 s. The arterial phase was performed 10 s after reaching 80 Hounsfield units with the ROI placed on the aorta at the level of celiac artery, and the portal venous phase was performed 90 s after the injection of iodine contrast medium. The arterial phases were captured for the upper and whole abdomen. All arterial-phase CT images were reconstructed every 5-mm slice.

**Texture analysis (TA).** A general surgeon performed measurements on a Picture Archiving and Communication Systems workstation under the guidance of a Board-certified abdominal radiologist. We

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Figure 2. An example of texture analysis of a neuroendocrine neoplasm in the pancreatic tail using an abdominal computed tomography image during the arterial phase. Texture analysis was performed with dedicated software for medical imaging processing (syngo.via Frontier Radiomics, Siemens Healthineers, Erlangen, Germany). After manual segmentation of the tumor, texture parameters were automatically calculated and are listed under the image.
Table I. Patient and tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=29)</th>
<th>1 (n=18)</th>
<th>2/3 (n=11)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range) 64 (44-81)</td>
<td>64 (44-80)</td>
<td>55 (49-81)</td>
<td>0.840</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 18 (62.1%)</td>
<td>12 (66.7%)</td>
<td>6 (54.5%)</td>
<td>0.697</td>
</tr>
<tr>
<td></td>
<td>Female 11 (37.9%)</td>
<td>6 (33.3%)</td>
<td>5 (45.5%)</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location, n (%)</td>
<td>Pancreatic head 11 (37.9%)</td>
<td>7 (38.9%)</td>
<td>4 (36.4%)</td>
<td>0.305</td>
</tr>
<tr>
<td></td>
<td>Pancreatic body 7 (24.1%)</td>
<td>6 (33.3%)</td>
<td>1 (9.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic tail 11 (37.9%)</td>
<td>5 (27.8%)</td>
<td>6 (54.5%)</td>
<td></td>
</tr>
<tr>
<td>Size, mm</td>
<td>Median (range) 18 (6-72)</td>
<td>14.5 (6-45)</td>
<td>34 (12-72)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Statistically significant p-values are shown in bold.

Previously confirmed that the measured values did not vary among the evaluators reading the images (16). The evaluators were aware that the patients had pNEN but were blinded to the assigned pathological grade. TA was performed with dedicated software for medical imaging processing (syngo.via Frontier Radiomics, Siemens Healthineers, Erlangen, Germany) (Figure 2).

All images were saved in the server of Digital Imaging and Communications in Medicine format. ROIs were manually set using the tumor on arterial-phase dynamic CT images to exclude visually detectable blood vessels from the ROI. The ROIs were carefully set to the tumor margin on each slice, and 3-D volumes-of-interest were constructed.

Based on our previous study, log-sigma 1.0 joint-energy data were extracted from the images as a feature of TA (14). The log-sigma 1.0 indicates the intensity of the Laplacian of Gaussian band-pass filter that is used to detect density changes. The sigma filter values were set to 1.0, 1.5, 2.0, and 2.5, with smaller sigma values indicating finer texture. The joint-energy is for second-order statistics, extracted by a gray-level co-occurrence matrix, which evaluates how often a pair of intensity levels is identified either horizontally, vertically, or diagonally to adjacent pixels. The joint-energy indicates homogeneous patterns in neighborhood intensity values within images. Histological grade was judged using the log-sigma 1.0 joint-energy extracted from the arterial phase of dynamic CT images as a feature of TA. The cut-off value of log-sigma 1.0 joint-energy was set to 0.42, and lesions with values above that were classified as TA-oriented G1 while those equal to or below it were classified as TA-oriented G2/3.

Ethical considerations. The study protocol was approved by the Ethics Committee of the Jikei University School of Medicine [27-177(2062)]. Written informed consent for participation and publication of this study was obtained from all subjects. A copy of the written consent is available for review upon request.

Statistical analysis. Differences in continuous data between patients with grade 1 (G1) and G2/3 pNEN were compared using the Mann-Whitney U-test, whereas differences in categorical data between the two groups were determined using Fisher’s exact test. These tests were also used for the comparison of quantitative and qualitative variables, respectively, between patients with G1 pNEN based on preoperative TA and those with G2/3 pNEN based on preoperative TA. The degree of concordance between preoperative tumor grade by TA and histological tumor grade was analyzed by McNemar’s test.

A receiver-operating characteristic curve was constructed to evaluate the discriminatory performance of the value derived by TA using the area under the curve (AUC), and an AUC of greater than 0.5 indicated that the value derived by TA was able to correctly identify G1 pNEN cases better than by chance. The Youden index was used to determine the optimal cutoff value for detecting G1 pNEN in the study cohort.

All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA), and values of p<0.05 were considered to indicate statistical significance.

Results

Patient and tumor characteristics. Table I shows the patient and tumor characteristics. There were 29 patients, including 18 males (62.1%) and 11 females (37.9%), with NF-pNEN detected by preoperative dynamic CT during the study period. The median age was 64 (range=44-81) years. The tumor was located in the pancreatic head, body, and tail in 11 (37.9%), 7 (24.1%), and 11 (37.9%) patients, respectively, and the median tumor diameter was 18 (range=6-72) mm.

The patient and tumor characteristics according to the tumor histological grade are shown in Table I. Pathologically, 18 (62.1%) and 11 (37.9%) patients had G1 and G2/3 tumors, respectively. The G1 and G2/3 tumors were commonly located in the pancreatic head and tail, respectively. The median diameter of G1 tumors was significantly smaller than that of G2/3 tumors (p<0.001).

Relationship between pathological factors and TA-oriented tumor grade. Table II shows the relationship between the
clinicopathological factors and TA-oriented tumor grade. Location of tumor, rates of neural invasion and extra-pancreatic invasion were comparable between the groups categorized according to the TA-oriented tumor grade. In contrast, tumor size and the rates of lymphatic and venous invasion were significantly greater in TA-oriented G2/3 tumors than in TA-oriented G1 tumors ($p<0.001$, $p=0.017$, and $p=0.035$, respectively). The mitotic rate and Ki-67 index were less than 2/10 high-power fields and 3%, respectively, in all 15 pNENs with TA-oriented G1. On the other hand, 10 (71.4%) tumors with TA-oriented G2/3 had a low mitotic rate (<2/10 2/10 high-power fields), significantly lower than for TA-oriented G1. The Ki-67 index was higher than 3% in 10 out of the 14 (71.4%) TA-oriented G2/3 tumors.

The positive predictive values of TA-oriented tumor grading for histological G1 and G2/3 pNENs were 100% and 78.6%, respectively. Using an optimal cut-off value of 0.217, the specificity and sensitivity of TA-oriented tumor grading for preoperative diagnosis of G1 pNEN were 1.00 and 0.889, respectively, and the AUC was 0.965 (95% confidence interval=0.901-1.000) (Figure 3).

**Discussion**

Despite substantial improvements in the past several decades (18), pancreatic surgery remains highly invasive. Importantly, pancreaticoduodenectomy has a high mortality rate of approximately 5% and a morbidity rate of up to 60% in experienced high-volume centers (19-21). Small, G1 pNENs rarely metastasize and have a favorable prognosis; therefore, the latest NCCN and ENETS guidelines in Western countries recommend follow-up as a clinical approach for small pNENs (10, 11). However, this strategy is not practical because accurate preoperative histological grading of pNENs is not always possible due to difficulties in the successful evaluation of small lesions using EUS-FNA. Numerous studies have reported that tumor size is associated with histological grade (22-29). In the present study, G2/3 pNENs were indeed larger than G1 pNENs. However, the determination of histological grade based only on tumor size and conventional diagnostic imaging modalities is limited.
TA is a new technique that allows the quantification of tissue heterogeneity using pixel intensity variations. As shown in Table II, grading by TA was not significantly associated with the mitotic rate or Ki-67 index and was considered to be a more comprehensive evaluation of histological tumor grade. Recent studies have demonstrated the utility of TA in differentiating benign and malignant tumors in various organs, including pancreatic adenocarcinoma (30, 31). Although several reports evaluated the utility of TA in grading pNENs, the specific imaging modality (CT versus magnetic resonance imaging) and phase (arterial versus portal venous phase) that were useful to determine TA were not clarified (26-29, 32, 33). We previously showed that there was no difference in the rate of diagnosis among radiologists and that TA based on the evaluation of the portal venous phase of dynamic CT was useful in detecting G2/G3 pNEN with 95% sensitivity, 73% specificity, and 88% accuracy (14). However, in the setting of clinical practice, it is necessary to exclude G2/3 lesions and high specificity is the most crucial aspect for the strategic observation of suspicious G1 pNEN lesions. In the present study, two out of the 11 patients with G2/G3 pNEN experienced postoperative recurrence. In our previous study, despite an excellent specificity of 100%, TA using arterial-phase dynamic CT had a sensitivity of 76%, which was lower than that determined using portal venous-phase dynamic CT (95%). In the present study, we validated the utility of TA using arterial-phase dynamic CT for accurate grade prediction of NF-pNEN in a multicenter setting.

In the present study including patients with NF-pNEN, TA exhibited high sensitivity for predicting G1 NF-pNEN and all TA-oriented G1 tumors were histologically proven to be G1 NF-pNENs. Three out of the 14 patients diagnosed with G2/3 NF-pNENs by TA were overdiagnosed as they were histological G1 NF-pNENs, whereas all 11 G2/3 tumors based on histological evaluation were correctly identified as G2/3 by TA, with a sensitivity of 1.00. This indicates a high positive predictive value of TA for histological G2/3 NF-pNEN, with some risk for the overdiagnosis of histological G1 lesions as G2/3 lesions. These data suggest that TA-oriented histological grading might be considered as a new minimally invasive modality and a follow-up strategy for patients with small NF-pNENs. However, the risk remains of occult hematogenous metastasis in patients with histological venous invasion, which was observed even in those with small, G1 tumors with a diameter of 9 mm (Table II) in the present study cohort. Therefore, a follow-up strategy should be optional while considering surgical resection for all NF-pNENs.

The major limitations of the present study were the retrospective design and the relatively small sample size. The performance of TA should be further evaluated in prospective studies. However, one major strength was the demonstration that a novel strategy of preoperative grade prediction using TA had a satisfactory specificity for NF-pNEN, a rare type of cancer. This method was not only non-invasive, it was also able to grade lesions correctly at a high rate. TA may enable smoother progress from diagnosis to treatment in future clinical applications. On the other hand, the performance of TA should be further evaluated in prospective studies. Furthermore, its efficacy as a diagnostic method could be further demonstrated by planning a study with a different design to investigate its ability to differentiate pNENs from other pancreatic neoplasms and its correlation with malignancy.

In conclusion, TA is a potential non-invasive diagnostic method for preoperative prediction of tumor grade in patients with NF-pNEN, especially those with G1 lesions, who are candidates for follow-up as a treatment strategy.

Conflicts of Interest

All the Authors have no conflicts of interest to declare in relation to this study.

Authors’ Contributions


Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP22K16547. The Authors would like to thank Enago (www.enago.com) for the English language review.

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Received June 20, 2023
Revised July 31, 2023
Accepted August 4, 2023