The Assessment of Specimens Procured by Endoscopic Ampullectomy

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Abstract

Endoscopic ampullectomy (EA) is increasingly used in the management of ampullary neoplasia. Although studies on the safety and efficacy of this procedure exist, no study has specifically addressed the histopathologic features of the specimens. We review our experience with 45 EA specimens assessed for the following: diagnosis, high-grade dysplasia (HGD), submucosal ampullary gland/ductule involvement, specimen integrity, and margin status. Familial adenomatous polyposis (FAP) status and the endoscopist's impression of completeness of removal were also ascertained. Previous biopsy diagnoses were compared with ampullectomy diagnoses, and histologic and clinical features were correlated with disease persistence. The histologic features of the ampullectomy specimens were as follows: diagnosis (no diagnostic abnormality, 3; reactive, 8; adenoma, 26; adenocarcinoma, 7; other, 1); HGD, 1; submucosal ampullary gland/ductule involvement, 20; specimen integrity (intact, 22; fragmented, 23); and margin status (positive, 20; negative, 2; could not be assessed, 12). Five patients had FAP, and EA was deemed complete in 21 (47%). The diagnostic agreement between preampullectomy biopsy and ampullectomy was 64%. Of the patients, 33 (73%) had documented persistent disease. None of the histologic or clinical features had a statistically significant relationship with disease persistence.

The ampulla of Vater is a complex anatomic structure composed of the distal-most, intraduodenal portions of the common bile duct and pancreatic duct, which usually join to form a common channel. These ducts are lined by pancreatobiliary-type epithelium. Viewed from the duodenal lumen, this structure projects as the duodenal papilla and is covered by small intestinal–type epithelium.[1]

The ampulla is recognized as a preferred site for development of duodenal epithelial neoplasia. In patients with familial adenomatous polyposis (FAP), the incidence of ampullary adenoma has been shown to approximately equal that for the remaining duodenum.[2] This is believed to reflect the anatomic complexity and function of the region; it is an epithelial transition zone bathed in pancreatic juice and bile.[3]

A variety of therapeutic options exist for the management of ampullary neoplasia. Pancreatoduodenectomy is considered the "gold standard." It is still the first choice for the treatment of most ampullary adenocarcinomas and, at many centers, for the management of large ampullary adenomas.[4] There has been a drive toward less invasive procedures, with the goal of minimizing morbidity and mortality. Transduodenal ampullectomy is an open surgical procedure that involves removal of the duodenal papilla with reimplantation of the distal common bile duct and pancreatic duct into the wall of the duodenum. This procedure is used at some centers in the management of large adenomas and a select population of low-stage, low-grade ampullary adenocarcinomas.[5,6]

Endoscopic ampullectomy (EA; also referred to as endoscopic papillectomy or endoscopic snare resection) obviates the need for laparotomy. Given technological advances and greater access to interventional endoscopy, this technique has been increasingly used in the last decade in the management

of ampullary adenomas. There are also scattered case reports of its use in small ampullary adenocarcinomas and neuroendocrine neoplasms.[7,8] (Often in these reports EA represents a "minimally invasive" alternative in patients deemed "poor surgical candidates.")

The endoscopist visualizes the papilla (and the attendant adenoma) with a side-viewing endoscope. Cholangiography and pancreatography are performed to assess for proximal extension of the lesion. Papillotomy can allow for access to intra-ampullary lesions. Saline or dilute epinephrine can be injected into the submucosa deep to the lesion, lifting the lesion and facilitating snare resection. Residual lesional tissue can be removed piecemeal with forceps or thermally ablated, typically with argon plasma coagulation. Finally, stents can be placed for ductal decompression.[9-11]

The goals of this study were several-fold. Fundamentally, we sought to describe the histologic features of specimens obtained by EA. Endoscopic biopsy of the ampulla has been criticized as inaccurate, with reported diagnostic accuracies ranging from 62% to 85%.[6,12-14] We explored this issue through the comparison of preampullectomy and ampullectomy diagnoses. We also have histologic follow-up for the majority of our cases, permitting a glimpse of what pathologists might expect to see in biopsy specimens following ampullectomy and allowing comment on the therapeutic usefulness of EA.

Materials and Methods

We identified a cohort of patients from an endoscopic retrograde cholangiopancreatography database at the University of Virginia Health System, Charlottesville, who underwent EA for presumed ampullary adenoma. Approximately half of the study patients had a previous ampullary biopsy specimen reviewed at our institution. Patients in whom endoscopy revealed a clinically malignant lesion, including cases in which submucosal injection failed to lift the lesion, were excluded, because in these cases, EA is aborted (instead, multiple forceps biopsy specimens are obtained to attempt to confirm the endoscopic impression).

Tissue had been routinely processed (formalin-fixed, paraffin-embedded, and slides cut at 5 μm and H&E stained). Ampullectomy specimens were assessed for the following histologic features (all original glass slides reviewed): diagnosis, presence of high-grade dysplasia (HGD), involvement of submucosal ampullary glands/ductules by adenoma, specimen integrity, and margin status. Adenomas were designated as tubular or tubulovillous (cases containing at least a 25% villous component). The diagnosis "adenomatous epithelium" was used when only a small fraction of the resected tissue appeared neoplastic. HGD was defined as significant cytoarchitectural abnormality (including loss of nuclear polarity, back-to-back glands, intraluminal necrotic debris) in the absence of stromal invasion. Cases were designated as intact (if the specimen consisted of one to a few well-oriented tissue fragments) or fragmented. When possible, margin status was assessed (in well-oriented, intact cases and in some fragmented cases consisting nearly entirely of lesional tissue). Patient FAP status and the endoscopist's impression of adequacy of lesion removal were also ascertained.

When available, preampullectomy and postampullectomy tissue diagnoses were recorded (via chart review). Also, the interval between preampullectomy biopsy and ampullectomy and the duration of histologic follow-up for postampullectomy specimens were noted. These diagnoses were correlated with the results of ampullectomy, allowing for assessment of the diagnostic accuracy of endoscopic biopsy preampullectomy and the efficacy of EA in eradicating ampullary neoplasia.

Statistics

A 1-tailed Mann-Whitney *U* test was used to compare the interval between preampullectomy biopsy and ampullectomy for ampullectomies with a "reactive" diagnosis vs all other diagnoses. The Fisher exact test was used to correlate histologic and clinical features with disease persistence or recurrence.

Results

We identified 45 patients (27 men and 18 women, ages 25-88 years) who underwent EA for presumed ampullary adenoma. In 22 cases, a preampullectomy tissue diagnosis was available, and in 37 cases we had histologic follow-up (consisting of 1 or more biopsy specimens or a resection specimen). Patient age and sex, FAP history, prior biopsy diagnoses, histologic features of the ampullectomy specimens, endoscopic impression of complete removal, and follow-up information are summarized in **Table 1**.

The histologic features of the 45 ampullectomy specimens were as follows: diagnosis (no diagnostic abnormality, 3; reactive atypia, 8; adenomatous epithelium, 2; tubular adenoma, 10; tubulovillous adenoma, 14; adenocarcinoma, 7; and gangliocytic paraganglioma [GCP], 1); HGD, 1; submucosal ampullary gland/ductule involvement, 20; specimen integrity (intact, 22; fragmented, 23); and margin status (positive, 20; negative, 2; could not be assessed, 12; not applicable, 11). Five patients had FAP, and there was an endoscopic impression of complete lesion removal in 21 (47%).

In 22 cases (49%), biopsy material had been previously reviewed. There was diagnostic agreement between the biopsy and the ampullectomy in 14 cases (64%). In the majority of the 8 discrepant cases, the biopsy had revealed adenoma, whereas the ampullectomy showed reactive atypia

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Table 1
Clinicopathologic Features of Patients Who Underwent Ampullectomy

Case No./ Sex/Age (y)	FAP	Previous Diagnosis	Ampullectomy Diagnosis	AG/DI	Margins	Microscopic ECR
1/M/57	N	Atypical, favor neoplastic	Reactive atypia	—	—	N
2/F/70	N	Adenoma	Adenocarcinoma	N	Positive	N
3/M/50	N	Adenoma	TVA*	Y	CNBA	Y
4/M/49	N	Adenoma	Submucosal fibrosis and reactive atypia	—	—	Y
5/M/47	N	Atypical	GCP	—	Positive	Y
6/F/71	Y	Adenoma	TVA*	Y	CNBA	N
7/F/62	N	Adenoma	Adenomatous epithelium*	N	Negative	Y
8/M/40	Y	Adenoma	TA*	Y	Positive	N
9/F/69	N	Adenoma	TA*	N	CNBA	Y
10/M/72	N	Adenoma	TA*	Y	CNBA	N
11/M/43	N	Adenoma	TA*	Y	Negative	Y
12/M/72	Y	Adenoma	Submucosal fibrosis	—	—	Y
13/F/75	N	Adenoma	Focal ulceration	—	—	Y
14/M/32	Y	Adenoma	TVA*	Y	Positive	Y
15/M/40	Y	Adenoma	TA*	N	CNBA	Y
16/M/86	N	Adenoma	TA*	Y	CNBA	N
17/M/82	N	Adenoma × 2	Ulceration and reactive atypia	—	—	Y
18/M/52	N	Adenoma × 2	TA*	N	CNBA	Y
19/M/51	N	Adenoma	TVA*	Y	Positive	N
20/M/78	N	At least adenoma	Adenocarcinoma*	N	Positive	N
21/M/58	N	Reactive × 2	Reactive atypia*	—	—	Y
22/M/44	N	Favor adenoma	NDA	—	—	Y
23/M/67	N	None	Adenocarcinoma	Y	Positive	N
24/F/82	N	None	NDA	—	—	N
25/F/59	N	None	TVA	Y	Positive	N
26/M/53	N	None	Adenomatous epithelium	N	CNBA	Y
27/M/58	N	None	TVA	N	Positive	Y
28/F/62	N	None	TA	Y	Positive	N
29/F/69	N	None	NDA	—	—	Y
30/F/88	N	None	Focal ulceration	—	—	Y
31/M/75	N	None	Adenocarcinoma	Y	Positive	N
32/M/79	N	None	TVA	N	Positive	Y
33/F/66	N	None	TVA	N	CNBA	Y
34/M/72	N	None	TVA	Y	CNBA	N
35/F/73	N	None	TA	Y	Positive	N
36/F/69	N	None	TVA	N	CNBA	N
37/M/58	N	None	TVA	Y	Positive	N
38/M/80	N	None	TVA	Y	Positive	N
39/F/82	N	None	TVA	Y	Positive	N
40/F/76	N	None	TA	N	CNBA	Y
41/M/25	N	None	Adenocarcinoma	Y	Positive	N
42/F/52	N	None	Adenocarcinoma	N	Positive	N
43/F/75	N	None	Adenocarcinoma	Y	Positive	N
44/F/50	N	None	Ulceration	—	—	N
45/M/59	N	None	TVA	Y	Positive	N

AG/DI, ampullary submucosal gland/ductule involvement; CNBA, could not be assessed; ECR, endoscopic impression of complete resection; FAP, familial adenomatous polyposis; FNA, fine-needle aspiration; GCP, gangliocytic paraganglioma; N, no; NDA, no diagnostic abnormality; TA, tubular adenoma; TVA, tubulovillous adenoma; Y, yes.
* Indicates agreement between previous diagnosis and ampullectomy diagnosis.

(4 cases) or no diagnostic abnormality (1 case). Two biopsy specimens were read as "atypical," and the corresponding ampullectomy specimens demonstrated reactive changes and GCP. Finally, in 1 case (case 2), although the biopsy specimen was diagnosed as adenoma, the ampullectomy specimen revealed a poorly differentiated adenocarcinoma (the subsequent pancreatoduodenectomy revealed a pancreatic ductal adenocarcinoma).

Histologic follow-up was available for 37 patients. The mean and median duration of follow-up were 1.25 years and 1 year, respectively. Of the 37 patients, 27 (73%) had documented persistent or recurrent disease. This includes 5 patients with an EA diagnosis of adenocarcinoma, in which the procedure would not be expected to extirpate the lesion. In 23 of these patients in whom ampullectomy revealed adenoma, there were 8 treatment successes (35%) and 15 lesions that ultimately persisted or recurred (65%). In 2 cases (cases 6 and 24) lesions progressed or were underdiagnosed by EA. In case 6, biopsy had revealed an adenoma and ampullectomy, a tubulovillous adenoma; 1.5 years later, peritoneal

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Persistence or Recurrence (Follow-up)
N (highly atypical; then favor reactive at 1 mo and 3 y)
Y (Whipple with pancreatic ductal adenocarcinoma at 4 mo)
N (reactive; then negative at 2 and 8 mo)
N (reactive × 2 at 6 mo)
N (NDA at 3 mo; reactive at 6 mo and 1 y)
Y (adenoma at 2 mo; peritoneal carcinoma on FNA at 1.5 y)
Y (adenoma × 4 out to 1.25 y; 1 interspersed reactive)
Y (adenoma × 4 out to 11 mo)
Y (adenoma × 5 out to 1.5 y)
Y (adenoma × 8 out to 2.5 years followed by 2 reactive out to 3.25 y)
Y (minimal residual adenoma at 6 mo; reactive at 2 y)
Y (NDA; then adenoma at 10 mo)
Y (reactive × 2; then small adenoma at 1.25 and 1.5 y)
Y (adenoma at 1 mo; then reactive × 2 at 1.5 y)
Y (adenoma at 1.25 y)
Y (adenoma at 4 mo)
Y (adenoma at 5 mo)
No follow-up
No follow-up
No follow-up
No follow-up
No follow-up
Y (Whipple with ampullary adenocarcinoma 5 d later)
Y (adenocarcinoma at 2.75 y followed by Whipple with ampullary adenocarcinoma)
N (NDA at 15 mo)
N (NDA; then reactive out to 1 mo)
N (NDA at 2.25 y)
N (NDA at 2.75 y)
— (NDA at 3 mo)
— (reactive at 1 mo)
Y (adenocarcinoma at 2 mo; reactive at 2.67 y after chemotherapy and radiation therapy)
Y (adenoma at 4 mo)
Y (adenoma × 3 out to 1.67 y)
Y (adenoma × 7 out to 5.5 y)
Y (NDA at 4 mo; then adenoma at 1.5 y)
Y (reactive at 1 mo then adenoma × 5 out to 1.5 y)
Y (adenoma at 1 mo; Whipple with adenoma 2 d later)
Y (adenoma at 2 and 4 mo)
Y (adenoma at 3 and 9 mo)
Y (adenoma × 2 at 6 and 7 mo)
Y (Whipple with ampullary adenocarcinoma at 1 mo)
Y (Whipple with ampullary adenocarcinoma at 2 mo)
No follow-up
No follow-up
No follow-up

carcinomatosis was diagnosed. In case 24, EA revealed no diagnostic abnormality; biopsy 2.75 years later revealed adenocarcinoma, and pancreatoduodenectomy confirmed an ampullary primary tumor.

The median intervals between preampullectomy biopsy and ampullectomy for "reactive" and for all other diagnoses were 33 and 29.5 days, respectively (P = .51). The presence of villous architecture (P = .71), submucosal ampullary gland/ductule involvement (P = 1), specimen integrity (P = 1), FAP status (P = .25), and endoscopic impression of complete removal (P = .25) had no statistically significant relationship to disease persistence or recurrence. Of note, all 5 patients with FAP experienced recurrence, and the lack of statistical significance probably reflects a combination of small sample size and overall frequency of recurrent disease.

Discussion

Given that study patients underwent EA for presumed ampullary adenoma, it is not surprising that the most common diagnosis in this group was some form of adenoma (26/45 [58%]). These were fairly evenly divided between tubular adenoma (10) and tubulovillous adenoma (14). Two cases consisted of scant fragments of superficial low-grade dysplastic epithelium, which we designated "adenomatous epithelium." **Image 1A** and **Image 1B** are taken from a typical adenoma.

The second most common category of diagnosis was "reactive atypia." Reactive changes consisted of some combination of ulceration, submucosal fibrosis, and reactive epithelial atypia (smudged chromatin, prominent nucleoli). Because the majority of patients will have had a tissue diagnosis established by preampullectomy forceps biopsy and because a significant number of patients with obstructive jaundice will have undergone stenting, that 18% of patients in this series demonstrated reactive changes is, again, not surprising.[9,10,15]

The third most common diagnosis in this series was adenocarcinoma (7 [16%]). Unfortunately, in 5 of these cases, a preampullectomy biopsy specimen was not available for review. Given the inclusion criteria of this study, though, the preampullectomy clinical impression was that of a benign lesion. Of note, one of the adenocarcinomas (case 2) proved to represent a pancreatic ductal adenocarcinoma at the time of pancreatoduodenectomy. Direct extension of pancreatic primary tumors to involve the ampulla is well described, and pathologists should keep this possibility in mind when evaluating ampullary specimens.[16]

In 3 cases, the ampullectomy demonstrated no diagnostic abnormality. This underscores the challenges inherent in endoscopically assessing the ampulla. By way of context, in a series of 114 patients with FAP enrolled in a duodenal/ampullary endoscopic surveillance program, although the papilla appeared normal at initial endoscopy in 67% of patients, in 54% of the patients with a normal-appearing ampulla, histologic examination revealed an adenoma. And although biopsy from an abnormal-appearing ampulla had a much higher chance of revealing an adenoma, it did not invariably do so; 4 (11%) of 37 patients had negative biopsy results.[2] In 1 of our 3 cases (case 29), EA was negative, as was a follow-up biopsy at 3 months; this would appear to reflect the aforementioned instance, a "clinical false-positive." In another of the cases

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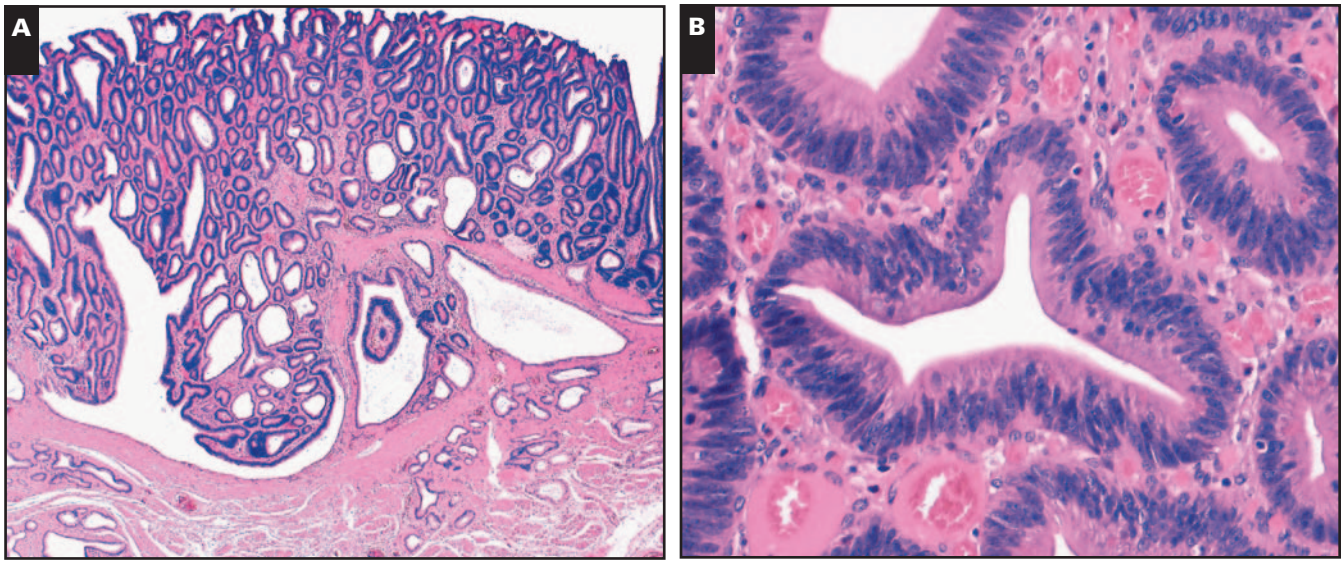

Image 1 Ampullary adenoma. **A**, Typical intestinal-type ampullary adenoma. Nearly all adenomas exhibit cytoarchitectural features indistinguishable from those seen in colonic adenomas (H&E, ×20). **B**, Nuclei are elongate, hyperchromatic, and pseudostratified (H&E, ×200).

(case 22), a preampullectomy biopsy diagnosis had favored adenoma, and there was no follow-up; it is possible in this case that biopsy, perhaps coupled with thermal ablation, eradicated the lesion, although without follow-up, this represents conjecture. The final of these 3 cases (case 24) represents a presumed diagnostic and therapeutic failure. Although the histologic features from EA were unremarkable, biopsy and subsequent pancreatoduodenectomy 2.75 years later revealed ampullary adenocarcinoma.

Finally, in 1 case (case 5), EA demonstrated a GCP. In this case, preampullectomy biopsy demonstrated an architecturally complex yet cytologically bland "atypical epithelial proliferation." Histologic follow-up out to 1 year failed to reveal residual GCP. GCP represents a rare and unusual neuroendocrine tumor of the periampullary region composed of varying proportions of spindled, epithelial, and ganglion cells.[17] This case is further discussed in a previously published report.[18] The distribution of ampullectomy diagnoses is summarized in **Table 2**.

Table 2
Distribution of Ampullectomy Diagnoses

Diagnosis	No. (%) of Cases
Adenoma	26 (58)
Reactive atypia	8 (18)
Adenocarcinoma	7 (16)
No diagnostic abnormality	3 (7)
Other	1 (2)

Regarding the remaining evaluated histologic features, HGD was noted in only 1 case (case 41), present simultaneously with invasive adenocarcinoma. Submucosal ampullary gland/ductule colonization was noted in 20 (61%) of 33 adenomas and adenocarcinomas. We consider this, along with overcalling reactive changes as neoplastic and thermal artifact as dysplasia, as potential diagnostic pitfalls **Image 2**. Knowledge of the frequency of this phenomenon and identification of a maintained lobular architecture and lack of desmoplasia will allow for correct diagnosis. Margins were frequently unevaluable (as specimens were often fragmented), and when they were, they were usually positive (20 [91%] in 22 applicable, evaluable cases). These observations correlate with the clinical practice of EA; lesions, especially larger ones, are frequently removed piecemeal, and margin status is not of paramount concern (because the procedure is generally used in lesions with less aggressive biologic behavior than those subjected to transduodenal ampullectomy or pancreatoduodenectomy and because of the relative ease of thermally ablating small foci of residual lesion). Finally, although not specifically evaluated, the vast majority of cases exhibited extensive thermal artifact; this again reflects ampullectomy practice, as the endoscopists are using snare cautery.[9-11]

Endoscopic biopsy of the ampulla has been criticized as inaccurate, with reported diagnostic accuracy rates ranging from 62% to 85%.[6,12-14] The inability to consistently identify adenocarcinoma has been frequently cited. For example, in a series of 123 patients at Memorial Sloan-Kettering Cancer Center (New York, NY) with nonfamilial periampullary

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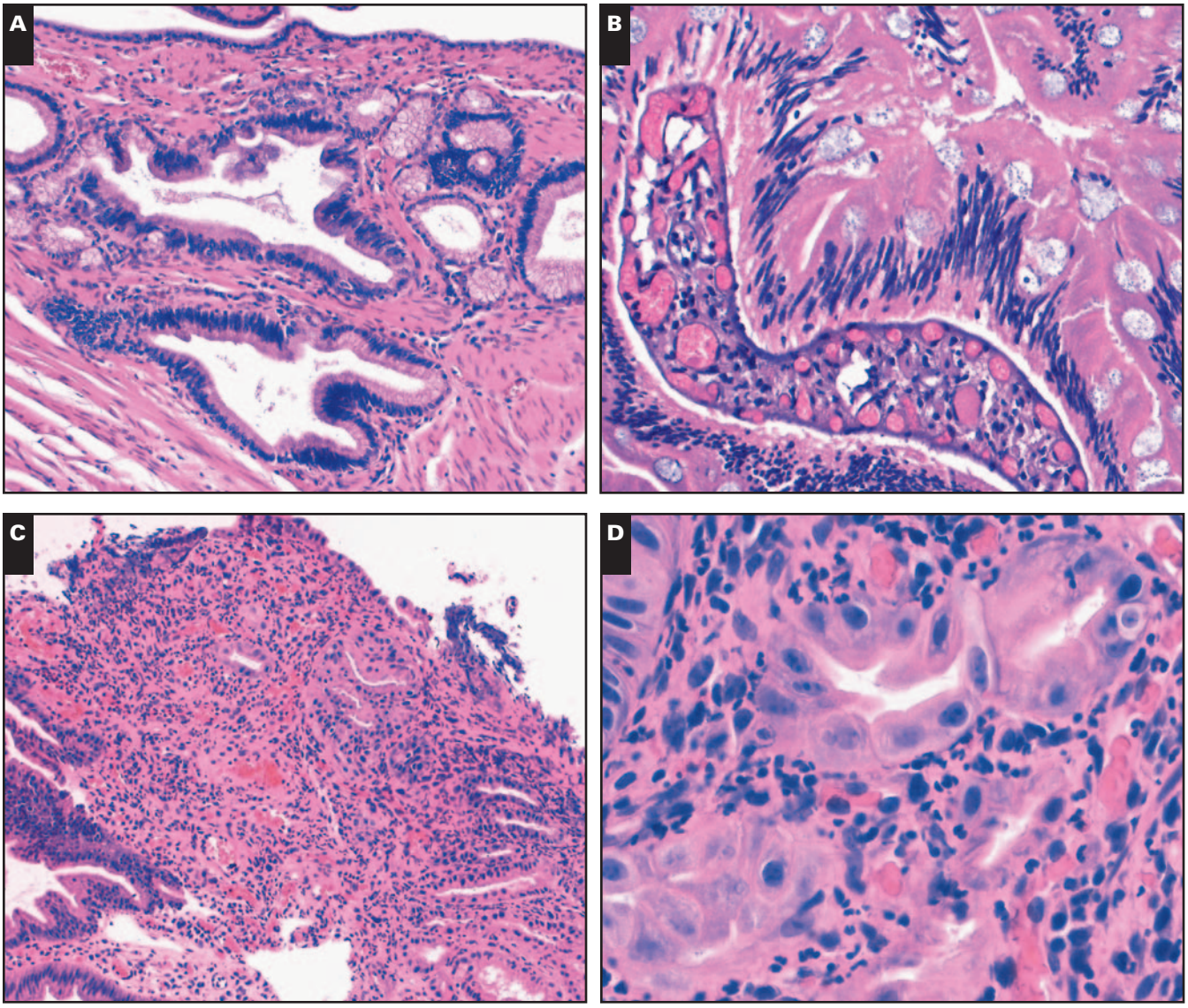

Image 2 Potential diagnostic pitfalls. **A**, Ampullary submucosal gland/ductule involvement. Adenoma frequently colonizes ampullary submucosal glands and ductules, simulating invasion. Maintenance of lobular architecture and lack of desmoplasia argue against malignancy (H&E, ×100). **B**, Cautery artifact. Cautery produces nuclear hyperchromasia and elongation, simulating adenomatous change (H&E, ×400). **C**, Reactive epithelial atypia. Biopsy demonstrates acutely inflamed polypoid mucosa with surface erosion (H&E, ×40). **D**, At high power, glands display smudged chromatin and prominent nucleoli. Biopsy 1 month earlier revealed adenoma; 2 subsequent biopsies demonstrated reactive changes (H&E, ×400).

neoplasms undergoing definitive surgical treatment, 27% of 99 patients with an ultimate surgical diagnosis of adenocarcinoma were underdiagnosed preoperatively.[6] Menzel et al[13] analyzed a group of 40 consecutive patients with polypoid ampullary tumors, and although their group realized an overall diagnostic accuracy of 62%, the sensitivity of endoscopic biopsy in establishing a diagnosis of adenocarcinoma was much lower (37%); 12 of 19 adenocarcinomas were diagnosed as adenoma or "reactive." The performance of multiple biopsies and papillotomy (providing access to intra-ampullary lesions) have each been shown to increase the diagnostic yield.[13,14]

This study is not ideally positioned to expose the weakness of endoscopic biopsy—its insensitivity in detecting adenocarcinoma. Theoretically, in patients with adenocarcinoma but with an endoscopic biopsy diagnosis or a clinical suspicion of adenoma, planned ampullectomies will be aborted when the lesion fails to lift or other modalities (endoscopic retrograde cholangiopancreatography, endoscopic ultrasound) suggest a more aggressive lesion. Nevertheless, as discussed, in 1 case, ampullectomy allowed for the diagnosis of adenocarcinoma. It also allowed for the adjudication of 3 atypical cases (one considered "at least adenoma" on biopsy, a "reactive" case,

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and the GCP). There were 5 other adenocarcinomas diagnosed on ampullectomy, but unfortunately, preampullectomy biopsy specimens were not available for these cases.

The relatively modest diagnostic agreement (64%) between preampullectomy biopsy and EA was largely attributable to 4 cases of biopsy-proven adenoma in which ampullectomy demonstrated only "reactive changes." We hypothesized that the interval between preampullectomy biopsy and EA would influence this phenomenon (as the time between these two procedures in this series was as little as 6 days), but this was not borne out, as the median interval for "reactive" and nonreactive cases was not statistically significant. Of note, of the 6 reactive cases with follow-up, 3 of the patients manifested recurrent adenoma; all 3 of them had a diagnosis of adenoma established on preampullectomy biopsy. Although given the results of this analysis, we cannot recommend a specific "cooling-off period" between forceps biopsy and EA, a reactive diagnosis, especially in the setting of a prior biopsy diagnosis of adenoma, should be regarded with caution. Close follow-up is recommended.

The reported therapeutic usefulness of EA in ampullary adenoma in most series is between 75% and 90%.[15,19-21] For example, Catalano et al[15] reviewed their experience with 103 consecutive patients with adenoma treated with EA. They cited an overall long-term success rate of 80%, with a higher success rate in sporadic vs FAP-associated lesions (86% vs 67%).[15] In our 23 patients in whom EA revealed adenoma and with available histologic follow-up, there were 8 patients in whom follow-up was negative for adenoma (35%), while 15 lesions ultimately persisted or recurred (65%). We attribute this seeming discrepancy in therapeutic usefulness to differences in the definition of "success." According to Catalano et al,[15] "Endoscopic success was defined as complete excision of the lesion *without regard to the number of sessions required* and the absence of recurrence or a *recurrence during long-term follow-up that was easily treated endoscopically*" [emphasis added]. For their 83 "successes" the authors state neither the number of sessions required nor the number of patients experiencing an "easily treatable" recurrence.[15] In the series by Desilets et al,[19] 12 of 13 patients underwent successful EA, with a mean of 2.7 endoscopic procedures; only 3 adenomas were completely removed with a single procedure. Our study of EA's therapeutic usefulness is unique in defining success or failure in terms of the absence or presence of histologic evidence of residual disease. We believe our results underscore the importance of enrolling patients in an endoscopic surveillance program.

Conclusions

EA is being increasingly used and represents a less invasive alternative in the management of ampullary neoplasia. Awareness of this procedure's diagnostic and therapeutic role and of some of its technical aspects should aid pathologists examining an EA specimen. Of particular interest, as EA often follows shortly after endoscopic biopsy, reactive changes may be encountered. Subsequent biopsies may reveal adenoma. That none of the evaluated histologic or clinical features correlated with disease persistence or recurrence would seem to reflect the overall high likelihood of microscopic residual disease. Tempering the enthusiasm of previous reports of EA's therapeutic usefulness, we have documented residual disease in 65% of patients in whom EA revealed adenoma. We believe it unrealistic to expect extirpation with a single procedure, and enrollment in an endoscopic surveillance program is strongly recommended.

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