The impact of preoperative endoscopic ultrasound on the surgical management of pancreatic neuroendocrine tumours

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BACKGROUND: Endoscopic ultrasound (EUS) is accurate in diagnosing pancreatic neuroendocrine tumours (PNETs), but its impact on surgical management is unclear.

OBJECTIVE: To determine whether preoperative EUS findings altered the decision for, and extent of, surgery in patients with PNETs.

METHODS: A retrospective review of patients referred for EUS because of suspected PNETs was conducted. The diagnosis of PNETs was confirmed by EUS-guided fine needle aspiration cytology, where indicated, or by surgical histology. EUS findings were compared with computed tomography (CT) findings to determine whether there was an impact on the decision for surgical management.

RESULTS: Fourteen patients (10 women), with a mean age of 44 years, underwent EUS for suspected PNETs. PNETs were seen with CT in 10 of 13 patients (77%) and with EUS in 14 of 14 patients (100%). One obese patient could not fit into the CT scanner. This patient had five PNETs on EUS. Three patients with a normal CT scan were determined to have one or two PNETs on EUS. Three patients with one or two PNETs on CT were found to have five to eight PNETs on EUS. EUS altered the decision for possible surgical management in five of 14 patients (36%), either by identifying a PNET or by finding multiple and multifocal PNETs that were not visualized on CT scans.

CONCLUSION: EUS is useful in the preoperative assessment of PNETs by providing information that significantly influences the decision for surgical intervention or changes the extent of the planned surgery.

Key Words: *Biopsy; Endosonography; Neuroendocrine tumour; Outcome; Pancreas*

Les répercussions de l'endoscopie préopértoire sur la prise en charge chirurgicale des tumeurs neuroendocriniennes du pancréas

HISTORIQUE : L'endoscopie est une méthode précise pour diagnostiquer les tumeurs neuroendocriniennes du pancréas (TNEP), mais on n'en connaît pas exactement les répercussions sur la prise en charge chirurgicale.

OBJECTIF : Déterminer si les résultats des endoscopies préopératoires modifient la décision d'opérer les patients atteints de TNEP et l'importance de la chirurgie.

MÉTHODOLOGIE : Les auteurs ont procédé à une analyse rétrospective des patients aiguillés en vue de subir une endoscopie à cause de TNEP présumées. Le diagnostic de TNEP était confirmé au moyen d'une cytologie par aspiration à l'aiguille guidée par endoscopie, au besoin, ou d'une histologie chirurgicale. Les auteurs ont comparé les résultats de l'endoscopie à ceux de la tomodensitométrie pour déterminer si la première avait des répercussions sur la décision de prise en charge chirurgicale.

RÉSULTATS : Quatorze patients (dix femmes) d'un âge moyen de 44 ans ont subi une endoscopie à cause de TNEP présumées. La tomodensitométrie a révélé des TNEP chez dix des 13 patients (77 %) et l'endoscopie, chez 14 des 14 patients (100 %). Un patient obèse ne pouvait pénétrer dans le tomodensitomètre. Ce patient avait cinq TNEP selon l'endoscopie. Chez trois patients dont la tomodensitométrie était normale, l'endoscopie a révélé une ou deux TNEP. Trois patients ayant une ou deux TNEP à la tomodensitométrie en avaient de cinq à huit à l'endoscopie. L'endoscopie a modifié la décision de possibilité de prise en charge chirurgicale chez cinq des 14 patients (36 %), que ce soit à cause de la découverte de TNEP ou de TNEP multiples et multifocales qu'on n'avait pas vues à la tomodensitométrie.

CONCLUSION : L'endoscopie est utile pour l'évaluation préopératoire de TNEP parce qu'elle fournit de l'information qui influe de manière significative sur la décision d'intervention chirurgicale ou qu'elle modifie l'importance de l'opération prévue.

Pancreatic neuroendocrine tumours (PNETs) are relatively uncommon and account for only 1% to 2% of all pancreatic neoplasms (1). They are commonly discovered between the fourth and fifth decades of life, with a slight female predominance (2).

PNETs can occur sporadically or may be associated with inherited syndromes, such as multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease, von Recklinghausen disease and tuberous sclerosis (3). Up to 30% of patients with MEN1 have clinically apparent PNETs or gastrointestinal neuroendocrine tumours. However, subclinical involvement can be demonstrated in up to 80% of patients (4). Gastrinomas and insulinomas are the most common functional PNETs in MEN1, accounting for 40% and 10% of patients, respectively (5).

Because PNETs are slow-growing tumours, their prognosis is good, and many patients can be cured with surgical resection. Despite various radiographic imaging techniques, such as transabdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography and octreotide scintigraphy, up to 30% of PNETs can be missed during preoperative evaluation (6). Published data suggest the superiority of endoscopic ultrasound (EUS) in detecting and localizing PNETs, particularly those smaller

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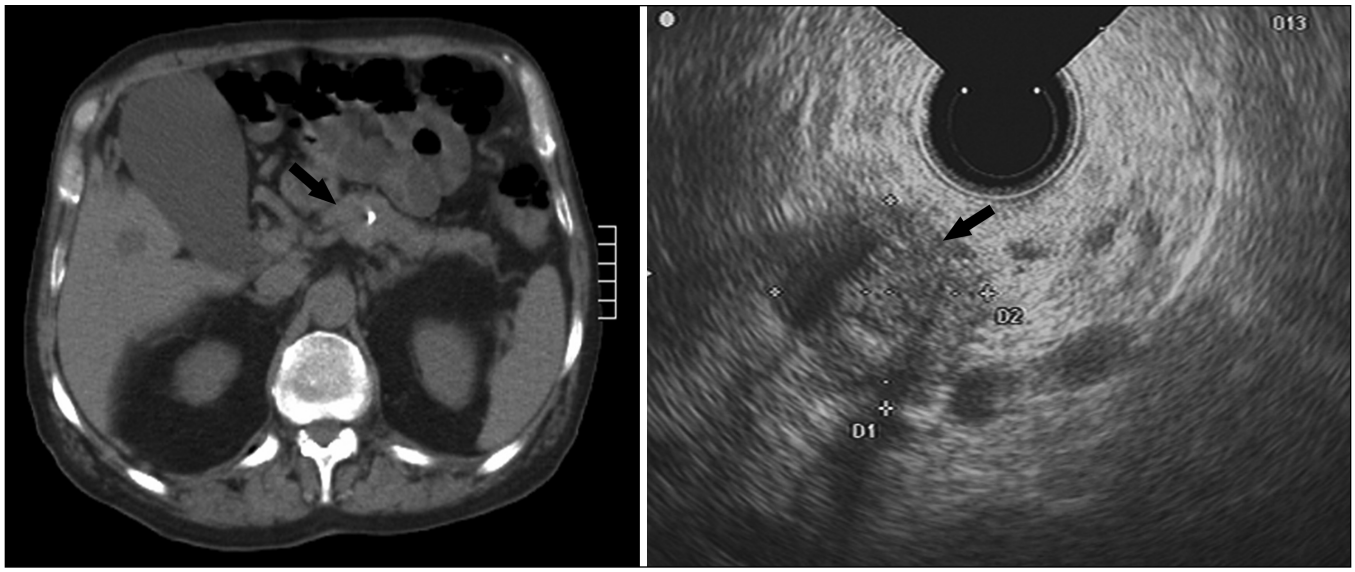

Figure 1) Left panel *Computed tomography image showing a 'calcified' focus within the body of a pancreas, but no definite mass was reported (arrow).* **Right panel** *Endosonographic image showing a discrete hypoechoic mass (arrow) within the body of a pancreas. Endoscopic ultrasound-guided fine needle aspiration from a mass reported as a neuroendocrine tumour*

than 2 cm in size, compared with ultrasound, CT, MRI and endoscopic retrograde cholangiopancreatography (7-9). In asymptomatic patients with MEN1, EUS was able to identify 82% of PNETs before the development of significant biochemical test abnormalities (4). EUS alone has a limited ability to differentiate between benign and malignant PNETs, but the diagnostic accuracy can be enhanced with EUS-guided fine needle aspiration (FNA), which can be performed in most patients (10). Despite the usefulness of EUS performed with or without FNA as an accurate diagnostic tool, there are limited data regarding its impact on the change in surgical management of PNETs.

The goal of the present study was to assess the impact of preoperative EUS on the decisions regarding surgical management of patients with PNETs.

METHODS

Patients

A retrospective chart review of patients with suspected PNETs who underwent EUS at the University of Alberta Hospital (Edmonton, Alberta) between February 2004 and January 2008 was performed. The diagnosis of PNETs was confirmed by EUS-guided FNA cytology and subsequent surgical pathology, where resection was indicated. Patients who were confirmed to have metastatic disease and were still considered for possible surgery had a tissue diagnosis obtained from the metastatic lesion and therefore may not have had EUS-FNA cytology or surgical histology. Relevant data, including patient demographics, radiographic imaging and surgical histology, were collected.

EUS examination

During the study period, all EUS procedures were performed by a single experienced endosonographer (Dr Sandha; experience with more than 1250 EUS procedures) using the Pentax EG3630UR radial echoendoscope (Pentax Precision Instruments, USA). PNETs were seen as well-encapsulated, homogeneous and isoechoic or slightly hypoechoic masses (Figure 1). When necessary, EUS-FNA was performed using the Pentax EG3630U or EG3630UT curvilinear array echoendoscope (Pentax Precision Instruments, USA) and a 22-gauge Wilson-Cook Echotip or Echotip-Ultra needle (Wilson-Cook Medical Inc, USA). All patients provided informed consent before undergoing the procedure. Procedures were performed in the endoscopy unit under conscious sedation with midazolam and meperidine.

Ethics

The study was approved by the Health Research Ethics Board at the University of Alberta, including a chart review of all patients.

RESULTS

Between February 2004 and January 2008, 14 patients suspected of having a PNET based on clinical features and/or radiographic imaging underwent EUS with or without FNA. The patient population included 10 women (71%), and the mean age of the study group was 44 years (range 23 to 69 years). Eight patients (57%) were known to have MEN1. The size of PNETs ranged from 0.4 cm to 2.5 cm in maximum diameter (Table 1). Most of the tumours were located in the body and/or tail of the pancreas (12 of 14 patients [86%]).

CT was performed in 13 of 14 patients and suggested the presence of a PNET in 10 of 13 patients (77%). Of these, nine patients had vascular enhancing lesions suggestive of a PNET. One morbidly obese patient could not fit into the CT scanner. Other imaging modalities performed included MRI in six of 14 patients with a PNET seen in four of six patients (67%) and an octreotide scan in eight of 14 patients, with a PNET identified in four of eight patients (50%).

EUS identified a PNET in 14 of 14 patients (100%). EUS-FNA was performed in 10 of 14 patients, with positive cytology in nine of 10 patients (90%). EUS-FNA cytology or surgical pathology confirmed EUS findings of a PNET in 12 of 14 patients. Two patients did not have EUS-FNA cytology or surgical histology to confirm the diagnosis because of the presence of metastatic disease to liver and lung, respectively, documented by tissue diagnosis.

TABLE 1
Demographic data of patient cohort

Patient	Age, years	Sex	MEN1 present	PNET identified by			Size of PNET	Surgery performed
				CT	EUS	EUS-FNA		
1	49	Female	Yes	Yes	Yes	Yes	0.9 cm, 1.5 cm	Yes
2	62	Female	No	Yes	Yes	No	1 cm	Yes
3	47	Female	Yes	Yes	Yes	ND	8 lesions, largest 1 cm	Yes
4	51	Female	No	Yes	Yes	Yes	1.2 cm	Yes
5	67	Male	No	No	Yes	Yes	2.5 cm	No (liver metastasis)*
6	23	Female	Yes	No	Yes	Yes	0.4 cm, 1 cm	Yes
7	38	Male	Yes	ND	Yes	Yes	5 lesions, largest 2.2 cm	No (awaiting surgery)*
8	50	Female	No	Yes	Yes	Yes	2.2 cm	Yes
9	33	Female	Yes	No	Yes	ND	0.8 cm	Yes
10	56	Female	No	Yes	Yes	Yes	1.6 cm	Yes
11	28	Female	Yes	Yes	Yes	Yes	7 lesions, largest 1 cm	Yes
12	34	Male	Yes	Yes	Yes	ND	5 lesions, largest 1.9 cm	No (liver metastasis)*
13	40	Male	Yes	Yes	Yes	ND	10 lesions, all <0.5 cm	No (lung metastasis)*
14	41	Female	No	Yes	Yes	Yes	1.8 cm	Yes

**Reason surgery was not performed. CT Computed tomography; EUS Endoscopic ultrasound; EUS-FNA EUS-guided fine needle aspiration; MEN1 Multiple endocrine neoplasia type 1; ND Not done; PNET Pancreatic neuroendocrine tumour*

The morbidly obese patient who could not have a CT scan was found to have five PNETs on EUS. These were confirmed by EUS-FNA. Three patients (two of whom had MEN1) reported to have a normal CT were found to have one or two PNETs by EUS. The PNETs were confirmed by EUS-FNA and/or surgical pathology. In three other patients, in whom CT identified one or two PNETs, preoperative EUS found five to eight PNETs, resulting in a change in the extent of the planned surgery from distal pancreatectomy to total pancreatectomy.

A definite diagnosis of a PNET or the finding of multiple and/or multifocal PNETs, not seen or appreciated on a CT scan, was only made during preoperative EUS in seven of 14 patients (50%). One of these patients (patient 7 in Table 1) was currently awaiting surgery. Another patient (patient 5 in Table 1) was not considered for surgery when subsequent metastasis to the liver was found. Surgical intervention was also not performed in a young patient (patient 12 in Table 1) who was initially considered for aggressive surgery despite having documented metastasis. Overall, the information obtained with a preoperative EUS examination had a definite impact on the decision for surgical intervention for PNETs in five of 14 patients (36%).

DISCUSSION

Neuroendocrine tumours are a heterogeneous group of neoplasms that originate from a common precursor cell population that shares a number of antigens with nerve elements, such as neuron-specific enolase and chromogranins (11). PNETs are uncommon tumours of the pancreas, accounting for only 1% to 2% of all primary pancreatic neoplasms. The incidence of PNETs has been estimated to be approximately 0.4 to 1.0 in 100,000 people. However, in autopsy and surgical series, up to 15% of pancreatic neoplasms have been identified as PNETs (11,12).

Most PNETs are well- to moderately differentiated, and can be classified as those associated with a clinical syndrome caused by excessive hormone production (functional or syndromic PNETs) or those without such an association (nonfunctional or nonsyndromic PNETs) (13). Between 70% and 85% of PNETs are functional, with insulinomas accounting for 40% to 60% and gastrinomas accounting for 20% to 30%.

PNETs vary in size, ranging from smaller than 1 cm to 5 cm or larger, and are benign in up to 40% of cases. Differentiation between benign and malignant PNETs can be difficult, although the presence of local invasion of adjacent organs or distant metastasis usually indicates malignant behaviour (14,15). Even in the face of metastatic disease, the prognosis of PNETs is more favourable than the more common pancreatic adenocarcinoma. Hence, a stepwise preoperative evaluation for PNET localization is very important for potentially curative surgery.

Despite the advances in imaging modalities, up to 30% of PNETs can be missed during a preoperative assessment. The sensitivity of transabdominal ultrasound for detecting PNETs ranges from 20% to 86% and increases with tumour size (16). Similarly, the sensitivity of nonhelical CT of the abdomen is reported to be 30% if the size of the primary tumour is between 1 cm and 3 cm, and 95% if it is larger than 3 cm, although a primary tumour smaller than 1 cm is rarely detected. The sensitivity of a CT scan can be enhanced using a multiphase and multidetector CT scanner. MRI is just as accurate as a CT scan for localizing PNETs. As with ultrasound and CT, tumour detection using MRI increases with tumour size. The overall sensitivity of MRI is between 85% and 94%, with a specificity of 78% to 100% (16-18). Because 80% to 90% of neuroendocrine tumours have somatostatin receptors, octreotide scintigraphy could potentially be the initial imaging procedure of choice. However, there are pitfalls in localizing small tumours and tumours that lack somatostatin receptors (19). Because these modalities are not accurate enough for preoperative visualization and identification of PNETs in the pancreas, which is paramount in planning the extent of surgery, intraoperative ultrasound (IOUS) has been used for direct examination of the pancreas (20). In this study (20), IOUS was found to localize 96% of PNETs and 58% of non-PNETs. The authors concluded that IOUS altered surgical management in 11% of gastrinomas, mainly by identifying additional gastrinomas or determining that the gastrinoma was malignant.

However, this modality requires laparoscopy or laparotomy, and decisions regarding the extent of surgical intervention required cannot easily be made and discussed with patients preoperatively.

EUS enables a high-frequency ultrasound probe to be placed in close proximity to the pancreas. Compared with other imaging modalities, EUS was more accurate in detecting and localizing PNETs, especially those smaller than 2.5 cm, with an overall accuracy between 89% and 97% (21-24). Varas Lorenzo et al (6) compared preoperative EUS with transabdominal ultrasound, CT, MRI, angiography and OctreoScan (Mid-South Imaging and Therapeutics, USA) in 37 patients suspected to have gastrointestinal neuroendocrine tumours. The sensitivity and specificity of EUS was 78% and 80%, respectively. EUS detected three PNETs (all insulinomas) that were smaller than 1 cm in size, which were missed by ultrasound, CT and MRI (6). In most cases, adding EUS-FNA to a basic EUS examination enhances the sensitivity of EUS by providing a cytological diagnosis without the risk of significant complications or the need for exploratory surgery (25). Jani et al (9) recently reported 41 patients with PNETs diagnosed by EUS-guided FNA. Interestingly, 85% of the tumours were nonfunctional and all of these nonfunctional tumours were discovered incidentally on CT scan. Surgical resection was performed in 78% of cases. Precise localization of the tumours in the body or the tail of the pancreas by EUS led to laparoscopic resection of these tumours in 34% of patients. Nine patients (22%) did not undergo surgery because of tumour metastasis, significant medical comorbidity or patient refusal (9).

Our study has some obvious limitations. It was a single-centre, retrospective review of a relatively small number of patients. However, our results suggest that preoperative EUS had a significant impact on the possible surgical management of 50% of patients and on definite surgical management in 36% of patients suspected of having PNETs. Patients with PNETs identified by EUS were then scheduled for surgery, and those who were found to have multiple and multifocal lesions underwent total pancreatectomy, instead of distal pancreatectomy, which was planned originally based on standard radiographic imaging. We currently do not routinely perform EUS-guided FNA in PNETs. This procedure is indicated only for those patients in whom a neuroendocrine tumour or syndrome, such as MEN1, is in doubt or when a CT scan has failed to localize a mass but one is suspected based on biochemical abnormalities.

Our results suggest that EUS with or without FNA is a very helpful diagnostic tool in the preoperative assessment of patients suspected of having PNETs, particularly in patients at risk for multifocal disease such as those with MEN1. The information obtained is important for surgeons to plan surgery in advance and preoperatively discuss the appropriate procedure with the patients.

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