—Original Article—

Characteristic endoscopic ultrasound findings of ampullary lesions that predict the need for surgical excision or endoscopic ampullectomy

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ABSTRACT

Background and Objectives: The management of ampullary lesions has evolved to include endoscopic ampullectomy (EA) as a curative approach to cancers of the ampulla of Vater. With this change comes a need to risk-stratify patients at initial diagnosis. **Materials and Methods:** Patients with verified ampullary lesions ($N = 50$) were analyzed in a case-control design. We evaluated endoscopic ultrasound (EUS) data to define characteristics that yield a high sensitivity in selecting candidates for EA. **Results:** Using data from previously published studies yielded a sensitivity of 0.765 in appropriately identifying the 34 surgical cases. Expanding these characteristics increased the sensitivity of EUS to 0.971 in identifying surgical candidates. Additionally, of advanced disease cases, the expanded characteristics correctly identified these cases with a sensitivity of 1.0-improved over 0.708 using prior published data. **Conclusion:** EA should be strongly considered if ampullary lesions are found to fit the following characteristics after EUS evaluation: lesion size <2.5 cm, invasion ≤4 mm, pancreatic duct dilatation ≤3 mm, ≤T1 lesion, no lymph nodes present, and no ductal stent in place. Furthermore, EUS data can be used to identify all high-risk lesions. With these characteristics identified, clinicians are better able to risk-stratify patients using EUS as either appropriate for or too high-risk for endoscopic resection.

Key words: Ampullary adenocarcinoma, ampullary adenoma, ampullary lesion, ampullary mass, endoscopic ampullectomy (EA), endoscopic ultrasound (EUS), surgical ampullectomy

INTRODUCTION

Lesions within the ampulla of Vater are amenable to treatment by pancreaticoduodenectomy (PD).[1-3] Since 1978, ampullary lesions have been treated with this radical approach.[2] However, recent advances in technology, procedure, and pathology suggest that a less radical approach may be feasible and potentially superior.[4] A mounting body of evidence supports the

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utility of endoscopic ampullectomy (EA) for resection of ampullary lesions both malignant and benign. Recent publications endorse endoscopic removal of ampullary lesions dependent on data gathered both prior to and after the endoscopic procedure.[4-11] Pending imaging, histopathological evaluation, and staging, there is the potential for patients with ampullary lesions to avoid the morbidity associated with PD.

The importance of defining proper intervention strategies for ampullary lesions lies in the fact that if patients survive 5 years after surgical resection, this is essentially a curative strategy.[12] Several studies show that cancers of the ampulla of Vater are rather uncommon, with ampullary carcinoma representing 2% of gastrointestinal (GI) malignancies.[13] Based on an evaluation of a large database, Surveillance, Epidemiology, and End Results (SEER), 5,625 cases of ampullary cancer were identified over a 32-year period; however, incidence is increasing.[14-15]

The current challenge in selecting candidates for EA rather than PD or surgical ampullectomy (SA) is defining the characteristics of ampullary lesions that necessitate surgery. PD is, by all accounts, the "Gold Standard" for eradication of pancreatic malignancy and, by association, malignancies of the ampulla of Vater.[3] Since 1992, the modality of endoscopic ultrasound (EUS) has been changing the management of these patients as it is the best imaging modality for ampullary lesions and generally more effective in delineating ampullary tumors than computed tomography, ultrasound, or magnetic resonance imaging.[16-23] Furthermore, EUS has been proven effective in identifying adenocarcinoma and as an effective tool for T-staging ampullary lesions.[24] Previous authors have shown that EA is possible with lesions <2.5 cm and without invasion past 4 mm.[8,11] The next step in determining the clinical significance of EA will be to reliably show the efficacy of EUS in determining candidates for endoscopic resection. As such, the aim of our study was to determine if EUS could appropriately stratify patients for EA by virtue of identifying ampullary lesions that necessitate surgical excision.

MATERIALS AND METHODS

Our analysis included procedures logged at an academic medical center between December 2003 and February 2014. We identified all patients who underwent EUS for the purpose of evaluating an ampullary mass or for staging (N = 534). This was performed using Crystal Reports (SAP, Walldorf, Baden-Württemberg, Germany) prior to a change in our electronic medical record system (occurred on September 24, 2012), and after the transition, endoPRO (Pentax Medical, Tokyo, Japan) was utilized. Because the search fields were necessarily broad in this retrospective chart review, 465 cases were not suitable for further evaluation; however, we identified 69 patients who underwent EUS for ampullary lesions, a majority of whom underwent subsequent intervention. There were a large number of cases that were referred to our medical center for further evaluation based on subtle findings within the duodenum, which were found to be either benign or a result of pancreatic pathology rather than a true ampullary lesion. All EUS procedures were performed using an Olympus GF-UE160, Olympus GF-UCT140, or GF-UC140P (Olympus America Corporation; Melville, NY, USA). Using a case-control design, we abstracted demographics, EUS findings and staging, pathological staging and diagnosis, end points of PD, SA, EA, or "other" from these cases, and 6-month follow-up data, if available. Standard TNM staging according to the American Joint Committee on Cancer (AJCC) 7th Edition was used.

We evaluated EUS data from successful EA and surgical cases with the purpose of stratifying patients at initial evaluation. We stratified the cases by surgery (PD and SA) and EA to define what characteristics predicted a need for surgery rather than an endoscopic removal. The decision to progress with EA was at the discretion of the clinician, and the decision points were evaluated retrospectively. When evaluating the data, two previously defined variables were utilized as predictors for successful EA: lesions <2.5 cm and/or invasion of less than or equal to 4 mm.[8,11] We define these as "prior established criteria." With a detailed retrospective review of the available data, the several variables were identified as common among surgical cases; we then tested to categorize these observations. We proposed that including the following additional characteristics would yield accurate decision-making: pancreatic duct dilatation ≤3 mm, tumor size ≤T1, no nodal metastasis, and no ductal stent in place.[19] We define these four additional data points in combination with the prior established criteria as "modified criteria."

Both the prior established criteria and the modified criteria were applied to the EUS data retrospectively. If

any of the characteristics were met, this indicated that this lesion should be surgically resected. We evaluated these criteria for their sensitivity in selecting the correct end-point.

Statistical evaluation was performed and included creating confidence intervals for the sensitivity of each assessment using Exploratory Software for Confidence Intervals (www.thenewstatistics.com; Cumming, 2013). McNemar's test was utilized for evaluating differences in the sensitivity of the two methods using SPSS (IBM Corporation, Version 21.0. Armonk, NY, USA).

In total, 19 of the 69 identified patients were excluded from analysis. Exclusion criteria included: Patients not deemed appropriate for surgical management, thus limiting further analysis; documentation errors; subjects lost to follow-up; anatomical variants, which excluded an endoscopic approach; and carcinoid tumors found on pathology. A majority (14) of the 19 exclusions were secondary to either a prohibitive risk of surgical intervention (7 subjects) or the patients were lost to follow-up (7 subjects). Furthermore, within the surgical group, there were five exclusions, two were the result of carcinoid pathology, one was not clearly identifiable via chart review, and three were the result of anatomical variants that made an endoscopic approach unreasonable.

RESULTS

In total, there were 534 endoscopic procedures for suspected ampullary lesions over the period of December 2003 to February 2014; of these, 69 patients had verified ampullary lesions. Of the 69 patients, 16 (23.1%) underwent EA, 29 (42.0%) underwent PD, 5 (7.2%) underwent SA, and 19 patients (27.5%) were omitted based on the guidelines as mentioned above, [Figure 1]. Hence, there were 50 patients with confirmed ampullary lesions in our analyses. Patients presented with a variety of clinical symptoms. Histopathological examination of the analyzed patients revealed 23 (46%) adenomas, 4 (8%) adenomas with high-grade dysplasia, 20 (40%) adenocarcinomas, and 3 (6%) "other" lesions (duodenitis, lipoma, and regenerative tissue) [Figure 2]. All adenocarcinomas were identified in patients undergoing surgical resection, but not all surgical resections were adenocarcinomas, [Table 1].

We also collected 6-month follow-up data on all patients with available records. In total, we were able

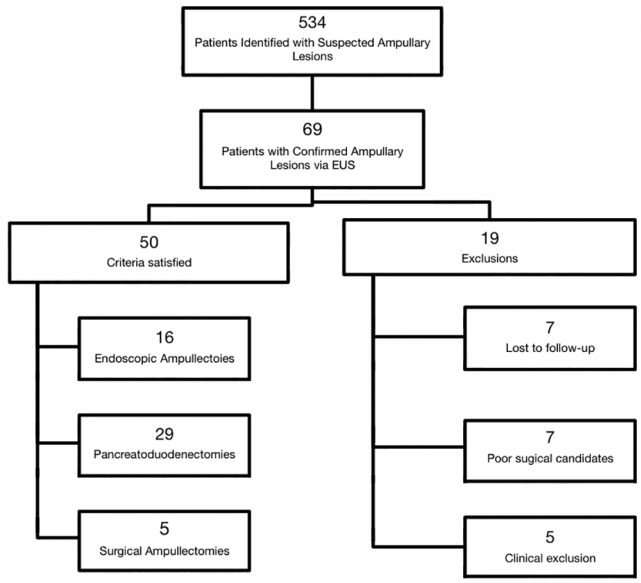

Figure 1. Distribution of all identified subjects

Table 1. EUS criteria findings in surgical cases with adenomatous disease compared with advanced disease

Number of Criteria Present	Adenomatous Disease	Advanced Disease
1	100%	100%
2	0	61%
3	0	12.5%

to obtain data on 38 of the 50 interventions used for analysis (76%). Of patients who had follow-up data available, 81% of surgical cases were disease-free at a time interval of at least 6 months, and 80% of EA cases were disease-free at that interval. There was a 19% and 20% rate for disease recurrence/presumed metastatic disease at the 6-month follow-up for surgical cases and EA cases, respectively.

Of the 34 surgical interventions, 24 (70.6%) had advanced disease defined as adenocarcinoma or adenoma with high-grade dysplasia. Of the 16 EAs, 13 (81.3%) were identified as adenomas and 3 (18.7%) were identified as "other" lesions. Within the patient group with confirmed adenomas, 13 (56.5%) were excised endoscopically and 10 (43.5%) went to surgery.

When the prior, established guidelines were applied to each individual case, 26 of the 34 lesions that required surgical intervention were identified — Showing a sensitivity of 0.765, 95% CI (0.600, 0.876). Using the modified criteria, EUS identified 33 of the 34 lesions that went to surgery, thus increasing the sensitivity to

0.971, 95% CI (0.851, 0.995) or a 21% increase in sensitivity. The modified criteria approach was superior to the old guidelines (P = 0.03).

Importantly, of the advanced disease cases identified (N = 24), the prior established guidelines identified 17 of the 24 advanced lesions, while the modified criteria identified all 24. Thus, the prior established guidelines identified 0.708, 95% CI (0.508, 0.851) of advanced disease, and this increased to 1.0, 95% CI (0.862, 1.0) with the modified criteria, a 29% increase in sensitivity, P = 0.01 [Figure 3].

DISCUSSION

Early research indicated that T1 lesions and/or lesions extending beyond the mucosa require surgical intervention.[5] More recent data have shown EA to be an appropriate intervention when there is no infiltration further than 4 mm, or if the mass was less than 2.5 cm.[8,11] Furthermore, the negative predictive value of EUS for muscularis invasion has been shown to be 90%.[9] EUS accurately identifies local staging of ampullary lesions and has been accepted as the best modality for evaluating ampullary lesions [Figure 4a and b].[24] This retrospective study demonstrates the clinical utility for EUS in predicting lesions suitable for EA.

The results of this study show that EUS is a very sensitive tool (97%) in identifying ampullary lesions necessitating surgery based on several characteristic findings. Thus, EUS is an effective tool in identifying ampullary lesions amenable to endoscopic intervention by virtue of its high sensitivity in identifying cases needing surgery. Furthermore, although the prior established guidelines were adequate at identifying patients with advanced disease, this was not the intent of their development. In adding additional characteristics, we improved the identification of advanced disease, or high-risk patients, from 70.8% to 100%. These findings have both statistical and clinical significance. As such, EA should be strongly considered if lesions are found to fit the following conditions: <2.5 cm, invasion ≤4 mm, pancreatic duct dilatation ≤3 mm, tumor size ≤T1, no nodal metastasis, and no ductal stent in place. Additionally, clinicians can be confident in their prediction of advanced pathology via EUS.

Our study does have several limitations. The analysis is confined to a single site with a limited number

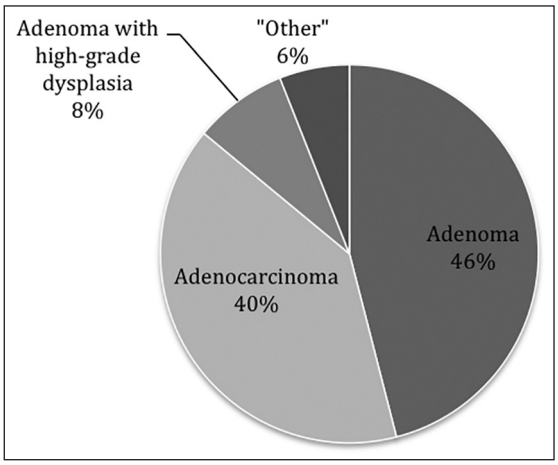

Figure 2. Final pathological diagnosis after surgery or ampullectomy

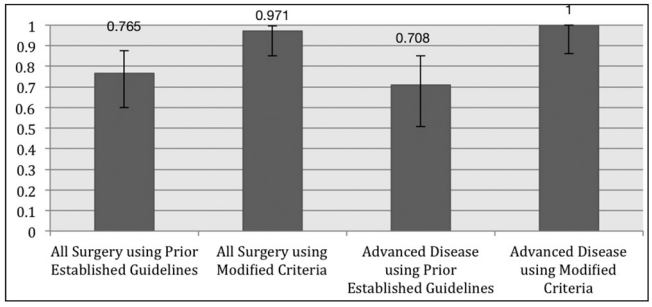

Figure 3. The sensitivity of Prior Established Guidelines and Modified Criteria by surgical intervention and advanced disease

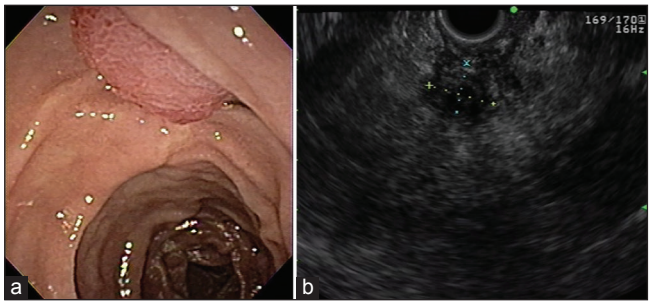

Figure 4. (a) Endoscopic image of an ampullary lesion (b) EUS image of a 1.3 cm × 1.0 cm ampullary lesion confined to the mucosa

of observed cases, and, as the institution where the interventions were performed is a tertiary medical facility, many of the referrals for care are for patients who are not established within our network of hospitals, making follow-up numbers limited. However, of note, the recurrence rates were similar among surgical and EA cases. The analysis was retrospective and unblinded, leaving open the possibility of rater bias. Additionally, EUS and its interpretation is intrinsically operator-dependent, so there may be difficulty in the reproducibility of EUS findings. Further research is warranted for long-term outcomes of patients who undergo EA in order to follow the progression of

disease and/or evaluate for the mortality among this relatively small patient population.

Despite the aforementioned limitations, the findings of this retrospective, subset analysis offer guidance to the management of ampullary lesions, and have the potential to facilitate fewer invasive surgical interventions in the future. Utilizing data collected from EUS in patients with ampullary lesions, a clinician is able to stratify patients at initial diagnosis and identify an appropriate definitive therapy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chareton B, Coiffic J, Landen S, *et al*. Diagnosis and therapy for ampullary tumors: 63 cases. *World J Surg* 1996;20:707-12.
2. Schlippert W, Lucke D, Anuras S, *et al*. Carcinoma of the papilla of Vater. A review of fifty-seven cases. *Am J Surg* 1978;135:763-70.
3. Yoon YS, Kim SW, Park SJ, *et al*. Clinicopathologic analysis of early ampullary cancers with a focus on the feasibility of ampullectomy. *Ann Surg* 2005;242:92-100.
4. Ceppa EP, Burbridge RA, Rialon KL, *et al*. Endoscopic versus surgical ampullectomy: An algorithm to treat disease of the ampulla of Vater. *Ann Surg* 2013;257:315-22.
5. Lee SY, Jang KT, Lee KT, *et al*. Can endoscopic resection be applied for early stage ampulla of Vater cancer? *Gastrointest Endosc* 2006;63:783-8.
6. Carter JT, Grenert JP, Rubenstein L, *et al*. Tumors of the ampulla of vater: Histopathologic classification and predictors of survival. *J Am Coll Surg* 2008;207:210-8.
7. Ito K, Fujita N, Noda Y, *et al*. Diagnosis of ampullary cancer. Dig Surg 2010;27:115-8.
8. Petrone G, Ricci R, Familiari P, *et al*. Endoscopic snare papillectomy: A possible radical treatment for a subgroup of T1 ampullary adenocarcinomas. *Endoscopy* 2013;45:401-4.
9. Azih LC, Broussard BL, Phadnis MA, *et al*. Endoscopic ultrasound evaluation in the surgical treatment of duodenal and peri-ampullary adenomas. *World J Gastroenterol* 2013;19:511-5.
10. El Hajj II, Coté GA. Endoscopic diagnosis and management of ampullary lesions. *Gastrointest Endosc Clin N Am* 2013;23:95-109.
11. Patel R, Davitte J, Varadarajulu S, *et al*. Endoscopic resection of ampullary adenomas: Complications and outcomes. *Dig Dis Sci* 2011;56:3235-40.
12. O'Connell JB, Maggard MA, Manunga J Jr, *et al*. Survival after resection of ampullary carcinoma: A national population-based study. *Ann Surg Oncol* 2008;15:1820-7.
13. Chan M, Adler DG. Ampullary cancer: Review and clinical update. *Commun Oncol* 2010;7:61-6.
14. Albores-Saavedra J, Schwartz AM, Batich K, *et al*. Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. *J Surg Oncol* 2009;100:598-605.
15. Benhamiche AM, Jouve JL, Manfredi S, *et al*. Cancer of the ampulla of Vater: Results of a 20-year population-based study. *Eur J Gastroenterol Hepatol* 2000;12:75-9.
16. Snady H, Cooperman A, Siegel J. Endoscopic ultrasonography compared with computed tomography with ERCP in patients with obstructive jaundice or small peri-pancreatic mass. *Gastrointest Endosc* 1992;38:27-34.
17. Rösch T, Braig C, Gain T, *et al*. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992;1:188-99.
18. Skordilis P, Mouzas IA, Dimoulios PD, *et al*. Is endosonography an effective method for detection and local staging of the ampullary carcinoma? A prospective study. *BMC Surg* 2002;2:1.
19. Cannon ME, Carpenter SL, Elta GH, *et al*. EUS compared with CT, magnetic resonance imaging, and angiography and the influence of biliary stenting on staging accuracy of ampullary neoplasms. *Gastrointest Endosc* 1999;50:27-33.
20. Mukai H, Nakajima M, Yasuda K, *et al*. Evaluation of endoscopic ultrasonography in the pre-operative staging of carcinoma of the ampulla of Vater and common bile duct. *Gastrointest Endosc* 1992;38:676-83.
21. Chen CH, Tseng LJ, Yang CC, *et al*. The accuracy of endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, computed tomography, and transabdominal ultrasound in the detection and staging of primary ampullary tumors. *Hepatogastroenterology* 2001;48:1750-3.
22. Müller MF, Meyenberger C, Bertschinger P, *et al*. Pancreatic tumors: Evaluation with endoscopic US, CT, and MR imaging. *Radiology* 1994;190:745-51.
23. Howard TJ, Chin AC, Streib EW, *et al*. Value of helical computed tomography, angiography, and endoscopic ultrasound in determining resectability of periampullary carcinoma. *Am J Surg* 1997;174:237-41.
24. Ridtidid W, Schmidt SE, Al-Haddad MA, *et al*. Performance characteristics of EUS for locoregional evaluation of ampullary lesions. *Gastrointest Endosc* 2015;81:380-8.