Diagnostic Accuracy of the Initial Endoscopy for Ampullary Tumors

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Background/Aims: Ampullary tumors come in a wide variety of malignant forms. We evaluated the diagnostic accuracy of endoscopy for ampullary tumors, and analyzed the causes of misdiagnosis.

Methods: We compared endoscopic imaging and biopsy results to final diagnoses. Types of endoscope, numbers of biopsy specimens taken, and final diagnoses were evaluated as possible factors influencing diagnostic accuracy.

Results: Final diagnoses were 19 adenocarcinomas, 18 normal or papillitis, 11 adenomas, two adenomyomas, one paraganglioma, and one neuroendocrine tumor. The diagnostic accuracy of endoscopic imaging or the initial biopsy was identical (67.3%). At least one test was concordant with the final diagnosis in all except two cases. Compared with the final diagnosis, endoscopic imaging tended to show more advanced tumors, whereas the initial biopsy revealed less advanced lesions. The diagnostic accuracy of the initial biopsy was influenced by the type of endoscope used and the final diagnosis, but not by the number of biopsies taken.

Conclusions: Endoscopy has limited accuracy in the diagnosis of ampullary tumors. However, most cases with concordant endoscopic imaging and biopsy results are identical to the final diagnosis. Therefore, in cases where both of these tests disagree, re-evaluation with a side-viewing endoscope after resolution of papillitis is required.

Key Words: Papillary tumors; Endoscopic examination; Diagnostic accuracy

INTRODUCTION

The number of cases diagnosed with ampullary tumors have recently increased because of the widespread use of routine endoscopy for health surveillance. A wide variety of tumors, including neoplasms such as neuroendocrine tumors, adenomas, and adenocarcinomas, as well as non-neoplasms such as inflammatory tumors, lipomas, lymphangiomas, fibromas, adenomyomas, and hamartomas, arise at the ampulla

of Vater (AoV).[1-6] Endoscopy is the most valuable method of identifying ampullary tumors. Observation of macroscopic appearance and biopsy specimens can be performed during routine endoscopy. However, the diagnostic accuracy of preprocedural biopsy has been reported as 62% to 76%,[7-12] which is insufficient to determine appropriate treatment modalities. Most reports about the diagnosis of ampullary tumors included patients who had received endoscopic or surgical resection. Because many inflammatory tumors do not require resection, these data may not represent the real diagnostic accuracy of the initial endoscopy. In addition, only a few studies have reported the relationship between endoscopic imaging and histological diagnosis.[13,14]

In this study, we evaluated the diagnostic accuracy of the initial endoscopy, including endoscopic imaging and forceps biopsy, for ampullary tumors. In addition, we analyzed the factors influencing diagnostic accuracy, such as the type of

endoscope used, the number of biopsy specimens taken, and the degree of malignant potentials.

MATERIALS AND METHODS

Among 267 patients who received endoscopic examination and biopsies for ampullary tumors during 2009 to 2012 at Chungbuk National University Hospital, 52 (39 men, 13 women; mean age, 60.3 years) who reached the final diagnosis stage were enrolled in this study. No patients received any treatment at the duodenal major papilla such as stenting or endoscopic sphincterotomy (ES). Reasons for endoscopy included cholangitis in 20 patients, suspicious papillary tumors on abdominal computed tomography (CT) in 18 patients, and

Table 1. Treatment Methods according to Final Diagnosis of Ampullary Tumors

Final diagnosis	No. of cases	Treatment methods
Normal or papillitis	18	Follow-up endoscopy
Adenoma	11	Surgical or endoscopic resection
Adenocarcinoma	19	Surgical resection
Adenomyoma	2	Endoscopic resection
Paraganglioma	1	Endoscopic resection
Endocrine tumor	1	Surgical resection

health surveillance in 14 patients. A final diagnosis was obtained by resected specimens in 33 patients, and by repeated biopsies (more than three) in 19 patients.

Ampullary tumors were treated by the Whipple's operation or pylorus-preserving pancreaticoduodenectomy in 21 patients, surgical ampullectomy in three patients, and endoscopic papillectomy in nine patients. The patients with inflammatory lesions, which were difficult to distinguish from neoplastic tumors, were included and received repeated endoscopy more than three times. Final diagnoses were 19 adenocarcinomas, 18 normal or papillitis, 11 adenomas, two adenomyomas, one paraganglioma, and one endocrine tumor (Table 1).

Endoscopy was performed using a forward-viewing endoscope (GIF-Q260; Olympus Optical Co., Ltd., Tokyo, Japan) in 21 patients or a side-viewing endoscope (TJF-240; Olympus Optical Co., Ltd.) in 31 patients by two endoscopists who were experts in pancreatobiliary diseases. Papillary lesions were diagnosed by endoscopic appearance as follows: papillitis, bulging, and edematous papilla with petechial;[15] adenoma, enlarged papilla covered with an even, granular, and discolored mucosa without ulcer or erosion; adenocarcinoma, enlarged papilla with an uneven granular or nodular appearance of the overlying mucosa associated with spontaneous bleeding, ulceration, and friable or indurated surface; adenomyoma, an enlarged papilla and villous granularities around the papillary
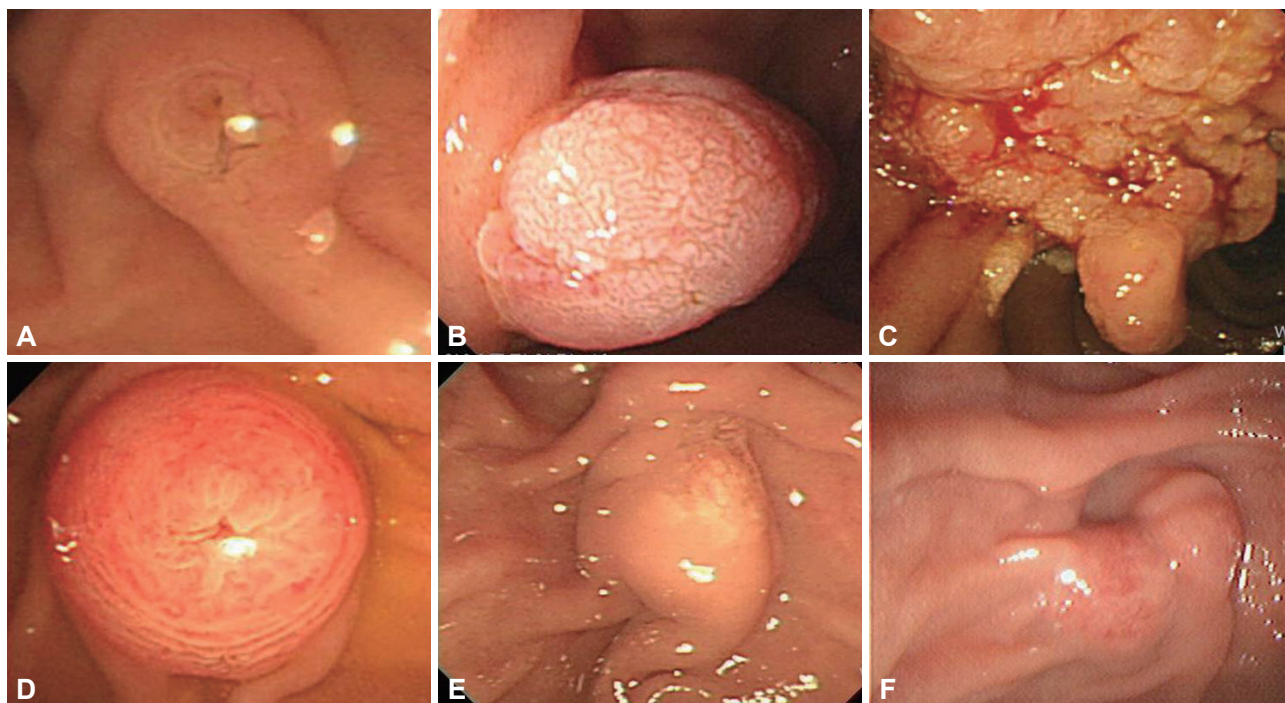

Fig. 1. Representative endoscopic imaging of ampullary tumors. (A) Papillitis, bulging, and edematous papilla with petechia. (B) Adenoma, discolored lobular/pine cone like tumor. (C) Adenocarcinoma, a reddish coarse nodular tumor associated with erosion and ready bleeding. (D) Adenomyoma, an enlarged major papilla and villous granularities around the papillary orifice. (E) Paraganglioma, even and firm nodular mass with a granular and villous mucosa. (F) Neuroendocrine tumor, bulging of the papilla, which has a smooth surface.

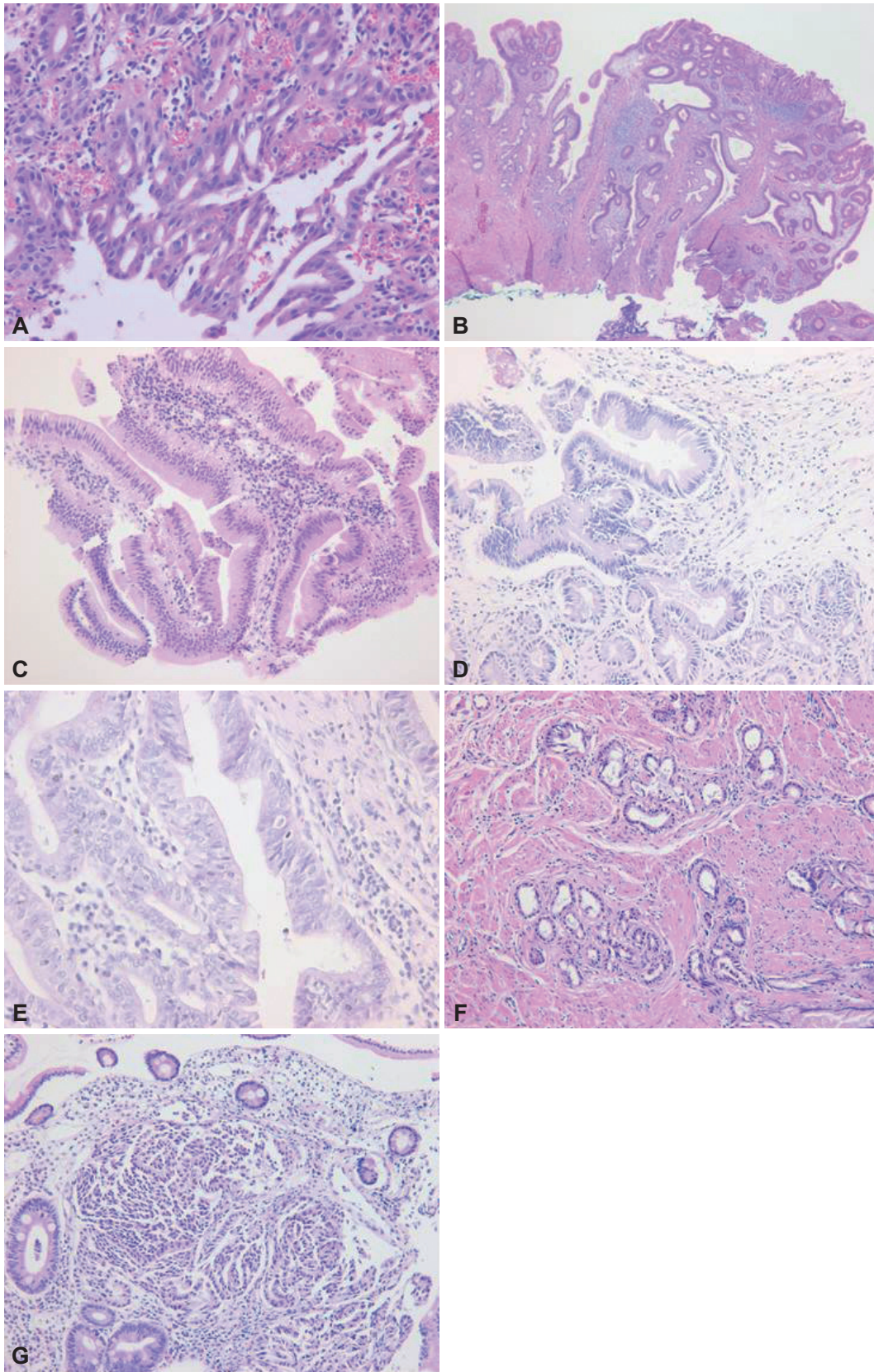**Fig. 2.** Representative pathologic findings of ampullary lesions. (A) Papillitis (H&E stain, ×200). (B) Tubular adenoma (H&E stain, ×50). (C) Villous adenoma (H&E stain, ×100). (D) Adenocarcinoma-intestinal type (H&E stain, ×100). (E) Adenocarcinoma-pancreaticobiliary type (H&E stain, ×100). (F) Adenomyoma (H&E stain, ×100). (G) Neuroendocrine tumor (H&E stain, ×100).

orifice; paraganglioma, even and firm nodular submucosal mass; neuroendocrine tumor, a round or oval tumor arising in the submucosa, sometimes with ulceration (Fig. 1).

Endoscopic biopsy was performed with forceps at the papilla when the major papilla looked abnormal. The number of biopsy specimens taken was two in 17 patients, three or four in 26 patients, and more than five in nine patients. Pathology was interpreted by an experienced pathologist. Final diagnoses were categorized as normal or papillitis, adenoma, carcinoma, and others (Fig. 2). The diagnostic accuracy of endoscopic imaging and the initial endoscopic biopsy were obtained with reference to the final diagnosis. We reviewed all cases that were misdiagnosed during the initial endoscopy. We analyzed the factors influencing the diagnostic accuracy of ampullary tumors such as final diagnosis, the type of endoscope used, and the number of biopsy specimens taken.

All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA), implementing Pearson chi-square test or linear-by-linear association. Statistical significance was defined as a $p<0.05$ (two-tailed).

RESULTS

Diagnostic accuracy of endoscopic imaging or the initial biopsy

Endoscopic imaging diagnoses included 20 adenomas, 20 adenocarcinomas, 11 normal or papillitis, and one adenomyoma. The diagnostic accuracy of endoscopic imaging was 67.3% (35/52) (Table 2). The most difficult diagnosis to make by endoscopic imaging was papillitis; 10 cases of papillitis were misdiagnosed as either adenoma (nine cases) or adenocarcinoma (one case), and two adenomas and one paraganglioma were misdiagnosed as normal or papillitis (Fig. 3). The diagnoses made during the initial biopsy were 24 normal or papillitis, 17 adenomas, nine adenocarcinomas, one endocrine tumor, and one paraganglioma. The diagnostic accuracy of the initial biopsy was 67.3% (35/52) (Table 3). The most difficult diagnosis to make by biopsy was carcinoma, which was misdiagnosed as adenoma in six cases and papillitis in four cases. Focal carcinoma within a background of adenoma was misdiagnosed as adenoma. Because biopsy specimens did not contain portions of focal cancerous change, they were diagnosed as high-grade dysplasia in four cases and low-grade dysplasia in two cases. In addition, adenocarcinomas covered with normal mucosa were diagnosed as papillitis in four cases. Their biopsy specimens contained only normal mucosa covering the cancer. Three adenomas were diagnosed as papillitis or vice versa in two cases. Differentiation between hyperplasia and dysplasia with severe inflammation is very difficult. Two of three adenomas posed technical problems in

papilla biopsies, for which no accurate tissues, only blood clots, could be obtained. Twenty-five of 30 cases were identical to the final diagnosis according to second biopsy. The diagnostic accuracy of second biopsy was 83.3%. Twenty of 22 cases concordant in endoscopic imaging and biopsy were identical to the final diagnosis (Table 4). Either endoscopic imaging or biopsy was concordant with the final diagnosis in all except two cases. Endoscopic imaging had a tendency to show more advanced tumors, whereas the initial biopsy showed less advanced lesions compared with the final diagnosis (Table 5).

Factors influencing diagnostic accuracy

The diagnostic accuracy of biopsy was influenced by the type of endoscope used (side-viewing vs. forward-viewing, 85.7% vs. 45.0%; $p=0.004$) (Fig. 4A) and the final diagnosis (normal or papillitis vs. adenoma vs. adenocarcinoma, 88.9% vs. 72.7% vs. 47.4%; $p=0.007$) (Fig. 4B), but not by the number of biopsy specimens taken (2 vs. $\geq$3, 56.3% vs. 75.0%; $p>0.05$) (Fig. 4C).

DISCUSSION

This study demonstrated that the diagnostic accuracy of endoscopy was 67.3% for endoscopic imaging and the initial biopsy, which was similar to that previously reported.[9] Either endoscopic imaging or biopsy was concordant with the final diagnosis in all except two cases. Therefore, a combination of these techniques may facilitate more accurate diagnoses.

This study showed that endoscopic biopsies may be falsely negative in a significant percentage of cases, and more so for carcinoma than for adenoma or inflammatory lesions. Biopsies were accurate in nine of 19 carcinomas (47.4%), which was lower than for inflammatory lesions (16/18, 88.9%) or adenomas (8/11, 72.7%). These data were similar to those previously reported,[7,9,16] where the diagnostic accuracy was 80% for adenomas[7] and 21% to 70% for carcinomas.[7,9] Yamaguchi et al.[7] reported that biopsy accuracy was different according to carcinoma type: 50% in the intramural protruding type, 64% in the exposed protruding type, and 88% in the ulcerating type.

Because endoscopic forceps biopsy of ampullary tumors does not rule out the possibility of deeper cancer,[17] many studies have recommended the harvesting of specimens from the depth of the papilla after ES to improve the diagnostic accuracy of biopsies from suspicious papilla.[9,16,18,19] However, one prospective study showed that sensitivity was 21% before and 37% after ES, and concluded that endoscopic forceps biopsies do not allow for reliable preoperative diagnosis of ampullary tumors.[9] Other techniques such as repeated biopsy or

Table 2. Diagnostic Accuracy of Endoscopic Imaging in 52 Patients with Ampullary Tumors

Endoscopic imaging	Final diagnosis, no. of case			
	Normal or papillitis (*n*=18)	Adenoma (*n*=11)	Adenocarcinoma (*n*=19)	Others (*n*=4)
Normal or papillitis (*n*=11)	8	2	0	1[a]
Adenoma (*n*=20)	9	8	1	2[b]
Adenocarcinoma (*n*=20)	1	1	18	0
Others (*n*=1)	0	0	0	1[c]

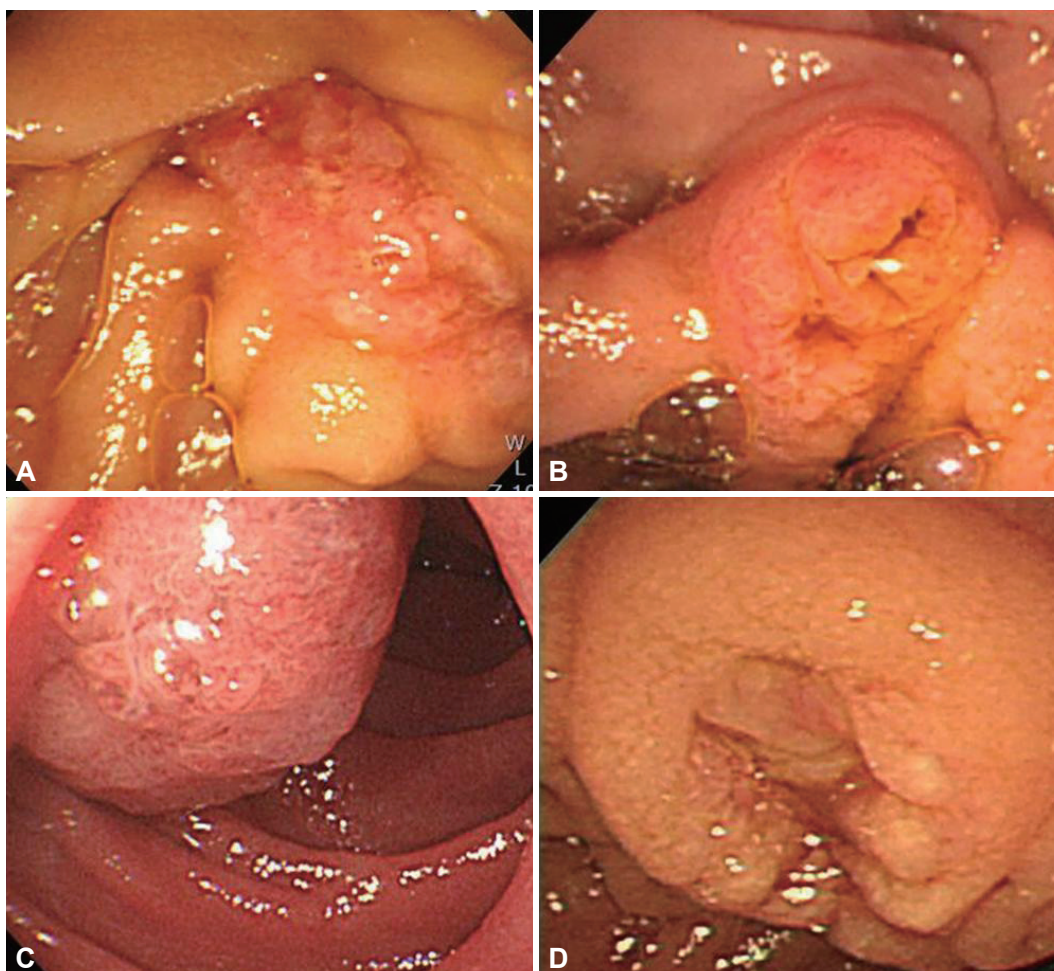[a]Paraganglioma; [b]Endocrine tumor and adenomyoma; [c]Adenomyoma.

Fig. 3. Endoscopic images of misdiagnosed cases by gross appearance. (A, B) Papillitis misdiagnosed as adenoma. (C) Adenoma misdiagnosed as carcinoma. (D) Carcinoma misdiagnosed as adenoma.

extensive use of papillectomy have also been recommended to improve diagnostic accuracy. Diagnostic accuracy was improved by repeated biopsy from 69% to 83%, and by papillectomy from 77% to 86%.[10] Our results showed that repeated biopsy can increase the diagnostic accuracy from 67.3% to 83.3%.

In the presence of inflammation, it is difficult to distinguish between neoplastic tumors and pseudotumors by endoscopy. Spontaneous bleeding, ulceration, friable or indurated surface, and unusual firmness are all endoscopic evidence of malignancy. However, inflammatory pseudotumors and adenomyomas are also frequently firm during forceps biopsy. One study reported that two of 11 patients with pseudotumors were treated with surgical excision biopsy because of suspicious histological features revealed through endoscopic biopsy.[20] On the other hand, adenomas may be diagnosed as inflammation. Because of a high incidence of concurrent cholelithiasis, many patients with a periampullary tumor seen during endoscopic retrograde cholangiopancreatography are misdiagnosed earlier as having choledocholithiasis only. One study reported

Table 3. Diagnostic Accuracy of First Endoscopic Biopsy in 52 Patients with Ampullary Tumors

First endoscopic biopsy	Final diagnosis, no. of case			
	Normal or papillitis (n=18)	Adenoma (n=11)	Adenocarcinoma (n=19)	Others (n=4)
Normal or papillitis (n=24)	16	3	4	1[a)]
Adenoma (n=17)	2	8	6	1[b)]
Adenocarcinoma (n=9)	0	0	9	0
Others (n=2)	0	0	0	2[c)]

[a)]Adenomyoma; [b)]Adenomyoma; [c)]Endocrine tumor and paraganglioma.

Table 4. Comparison of Diagnosis by Endoscopic Imaging and First Biopsy in 52 Patients with Ampullary Tumors

First endoscopic biopsy	Endoscopic imaging, no. of case			
	Normal or papillitis (n=11)	Adenoma (n=20)	Adenocarcinoma (n=20)	Others (n=1)
Normal or papillitis (n=24)	6	12	5	1[a)]
Adenoma (n=17)	4	7	6	0
Adenocarcinoma (n=9)	0	0	9	0
Others (n=2)	1[b)]	1[c)]	0	0

[a)]Adenomyoma; [b)]Paraganglioma; [c)]Endocrine tumor.

Table 5. Comparison of Final Diagnosis and Endoscopic Imaging or First Biopsy in Patients with Normal or Papillitis, Adenoma, and Carcinoma

Endoscopic imaging	First endoscopic biopsy, no. of case		
	Over diagnose[a)] (n=2)	Concordant (n=33)	Underdiagnosed (n=13)
Over diagnosed (n=11)	1	10	0
Concordant (n=34)	1	21	12
Underdiagnosed[b)] (n=3)	0	2	1

p=0.045 by linear by linear association.
[a)]Over diagnosis means diagnosis as more advanced tumors compared to final diagnosis; [b)]Underdiagnosis means diagnosis as less advanced tumors compared to final diagnosis.
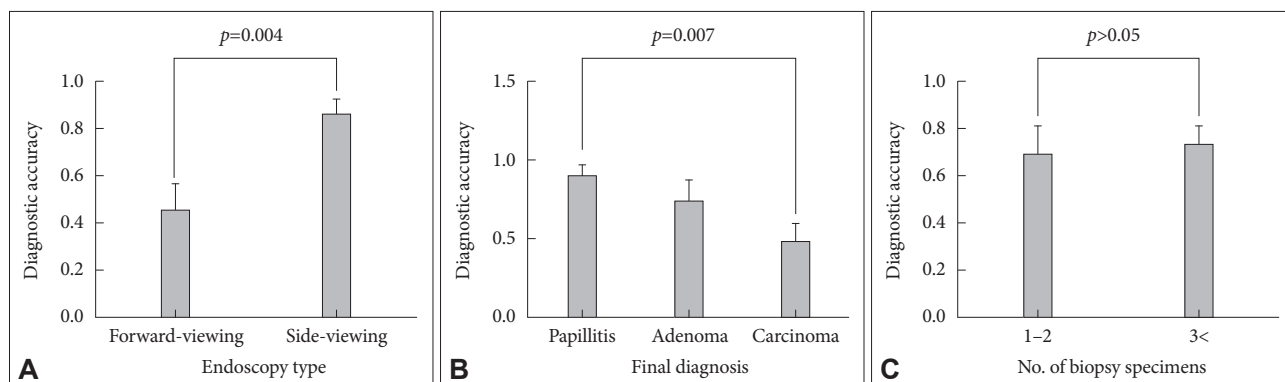

Fig. 4. The diagnostic accuracy of biopsy was influenced by the type of endoscope used. (A) Side-viewing versus forward-viewing endoscope (85.7% vs. 45.0%, p=0.004). (B) Final diagnosis, normal or papillitis versus adenoma versus adenocarcinoma (88.9% vs. 72.7% vs. 47.4%, p=0.007). (C) Number of biopsy specimens (2 vs. ≥3, 56.3% vs. 75.0%; p>0.05).

that eight of 21 (38%) patients with ampullary or periampullary neoplasms also had gallstones.[13] Therefore, enlarged and nodular papillae associated with cholangitis require repeated endoscopy after resolution of inflammation.

The diagnostic accuracy was higher with the side-viewing endoscope than with the forward-viewing endoscope, which was identical the results of previous studies.[3,18] Therefore, sus-

picious neoplastic tumors revealed during routine endoscopy require repeated examination with a side-viewing endoscope. However, many endoscopists are not familiar with the use of side-viewing endoscopes. We previously reported the usefulness of a cap-assisted forward-viewing endoscope.[13] This can increase the diagnostic accuracy of a forward-viewing endoscope and decrease the need for a side-viewing endoscope.

Although the diagnostic accuracy improved for a higher number of biopsies, this was not statistically significant. This result means that the most important factor during biopsy is not the number of biopsies, but the selection of accurate biopsy sites. Because ampullary cancer usually derives from the ampullary portion of the bile duct and pancreatic duct or the common channel, a forceps biopsy specimen should be obtained from the bile duct and pancreatic duct orifice. The risk of complications during biopsy from the AoV is thought to be low. There were no complications related to biopsy of the major papilla in this study. However, one case report showed that acute pancreatitis developed because of mucosal edema and subsequent pancreatic duct obstruction.[21]

There are series with more accurate diagnoses by endoscopic appearance than by histology from the endoscopic biopsy of the papilla.[13,22] Correlation of the pathologic features of biopsy specimens with endoscopic appearances may result in more accurate diagnoses.[23] In this study, endoscopic imaging was not superior to biopsy. However, considering both results together, an accurate diagnosis can be achieved. Therefore, papillitis diagnosed by endoscopic imaging and biopsy does not require repeated endoscopy. However, when ampullary neoplasm was suspicious under either test, re-evaluation with a side-viewing endoscope and repeated biopsy were needed.

Abdominal CT,[24] abdominal magnetic resonance imaging (MRI),[25] and positron emission tomography (PET)[26] have been used as the modalities of choice for diagnosing ampullary tumors. Abdominal CT can be used to identify bulging papilla, but is inferior compared to abdominal MRI for distinguishing the underlying cause.[24] Despite high sensitivity and specificity in diagnosing periampullary malignancy, PET does not change the clinical management in the vast majority of patients previously evaluated by CT.[26] Recently, new diagnostic methods including endoscopic ultrasonography (EUS), narrow band imaging systems, and intraductal EUS have shown promise.[27,28] However, these methods cannot replace routine endoscopic examination, and should be used as adjunctive methods for the evaluation of abnormal ampullary tumors. A study reported that using a side-viewing duodenoscope with biopsies combined with EUS is not accurate enough to preoperatively ensure that an ampullary tumor is benign, even after ES.[28] Therefore, a more accurate method of endoscopic biopsy and safe management strategy is needed.

Endoscopic biopsy has many limitations as a diagnostic method for ampullary tumors. However, there are no methods capable of replacing endoscopy. Therefore, management strategies are determined by the results of endoscopic biopsy. On the basis of this study, we recommend that cases in which the results of endoscopic imaging and biopsy disagree should be re-evaluated with a side-viewing endoscope once inflammation has been resolved. When intramural cancer is suspected, a repeat biopsy after ES or the extensive use of papillectomy should be considered before determining treatment methods.

Conflicts of Interest

The authors have no financial conflicts of interest.

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