Case Series

# Clinical Usefulness of Endoscopic Ultrasonography With or Without Fine Needle Aspiration in the Diagnosis and Staging of Pancreatic Carcinoma

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## Abstract

**Introduction: The aims of this study was to show the accuracy and clinical usefulness of endoscopic ultrasonography (EUS) with EUS-guided fine needle aspiration (FNA) in the diagnosis and staging of pancreatic cancer not obvious in computed tomographic (CT) scan abdomen imaging. Materials and Methods: Five male patients were evaluated; 4 presented with obstructive jaundice and 1 had unexplained loss of weight. The mean age was 66 years (range, 40 to 77). All had CT scan abdomen imaging which did not show any obvious pancreatic tumour. EUS with FNA was done for all cases when indicated. Surgical findings, if any, were obtained and compared to EUS findings. Results: EUS easily detected the pancreatic tumour in all 5 cases. The tumour sizes detected ranged from 27 to 40 mm in diameter. These corresponded fairly accurately with that of surgical findings for all 3 who had surgery. EUS reported 3 cases with pathological lymph node involvement. All 5 cases were confirmed by FNA or surgery. EUS was also accurate in 4 cases, which reported the absence of portal vein or superior mesenteric vein invasion. Surgical documentation could not verify the fifth case. There were no complications at all from the EUS with/without FNA. Conclusion: This case series showed that EUS with/without FNA appears to be useful and safe in diagnosing and staging pancreatic head tumours not detectable by CT scanning.**

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**Key words: Endoscopic ultrasound, Fine needle aspiration, Pancreatic cancer**

## Introduction

Pancreatic cancer is notoriously known to be diagnosed in the later stages and this carries with it a poor prognosis. In particular, tumours involving the head of pancreas are particularly difficult to diagnose early and computed tomography (CT) scanning often fails to detect an early tumuor at that site. In many instances, "bulkiness of the head of pancreas" was reported by the radiologist when a tumour was not evident.

Endoscopic ultrasonography (EUS) has revolutionised endoscopic diagnosis and management and has been objectively proven to be superior to other forms of radiological imaging [conventional ultrasonography, CT scanning, magnetic resonance imaging (MRI)] in terms of sensitivity and specificity in T staging of cancers of the gastrointestinal tract, especially that of the oesophagus, pancreas and the rectum. It is also superior to CT scanning in detecting early head of pancreas tumours which are not easily seen radiologically.

This is a case series of 5 patients who presented with common bile duct strictures (secondary to head of pancreas tumour) which were all not detected by CT scanning, but by EUS and proven by fine needle aspiration (FNA) of the lesions.

## Case Series

*Patient A*

A 77-year-old Chinese man with a history of non-insulin-dependent diabetes mellitus was admitted for the problem of obstructive jaundice. Abdominal examination revealed no organomegaly. Liver function test showed a cholestatic picture [bilirubin (bil) = 171 umol/L, albumin (alb) = 37 g/dL, alkaline phosphatase (ALP) = 299 U/L, alanine aminotransferase (ALT) = 406 U/L, aspartate amino-

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transferase (AST) = 308 U/L, gamma-glutamyl transpeptidase (GGT) = 877 U/L, CA 19-9 = 530 U/mL and carcinoembryonic antigen (CEA) = 2.4 ug/L. CT scan of the abdomen showed moderate dilatation of the intrahepatic, extrahepatic and pancreatic ducts. A small irregular hyperdensity was seen in the distal common bile duct near the insertion into the duodenum. However, no definite pancreatic mass was reported (Fig. 1).

Endoscopic retrograde cholangio-pancreaticography (ERCP) showed a normal-looking ampulla, but with an adjacent submucosal bulge. Contrast injection revealed a short, smooth stricture at the lower end of the common bile duct with proximal dilatation. The pancreatic duct was not opacified. Biopsy of the ampulla and deployment of a stent were done. The ampullary histology came back as chronic inflammation with no specific features.

EUS was done with a Pentax EG 3630 UR radial echoendoscope (Pentax Corporation, Tokyo, Japan) and a Hitachi EUB 6500 ultrasound scanner (Hitachi Medical, Tokyo, Japan), where good sonographic images were obtained. A definite hypoechoic, irregular mass (about 40 mm in diameter) was seen at the head of pancreas. This appeared to abut on the portal vein, but no definite vascular invasion was present. A 10-mm peri-pancreatic lymph node was also detected (Fig. 2). The pancreatic duct was dilated to about 10 mm. The rest of the pancreas appeared normal. No coeliac axis lymphadenopathy was detected. The EUS staging was T2N1MX. The scope was removed and a Pentax EG 3630 U convex echoendoscope was passed into the duodenum. The mass was located, and colour and flow Doppler were used to ensure the absence of intervening blood vessels before FNA was carried out. This was done successfully with a Wilson Cook 22G Echotip FNA needle (Wilson Cook Medical Inc., Salem, NC, USA) under real-time ultrasound guidance. A total of 4 passes were made. Cytological examination showed a high cellular yield with uniform, benign pancreatic ductal cells present in monolayer sheets. However, atypical cells were also present in discohesive sheets, clusters and papillary structures. The atypical cells were pleomorphic with crowded nuclei, prominent nucleoli and cytoplasmic vacuolisation. These cellular features were consistent with an adenocarcinoma (Figs. 3 and 4).

The patient was referred to the surgeon and a laparotomy done a few weeks later revealed a locally advanced pancreatic cancer (50 mm in diameter) in the uncinate process with extension into the head/neck. The tumour extended to the proximal branches of the superior mesenteric vein with multiple enlarged hepatic artery and retro-pancreatic lymph nodes. A palliative triple bypass was performed in view of the advanced stage of the cancer. Peritoneal fluid cytology further confirmed metastatic adenocarcinoma. The patient passed away 7 months after the date of diagnosis.

*Patient B*

A 72-year-old Chinese man presented with central abdominal discomfort and loss of appetite and weight over the past few weeks. Hb was 10.4 g/dL, Alb 37 g/L, ALP 178 U/L, Bil 23.2 mmol/L, ALT 8 U/L, CEA 117.6 ug/L, CA19-9 <2 U/mL. Oesophago-gastro-duodenoscopy (OGD) (gastroscopy) showed an ulcerative mass at D1D2 junction, but biopsy of the lesion revealed no diagnostic features. CT scan of the abdomen (Fig. 5) showed slight thickening of the duodenal wall which might be due to under-distension. A small amount of fluid was seen between the medial wall of the second part of the duodenum and the pancreatic head. This might be due to the duodenal biopsy done a few hours earlier. There was no definite mass within the pancreatic head. A few small, low-density lobular soft tissue masses were seen surrounding the coeliac axis and the peripancreatic region; these were thought to be possible signs of lymphadenopathy.

However, due to an appropriately high index of suspicion, the patient was referred to the gastroenterologist for an EUS/FNA. Endoscopically, a large ulcerative duodenal lesion was seen and biopsies were re-taken. Sonographic images showed a lobulated, bulky and heteroechogenic head of pancreas (Fig. 6). The tumour appeared to abut on part of the portal vein. Coeliac lymph nodes measuring 9 mm in diameter were also detected (EUS staging T2N1MX). Duodenal biopsies showed poorly differentiated adenocarcinoma in the lamina propria of the duodenal mucosa. The FNA of the pancreatic head and the coeliac lymph nodes revealed clusters of atypical cells suspicious of carcinoma (Fig. 7).

After some discussion, a decision was made by the patient to adopt a conservative and palliative approach to the advanced cancer. Subsequently, the patient underwent an ERCP (Fig. 8), where a self-expanding metallic wallstent was deployed across the bile duct stricture to relieve obstruction. He was discharged in a stable condition, but passed away at the next admission a few months later.

*Patient C*

The third patient was a 40-year-old Chinese man who presented with obstructive jaundice confirmed by liver function test (bil = 265 mmol/L, ALP = 511 U/L, ALT = 478 U/L, AST = 253 U/L, GGT = 761 U/L). Ultrasound of the abdomen showed intra- and extrahepatic duct dilatation with no obvious ductal stone; pancreatic duct was also dilated. No definite pancreatic head mass was reported. Some small gallbladder stones or polyps were present. CT scan of the abdomen showed intrahepatic

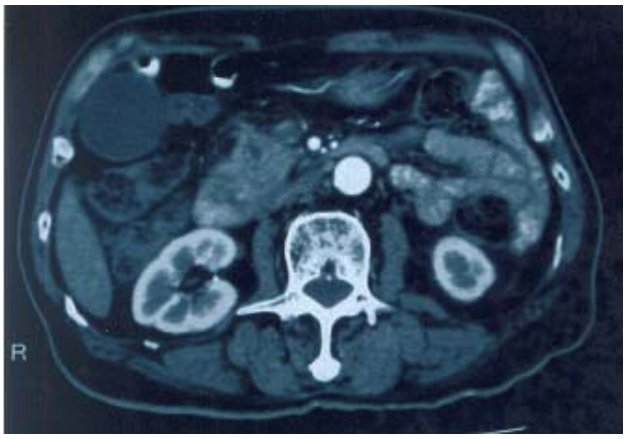


Fig. 1. CT scan of the abdomen of patient A shows vaguely the dilated pancreatic (small arrow) and common bile duct (big arrow), but no definite pancreatic mass was seen.

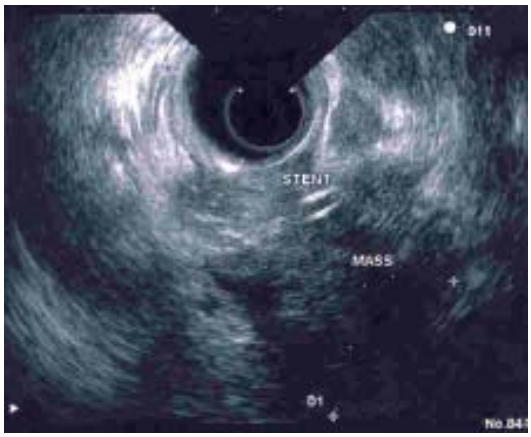


Fig. 2. Radial EUS image of patient A shows the irregular heteroechogenic pancreatic head mass with the biliary stent (previously deployed) seen in situ.

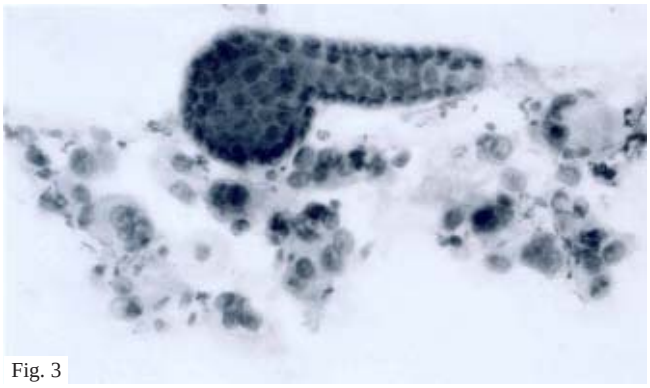

Fig. 3

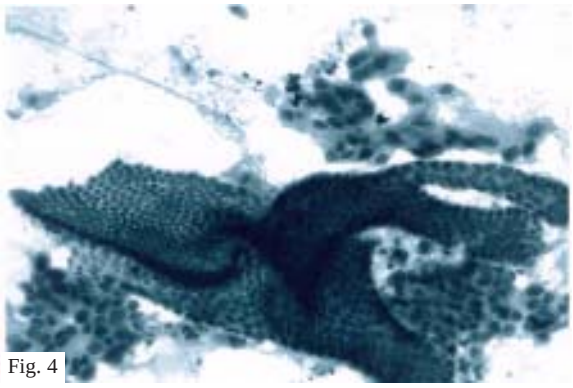

Fig. 4

Figures 3 and 4. Cytology specimens from FNA of the pancreatic head mass of patient A show high cellular yield with uniform, benign pancreatic ductal cells present in monolayer sheets. Atypical cells that were pleomorphic with crowded nuclei, prominent nucleoli and cytoplasmic vacuolisation consistent with adenocarcinoma were also present.

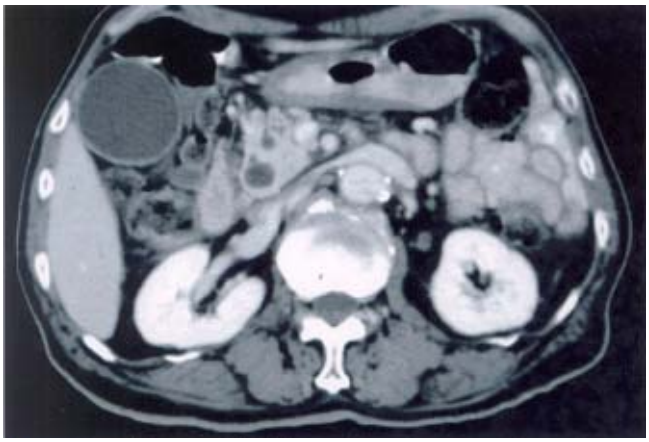

Fig. 5. CT scan of the abdomen of patient B shows the dilated common bile (big arrow) and pancreatic duct (small arrow), but no definite pancreatic mass was seen.

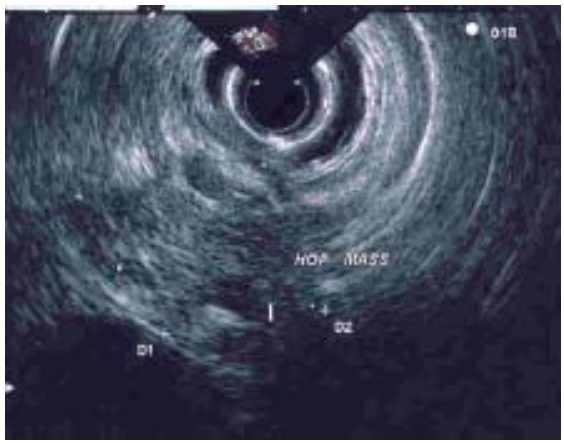


Fig. 6. Radial EUS image of patient B's pancreatic head shows a heteroechogenic mass with ill-defined border.

ductal dilatation terminating abruptly at the proximal common bile duct. No pancreatic mass was reported. ERCP showed irregular narrowing of the pancreatic duct towards the side of the ampulla, with narrowing of the dilated common bile duct at its distal end. The ampulla appeared normal endoscopically. Brushings of pancreatic and common bile duct strictures showed atypical cells equivocal for malignancy. EUS showed an ill-defined

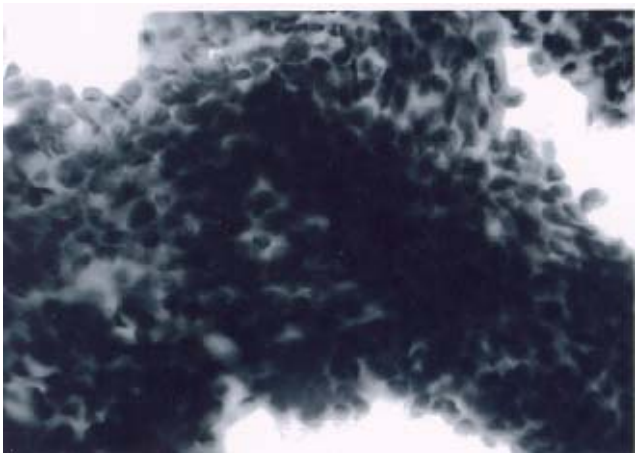

Fig. 7. Cytology specimens from FNA of the pancreatic head mass of patient B shows a cluster of atypical cells suspicious of carcinoma.

mass at the pancreatic head measuring about 3 to 4 cm in diameter with some peripancreatic lymph nodes (EUS staging T2N1MX). The splenic and portal veins were not involved. FNA of the peripancreatic lymph nodes showed lymphocytes, benign cells and atypical cells suspicious of malignancy. FNA of coeliac lymph node showed lymphoid yield with benign and atypical cells that were also suspicious of malignancy. FNA of the pancreatic lesion showed cellular yield of columnar cells and occasional group of atypical cells indicative of malignancy.

The patient was referred to the surgeon for surgery, but preoperative assessment with CT scan of the thorax showed consolidation in the left posterior inferior segment of the lung. Percutaneous biopsy of the left lung lesion was done and this showed atypical cells. Surgery was postponed and a CT scan of the abdomen 2 months later showed a more prominent head of pancreas tumour, superior mesenteric vein thrombosis, a left adrenal nodule, small indeterminate lesions in the liver and an increase in the size of the previous lung lesions. He was not deemed a suitable surgical candidate and was referred to the oncologist for chemotherapy. Despite chemotherapy and the deployment of a self-expanding metallic wallstent, he deteriorated and passed away 11 months after the date of diagnosis.

*Patient D*

The fourth patient was a 69-year-old man who presented with obstructive jaundice secondary to bile duct stricture; CT scan of the abdomen was normal. EUS showed a 27 x 30-mm hypoechoic, irregular pancreatic head mass with no portal vein invasion or lymphadenopathy (EUS staging T2N0M0). FNA of the lesion showed many clusters of neoplastic cells with pleomorphic, hyperchromatic nuclei consistent with that of adenocarcinoma. A biliary stent was deployed via percutaneous transhepatic cholangiography and this was internalised via a rendezvous ERCP.

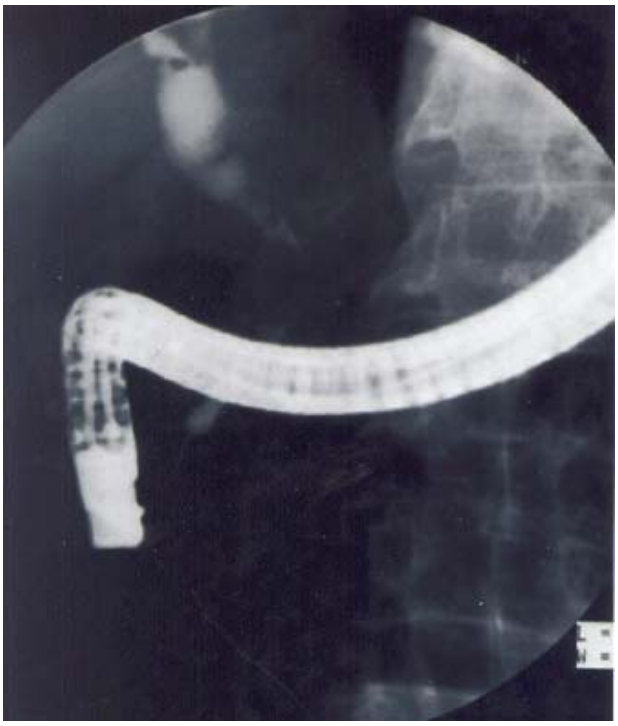

Fig. 8. ERCP image of patient B shows a stricture at the distal common bile duct secondary to pancreatic head tumour.

After some delay by the patient (partly because of the severe acute respiratory syndrome outbreak), he underwent a planned Whipple's operation a few months later. The operative findings include a 30-mm tumour at the head of pancreas extending to the lower portal hepatis and the likely encasement of the portal vein. Multiple small peripancreatic lymph nodes were seen. The pancreatic body and tail felt firm on palpation (which might have been chronic pancreatitis). Small, hard lymph nodes were seen at the neck of the gallbladder; these were excised for histology which reported reactive lymphoid hyperplasia with no evidence of malignancy. The planned Whipple's operation was abandoned in view of the operative findings. A Bard biliary self-expanding metallic stent (Bard Singapore Pte Ltd) was deployed to relieve biliary obstruction. He underwent chemo-radiation therapy, but passed away 8 months after the diagnosis of cancer.

*Patient E*

The last patient was a 72-year-old Chinese man with a long history of diabetes mellitus who presented with painless obstructive jaundice. CT scan of the abdomen showed no definite pancreatic mass. ERCP showed a bulky ampulla, dilated common bile duct and pancreatic duct with a short stricture at the distal end of the bile duct. Brushings showed atypical cells. An EUS was done and this showed an irregular, predominantly hypoechoic mass at the pancreatic head measuring about 27 x 33 mm in diameter. The tumour

Table 1. Characteristics of Patients with Pancreatic Head Cancer Diagnosed by EUS

| No. | Age (y) | Sex | Size (mm) | Vessel invasion | Lymph node | EUS staging | Cytology | Surgery/Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 77 | M | 39 x 40 | No | Yes | T2N1MX | Adenocarcinoma | Palliative surgical bypass | Died 7 months later |
| 2 | 72 | M | 30 x 30 | No | Yes | T2N1MX | Carcinoma | Palliative biliary wallstent | Died 3 months later |
| 3 | 40 | M | 30 x 40 | No | Yes | T2N1MX | Atypical cells suspicious of malignancy | Refused operation; undergone chemotherapy | Died 11 months later |
| 4 | 69 | M | 27 x 30 | No | No | T2N0M0 | Adenocarcinoma | Exploratory laparotomy done showed likely PV encasement; Whipple's abandoned; Wallstent deployment and radiation therapy | Died 8 months later |
| 5 | 72 | M | 27 x 33 | Yes | No | T3N0M0 | Atypical cells suspicious for malignancy | Whipple surgery = 4 x 4 x 3.5 mm tumour with no SMV involvement but tumour next to SMA. Coeliac LN resected but negative for malignancy from histology | Had adjuvant chemo RT and still well as of today |

EUS: endoscopic ultrasound; LN: lymph node; PV: portal vein; RT: radiation therapy; SMA: superior mesenteric artery; SMV: superior mesenteric vein

appeared to have invaded into the adjacent portal vein. No coeliac lymph nodes were detected. EUS staging was T3N0M0. FNA of the lesion showed atypical cells suspicious for malignancy.

The patient underwent a Whipple's operation which showed a bulky tumour in the uncinate process of the pancreas (40 x 40 x 35 mm). There was common bile duct dilatation and enlarged peripancreatic and coeliac lymph nodes. There was pancreatic body thickening next to the superior mesenteric artery, but the tumour did not involve the superior mesenteric vein. No mention was made of the portal vein. There were no ascites or liver metastases. Histology confirmed moderately differentiated adenocarcinoma with peripancreatic lymph nodes involved by tumour. There was, however, no evidence of malignancy in the resected coeliac lymph nodes. The patient underwent adjuvant chemo-radiation therapy and, at the time of writing, is still stable and well.

## Discussion

It is clear that EUS can diagnose pancreatic tumours with high sensitivity and specificity.[1-5] There are numerous reports of EUS being superior to ultrasonography and CT scan in detecting large pancreatic tumours with sensitivity nearing 100%.[2,3] In tumours measuring <3 cm, EUS has proven to have higher detection rates. T staging accuracy varies from 78% to 94% and N staging ranges from 64% to 82%. [6-11] However, its specificity is not as good as its sensitivity as EUS cannot reliably differentiate malignant from benign lesions.[3,4] This is especially true for chronic inflammatory pancreatitis cases.

However, EUS-guided FNA for tissue diagnosis greatly increases the diagnostic accuracy of pancreatic cancer and nodal staging. The overall yield in many studies reported a high of 80s and low of 90s.[6,12] The advantage of EUS-guided FNA over CT-guided FNA is that it can be performed during the same staging procedure and it carries a very small risk of pancreatitis.[12-14] EUS-guided FNA is also associated with shorter insertion length, continuous real-time visualisation of needle tip during aspiration and the use of Doppler ultrasonography to avoid adjacent vascular structures. Though needle tract malignant seedling is a possibility after EUS FNA, the track created is shorter compared to CT-guided FNA. Furthermore, for a pancreatic head tumour, the FNA puncture is usually at the duodenal bulb which would have been removed by surgery if the tumour was resectable.

Sensitivity for detecting vascular invasion and predicting surgical resectability is >90% in some studies.[1,6,7] The vessels typically involved are the portal vein, portal confluence, superior mesenteric vein and artery, splenic vein and artery, hepatic artery and coeliac artery. It is easy to assess portal and splenic vein invasion, but difficult with regards to the superior mesenteric vein and artery.[1,2] For determination of portal and splenic vein invasion, EUS has been reported to be superior to angiography with accuracy rates ranging from 77% to 85% depending on criteria for involvement.[15]

Finally, with regards to accuracy of N staging via EUS, this ranges from 64% to 82%. However, the use of EUS FNA to obtain cytological diagnosis increases the specificity and, hence, the overall diagnostic accuracy.

In this case series, EUS easily detected the pancreatic tumour in all 5 cases (which were all missed by CT scanning). EUS for tumour size assessment was compared with surgical findings (if any) and they were, respectively, 40 mm vs 50 mm; 30 x 27 mm vs 30 mm and finally 33 x 27 mm vs 40 x 35 mm. This is a fairly accurate assessment and it must be emphasised that the surgeries were done a few weeks to a few months after EUS due to various reasons.

With regard to EUS in lymph node assessment, 3 cases were correctly reported as pathological (confirmed by FNA cytology). The fourth case, where lymph nodes were not sonographically detected, was also correctly confirmed by surgical findings. Though the fifth case's surgical findings reported coeliac lymph nodes (not seen at EUS), examination of the resected coeliac lymph node specimens showed no malignancy at all. However, some of the peripancreatic lymph nodes resected (also not seen at EUS) were found to be involved with tumour.

For vascular assessment, EUS was accurate in 4 cases which stated no portal vein or superior mesenteric vein invasion. In the fifth case, EUS reported possible invasion of the adjacent portal vein, but this was reported as tumour next/adjacent to the superior mesenteric artery and vein (portal vein not mentioned).

Accurate staging for determination of resectability is crucial to reduce unnecessary exploratory surgery. Improved staging of pancreatic cancer provided by EUS might lead to favourable clinical and economic outcomes. Though there is little data from prospective trials, decision analytic models were used to answer this question.[16] We compared 4 strategies used for evaluating patients with pancreatic cancer. EUS followed by laparoscopy (for patients without local invasion by EUS) resulted in the lowest cost per patient and reduced the number of open explorations by 71%. When angiography was used to confirm local invasion determined by EUS, the rate of curative resections was increased by 2.4 per 100 patients staged, albeit at a cost of S$110,000 per resection.

Our series, though small, aims to educate physicians about the safety and clinical usefulness and accuracy of EUS FNA for diagnosis and staging of pancreatic head cancer. In all the cases, CT scan imaging could not detect the tumours and EUS was done in view of a high index of clinical suspicion of a pancreatic head tumour. No complications occurred in all the cases and all of them were also performed on an outpatient basis. A cytology technician was present in all our cases to process the specimens immediately and to verify adequate cellular yield. This is important as it increases the accuracy yield and minimises the number of FNA passes made (which translates into fewer complications).

## Conclusion

This case series showed that EUS with/without FNA is very useful to diagnose pancreatic head tumours not detectable by CT scanning of the abdomen. It appears to be safe and reasonably accurate in cancer diagnosis and staging. However, only a large prospective study can provide a quantitative assessment of the sensitivity and specificity of the technique. FNA provides a high yield of histological confirmation and can be carried out easily and safely on an outpatient basis. EUS with/without FNA should be advocated in all cases of painless obstructive jaundice, refractory duodenal ulcer or unexplained loss of weight.

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