Advancing the diagnostic and therapeutic role of EUS in pancreaticobiliary disease: Hopkins Lecture 2016

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INTRODUCTION

Linear endoscopic ultrasound (EUS) has become established as a key diagnostic and therapeutic tool in pancreaticobiliary medicine over the last 20 years. EUS/EUS-fine needle aspiration (FNA) is used in the diagnosis and staging of pancreatic and biliary masses, the diagnosis of unexplained dilatation of the bile and pancreatic ducts and the diagnosis of pancreatic cysts. Interventional EUS has developed rapidly with the EUS-guided drainage of pancreatic fluid collections, now the most commonly used EUS-guided intervention. In this article, I will set out the results of a series of studies performed over the last 12 years that have

1. helped develop the role and establish the utility of diagnostic linear EUS/EUS-FNA
2. developed and refined the techniques for EUS-guided pancreatic necrosectomy.

DIAGNOSIS

The question of whether to further investigate patients with asymptomatic unexplained duct dilatation (after CT and/or magnetic resonance cholangiopancreatography (MRCP)) and normal liver function tests (LFT) is controversial and a growing problem due to the increase in the incidental finding in patients undergoing cross-sectional imaging. In a study that I initiated, a significant and clinically relevant yield was demonstrated in 17% of such patients with unexplained common bile duct (CBD) dilatation.¹ We also demonstrated that previous cholecystectomy is significantly associated with no cause found on EUS in those with isolated CBD dilatation, and that the yield in those with CBD and pancreatic dilatation was low. This study helps to elucidate which

asymptomatic patients, with normal LFT and unexplained dilated ducts, should undergo further investigation with EUS.

Elastography is an ultrasound technique that allows assessment of the elasticity or firmness of a given tissue relative to that of adjacent normal tissue by measuring the strain or displacement generated in response to compression or vibration. The magnitude of the strain generated reflects the histological composition; inflammation is generally softer, that is, more strain, and malignancy generally harder, that is, less strain.

Quantitative EUS elastography is a novel technique that enables real-time quantification of tissue stiffness, and may help differentiate benign from malignant solid pancreatic masses. An initial study reported outstanding diagnostic performance.² I subsequently led a large single-centre study³ in patients with pancreatic masses. We documented an excellent sensitivity but poor specificity, suggesting that this technique, while a useful adjunct to tissue acquisition, requires further refinement before it could replace tissue diagnosis.

Initial reports of EUS-FNA invariably reported high unsatisfactory aspiration rate of 15%–25% at the outset of a service significantly impairing the diagnostic performance of the test. Rapid onsite examination (ROSE) by a cytopathologist or technician of an air-dried slide to perform adequacy assessment has been suggested as critical to improving the yield in EUS-FNA. In one early study, a cytopathologist was shown to improve accuracy from 52% to 78%.⁴ A recent survey of international practice documented its use by 98% of US respondents vs 51% in Europe and Asia.⁵

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In a study comparing diagnostic performance with and without cytopathology adequacy assessment,⁶ we found this not to make a difference in a high-volume, experienced unit with a baseline low inadequate aspiration rate. This was one of the first studies to challenge the conventional wisdom of the utility of ROSE. A recent randomised controlled trial arrived at the same conclusion.⁷ ROSE may however have a role during training and in centres with a low adequacy rate.⁸ Our study highlights the importance of carefully analysing global service performance before selecting the appropriate intervention to improve outcomes.

In a study comparing biliary brushings and EUS-FNA performed under the same sedation,⁹ we demonstrated that combining therapeutic endoscopic retrograde cholangiopancreatography (ERCP) and EUS-FNA under the same conscious sedation is feasible, with a complication rate similar to that of ERCP alone. This approach has potential benefits in reducing the costs and delays in the patient journey.

ERCP with biliary brushings is routinely used for the diagnosis of biliary strictures; however, the yield is low and the risk not insignificant particularly in non-jaundiced patients. EUS-FNA is less invasive and has a significantly lower complication rate than ERCP. In a study of EUS/EUS-guided FNA of proximal biliary strictures,¹⁰ we found the diagnostic performance to be better than that seen with brush cytology. EUS is now an established investigation in the management of indeterminate biliary strictures.^{11 12}

The management of pancreatic cysts is a significant challenge in modern pancreatology. Pancreatic cysts are increasingly identified incidentally because of the use of high-quality cross-sectional imaging to investigate disparate abdominal symptoms. The majority of pancreatic cysts referred to tertiary centres are asymptomatic and incidental findings. The issues and complexities of management revolve around the difficulty of making an accurate diagnosis. An important distinction is between mucinous and non-mucinous cysts.

Cyst fluid carcinoembryonic antigen (CEA) is suggested to be an accurate predictor of mucinous cysts, and the cut-off value of 192 ng/mL proposed as more sensitive than any other single/combined EUS-derived test. This cut-off is commonly used to differentiate mucinous from non-mucinous cysts. In a recently published study of cyst fluid CEA¹³ that I led, we have shown that the recommended cut-off of 192 ng/mL is significantly less accurate than EUS morphology and that combining cytology, CEA and EUS results in excellent diagnostic performance. This study highlighted the problem of over-reliance on CEA as a marker in cyst fluid. In another pancreatic cyst study,¹⁴ cyst size as assessed by EUS and CT was compared with resection histology as the gold standard. We documented good correlation between EUS, CT

and histology. This study provided the first evidence that measurement on these different modalities could be used interchangeably.

Tissue acquisition by means of EUS-FNA is considered the standard of care for the tissue diagnosis of pancreatic masses. However, when strict cytological criteria are used, the sensitivity of EUS-FNA for the diagnosis of malignant pancreatic masses even in expert hands has been reported to be as low as 77%.¹⁵ This forces a significant proportion of patients to undergo a second procedure and/or interval imaging with potentially detrimental delays to definitive management. Fine core biopsy needles have been developed in an attempt to overcome the limitations of EUS-FNA, preserve tissue architecture and improve sample adequacy and diagnostic accuracy. However, multiple studies have failed to demonstrate superior tissue adequacy or diagnostic performance when compared with FNA. In the first large single-centre cohort study, we have demonstrated that a second generation core biopsy needle with a novel tip, bevel and sheath design afforded significantly superior tissue yield (99% vs 87%) and sensitivity (91.1% vs 71.1%) than the most commonly used counterpart.¹⁶ If substantiated by randomised controlled trials, needles of this type could become the standard of care.

TRAINING

There is paucity of data on the training requirement for competency in EUS-FNA of the pancreas. We studied the experience in our unit and training fellowship¹⁷ and demonstrated that a formal 1-year training programme in pancreaticobiliary EUS produced procedural performance at the outset of independent practice comparable with that of an experienced endosonographer, and significantly better than that achieved without training. This study provides evidence to underpin recommendations for a formal period of high-volume training.

INNOVATION IN THERAPEUTIC EUS

The development of pancreatic necrosis and particularly infected necrosis is associated with worsening prognosis. Historically, open necrosectomy was performed, but this is associated with significant mortality.¹⁸

Minimally invasive techniques may reduce the adverse effects of the treatment of infected necrosis. Infected necrosis is often walled off and applied to the posterior wall of stomach, making it amenable to a transgastric approach. Working with Richard Charnley, we were among the first to develop EUS-guided necrosectomy. The technique involves using EUS to assess the walled-off necrosis, select a suitable place for puncture and guide puncture. The tract is then dilated, and either at the index or subsequent procedures, a variety of devices (basket, snare, forceps) used for debridement. Cavity endoscopy to aid debridement can also be performed. At the end of

each necrosectomy procedure, plastic pigtail stents are placed to maintain tract patency. Repeat procedures are performed as required.

EUS-guided endoscopic necrosectomy is the first true natural orifice transluminal endoscopic surgery procedure and has revolutionised the management of this condition. It offers a minimally invasive, yet aggressive, approach to the debridement of infected necrosis. We established that the technique as described above was feasible and associated with lower morbidity and mortality compared with conventional surgery.¹⁹ We have continued to evolve the technique and recently demonstrated the utility of a novel fully covered self-expanding removable metal stent for endoscopic necrosectomy.²⁰ Use of such stents has the potential to reduce cost (by reducing the number of procedures required), reduce the time to resolution and reduce complications. Endoscopic necrosectomy is not a procedure in isolation, but part of the repertoire of a specialist pancreatic unit, and specialist multi disciplinary team (MDT) discussion is critical. A new generation of single device lumen apposing metal stents has recently become available; the UK experience of its use for drainage of pancreatic fluid collections²¹ has recently been presented. We have also demonstrated that it can be used for EUS-guided drainage of the gall bladder.²²

CONCLUSION

The work described here has been possible because I have been fortunate to have supportive colleagues, and to be part of a cohesive hepato pancreaticobiliary (HPB) team committed to multidisciplinary working has facilitated therapeutic innovation as well as studies on the role of EUS in pancreaticobiliary disease.

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REFERENCES

- Oppong KW, Mitra V, Scott J, *et al.* Endoscopic ultrasound in patients with normal liver blood tests and unexplained dilatation of common bile duct and or pancreatic duct. *Scand J Gastroenterol* 2014;49:473–80.
- Iglesias-Garcia J, Larino-Noia J, Abdulkader I, *et al.* Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. *Gastroenterology* 2010;139:1172–80.
- Dawwas MF, Taha H, Leeds JS, *et al.* Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. *Gastrointest Endosc* 2012;76:953–61.
- Klapman JB, Logrono R, Dye CE, *et al.* Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol* 2003;98:1289–94.
- van Riet PA, Cahen DL, Poley JW, *et al.* Mapping international practice patterns in EUS-guided tissue sampling: outcome of a global survey. *Endosc Int open* 2016;4:E360–70.
- Nayar MK, Chatterjee S, Wadehra V, *et al.* Does on-site adequacy assessment by cytotechnologists improve results of EUS guided FNA of solid pancreaticobiliary lesions? *JOP* 2013;14:44–9.
- Wani S, Mullady D, Early DS, *et al.* The clinical impact of immediate on-site cytopathology evaluation during endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: a prospective multicenter randomized controlled trial. *Am J Gastroenterol* 2015;110:1429–39.
- Wani S, Muthusamy VR, Komanduri S. EUS-guided tissue acquisition: an evidence-based approach (with videos). *Gastrointest Endosc* 2014;80:939–59.e7.
- Oppong K, Raine D, Nayar M, *et al.* EUS-FNA versus biliary brushings and assessment of simultaneous performance in jaundiced patients with suspected malignant obstruction. *JOP* 2010;11:560–7.
- Nayar MK, Manu NK, Manas DM, *et al.* Role of EUS/ EUS-guided FNA in the management of proximal biliary strictures. *Hepatogastroenterology* 2011;58:1862–5.
- Bowlus CL, Olson KA, Gershwin ME. Evaluation of indeterminate biliary strictures. *Nat Rev Gastroenterol Hepatol* 2016;13:28–37.
- Dawwas MF, Oppong KW, Webster GJ. Endoscopic assessment and management of biliary strictures. *Frontline Gastroenterol* 2016;7:170–5.
- Oppong KW, Dawwas MF, Charnley RM, *et al.* EUS and EUS-FNA diagnosis of suspected pancreatic cystic neoplasms: Is the sum of the parts greater than the CEA? *Pancreatol* 2015;15:531–7.
- Leeds JS, Nayar MN, Dawwas M, *et al.* Comparison of endoscopic ultrasound and computed tomography in the assessment of pancreatic cyst size using pathology as the gold standard. *Pancreatol* 2013;13:263–6.
- Turner BG, Cizginer S, Agarwal D, *et al.* Diagnosis of pancreatic neoplasia with EUS and FNA: a report of accuracy. *Gastrointest Endosc* 2010;71:91–8.
- Nayar MK, Paranandi B, Dawwas MF, *et al.* Comparison of the diagnostic performance of 2 core biopsy needles for EUS-guided tissue acquisition from solid pancreatic lesions. *Gastrointest Endosc* Published Online First: 12 Sep 2016. doi:10.1016/j.gie.2016.08.048
- Nayar M, Joy D, Wadehra V, *et al.* Effect of dedicated and supervised training on achieving competence in EUS-FNA of solid pancreatic lesions. *Scand J Gastroenterol* 2011;46:997–1003.
- Bassi C, Butturini G, Falconi M, *et al.* Outcome of open necrosectomy in acute pancreatitis. *Pancreatol* 2003;3:128–32.
- Charnley RM, Lochan R, Gray H, *et al.* Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. *Endoscopy* 2006;38:925–8.

- 20 Huggett MT, Oppong KW, Pereira SP, *et al.* Endoscopic drainage of walled-off pancreatic necrosis using a novel self-expanding metal stent. *Endoscopy* 2015;47: 929–32.
- 21 Venkatachalapathy S, Makin A, Pereira S, *et al.* OC-073 The first multicentre experience from the UK and Ireland of the use of the hot Axios system for transluminal drainage of pancreatic fluid collections. *Gut* 2016;65:A44.
- 22 Paranandi B, Nayar M, Scott J, *et al.* Endoscopic cholecystogastrostomy in a patient with gallbladder empyema secondary to cholangiocarcinoma. *Endoscopy* 2016;48(Suppl 1):E163.