

Linear endoscopic ultrasonography vs magnetic resonance imaging in ampullary tumors

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using the results of surgical or endoscopic treatment as a benchmark.

RESULTS: A suspicion of ampullary tumor was present in 75% of MRI and all L-EUS examinations, with 80% agreement between EUS and histological findings at endoscopy. However, L-EUS and histological TN staging at surgery showed moderate agreement ($\kappa = 0.54$).

CONCLUSION: L-EUS could be a useful adjunct as a diagnostic tool in the evaluation of patients with suspected ampullary tumors.

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Key words: Ampullary tumors; Endoscopic ultrasound; Magnetic resonance imaging

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Abstract

AIM: To assess linear endoscopic ultrasound (L-EUS) and magnetic resonance imaging (MRI) in biliary tract dilation and suspect small ampullary tumor.

METHODS: L-EUS and MRI data were compared in 24 patients with small ampullary tumors; all with subsequent histological confirmation. Data were collected prospectively and the accuracy of detection, histological characterization and N staging were assessed retrospectively

INTRODUCTION

Ampullary tumors are infrequent entities that represent about 0.2% of gastrointestinal malignancies^[1]. However, these neoplasms are considered as diagnostic challenges, because they display a wide array of pathological features, from mild dysplasia to high-grade dysplasia and invasive

carcinoma^[2]. Clinical presentation includes vague abdominal pain, liver enzyme elevation, jaundice, recurrent pancreatitis, or uncommon symptoms such as gastrointestinal bleeding or duodenal obstruction^[3,4].

Although endoscopic papillectomy represents a possible treatment^[5], most ampullary tumors still undergo a surgical approach^[6,7]. Thus, the diagnostic evaluation must be as careful as possible^[8], because ampullary carcinoma is difficult to diagnose at an early stage and multiple imaging techniques should be carried out appropriately to establish a diagnosis and improve prognosis^[9]. In fact, neither definitive methods for early diagnosis nor specific markers are available for this disease^[10].

In recent years, endoscopic ultrasound (EUS) has been shown to be superior to computed tomography (CT)^[11] and conventional ultrasound scans^[12], and equivalent to magnetic resonance imaging (MRI) for tumor detection and T and N staging of ampullary tumors^[13].

Echoendoscopes are classified into radial and linear instruments^[14]: to date, almost all information available on detection and staging of ampullary tumors has been obtained with radial echoendoscopes, and there are no studies with linear EUS (L-EUS) for this purpose.

The aim of the present study was to compare L-EUS and MRI in the diagnostic evaluation of patients with suspected ampullary neoplasms.

MATERIALS AND METHODS

In a consecutive series of 1205 L-EUS biliopancreatic examinations carried out in the period July 2007 to August 2009, there were 44 symptomatic patients (referred for increasing liver enzymes, jaundice, abdominal pain or dilation of the biliary tract) who were evaluated for suspicion of ampullary tumors. In 20 of these, the ampullary tumor was excluded by L-EUS that revealed other causes for their symptoms (four stones, four mediocholedocal stenoses, and 12 pancreatic cephalic small cancer). In the remaining 24 patients, data were collected prospectively and the accuracy of detection, histological characterization, and N staging were assessed retrospectively using the surgical or endoscopic results as a benchmark.

The following inclusion criteria were adopted: (1) cholestatic syndrome with previous negative or uncertain conventional US and CT imaging; (2) absence of previously known biliary and/or pancreatic diseases; (3) absence of advanced ampullary tumors; (4) histological diagnosis of the resected specimen; (5) MRI (axial, coronal and radial sequences, T2 single-shot, performed by a radiologist with experience of the biliary tree); and (6) L-EUS. Exclusion criteria included previously known biliary or pancreatic disease, and the presence of evident, large ampullary tumors at endoscopy.

L-EUS was carried out by means of a linear array echoendoscope (Pentax EG 33830UT or Pentax EG 3870UTK; Hamburg, Germany) that was inserted into the second

part of the duodenum after intravenous midazolam and meperidine titrated to obtain conscious sedation. Keeping the tip of the echoendoscope in touch with the duodenal mucosa, the echoendoscope was torqued counterclockwise and slowly withdrawn into the duodenal bulb^[14], and after visualization of the papilla of Vater, its endoscopic aspect was considered and recorded.

Ampullary carcinoma visualized by EUS was staged according to the TN classification^[15]: T1 if the tumor echo was limited to the main duodenal papilla; T2 if the tumor echo invaded the duodenal muscularis propria layer; T3 if the tumor echo invaded the pancreas; and T4 if the tumor echo invaded peripancreatic soft tissues or other adjacent organs or vascular structures. EUS criteria for lymph node metastasis, classified as N1, were circularity, at least 10 mm in size, and hypoechogenicity.

Ethical considerations

This was a retrospective study and no study-driven clinical intervention was performed. Simplified Institutional Review Board approval for retrospective studies was obtained.

Statistical analysis

Differences in percentage of detection of ampullary tumors between MRI and L-EUS and between L-EUS and histology were assessed by the χ^2 test. Values of $P < 0.05$ were chosen for rejection of the null hypothesis. Moreover, a κ value for agreement between endoscopic and surgical histology and L-EUS and histological TN staging was calculated. The value was scored according to standard criteria^[16].

RESULTS

Data from 24 patients (17 men and seven women, aged 60 ± 12 years, range: 42-88 years) fulfilled the entry criteria and were evaluated. Demographic data, referral reasons, clinical, radiological and histological features are summarized in Tables 1 and 2. Abdominal pain was the common symptom in all patients; jaundice was present in 13 (54%) and liver enzyme elevation was detected in 12 (50%). One patient was evaluated due to dilation of both extrahepatic and main pancreatic ducts. Multiple endoscopic forceps biopsies were taken from all cases during L-EUS evaluation. In one case, it was impossible to analyze the sample due to material not being available in the test-tube. Agreement between endoscopic and histological results was very good ($\kappa = 0.81$).

All patients underwent surgery except for two (stage T1N0) who were treated by endoscopic ampullectomy, and histological results were available for the entire group (Figure 1). Average diameter of the ampulla was 2 ± 0.8 cm (range: 1.5-2.6 cm).

MRI examination was negative in 6 (25%) cases, showed indirect signs (dilatation of intrahepatic and extrahepatic bile ducts) of space occupying lesions of the ampulla in

Table 1 Demographic data and reasons for referral of patients with ampullary tumors

Patient No.	Sex/age (yr)	Referral reason
1	M/53	Liver enzymes elevation + jaundice
2	F/47	Abdominal pain
3	M/71	Liver enzymes elevation + jaundice
4	M/62	Liver enzymes elevation + jaundice
5	F/53	Liver enzymes elevation
6	F/67	Liver enzymes elevation
7	M/45	Liver enzymes elevation
8	M/73	Liver enzymes elevation
9	M/80	Liver enzymes elevation
10	F/44	Liver enzymes elevation
11	F/50	Liver enzymes elevation + jaundice
12	M/48	Liver enzymes elevation + jaundice
13	M/66	Liver enzymes elevation
14	M/67	Liver enzymes elevation + jaundice
15	M/59	Liver enzymes elevation
16	M/67	Liver enzymes elevation + jaundice
17	F/60	Liver enzymes elevation
18	M/63	Liver enzymes elevation + jaundice
19	F/54	Liver enzymes elevation + jaundice
20	M/65	Liver enzymes elevation
21	M/64	Liver enzymes elevation + jaundice
22	M/42	Liver enzymes elevation + jaundice
23	M/47	Liver enzymes elevation + jaundice
24	F/88	Liver enzymes elevation + jaundice

17 (71%) cases, and an actual space occupying lesion of the ampulla in 1 (8%) case (Figure 2).

L-EUS detected ampullary tumors in all 24 (100%) patients ($P < 0.03$ vs MRI) (Figure 2).

In 19 (80%) cases, Histological analysis revealed intestinal-type adenocarcinoma in 19 (80%) cases (stage T2N0 in 14 and T2N1 in five) CDX2 positive, adenoma with high-grade dysplasia in 2 (8%), and adenoma with low-grade dysplasia in the remaining 3 (12%) (Figure 3).

No biliary/pancreatic-type tumors were found. Thus, L-EUS was able to detect malignant lesions in 87% of ampullary lesions ($P = 0.21$ vs histological results), with sensitivity of 87.5% and specificity of 100% and a moderate agreement ($\kappa = 0.54$) between L-EUS and TN histological staging.

DISCUSSION

Although MRI is regarded as the most reliable noninvasive diagnostic imaging modality for the evaluation of pancreatobiliary lesions^[17,18], and is considered as a substitute for diagnostic endoscopic retrograde cholangiopancreatography^[19], it cannot provide biopsy samples and rarely identifies whether the obstruction is benign or malignant, especially when lesions are small. The ampulla of Vater is a possible blind spot for MRI because of its small size and the tapering of the intramural ducts that contain little fluid^[9,18,20]. Thus, other investigative modalities have been added to the diagnostic armamentarium; among these, EUS has proved to be useful and reliable. Generally, radial EUS is considered the gold standard^[17,18] whereas L-EUS performance has never been studied.



Figure 1 Endoscopic aspect (A) and resected surgical specimen (B) of a small ampullary tumor.

This is believed to be the first study to report L-EUS as a useful diagnostic tool for detection and staging of small ampullary tumors. In our experience, also supported by histological findings, this technique was able to raise a suspicion of ampullary neoplasm when other imaging techniques, including MRI, were not. Indeed, a suspicion of ampullary neoplasms was observed in 75% of MRI investigations compared with 100% of L-EUS scanning; the latter proved to be accurate, identifying > 80% of these lesions as malignant. The accuracy of EUS in the TNM staging of ampullary tumors remains controversial^[17,21]. Histological grade is the gold standard, with the possibility to differentiate between ampullary tumor of intestinal type and those originating from the biliary or pancreatic ducts; however, it is worthy of note that a discrete correlation was found between L-EUS and histological TN staging in the present study. The discrepancies were due more to overstaging in 6 (25%) patients than to understaging in 3 (12%) patients. Overstaging can occur in the presence of peritumoral inflammation, whereas understaging can occur in the presence of minimal malignant infiltration of the pancreas^[9,22]. Other recent experience also suggests that EUS is an accurate diagnostic test and exhibits a high level of agreement with surgical pathology^[23].

However, L-EUS provided several advantages compared to MRI, such as the possibility of obtaining direct endoscopic visualization of the major duodenal papilla, and to depict the layered structures of the periampullary area. Thus, it is often possible to give a judgment on a pos-

Table 2 Clinical-radiological variables and histological features of ampullary tumors

Patients	US	CT-scan	MRI	L-EUS	Endoscopic imaging + biopsies	Surgery	Definitive staging and histology
1	Not done	Neg	Suspicion:dilation CBD + WD	T2N0	Visible lesion 1.6 cm-HGD	DCP	PT2N0, ADK
2	Uncertain	Neg	Suspicion:dilation CBD + WD	T2N0	Visible lesion 2.0 cm-HGD	DCP	PT2N1, ADK
3	Not done	Neg	Suspicion:dilation CBD + WD	T2N0	Visible lesion 1.8 cm-HGD	DCP	PT2N0, ADK
4	Not done	Not done	Suspicion:dilation CBD + WD	T2N0	Visible lesion 2.0 cm -HGD	DCP	PT2N0, ADK
5	Not done	Not done	Suspicion:dilation CBD + WD	T2N0	Visible lesion 1.5 cm-HGD	DCP	PT2N0, ADK
6	Neg	Neg	Neg	T1N0	Visible lesion 2.0 cm-LGD	EMR	PT1N0, LGD
7	Not done	Neg	Neg	T1N0	Visible lesion 2.0 cm-LGD	EMR	PT1N0, LGD
8	Neg	Not done	Neg	T2N0	Visible lesion 2.0 cm -HGD	SA	PT1N0, HGD
9	Neg	Neg	Suspicion:dilation CBD	T2N0	Visible lesion 2.0 cm-ADK	DCP	PT2N0, ADK
10	Neg	Neg	Neg	T2N0	Visible lesion 2.0 cm HGD	DCP	PT2N0, ADK
11	Neg	Neg	Suspicion:dilation CBD + WD	T2N0	Visible lesion 2.0 cm-ADK	DCP	PT2N0, ADK
12	Neg	Neg	Suspicion:dilation CBD + WD	T2N0	Visible lesion 2.6 cm-ADK	DCP	PT2N1, ADK
13	Not done	Neg	Neg	T1N0	Visible lesion 1.5 cm-LGD	SA	PT1N0, LGD
14	Neg	Not done	Suspicion:dilation CBD	T2N0	Visible lesion 2.5 cm-ADK	DCP	PT2N0, ADK
15	Neg	Not done	Suspicion:dilation CBD	T2N1	Visible lesion 2.0 cm-HGD	DCP	PT2N0, ADK
16	Neg	Uncertain	Suspicion:dilation CBD	T2N1	Visible lesion 2.0 cm-HGD	DCP	PT2N0, ADK
17	Neg	Neg	Suspicion:dilation CBD	T2N1	Visible lesion 2.0 cm-ADK	DCP	PT2N0, ADK
18	Neg	Neg	Suspicion:dilation CBD	T2N1	Visible lesion 1.5 cm-ADK	DCP	PT2N1, ADK
19	Not done	Neg	Suspicion:dilation CBD + WD	T2N1	Visible lesion 2.0 cm-ADK	DCP	PT2N1, ADK
20	Neg	Neg	Suspicion:dilation CBD	T1N0	Visible lesion 1.5 cm-HGD	DCP	PT2N0, ADK
21	Not done	Neg	Neg	T2N1	Visible lesion 2.0 cm-ADK	DCP	PT2N0, ADK
22	Not done	Not done	Suspicion:dilation CBD	T2N0	Visible lesion 2.5 cm-not available	DCP	PT1N0, HGD
23	Uncertain	Neg	Suspicion:dilation CBD + WD	T2N1	Visible lesion 2.5 cm-ADK	DCP	PT2N1, ADK
24	Neg	Neg	Suspicion:dilation CBD + WD	T2N1	Visible lesion 2.0 cm-ADK	SA due to age	PT2N0, ADK

ADK: Adenocarcinoma; CBD: Common bile duct; DCP: Duodeno-cephalo-pancreasectomy; HGD: High grade dysplasia; LGD: Low grade dysplasia; Neg: Negative for ampullary tumor; SA: Surgical ampullectomy; WD: Wirsung duct; US: Ultrasound; CT: Computed tomography; MRI: Magnetic resonance imaging; L-EUS: Linear endoscopic ultrasound; EMR: Endoscopic mucosal resection.

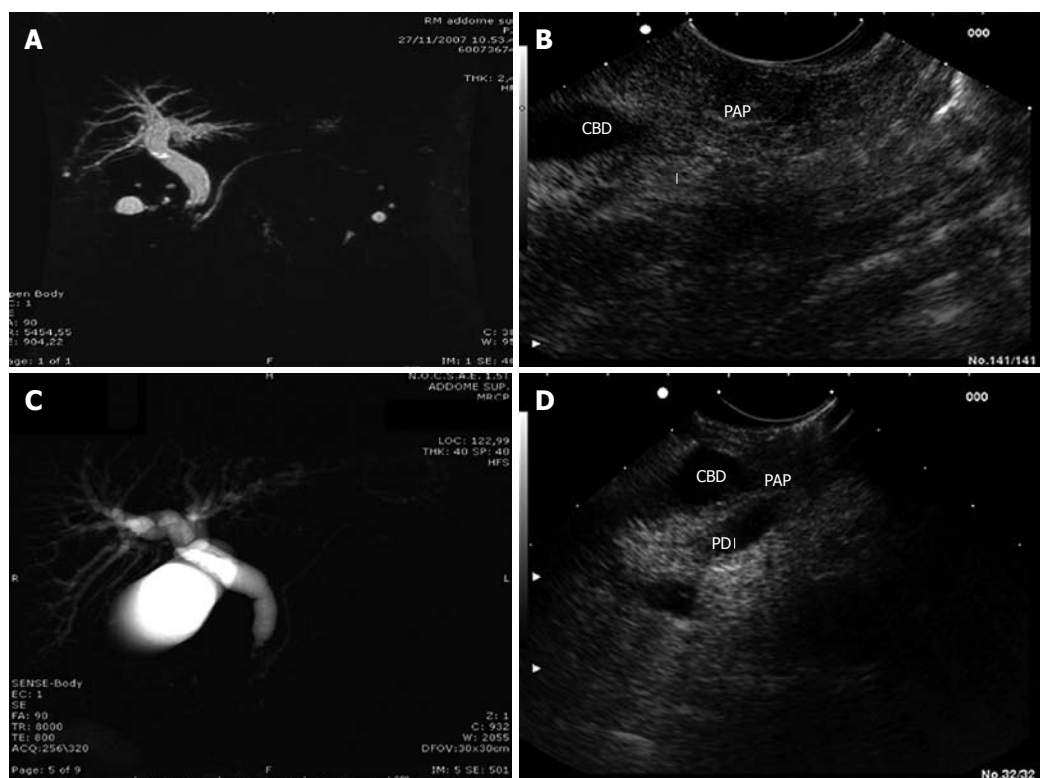


Figure 2 Ampullary tumor, stage 1. A: Magnetic resonance imaging (MRI) showed dilation of the common bile duct and Wirsung's duct, without space-occupying lesions of the ampulla; B: Linear endoscopic ultrasound (L-EUS) of the same patient. Ampullary tumor, stage 2; C: MRI showed dilation of the common bile duct and normal appearance of Wirsung's duct; D: L-EUS scan of the same patient, which showed duodenal wall disruption without pancreas invasion. CBD: Common bile duct; PAP: Papilla (Vater's papilla); PD: Pancreatic duct.

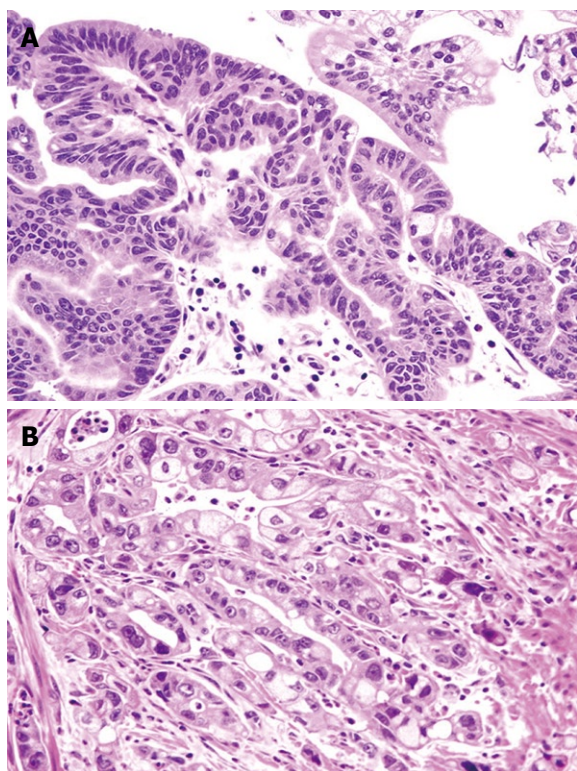


Figure 3 Ampullary tumor, low-grade dysplasia (A) and ampullary adenocarcinoma (B). Hematoxylin and eosin (HE), original magnification 40 ×.

sible endoscopic approach, because it also demonstrates intracholedochal growth. Limitations of this technique include inability to differentiate early malignant from benign tumors and to demonstrate distant metastases, in addition to being an invasive method.

The present study had some limitations. It was retrospective, the patient cohort was relatively small, and it was carried out in a setting with particular expertise in EUS. It remains to be established whether these results can be translated to a more general setting.

In conclusion, L-EUS appears to be a valid diagnostic tool to identify and stage small ampullary tumors, and might yield results that are superior to those of other diagnostic techniques. Further prospective studies are clearly needed to confirm these observations.

COMMENTS

Background

Ampullary tumors are rare and difficult to diagnose. The correct diagnosis is often reached after serological, radiological and/or endoscopic tests. Recently, endoscopic ultrasound (EUS) has been demonstrated as being as useful as magnetic resonance imaging (MRI) for detection of these neoplasms.

Innovations and breakthroughs

No previous study has been previously conducted with L-EUS in this setting, and this study by Manta *et al* showed that this appears to be a valid diagnostic tool to identify and stage small ampullary tumors, and might yield results that are superior to those with other diagnostic techniques.

Terminology

EUS and L-EUS: techniques that combine endoscopic and echographic approaches for detecting lesions of the gastrointestinal tract. MRI: a technique

that employs nuclear resonance imaging to visualize abdominal sections without exposing the subject to radiation.

Peer review

This is a retrospective study with a small sample size. Despite this, it is a novel and well-designed study that is likely to influence clinical practice.

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