Endoscopic ultrasound assessment of lesions of the ampulla of Vater is of particular value in low-grade dysplasia

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Abstract

Background: The accurate diagnosis of dysplasia or carcinoma within ampullary lesions can be difficult, but, when possible, identifies patients who require endoscopic or surgical resection, respectively. The role of endoscopic ultrasound (EUS) in diagnosing these lesions and the degree of dysplasia is unclear.

Methods: Patients with lesions of the ampulla were identified over 5 years. Patients who did not undergo EUS were compared with those who did.

Results: A total of 27 of 58 (47%) patients were investigated with EUS. Pretreatment diagnoses were correct in 93% of the EUS group vs. 78% of the no-EUS group. Rates of diagnostic accuracy in low-grade dysplasia (LGD), high-grade dysplasia (HGD) and adenocarcinoma (ADC) were 72%, 20% and 96%, respectively, in the no-EUS group, and 93%, 50% and 100%, respectively, in the EUS group. Every diagnosis of LGD in the EUS group was correct, whereas these diagnoses accounted for the majority of errors (eight of 13) in the no-EUS group. High-grade dysplasia was frequently misdiagnosed. More patients were treated by endoscopic resection in the EUS group (12 of 27 vs. five of 31; \( P = 0.025 \)).

Conclusions: Endoscopic ultrasound increases the accuracy of preoperative diagnosis of ampullary lesions and is particularly useful in patients with LGD because it permits safe endoscopic management. Patients with HGD must be reviewed carefully and considered for pancreatoduodenectomy.

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Introduction

Tumours of the ampulla of Vater are uncommon and represent only 0.2% of gastrointestinal tract tumours.1 Lesions display cellular atypia that progress from low-grade dysplasia (LGD) to invasive adenocarcinoma (ADC).2 Accurate preoperative diagnosis is essential as the management of dysplastic lesions can be achieved with endoscopic means, whereas resectable carcinoma requires pancreaticoduodenectomy.2,3 Furthermore, the identification of patients with metastatic disease avoids unnecessary surgery and morbidity. The accurate diagnosis and staging of ampullary lesions rely heavily upon the interpretation of radiological information and biopsy material.4,5 The presence of jaundice may represent malignant change in an ampullary adenoma, although benign adenomas are often identified incidentally when jaundice of other causes is investigated.5 In comparison with computerized tomography (CT) and magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) has the ability to demonstrate in higher spatial resolution the ampulla, closely related anatomical structures including lymph nodes, and the interface between the duodenal wall and pancreas.7,8 For these reasons the sensitivity and specificity of EUS in performing preoperative tumour (T) and node (N) staging are superior to those of MRI or CT.9 However, EUS can be a technically challenging procedure and although it is widely available, is very much operator-dependent. Dysplastic ampullary adenomas are considered premalignant although the time to progression remains uncertain. Given that the management of patients with LGD is better served with local resection (endoscopic or surgical), EUS is an important tool with
which to define the degree of dysplasia within ampullary lesions. This study sought to identify the accuracy of preoperative diagnosis and staging in patients with ampullary lesions and, in particular, to identify which patients benefit most from EUS.

Materials and methods

Patients with ampullary adenomas or adenocarcinomas were identified from a surgical departmental database and pathology records. Both sets of records were cross-checked to establish the suitability of patients for inclusion and to ensure that no patients were missed. The study period was January 2006 to December 2011. Patients in whom the lesion arose from a location other than the ampulla were excluded. Presenting complaints, preoperative investigations, patient demographic details, and data on operative or endoscopic management, complications and outcome were recorded. All patients were presented and reviewed at a multidisciplinary meeting (MDT). Tumours were classified using the tumour–node–metastasis (TNM) classification and dysplasia was defined as being of low (LGD) or high (HGD) grade. All pathological specimens were analysed by consultant histopathologists within a specialist hepatopancreatobiliary unit.

Patients were divided into two groups, comprising, respectively, those in whom preoperative investigations included EUS and those in whom EUS was not performed. There was no standard algorithm to investigate or manage these patients. Preoperative investigations included a combination of CT, MRI and endoscopic retrograde cholangiopancreatography or oesophagogastroduodenoscopy. Management comprised endoscopic resection or transduodenal resection for LGD and pancreaticoduodenectomy for HGD and ADC if the patient was considered fit enough. The preoperative diagnosis was compared with the final pathological diagnosis to identify sensitivity, specificity, and negative and positive predictive values. Endoscopic ultrasound was performed after multidisciplinary review for each patient. Thus, for patients in both the no-EUS and EUS groups, a preoperative diagnosis without EUS information was available for comparison with postoperative findings. The preoperative diagnosis was established based upon histological findings presented to the MDT; when tissue for histology was unavailable or the diagnosis was questionable, the MDT’s diagnosis was based on the interpretation of radiological and clinical information. The pathological spectrum included LGD, HGD, carcinoma in situ (Cis) and ADC. Carcinoma in situ was grouped with HGD. A preoperative diagnosis of HGD was treated as a diagnosis of ADC because invasive ADC was frequently found within HGD after formal resection and because there is a risk for lymph node metastasis in T1 ampullary tumours.

All EUS procedures were performed by a single operator (BSM) with the patient under conscious sedation administered by the endoscopist. Linear echoendoscopes (GF-UCT240 and 260-AL5; Olympus Corp., Tokyo, Japan) were used for all procedures. Intravenous buscopan (20 mg) was used to inhibit duodenal peristalsis during the procedure. A total of 40–80 ml of water was infused into the duodenum to create negative contrast for ultrasound imaging. Tissue samples were obtained from a combination of fine needle aspiration performed with EchoTip® 22-G or 19-G needles (Cook Medical Inc., Bloomington, IN, USA) and mucosal biopsies obtained with Radial Jaw® 4 Jumbo Biopsy Forceps (Boston Scientific Corp., Natick, MA, USA). The samples were deposited in CytoRich® Red (TriPath Imaging, Inc., Burlington, NC, USA) prior to cytological analysis.

Data are expressed as the median (range). Continuous variables were assessed using the Mann–Whitney test and categorical variables with the chi-squared test or Fisher’s exact test when one or more frequencies did not exceed 5. Significance was indicated by a P-value of <0.05 and analyses were performed using PASW Version 18 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 58 subjects were found to meet the inclusion criteria. Computed tomography was performed in 52 patients, MRI in six and upper gastrointestinal endoscopy (UGIE) in 51. An EUS was performed in 27 patients. The median age of the entire cohort was 67 years (range: 19–85 years). The cohort included 37 men (64%). The final pathological diagnosis was LGD in 23 patients, HGD in three patients, and ADC in 32 patients. In the latter group, one patient had a malignant neuroendocrine tumour and the remaining 31 patients had intestinal type ADC (Table 1).

Both the EUS and no-EUS groups were comparable with respect to age, gender and presenting complaints (Table 1). A significantly greater proportion of endoscopic mucosal resections (EMRs) were performed amongst the EUS group (12 of 27 vs. five of 31 patients; P = 0.025). To date, none of the patients who underwent endoscopic resection have developed malignant tumours. Of the 12 patients in the EUS group in whom curative resection was attempted, three were identified as having unresectable distant disease at operation. The median follow-up was 18 months (range: 1–65 months). Table 1 summarizes management strategies and outcomes in the EUS and no-EUS groups.

Accuracy of preoperative investigations

The overall accuracy of the preoperative diagnoses in the no-EUS and EUS groups is shown in Table 2. Sensitivity, specificity, and negative and positive predictive values for the diagnosis of LGD, HGD and ADC in the no-EUS and EUS groups are given in Table 3.

The 13 patients in the no-EUS group for whom the preoperative diagnosis was found to have been incorrect were identified on EUS as having LGD (n = 8), HGD (n = 4) or ADC (n = 1). The two patients in the EUS group for whom the preoperative diagnosis was found to have been incorrect had been diagnosed with adenoma (n = 1; the lesion was seen but the tissue obtained for
A preoperative diagnosis of HGD tended to understage these lesions: three of five cases were subsequently identified as ADC. One case was found to represent LGD. Of the cancers, two cases following resection were classified as T2N0M0, but one was rendered inoperable by peritoneal disease (TxNxM1).

There was a significant difference between the groups in terms of management. Fewer patients in the EUS group underwent surgical resections and more underwent endoscopic resection ($P = 0.025$) (Table 1). The numbers of patients undergoing planned pancreateoduodenectomy, transduodenal resection and EMR, respectively, were 24, two and five in the no-EUS group, and 12, three and 12 in the EUS group. Three patients in the EUS group were found to have inoperable disease at pancreateoduodenectomy as a result of occult liver metastases or peritoneal disease.

The presence of jaundice was a predictor of malignancy (25 of 32 cases with a bilirubin level of >20 μmol/l; $P < 0.001$), although eight patients with a normal bilirubin level received a final diagnosis of ADC and a further two were diagnosed with HGD.
Comparison of UGIE with EUS
The ability of EUS to correctly identify LGD, HGD or ADC at endosonography was 85% (based upon the depth of invasion) and from the material obtained for histological assessment was 92%. The ability of UGIE to correctly identify LGD, HGD or ADC at endoscopy was 62% (based upon the macroscopic appearance) and from the material obtained for histological assessment was 60%. The difference in diagnostic accuracy following pathological assessment was significant ($P = 0.006$).

Discussion
This study aimed to identify whether the addition of EUS to standard tests investigating lesions of the ampulla affects the accuracy of preoperative diagnosis. Near-perfect accuracy was observed in patients undergoing EUS. The main difference appeared to concern the strength of EUS to correctly identify LGD, which was diagnosed correctly in every patient in the EUS group. This contrasted with the no-EUS group, in which a diagnosis of LGD was responsible for the majority of incorrect diagnoses (eight of 13). However, a diagnosis of ADC in the no-EUS group was correct in all but one case. It appears that a preoperative diagnosis of HGD should be interpreted with caution in view of a high false negative rate observed in the present data and by others.10 The management of early ampullary tumours is controversial. Ampullectomy for HGD, Cis or T1 ADC has been advocated over pancreateoduodenectomy because the former facilitates decreases in procedural morbidity, mortality and length of stay.11–14 The oncological outcome, however, is unsatisfactory. Although limited series of patients undergoing endoscopic resection without recurrent disease, including patients with T1 tumours, have been reported,12,13 other researchers have reported that recurrent disease affects nearly 20% of patients.14 In the largest single series of patients ($n = 435$) undergoing pancreateoduodenectomy for ampullary neoplasms, 28% of patients with T1 tumours were found to have lymph node metastases.11 The number of patients in the present series is too small to support conclusions on the role of EUS in the accuracy and pre-

Figure 1 Proposed algorithm for the investigation and subsequent management of a suspected lesion of the ampulla of Vater. EUS, endoscopic ultrasound; EMR, endoscopic mucosal resection; LGD, low-grade dysplasia; HGD, high-grade dysplasia; ADC, adenocarcinoma; R0, resection margin clear of disease.
...dictive values of diagnosing and assessing HGD. The accuracy of EUS in staging "T" disease is thought to be lowest in T1 lesions (0–100%) and to increase by T-stage to 45–100% for T2 lesions and 75–100% for T3–T4 lesions. Thus, the tendency for HGD to be understaged and for lymph node metastases to develop in early tumours has clear implications for the management of patients with a preoperative diagnosis of HGD or early cancer. Although there is no agreed consensus on the management of these lesions, for the reasons given, the present authors advocate pancreateoduodenectomy. If a subject with HGD does undergo endoscopic resection, thorough pathological sampling is required. In patients in whom resection margins are incomplete or in whom foci of invasive carcinoma are identified, pancreateoduodenectomy should be performed. In patients treated by local resection, even with clear margins, surveillance must be performed in view of the risk for recurrent disease.

Evidence for the impact of EUS upon the management of patients is seen in the significantly greater proportion of patients treated by EMR in the EUS group.

The limitations of this study include the short follow-up of patients with LGD in whom local resection was performed. Although no patients have been found to exhibit recurrent disease to date, this may reflect a lead time bias. Further limitations include the low number of subjects with HGD or early tumours. This reflects the nature and spectrum of this disease and is observed in similar cohorts of presented cases. The role of EUS in staging these lesions could be addressed by either a multi-institutional study or a systematic review.

According to the current findings, a simple diagnostic algorithm is presented (Fig. 1). This can be summarized as: a diagnosis of LGD merits an investigation with EUS; a diagnosis of HGD must be regarded with caution regardless of the investigation modality, and a patient with a diagnosis of ADC does not benefit from EUS. Patients with HGD should undergo pancreateoduodenectomy if they are fit enough to do so and EMR if they are unfit for radical resection. Endoscopic ultrasound could be used to assess local invasion. Although EUS permits accurate local staging, it did not assist in three patients in whom ADC was understaged and in whom distant peritoneal disease developed, who received inappropriate laparotomy and attempts at curative resection.

Conflicts of interest
None declared.

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