Diagnosis and Localization of Insulinoma in Thai Patients: Performance of Endoscopic Ultrasonography Compared to Computed Tomography and Magnetic Resonance Imaging

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Background: *Endoscopic ultrasonography (EUS) has now been accepted as the most sensitive method to localize insulinoma. However, the data in Thai patients is lacking and the diagnostic performances of EUS comparing to computed tomography (CT) and magnetic resonance imaging (MRI) is unknown.*

Material and Method: *Retrospective analysis of 19 patients with recurrent hypoglycemia suggestive of insulinoma who underwent EUS, CT and MRI for tumor localization during 2007 to 2012. Surgical pathology or long-term follow-up was used as gold standard.*

Results: *There were 14 patients with 15 insulinoma lesions and 5 patients without insulinoma (2 nesidioblastosis and 3 without lesion). EUS, CT and MRI were performed in 19, 11 and 10 patients, respectively. EUS could detect insulinoma with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 93%, 80%, 93% and 80%, respectively. The corresponding performances for CT were 78%, 100%, 100%, 50% and MRI were 71%, 33%, 71%, 33%, respectively. In patients with positive CT, subsequent EUS did not change diagnosis. However, EUS was able to detect insulinoma in 50% of patients with negative CT. On the other hand, in patients with positive MRI, EUS changed and corrected the diagnosis of MRI in 29% and was able to detect insulinoma in 67% of patients with negative MRI. EUS, CT and MRI correctly localized insulinoma in 87%, 67% and 57%, respectively. The most common incorrect localization was between pancreatic body and tail.*

Conclusion: *EUS has the best diagnostic performance in detection and localization of insulinoma. CT is less sensitive but very specific, therefore positive CT may preclude the need of EUS. MRI, however, is less sensitive and specific than CT. Either positive or negative MRI may require further EUS.*

Keywords: *Computed tomography, Endoscopic ultrasound, Insulinoma, Localization, Magnetic resonance imaging, Thai*

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Insulinoma is the most common neuroendocrine tumor (NET) of the pancreas. However, it remains a rare disease with an annual incidence ranging from 1 to 5 cases per million[1]. Most patients present with neuroglycopenic symptoms from recurrent hypoglycemia, accompanied with elevated insulin level and c-peptide. Diagnosis and localization of insulinoma is a challenging problem for clinician because the tumor is usually small and the sensitivity of the current diagnostic imaging studies, e.g. computed tomography (CT) and magnetic resonance imaging (MRI) are unsatisfactorily low. Accurate localization of the insulinoma is important because it may help surgeons' decision making allow for planning of less invasive operations, e.g. laparoscopic, robotic pancreatic resection or tumor enucleation, which have lower post-operative morbidity compared to conventional open surgeries.

Endoscopic ultrasonography (EUS) is an endoscope with an ultrasound tip. The close proximity between the pancreas and stomach and duodenum allows visualization of the pancreas once the echoendoscope is placed inside the gastroduodenal lumen. Rosch, et al[2] firstly described the use of EUS to diagnose pancreatic NET in 1992. Since then, there

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have been many case series reporting the moderately high sensitivity of EUS (57-94%) in the diagnosis of insulinoma[3-14] and EUS was noted to be superior to other diagnostic modalities. However, EUS is operator dependent and not widely available outside tertiary care centers, therefore limiting its use in general practice. Although recent studies have shown better performance with the current CT and MRI technology[15], EUS is still accepted as the most sensitive method to detect insulinoma.

Siriraj Hospital has offered EUS service since 2004. In early years, we observed that the performance of EUS in detection of insulinoma was lower than expected, likely due to the poor image resolution of the first generation EUS system (i.e. mechanical radial EUS) and the limited-experience endosonographers. The combination of currently available electronic radial and curvilinear EUS and experience of dedicated EUS-trained endoscopists gained after 2007, the performance of EUS has improved significantly. Given the lack of data on diagnostic performance of EUS in localization of insulinoma in Thai patients, we conducted a retrospective study to explore the ability of EUS to diagnose and localize insulinoma as compared to CT and MRI.

Material and Method

Patients

Patients presented with recurrent hypoglycemia (fasting plasma glucose concentration less than 2.5 mmol/L or 45 mg/dL) and elevated insulin level (immunochemiluminometric plasma insulin concentrations greater than 18 pmol/L or 3 μU/mL) raising suspicion of insulinoma, who underwent electronic radial or linear EUS in Siriraj Hospital, Bangkok, Thailand during 2007 to 2012 were identified using patient database of the Endocrinology Clinic and the endoscopic database of the Vikit Viranuvatti Endoscopic Center, Siriraj Hospital. Patients who did not undergo EUS were not included in the present study. Patients' demographics, clinical presentations, laboratory results and EUS reports were reviewed and analyzed.

Insulinoma group

This group comprised of 14 patients. Definite diagnosis was made by surgical pathology.

Non-insulinoma group

Five patients who did not have insulinoma, either by surgery (n = 4) or by spontaneous improvement of hypoglycemia after long-term follow-up (n = 1). Two patients had nesidioblastosis or beta-cell hyperplasia diagnosed by surgery. Two patients had no insulinoma found during surgery and 1 patient improved spontaneously without surgery. All 5 cases were classified as control.

EUS

All EUS was performed by one of the authors (SP, NP and VP) using an electronic radial EUS (GF UE 160P, Olympus, Tokyo, Japan) or curvilinear EUS (GF UC 140P, Olympus, Tokyo, Japan). The decision to use radial or linear EUS with or without water balloon were up to the endosonographers.

CT and MRI

All CT scans were contrast-enhanced CT. However, details of the CT protocol (i.e. whether it was pancreatic protocol) were not available. All MRIs were performed in Siriraj Hospital with a 1.5 T MR imagers (Philips®) and the protocol included T1W, T2W and post gadolinium injection.

Location of insulinoma

Location of insulinoma was classified as pancreatic head (proximal to the portal vein confluence), neck (anterior to the portal vein confluence), body (distal to the portal vein confluence to the lateral border of left kidney) and tail (distal to the lateral border of left kidney).

Statistical analysis

Patients' characteristics, plasma glucose, insulin level and hemoglobin A_1C (HbA_1C) level were described as mean, standard deviation (mean $\pm$ SD), frequency and percentage. Comparison between groups used Chi-square test, Fisher-exact test or one-way ANOVA test as appropriate. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each diagnostic modality in the detection of insulinoma were calculated. The accuracy for each diagnostic modality was presented. SPSS statistics version 17.0 was used in the analysis.

Ethics

The present study was approved by Siriraj Institutional Review Board.

Results

Patients' characteristics

Characteristics of the 14 patients with insulinoma and 5 with non-insulinoma were demonstrated in

Table 1. Age of the patients with insulinoma was significantly older than those without (55 years vs. 37 years, p = 0.016). Both groups were predominantly female and all presented with neuroglycopenic symptoms. Mean duration of symptoms were similar. Means lowest plasma glucose and insulin level were not statistically different between the two groups. However, HbA_{1c} was lower in the insulinoma group (5.3% vs. 5.6%, p = 0.011).

Characteristics of insulinoma at surgery

Among the 14 patients with insulinoma, there were 15 insulinoma lesions demonstrated at surgery (there was 1 patient who had 2 lesions, both in the pancreatic tail). The mean maximum diameter of the lesions was 13 ± 5 mm (range 6-25 mm). Three lesions (20%) were smaller than 10 mm (6 mm, 8 mm and 8 mm). Locations of the insulinoma were as follows: 4 at pancreatic head (27%), 2 at neck (13%), 3 at body (20%) and 6 at tail (40%). One patient had malignant insulinoma with liver metastasis at presentation.

Endosonographic features of insulinoma

Fifteen insulinoma were detected by EUS. All were oval or round in shape. The echogenicity was hypoechoic in 9 (60%), hyperechoic in 2 (13%), isoechoic in 2 (13%) and mixed echogenicity in 1 (7%). These 4 EUS features are illustrated in Fig. 1.

Performance of EUS

EUS was performed in all 19 cases and could detect insulinoma in 14 of the 15 lesions (sensitivity 93%). The missed lesion was a 1-cm insulinoma located at the pancreatic neck. This patient's pancreas, however, had a background of suggestive chronic pancreatitis according to the Rose mont classification[16]. In contrast, EUS was negative in 4 out of the 5 patients without insulinoma (specificity 80%). The PPV and NPV were 93% and 80%, respectively. EUS correctly localized the sites of insulinoma in 13 out of 15 lesions (accuracy 87%). One case was EUS negative and in another EUS falsely located insulinoma from pancreatic tail to pancreatic body.

Performance of CT scan

CT scan was performed in 9 cases of insulinoma and 2 cases of those without insulinoma. CT detected insulinoma in 7 of the 9 lesions (sensitivity 78%) and none in the 2 controls (specificity 100%). The PPV and NPV were 100% and 50%, respectively. CT correctly localized insulinoma in 6 of 9 lesions (accuracy 67%). Two cases were CT negative and one case CT falsely located the lesion from pancreatic tail to pancreatic body.

Performance of MRI

MRI scan was performed in 7 cases of insulinoma and 3 cases of those without insulinoma.

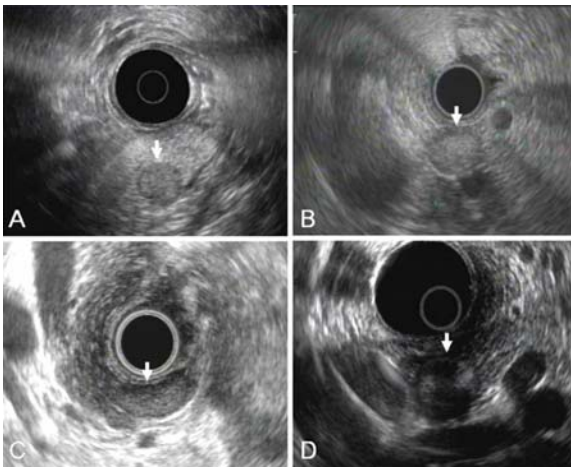

Fig. 1 The 4 endosonographicfeatures of insulinomaby EUS. A) hypoechoic nodule B) hyperechoicnodule C) isoechoic nodule D) mixed echogenicity nodule

Table 1. Characteristics of 14 patients with insulinoma and 5 patients without insulinoma

Characteristics	Insulinoma (n = 14)	Non-insulinoma (n = 5)	p-value
Age (year), mean ± SD	55.1 ± 13.6	37.2 ± 10.3	0.016
Female, n (%)	11 (78.6)	5 (100)	0.530
Neuroglycopenic symptoms, n (%)	14 (100)	6 (100)	1.000
Duration before diagnosis (mo), mean ± SD	16 ± 21	9.6 ± 15	0.544
Lowest plasma glucose (mg/dL), mean ± SD	34 ± 10	28 ± 9	0.256
Insulin level (μIU/mL), mean ± SD	30.1 ± 25.1	49.1 ± 45.5	0.221
Hemoglobin A1c (%), mean ± SD	5.3 ± 0.2	5.6 ± 0.2	0.011

MRI was able to detect insulinoma in 5 of the 7 lesions (sensitivity 71%) and 2 of the 3 controls (specificity 33%). The PPV and NPV were 71% and 33%, respectively. MRI localized insulinoma correctly in 4 of the 7 lesions (accuracy 57%). Two cases were MRI negative and one case MRI falsely located the lesion from pancreatic tail to pancreatic neck.

Performance of EUS, CT and MRI according to the size of insulinoma

The mean sizes of insulinoma detected by EUS, CT and MRI were 13 $\pm$ 5 mm, 13 $\pm$ 6 and 16 $\pm$ 4 mm, respectively, which were not statistically different (p = 0.418). Among the 3 insulinoma smaller than 10 mm (diameter 6, 8 and 8 mm each), EUS and CT similarly detected 2 out of the 3 lesions (67%). The missed lesion by both EUS and CT was 6 mm in size. MRI was not done in these 3 patients.

Value of EUS after performing CT or MRI

When considering the results of EUS after performing of CT, EUS changed the diagnosis or localization by CT in 2 of the 11 cases (18%). If CT was positive, EUS did not change any diagnosis or localization. In contrast, EUS was able to localize the lesion in 2 of 4 cases (50%) with negative CT scan. In MRI positive patients, EUS correctly changed the results in 2 out of 7 lesions (29%). If MRI was negative, EUS would provide the diagnosis in 2 of the 3 cases (67%). Thus, EUS correctly changed the diagnosis and localization of the lesion in 4/10 cases (40%) when being performed after MRI.

Discussion

The diagnosis and localization of insulinoma remains a diagnostic challenge for clinician. In the present study, we demonstrated that EUS was the most sensitive method (93%), followed by CT (78%) and MRI (71%). Specificity of EUS was lower (80%) than CT scan (100%) but higher than MRI (33%). Furthermore, EUS would make the diagnosis in 50% and 67% of the CT- or MRI- negative cases, respectively.

In the present study, we had 14 patients with insulinoma over a 6-year-period. There were 2 other patients already diagnosed with insulinoma by CT without the need for EUS, thus they were not included in the study. Detection of 16 insulinomas over the course of 6 years confirms the rarity of the disease. The mean age of the 14 insulinoma patients was 55 years and 79% were female. These numbers were comparable with those from the largest case series of insulinoma to date which included 224 patients and showed a mean age of 47 years and that 60% were female[1]. The 5 patients who eventually did not have insulinoma in the present study were younger and had higher level of HbA_{1C}. These probably reflected the fewer or milder episodes of hypoglycemia in the non-insulinoma group.

The sensitivity of EUS for insulinoma in the present study (93%) was comparable to those have been reported in the literature (57-94%)[3-14] and meta-analysis (75%)[17]. The only case missed by EUS had chronic pancreatitis in the background of the pancreas according to Rosemont classification[16]. It is well known that the presence of chronic pancreatitis can obscure the detection of pancreatic neoplasm by EUS[18]. Therefore, in addition to the current knowledge on the risk factors of false-negative EUS for insulinoma, which were low BMI[19], young age[19], female gender[19] and pancreatic tail lesion[7,12,14], the presence of chronic pancreatitis is probably another risk.

The sensitivity of CT scan in the present study (78%) was higher than most reports that used an older version of CT (0-73%, average 32%)[4,5,10,12,13,20], but lower than those of the recent studies which used multidetector CT (94-100%)[13,15]. The authors did not have complete information on the details of the CT techniques used in our patients, particularly patients who had CT from the outside hospitals. Nevertheless, it is likely that some cases did not undergo mutidetector CT and this might explain the lower sensitivity of CT in the present study. The sensitivity of MRI in the present study (71%) was higher than those from the past studies (7-25%)[5,10] but lower than in a recent study that reported a 100% sensitivity of MRI[15]. The differences in the MRI machines and protocols probably explained these discrepancies. Notably, the numbers of CT and MRI done in the present study were very small. Thus, a further larger study is required to confirm the results.

The authors found that size of insulinoma may not be an important factor that determines the diagnosis yield of each test since the mean size of insulinoma detected by each modality was not different. In fact, EUS and CT equally detected 2 of the 3 small insulinoma that were smaller than 1 cm.

Little is known about the specificities of EUS, CT and MRI for insulinoma because most of the previous studies focused mainly on the sensitivity. The specificity of EUS in the present study (80%) was lower than the 2 previous reports that showed a 95-100%

specificity[2,11]. In the present study, EUS falsely diagnosed insulinoma in 1 out of the 5 controls. This lesion was detected at the surface of the pancreatic head and indeed was labeled as equivocal by the endosonographer. Therefore, the true specificity of EUS in the present study would be considered higher. The present study showed that CT had higher specificity (100%) than EUS and MRI. This finding was probably not unexpected since CT findings of insulinoma are arterial enhancing lesion and/or blushing, which are quite specific and rare for other pancreatic pathologies. MRI, however, was shown to have poor specificity in the present study. The reason is unclear but the visualization of the pancreas by MRI is often more difficult and more confusing than CT and is a similar problem as MRI in acute pancreatitis, which has not gained acceptance as CT[21]. However, because the numbers of CT and MRI in the present study were very small, the result should be interpreted with caution.

The accuracies of EUS and CT to locate insulinoma were excellent. If the lesion was detected, it was correctly localized. The only case of falsely localized insulinoma by both EUS and CT was mistaken from pancreatic tail to pancreatic body. On the review, this mass lay between the body and tail. Therefore, it might be erroneously localized because currently the landmark dividing pancreatic body and tail is still arbitrary and probably differs among clinicians. The present study did not support the belief that EUS often misses insulinoma at pancreatic tail (sensitivity 83% in the present study vs. 40-50% in the literatures)[7,12,14]. The reasons might be due to the small number of the tail lesions (6 cases) and the higher level of awareness of the endosonographers in Siriraj Hospital about the weakness of EUS in pancreatic tail. Thus, our endosonographers usually pay great attention at this area.

Using the above information and the data on the value of EUS after performing CT or MRI, the authors suggested that 1) EUS should be the first-line investigation due to the excellent sensitivity (93%) and good specificity (80%). 2) Positive EUS may require no further test because the PPV is high (93%). However, the NPV of EUS is not good enough (80%), thus negative EUS requires further work-up, *i.e.*, MDCT. 3) Positive CT has a very high specificity and PPV (100%), hence, may preclude further tests, while negative CT should be further backed up with EUS. 4. MRI is neither sensitive (71%) nor specific (33%), thus, either positive or negative MRI requires EUS, unless a better quality MRI is available.

In the present study, the authors also confirmed the observation by others that the most common feature of insulinoma by EUS is a hypoechoic nodule[20] and larger masses may appear hyperechoic or mixed echoic[20]. It is also suggestive that insulinoma has no site preference. The present study showed the tail preponderance (40%), followed by head (27%). Some previous studies also showed the more common tail lesions as did ours[5]. However, some differently showed head preponderance[11,14]. The main reason is likely the small number of cases in each study. The exact distribution of insulinoma remains unknown and needs a larger study or a systematic review.

There were some weaknesses of the present study. First, the number of cases was small and the present study is retrospective. However, this is difficult to avoid due to the rarity of the disease. Second, some data was missing, e.g. the details of the CT technique. The strength of our study was that most patients had surgery and negative cases allowed us to evaluate the specificity and the predictive values of EUS, CT and MRI.

In conclusion, EUS had the best overall performance to detect and localize insulinoma. CT was less sensitive but very specific. Positive CT may preclude the need of EUS. MRI is less sensitive and specific than CT. Either positive or negative MRI require further EUS.

Potential conflicts of interest

None.

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การวินิจฉัยและบอกตำแหน่งของอินซูลินโนมาในคนไทยด้วยการส่องกล้องอัลตราซาวนด์เทียบกับการตรวจเอกซเรย์คอมพิวเตอร์ และการตรวจคลื่นแม่เหล็ก

สุพจน์ พงศ์ประสบชัย, ระวีวรรณ เลิศวัฒนารักษ์, นนทลี เผ่าสวัสดิ์, วรายุ ปรัชญกุล

***ภูมิหลัง**: การส่องกล้องอัลตราซาวนด์ได้รับการยอมรับว่าเป็นการตรวจที่ไวที่สุดในการหาอินซูลินโนมา แต่ข้อมูลในคนไทยรวมทั้งความแม่นยำเมื่อเทียบกับเอกซเรย์คอมพิวเตอร์หรือการตรวจคลื่นแม่เหล็กยังไม่ทราบแน่ชัด*

***วัสดุและวิธีการ**: เป็นการศึกษาแบบย้อนหลังในผู้ป่วย 19 รายที่มาด้วยอาการน้ำตาลในเลือดต่ำซ้ำๆ ที่สงสัยอินซูลินโนมาและได้รับการส่องกล้องอัลตราซาวนด์ ร่วมกับเอกซเรย์คอมพิวเตอร์หรือการตรวจคลื่นแม่เหล็กเพื่อหารอยโรคตั้งแต่ปี พ.ศ. 2550 ถึง พ.ศ. 2555 โดยถือผลจากการผ่าตัดหรือผลจากการติดตามระยะยาวเป็นการวินิจฉัยสุดท้าย*

***ผลการศึกษา**: มีผู้ป่วยอินซูลินโนมาทั้งหมด 14 ราย ซึ่งมีอินซูลินโนมา 15 ตำแหน่ง และผู้ป่วยที่ไม่ใช่อินซูลินโนมา 5 ราย (2 รายเป็นเนซิดิโอบลาสโตสิส และ 3 รายไม่พบสาเหตุ) ผู้ป่วยได้รับการตรวจส่องกล้องอัลตราซาวนด์ เอกซเรย์คอมพิวเตอร์ และคลื่นแม่เหล็ก 19 ราย, 11 ราย และ 10 รายตามลำดับ การส่องกล้องอัลตราซาวนด์สามารถตรวจพบ อินซูลินโนมาด้วยความไว ความจำเพาะ คำทำนายเมื่อผลบวก และคำทำนายเมื่อผลลบร้อยละ 93, 80, 93 และ 80 ตามลำดับ, เอกซเรย์คอมพิวเตอร์ร้อยละ 78, 100, 100 และ 50 ตามลำดับ และการตรวจคลื่นแม่เหล็กร้อยละ 71, 33, 71 และ 33 ตามลำดับ ในผู้ป่วยที่เอกซเรย์คอมพิวเตอร์พบรอยโรคแล้วการส่องกล้องอัลตราซาวนด์ไม่ได้เปลี่ยนแปลงการวินิจฉัยใดๆ แต่หากเอกซเรย์คอมพิวเตอร์ไม่พบรอยโรค การส่องกล้องอัลตราซาวนด์พบอินซูลินโนมาได้ร้อยละ 50 ในผู้ป่วยที่ตรวจคลื่นแม่เหล็กพบรอยโรคแล้วการส่องกล้องอัลตราซาวนด์เปลี่ยนแปลงการวินิจฉัยร้อยละ 29 ถ้าการตรวจคลื่นแม่เหล็กไม่พบรอยโรคการส่องกล้องอัลตราซาวนด์จะพบอินซูลินโนมาได้ร้อยละ 67 การส่องกล้องอัลตราซาวนด์เอกซเรย์คอมพิวเตอร์ และการตรวจคลื่นแม่เหล็กบอกตำแหน่งของอินซูลินโนมาได้ถูกต้องร้อยละ 87, 67 และ 57 ตามลำดับ ความผิดพลาดที่พบบ่อยที่สุดคือการบอกตำแหน่งระหว่างตับอ่อนส่วนตัวและหาง*

***สรุป**: การส่องกล้องอัลตราซาวนด์มีความแม่นยำมากที่สุดในการวินิจฉัยและบอกตำแหน่งของอินซูลินโนมา เอกซเรย์คอมพิวเตอร์มีความไวน้อยกว่าแต่จำเพาะมากกว่า หากตรวจพบรอยโรคอาจไม่ต้องตรวจส่องกล้องอัลตราซาวนด์ต่อการตรวจคลื่นแม่เหล็กมีความไวและความจำเพาะน้อยกว่าเอกซเรย์คอมพิวเตอร์ทำให้ไม่ว่าจะพบหรือไม่พบรอยโรคควรได้รับการส่องกล้องอัลตราซาวนด์ต่อไป*