

Heterotopic pancreas: the added value of endoscopic ultrasound with Computed Tomography for diagnosis

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Abstract

Aims: To investigate the added value of endoscopic ultrasound (EUS) with computed tomography (CT) in distinguishing heterotopic pancreas (HP) from other pathologies, when gastroduodenal subepithelial tumors (SETs) are suspected on an upper endoscopic examination. **Material and methods:** We retrospectively included 54 consecutive patients with gastroduodenal SETs who had undergone both abdominal CT and EUS within a 3-month interval. All EUS, endoscopy, and CT images were reviewed and evaluated in a blinded manner by an endoscopist and a radiologist, respectively. Univariate and multivariate analyses were performed to identify EUS/CT findings related to HP. Diagnostic performance of CT only and CT combined with EUS was compared for distinguishing HP from other SETs. **Results:** We included patients with HP (n=17; pathologically confirmed, n=6), gastrointestinal stromal tumor (GIST, n=24), and other pathologies (n=13). Multivariate logistic regression analyses revealed that irregular margin, origin from submucosal layer, internal microcystic-tubular structure, and oval shape were independent factors in diagnosing HP by EUS, whereas a micro-lobulating contour was the only significantly independent factor in CT. In assessments of diagnostic performance, CT combined with EUS showed significantly superior diagnostic performance in comparison with CT only (area under the curve, 0.961 vs. 0.833, p=0.028) in the consensus interpretation of an endoscopist and a radiologist. **Conclusions:** CT combined with EUS with a comprehensive and complementary interpretation showed significant added value compared to CT only in diagnosing gastroduodenal HP.

Keywords: endosonography; multidetector Computed Tomography; heterotopic pancreas

Introduction

Heterotopic pancreas (HP) is a congenital anomaly in which pancreatic tissue appears separate from the orthotopic pancreas without ductal or vascular continuity. Since HP is typically asymptomatic, it is usually discovered incidentally during endoscopic examinations,

imaging studies, or an unrelated surgery. Although its exact prevalence is not known, previous autopsy series revealed that the most common location of HP is the upper gastrointestinal tract (prevalence, 0.5%–13.7%) [1,2]. HP shows extremely low malignant potential [3] and rarely causes symptoms. However, to avoid unnecessary surgery, noninvasive distinction of HP from other subepithelial tumors (SETs) with a high accuracy is crucial.

Gastrointestinal SETs are frequently detected using computed tomography (CT), which enables complete delineation of tumors as well as assessments of locoregional invasion or distant metastasis. According to the previous literature, HP can be differentiated from gastrointestinal stromal tumor (GIST) and leiomyoma with relatively high accuracy with CT [4]. However, CT still has limited value in evaluating the layers of the gastrointestinal tract and the origin of SETs. In contrast, endoscopic

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ultrasound (EUS) enables the determination of the layer of origin and more accurate differentiation of SETs from extrinsic compression, which makes it a useful tool for differential diagnosis of gastrointestinal SETs. However, to the best of our knowledge, there has been no literature regarding the diagnostic accuracy of EUS for HP.

In addition, although HP commonly originates from and is limited to the submucosal layer, it often extends into the proper muscle or subserosal layer, making it difficult to differentiate from other SETs by imaging studies [5]. Thus, in actual clinical practice, a multimodal approach may address the shortcomings of single diagnostic methods and improve diagnostic accuracy, especially when the differential diagnosis of gastrointestinal SETs is challenging. Considering the substantial recent development in imaging and endoscopic techniques, a diagnostic approach integrating EUS and CT might yield better diagnostic performance than that achieved with CT only. Accurate diagnosis of HP with noninvasive techniques may preclude invasive procedures and unnecessary surgeries. In this study, we investigated the value of EUS combined with CT in distinguishing HP from other pathologies in patients with endoscopically suspected gastroduodenal SETs.

Material and methods

This retrospective study was reviewed and approved by our institutional review board, and the requirement for informed consent was waived (IRB No. 1907-004-16271).

Patients

We retrospectively included 196 consecutive patients with gastroduodenal SETs that had undergone both abdominal CT and EUS within a 3-month interval between April 2010 and April 2019 at Chung-Ang University Hospital, a tertiary referral teaching hospital, by reviewing the electronic medical database. Among these, we excluded patients without pathologic confirmation of the SET lesion (n=153), except cases that showed a very high clinical possibility of HP by meeting the following criteria [(3) and any of (1) or (2)] (n = 11): 1) endoscopic findings showing typical umbilication or duct opening on the surface and location in the antrum of the stomach, 2) specific findings highly suggestive of HP on CT or EUS, and 3) no change in size and characterization on CT during a follow-up period over 3 years, confirmed by a 9-year experienced abdominal radiologist. Finally, we included 54 patients in this study.

Endoscopic ultrasound and analysis

EUS examination was performed by one of three experienced endoscopists using a radial-scanning-echoendoscope (GF-UM2000 or GF-UE260; Olympus Co. Ltd.) or a 12MHz 2.5mm radial miniprobe (UM-DP12-25R;

Olympus Co. Ltd.). These were connected to an endoscopic ultrasonic observation unit (EU-M2000; Olympus Co. Ltd.). A water-fillable balloon was attached to the radial echoendoscope around the transducer. Which EUS scope to use or whether to use a water-filled balloon was at the discretion of the endoscopist. After the patient was placed in the left lateral decubitus position, the echoendoscope was advanced into the stomach and deaerated water was instilled to allow observation of the target lesion. All endoscopic procedures were performed under moderate sedation in the endoscopy unit.

All EUS and endoscopic images were reviewed and evaluated by an endoscopist with 6 years of experience in a blinded manner, and the following EUS findings were recorded for all SETs: (1) location (upper, middle, and lower third of the stomach and duodenum), (2) size (long diameter [LD] and short diameter [SD]), (3) layer of origin (muscularis mucosa, submucosa, muscularis propria, and subserosa/serosa), (4) echogenicity, (5) heterogeneity in echotexture, (6) margin, (7) presence of microcystic (anechoic duct-like) structure (<3 mm), (8) presence of macrocystic structure (≥ 3 mm). Echogenicity of SETs on EUS was evaluated in comparison to the echogenicity of the proper muscle layer and submucosal layer. The echogenicity was scored as follows: 0 (anechoic, similar to that of a cystic lesion), 1 (markedly hypoechoic, between 0 and 2), 2 (hypoechoic, similar to that of the proper muscle layer), 3 (isoechoic, between 2 and 4) and 4 (hyperechoic, similar to that of the submucosal layer). The endoscopist also recorded whether the SET showed heterogeneous or homogeneous echogenicity. Since all patients underwent upper endoscopic examination before EUS and endoscopic gross findings are always considered together with EUS results in the interpretation of test results in actual clinical practice, the following endoscopic findings of SETs were also evaluated: presence of central umbilication, ulceration, or surface erosion.

Computed tomography acquisition and analysis

CT images were obtained by using a 256-detector row CT scanner (Brilliance iCT, Philips Healthcare) or 64-detector row CT scanners (Brilliance 64, Philips Healthcare and Optima660, GE Healthcare). Each patient received 1.5 mL/kg of nonionic contrast material through an 18-gauge angiocatheter inserted into a forearm vein; a mechanical injector was used to obtain a flow rate of 3.0 mL/s. Acquisition parameters were as follows: beam thickness, 0.625-1 mm; table pitch, 1; reconstruction interval, 3 mm; and multi-planar reformatting using coronal and sagittal planes. We obtained pre-contrast CT images followed by arterial-phase images using a bolus tracking method and portal venous phase images taken approximately 60-70 s after the administration of con-

trast material. For optimal evaluation, all patients fasted for at least 6 hours, and later consumed 6 g of effervescent granules with sips of water or 300 mL of water right before the examination to distend the stomach.

One experienced abdominal radiologist (9 years of experience) reviewed the CT dataset in a blinded manner to assess the following items: 1) location, 2) long and short diameters, 3) enhancement degree on the portal venous phase compared to the orthotropic pancreas, 4) micro-lobulating contour, 5) presence of fatty halo, 6) presence of microcystic (anechoic duct-like) structure (<3 mm), 7) presence of macrocystic structure (≥ 3 mm), 8) heterogeneity in texture.

Diagnostic performance test

Based on the results from prior EUS and CT image analyses, two rounds of diagnostic performance tests were conducted by one endoscopist and one abdominal radiologist in consensus. In the first round, the reviewers rated the possibility of HP using a 5-point scale scoring system (1, no possibility; 2, probably not; 3, intermediate probability for HP; 4, probably; 5, definitely HP) on CT images. In the second round of review, they conducted a diagnostic performance test by using EUS with CT images together in the same manner. To avoid recall bias, the second round of review was performed three weeks after the first one.

Statistical analysis

The differences in the demographic data between the HP and non-HP SET groups, including age and sex, were evaluated. The Student's *t*-test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables. To determine which findings on EUS or CT were significantly related to HP, univariate and multivariate analyses were performed using Fisher's exact test and multiple regression analysis test, respectively. Significant factors from the univariate analysis were evaluated in the multivariate analysis. *p* values <0.05 were considered statistically significant. To obtain the optimal cutoff value of the LD/SD ratio and to confirm the diagnostic performance, receiver operating characteristic (ROC) curves were generated. The area under the ROC curve (AUC) was measured to evaluate the diagnostic accuracy of imaging modalities in distinguishing HP from non-HP SETs. All statistical analyses were performed using MedCalc® software version 19.0.4 (MedCalc Software bvba).

Results

Demographic data

We eventually included 54 patients (M:F = 22:32; mean age, 57.8 years; range, 24–84years) with gastrodu-

odenal SETs, including HP (n=17; surgery-confirmed, n=6), GIST (n=24), leiomyoma (n=3), neuroendocrine tumor (NET, n=3), schwannoma (n=2), Castleman's disease, lymphoma, exophytic focal nodular hyperplasia of the liver, duplication cyst, and glomus tumor (n=1 each). The mean age of patients in the non-HP group was significantly higher than that in the HP group (61.1 vs. 50.6 years, *p*=0.025) (Table I).

Image analysis with EUS and CT

All SETs showing central umbilication on esophago-gastroduodenoscopy (EGD) were HP and accounted for 31.5% (n=5, *p*=0.002) of all HP cases. Multiple variables related to the EUS and CT findings were taken into consideration and analyzed to distinguish HP from other SETs. Irregular margin, origin from the submucosal layer, greater hyperechogenicity than the muscle layer, heterogeneous echotexture, internal microcystic-tubular structure, and oval shape (LD/SD ratio >1.64) were significant EUS features (*p*<0.05) in the univariate analysis. In contrast, a micro-lobulating contour, iso-attenuation with the pancreas on the portal venous phase, homogeneous enhancement pattern, and absence of macrocystic structure were identified as significant CT features (*p*<0.05) in the univariate analysis (Table I). The optimal cutoff LD/SD ratio in CT was >1.25, but this value was not statistically significant. Multivariate logistic regression analysis revealed that irregular margin (*r*=0.63, *p*<0.001), origin

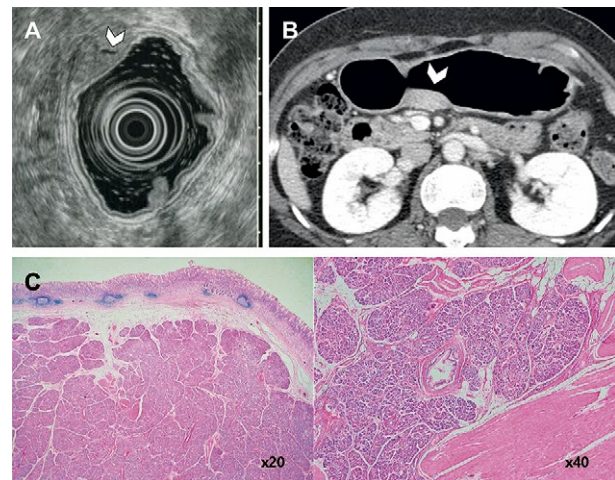


Fig 1. A 57-year-old female patient with heterotopic pancreas. A, Endoscopic ultrasound shows an isoechoic mass in the submucosal layer with an ill-defined margin. The lesion contains a microcystic structure (arrowhead) correlating with the pancreatic duct. B, On computed tomography, a homogeneously enhancing ovoid mass is located in the posterior wall of the gastric lower body (arrowhead). C, Histologic examination of resected specimen shows heterotopic pancreatic tissue in the submucosa with overlying gastric mucosa. The heterotopic pancreas contains ducts and acinar cells.

from the submucosal layer ($r=0.31$, $p<0.001$), internal microcystic-tubular structure ($r=0.30$, $p<0.001$), and oval shape ($r=0.21$, $p=0.015$) were independent findings for diagnosing HP using EUS (fig 1 and 2). In CT, a micro-lobulating contour was identified as the only significantly independent factor suggestive of HP ($r=0.66$, $p<0.001$).

Diagnostic performance study

In the diagnostic performance study, the first round of consensus review with CT showed a good performance with an AUC value of 0.833 (sensitivity, 64.86%; specificity, 94.12%). When we combined EUS findings with CT images to discriminate between HPs and non-HP SETs in the second round of consensus review, the AUC reached 0.961, which indicates an excellent performance, with a sensitivity of 91.89% and specificity of 94.12%. While distinguishing HP from other SETs, the diagnostic performance improved significantly when EUS find-

ings were interpreted together with CT, compared to that when diagnosis was made by CT only ($p=0.028$) (fig 3).

Sensitivity analysis

As some degree of heterogeneity could exist among the patients with HP between the pathologically confirmed group ($n=6$) and the clinically confirmed group ($n=11$), sensitivity analysis was additionally performed. For this purpose, the diagnostic performance study was conducted again, this time only including the patients with pathologically confirmed SETs ($n=43$), excluding 11 patients with HP without pathologic confirmation. The first round of consensus review with CT showed good performance in discriminating between HPs and non-HP SETs with an AUC value of 0.662 (sensitivity, 33.33%; specificity, 91.89%). When EUS findings and CT images were combined in the second round of consensus review, the AUC reached 0.833, which indicates excellent per-

Table I. Demographic characteristics and imaging findings

| | | Heterotopic Pancreas (n = 17) | Non-heterotopic Pancreas (n = 37) | p values |
|-----|-------------------------------|----------------------------------|--------------------------------------|----------------------------|
| | M:F | 7:10 | 15:22 | |
| | Mean age (years) | 50.6 | 61.1 | 0.025 |
| EUS | Mean size (mm) | 17.95 (10.0-27.0) | 26.68 (7.4-64.0) | 0.002 |
| | LD/SD ratio | 1.84 (1.20-2.77) | 1.50 (0.94-3.17) | 0.015‡ |
| | Location | | | |
| | Cardia | 0 | 3 | |
| | Fundus | 0 | 6 | |
| | Body | 4 | 17 | |
| | Antrum | 7 | 9 | |
| | Pylorus | 1 | 1 | |
| | Duodenum | 5 | 1 | |
| | Central umbilication | 5 | 0 | 0.002 |
| | Layers† | | | Submucosal origin <0.0001‡ |
| | Mucosa | 3 | 2 | |
| | Submucosa | 12 | 4 | |
| | Proper muscle | 7 | 24 | |
| | Subserosa/serosa | 1 | 5 | |
| | Extragastric | 0 | 3 | |
| | Echogenicity | | | Brighter than MP <0.0001 |
| | Anechoic | 0 | 3 | |
| | Marked hypoechoic | 0 | 2 | |
| | Hypoechoic | 2 | 24 | |
| | Isoechoic | 14 | 8 | |
| | Hyperechoic | 1 | 0 | |
| | Heterogeneous echogenicity | 12 | 11 | 0.007 |
| | Ill-defined margin | 10 | 5 | <0.0001‡ |
| | Microcyst/duct-like structure | 9 | 2 | 0.0002‡ |
| | Macrocyt (≥ 3 mm) | 0 | 4 | 0.3 |
| CT | Mean size (mm) | 19.53 (12.0-35.0) | 28.73 (7.0-9.0) | 0.003 |
| | LD/SD ratio | 1.60 (1.15-2.33) | 1.47 (1.04-2.73) | 0.26 |
| | Homogeneous enhancement | 11 | 23 | 0.002 |
| | Micro-lobulating contour | 12 | 7 | <0.0001‡ |
| | Microcyst/duct-like structure | 2 | 1 | 0.23 |
| | Macrocyt (≥ 3 mm) | 0 | 9 | 0.04 |

CT, computed tomography; EUS, endoscopic ultrasound; LD, long diameter; SD, short diameter; MP, muscularis propria; †, counting of all involved layers in cases of multi-layer involvement; ‡, significant finding in multivariate analysis

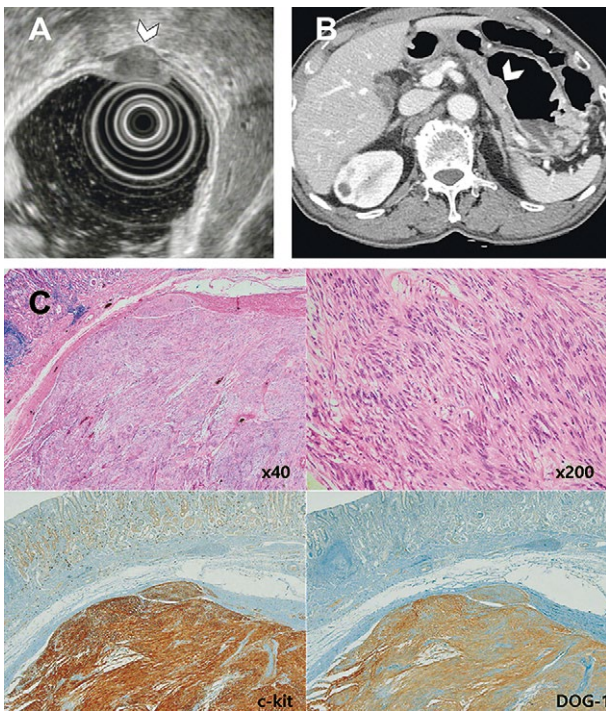


Fig 2. A 78-year-old male patient with gastrointestinal stromal tumor. A, Endoscopic ultrasound shows a hypoechoic well-defined mass (arrowhead) originating from the proper muscle layer of the stomach. B, On the portal venous phase of computed tomography, a homogeneously enhancing ovoid mass can be seen in the posterior wall of gastric lower body (arrowhead) with the same degree of enhancement as the orthotropic pancreas. C, Histologic examination of resected specimen shows submucosal proliferation of spindle cells arranged into short fascicles, with occasional cytoplasmic vacuoles. Immunohistochemistry confirmed GIST with strong positive staining for c-Kit, and DOG-1.

formance, with a sensitivity of 83.33% and specificity of 81.08%. This sensitivity analysis showed that even when only pathologically confirmed cases were included, the diagnostic performance for distinguishing HP from other SETs improved significantly when EUS findings were interpreted together with CT, compared to when diagnosis was made by CT only ($p=0.018$) (fig 4).

Discussions

In this study, we investigated several characteristic EUS and CT features for distinguishing HP from other SETs. Irregular margin, origin from the submucosal layer, internal microcystic-tubular structure, and oval shape were independent EUS features for diagnosing HP, while a micro-lobulating contour was the only independent finding on CT. Moreover, CT combined with EUS showed significantly superior diagnostic performance over CT alone in consensus-based interpretations.

In routine clinical practice, most gastroduodenal SETs are asymptomatic and incidentally found on EGD or abdominal CT. Although definitive diagnosis of SETs can be achieved by pathologic confirmation, obtaining adequate tissue is sometimes difficult and the diagnostic yield with the conventional endoscopic biopsy method is quite low. While tissue acquisition via more invasive endoscopic techniques, such as endoscopic mucosal/submucosal resection or EUS-fine needle aspiration (FNA), is effective, these procedures are not routinely performed and have not been sufficiently investigated for diagnosis of HP [6-8]. Moreover, they may not be widely available

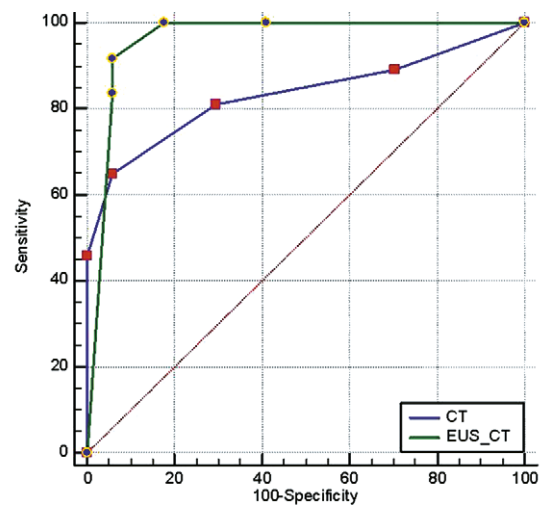


Fig 3. Receiver operating curves showing the diagnostic performance of consensus readings in CT and combined EUS-CT assessments.

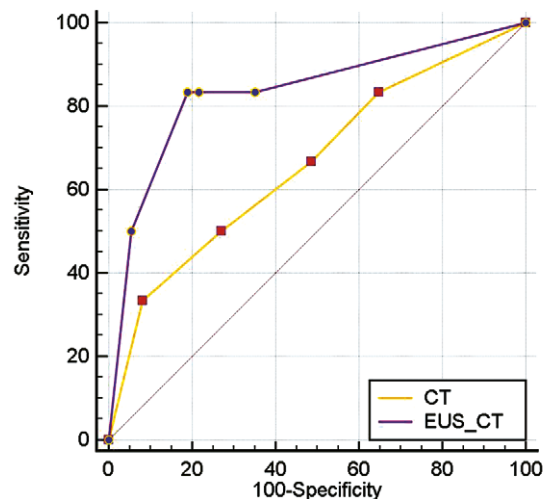


Fig 4. Receiver operating curves showing the diagnostic performance of consensus readings in CT and combined EUS-CT assessments, when only pathologically confirmed SETs were included.

in some centers and sometimes procedure-related complications can occur, such as acute pancreatitis, infection, bleeding, or perforation [9].

HP is frequently encountered during EGD, and does not usually require any further treatment, including surgery. On EGD, HP is often observed as a SET with central umbilication, which is typically located in the antrum or proximal duodenum [5]. However, not all HPs exhibit the features described above, and vice versa. On the basis of EUS findings, HP can be divided into two types: the shallow type, which originates from and is limited to the mucosal and/or submucosal layer, and the deep type, which extends into the muscle or subserosal layer. The latter type is often difficult to differentiate from other SETs such as glomus tumor or GIST [5,10]. This atypical presentation of HP sometimes makes it difficult to distinguish HP from other pathologies without histologic confirmation [11].

Although there is no definite consensus guideline for further evaluation and follow-up of gastroduodenal SETs, CT or EUS is not usually recommended for very small SETs [12]. For these lesions, endoscopic follow-up is sufficient in most cases [13]. However, for larger SET lesions, especially when premalignant or malignant potential cannot be ruled out, further evaluation with advanced diagnostic modalities is often needed. CT and EUS are not only useful tools, but also the most commonly used modalities for this purpose.

The ill-defined, irregular margin on EUS or the micro-lobulating contour on CT images correspond to the lobular morphology of the acinar component of HP in histologic specimens. An internal microcystic-tubular structure (<3 mm) was a significant finding on EUS, whereas absence of macrocystic structure was identified as a significant CT feature in our study. One possible reason why microcystic structure was not a significant finding on CT might be the limited resolution of CT. On the other hand, evaluation of macrocystic structure could have been suboptimal on EUS in comparison with CT, since there is a trade-off between resolution and penetration in ultrasound. This limitation is especially problematic in large tumors, since central necrosis of GIST or NET and cystic degeneration of schwannoma usually occur in a relatively large tumor. Another interesting result of our study was the difference in optimal L/S ratios between EUS and CT (1.64 vs. 1.25) to distinguish HP from other SETs, even though there was no statistical significance. The higher cutoff value of the L/S ratio could be explained by the inherent differences in the diagnostic modalities. During EUS, compression by the endosonographic probe could make the lesion more elliptical, and filling the lumen with water also leads to the extension of

the gastrointestinal wall and the lesion itself, exaggerating the L/S ratio of the SET lesion. Previous studies have shown that the characteristic EUS features of the HP: unifying the expressions include indistinct borders, heterogeneous echogenicity, anechoic ductal structures, and localization within two or more layers, mostly including the submucosal layer [14,15], most of which were confirmed in our study.

Nevertheless, each imaging modality has its strengths and limitations, which may undermine its diagnostic accuracy for SET lesions. We have shown that the diagnostic performance of CT with EUS in distinguishing HP from other SETs was significantly better than that of CT alone. This discrepancy in diagnostic accuracy could be primarily attributed to the ability to evaluate the layer of origin, which is an important factor in distinguishing SET lesions. Similar to previous studies [15,16], most HPs originated from the submucosal layer and half of them involved one more adjacent layer of the gastroduodenal wall, including the muscularis mucosa or muscularis propria [5,15,16] in our study. Only one non-HP SET (glomus tumor) showed involvement of the muscularis mucosa and submucosa simultaneously. In the non-HP SET group, only four lesions (glomus tumor, duplication cyst, NET, and GIST) originated from the submucosal layer. The addition of EUS greatly improved the diagnostic accuracy in comparison with evaluations made by CT alone. When the differential diagnosis of gastrointestinal SETs is challenging, this multimodal approach could be particularly useful to overcome the inherent limitations of single diagnostic methods, thereby improving the diagnostic ability. Distinguishing HP from other SETs accurately with combinations of noninvasive techniques is clinically important, since this can preclude the need for invasive procedures and unnecessary surgeries. However, very few studies have performed comprehensive assessments of EUS and CT findings for SETs, even though those two modalities are often performed together for initial or subsequent diagnoses in cases of equivocal lesions on EGD. One possible obstacle to a comprehensive interpretation of these two modalities may be the need for different operators, i.e., endoscopists and radiologists, with both operators lacking a full understanding of the limitations and strengths of the method interpreted by the counterpart. This could undermine the comprehensive assessments derived by the consensus of a radiologist and an endoscopist.

There are several limitations in our study. First, the sample size was relatively small, and some non-pathologically proven HP cases were included. The results must therefore be interpreted with caution. Nevertheless, we meticulously selected only those cases where the pos-

sibility of HP was very high, showing typical imaging features for HP and no change over a follow-up period of more than 3 years. In addition, the sensitivity analysis performed only on pathologically confirmed cases also proved the additional value of EUS in the diagnostic performance. Second, EUS and CT protocols were heterogeneous because of the retrospective study design implemented over a long-term study period. EUS was performed by three different operators, which could be a confounding factor, since EUS is a highly operator-dependent procedure. However, an experienced endoscopist reviewed all the EUS images and the same effort was made for CT images by an experienced radiologist to minimize this subjectivity.

In **conclusion**, EUS combined with CT and a comprehensive and complementary interpretation showed significant added value in distinguishing gastroduodenal HP from other SETs, in comparison to CT only.

Conflict of interest: none

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