Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis

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Background: Current guidelines recommend CT scan or magnetic resonance imaging as the initial imaging modalities for the work-up of suspected pancreatic neuroendocrine tumors (PNETs).

Objective: To determine the incremental benefit of preoperative EUS (IB_{EUS}) for the detection of suspected PNETs after other investigative modalities have been attempted.

Design: This systematic review searched MEDLINE, EMBASE, bibliographies of included articles, and conference proceedings for studies reporting original data regarding the preoperative detection of PNETs. Pooled IB_{EUS} was calculated by using random effects models. Heterogeneity was explored by using stratified meta-analysis and meta-regression. Evidence of small-study effects was assessed by using funnel plots and the Begg test.

Patients: Patients with suspected PNETs.

Interventions: EUS evaluation.

Main Outcome Measurements: The pooled IB_{EUS} for the detection of PNETs after CT scan, with or without additional investigative modalities.

Results: Among 4505 citations identified, we included 17 cohort studies (612 patients). EUS identified PNETs in 97% of cases. Improved PNET identification with EUS was observed in all of the studies. After adjusting for small-study effects, meta-analysis showed that EUS alone could identify PNETs in approximately 1 in 4 patients (adjusted IB_{EUS} 26%; 95% confidence interval, 17%-37%). The pooled IB_{EUS} varied based on the study design, study size, type of CT scan used, and the number of modalities used prior to EUS.

Limitations: The majority of included studies were retrospective. Small-study effects were observed.

Conclusion: Preoperative EUS is associated with an increase in PNET detection after other modalities are attempted. (Gastrointest Endosc 2015;81:848-56.)

Abbreviations: IB_{EUS}, incremental benefit of preoperative EUS; MEN-1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PET, positron emission tomography; PNET, pancreatic neuroendocrine tumor.

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Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms, with a prevalence of 1 to 2/100,000 people.[1] There has been an increase in the diagnosis of PNETs,[2] which has been attributed to the ability of modern imaging modalities to detect otherwise silent tumors.[3] Data from autopsy series report that the incidence of small (<1 cm) PNETs ranges from 0.8% to 10%.[4]

Although there is some evidence that small, asymptomatic tumors can be managed with regular observation,[5] complete surgical resection is the only potential curative therapy for PNETs.[6] In order to optimize surgical management, correct preoperative localization and staging of PNETs is ideal. Current guidelines recommend CT or magnetic resonance imaging (MRI) as the initial imaging modality for the initial work-up for suspected PNETs.[7-12] These imaging techniques are able to detect PNETs with an estimated sensitivity of 40% to 80%.[6,7] Somatostatin receptor scintigraphy is highly sensitive (up to 90%) to PNETs expressing somatostatin receptors.[13] Benign insulinomas, however, often do not express somatostatin receptors sufficiently, and thus somatostatin receptor scintigraphy sensitivity for their detection falls to below 60%.[14] Positron emission tomography (PET) has excellent spatial resolution and is able to quantify tracer uptake. Several specific tracers have been used for the detection of PNETs, among which ^{68}Ga-labeled DOTA-D-Phe^{1}-Tyr^{3}-octreotide is the most widely used.[15] ^{11}C-5-hydroxy-L-tryptophan can identify up to 90% of well-differentiated PNETs and seems to have the optimal properties for staging PNETs; however, it is not widely available.[16] Selective intra-arterial injection of secretin or calcium during angiography with hepatic venous sampling has been shown to have a wide range of sensitivities for detecting PNETs, carries the risk of angiography, and is resource-intensive.[7,17]

EUS has an excellent sensitivity and specificity for the detection of pancreatic PNETs,[18] although this may not translate into EUS being clinically beneficial after other technologies have been used to detect PNETs. There are several reports demonstrating that EUS correctly identifies PNETs missed on previous imaging modalities; however, the study settings, designs, and results vary. Further, the incremental benefit of using EUS to detect PNETs after other radiologic modalities have been attempted has not previously been quantified. We therefore conducted a systematic review and meta-analysis to determine the incremental benefit of preoperative EUS (IB_{EUS}) for the detection of suspected PNETs.

METHODS

This study was conducted by using a detailed protocol created a priori in accordance with guidelines for systematic reviews and meta-analyses of observational studies.[19]

Search strategy

Two investigators (P.J., M.Z.) created an initial electronic bibliographic database search strategy, which was subsequently refined by a medical librarian with extensive systematic review experience. On January 18, 2014, we conducted unrestricted searches of MEDLINE and EMBASE from their first available date for studies reporting on the association between EUS and patients with neuroendocrine tumors. We also searched the reference lists of conference proceedings published over the previous 3 years by representative organizations (the American College of Gastroenterology, the American Gastroenterology Association, the American College of Surgeons, the Canadian Association of Gastroenterology, and the European Neuroendocrine Tumour Society) and contacted relevant field experts. We reviewed full-text and abstract publications. Articles published in all languages were considered.

In MEDLINE, we created 4 comprehensive search themes. The first theme, *endoscopic ultrasound,* combined exploded versions of the medical subject heading terms *endoscopic ultrasound-guided fine-needle aspiration* or *endosonography*. The second theme, *pancreatic neoplasms*, was aimed at including all studies that could consider PNETs for their main or sub-analyses. The theme combined exploded versions of medical subject heading terms *pancreatic cyst, mucinous and serous neoplasms, carcinoma in situ, pancreatic ductal carcinoma, papillary carcinoma, papillary adenocarcinoma, mucinous adenocarcinoma, mucinous cystadenocarcinoma, noninfiltrating intraductal carcinoma, bile duct neoplasms, acinar cell carcinoma, neuroendocrine tumors, endocrine gland neoplasms, islet cell adenoma, gastrinoma, vipoma, glucagonoma.* The third theme, *general surgery*, combined exploded versions of medical subject heading terms *operatic surgical procedures, pancreatectomy, laparotomy, pancreaticoduodenectomy*. The *endoscopic ultrasound*, *pancreatic neoplasms,* and *general surgery* search themes were combined by using the Boolean operator "and."

Study selection

Two reviewers (P.J., M.Z.) independently reviewed abstracts and titles to identify potentially relevant articles that appeared to report original data on the influence of EUS on the localization of PNETs. The same reviewers (P.J., M.Z.) subsequently read all potentially relevant articles independently and in full. We used the following inclusion criteria: (1) the study population involved adult patients ≥18 years with PNET; (2) the intervention was preoperative use of EUS; (3) the comparator was exposure to a CT scan with or without other imaging modalities, including MRI, abdominal US, and PET scan; and (4) the outcome included the detection of PNETs. Both published and unpublished studies were eligible for inclusion. Studies with insufficient or duplicate data were excluded.