Turk J Gastroenterol *2014; 25: 563-7*

Endoscopic papillectomy for carcinoma of the ampulla of Vater: Possible standardization based on endoscopy and immunohistochemistry

ENDOSCOPY

Hamada Yoshihiro[1], Maeshiro Kensei[2], Nakayama Yoshifuku[3]

[1]Department of Pathology, Fukuoka University Faculty of Medicine, Fukuoka, Japan
[2]Department of Surgery, St. Maria Hospital, Kurume, Japan
[3]Department of Laboratory Medicine, Kyushu Medical Center, Fukuoka, Japan

Original Article

ABSTRACT

Background/Aims: Clinicopathological investigation of the indications for the use of endoscopic papillectomy as a treatment for carcinoma in situ of the ampulla of Vater (CAV).

Materials and Methods: Of 97 patients diagnosed with CAV in our department over the last 15 years, the 5 patients who received a carcinoma in situ diagnosis and were included in this retrospective study.

Results: The lesions in the patients were classified as either the superficial or luminal type, based on endoscopic findings. Histological findings showed that the major duodenal papilla (Ad) was the main site of CAV in the superficial type and that the common duct into the duodenal lumen (Ac) was the primary site in the luminal type. Immunohistochemical staining showed that the superficial-type lesions were positive for cytokeratin 20, suggesting development of the cancer from the Ad. The luminal-type lesion was positive for cytokeratin 7 and negative for cytokeratin 20, suggesting an origin in the pancreatobiliary duct. Mucin-2 was expressed in the superficial type, and mucin-1 in the luminal type.

Conclusion: Superficial-type lesions, which are principally located in the Ad, exhibit little tendency to invade surrounding tissues, whereas the luminal-type lesions, which are predominantly located in the Ac, may tend to be more invasive. Although endoscopic papillectomy might be indicated for the superficial-type lesions, caution is needed in the determination of the extent of luminal-type lesions.

Keywords: Ampulla of Vater, endoscopic papillectomy, carcinoma

INTRODUCTION

Since the 1980s, endoscopic papillectomy (EP), which can also be used for the diagnosis of tissue cancers, has been performed to treat papillary tumors (mainly adenomas). In recent years, the indications for EP have been extended to include benign/malignant borderline lesions and early cancers (1-5). Although EP is expected to be useful as a minimally invasive treatment for carcinoma of the ampulla of Vater (CAV) that is confined to a limited area, its conduct requires that the localized invasion of the cancer be carefully determined, preoperatively. With the introduction of endoscopic ultrasonography (EUS) and intraductal ultrasonography (IDUS), the diagnostic evaluation of the extent of CAV has markedly improved compared with that possible using other techniques, such as endoscopic retrograde cholangiopancreatography (ERCP). However, because only a small number of patients with carcinoma in situ (pTis), biological behavior and the patient prognosis after local excision remain incomplete.

Various immunohistochemical techniques have been introduced for the classification of ampullary tumors and the evaluation of their malignancy. Based on the primary tumor site, Zhou et al. (6) classified papillary tumors as intestinal and pancreatobiliary types, using the results of cytokeratin (CK) staining. A correlation has also been reported between a classification based on the pattern of mucous expression, using staining for apomucin, and patient prognosis (7,8).

Address for Correspondence: Hamada Yoshihiro, Department of Pathology, Fukuoka University Faculty of Medicine, Fukuoka, Japan
E-mail: yhamada@fukuoka-u.ac.jp
Received: 13.2.2014 **Accepted:** 19.8.2014

In this study, we investigated EP from a clinicopathologic standpoint to explore the possibility of expanding its indications, from being utilized mainly as a diagnostic modality for adenomas and benign/malignant borderline lesions, to include it as a treatment for CAV.

MATERIALS AND METHODS

A total 97 patients with CAV underwent surgical resection and pathological diagnosis in Fukuoka University Hospital during 15 years. The present study included 5 patients with histologically diagnosed pTis. The patients' clinical characteristics and postoperative survival periods were obtained from patient records. Based on their endoscopic findings, tumors were morphologically classified into 2 types: (1) the superficial type with a nodular mucosal pattern reaching the papillary opening and extending to the duodenal lumen, and (2) the luminal type in which part of the tumor has grown mainly in the ampullary region and is exposed near the orifice.

All resected specimens were subjected to hematoxylin and eosin (H&E) staining, as well as immunohistochemical staining to detect cytokeratin and apomucin. The areas of the ampulla of Vater were defined according to the Classification of Biliary Tract Carcinoma (Figure 1) (9).

Fisher's exact probability test was employed to determine the association between clinicopathological factors of superficial and liminal type of CAV using StatView ver. 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

The mean age of the 5 patients was 66.5 (52-72) years; 4 were women. The postoperative follow-up duration was 36-132 months; all patients remain alive, without recurrence, at the time of this writing. Upper abdominal pain was observed as an initial symptom in 1 patient; the other 4 patients were asymptomatic, with their cancers detected using upper gastrointestinal tract endoscopy (Table 1). The endoscopic examination of the ampullary region revealed superficial tumor patterns (Figure 2a) in Patients 1, 3, 4, and 5, and a luminal pattern (Figure 2b) in Patient 2.

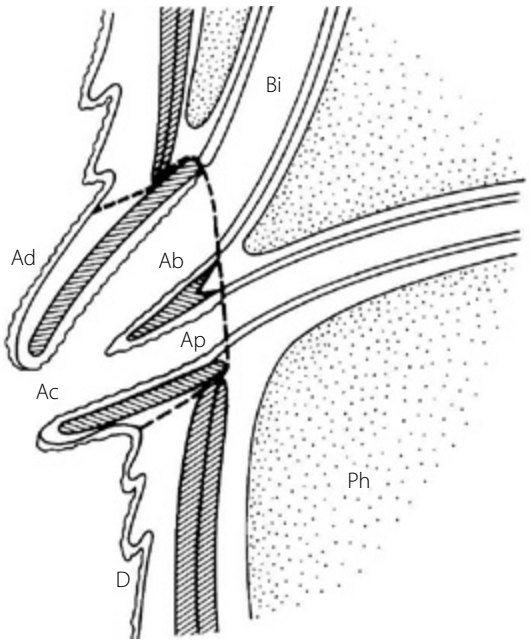

Figure 1. Portions of the papilla of Vater. Ab, bile duct portion; Ap, bile duct portion; Ac, Portion of the common duct into the duodenal lumen; Ad, major duodenal papilla; Ph, pancreatic head; D, duodenum.

The macroscopic types, judged from fixed samples, indicated that 4 patients had exposure-type tumors and 2 had non-exposure-type tumors. The mean histological tumor size was 11.0 mm. Based on H&E staining, the cancer sites were located in the common duct into the duodenal lumen and in the major duodenal papilla (Ad). Additionally, a comparison between the endoscopic findings and the main lesion locations revealed that the 4 patients with superficial-type tumors were consistent with an Ad location (Figure 3a), whereas that for the patient with a luminal type tumor was consistent with an Ac location (Figure 3b). CK immunohistochemistry of the superficial-type tumors in patients showed positive CK7 staining in only 2 of the 4 patients; CK20 staining was positive in all 4

Table 1. Clinical features of 5 cases of carcinoma of the ampulla of Vater

	n	Superficial	Luminal
Age, mean, y		66	52
Sex (M/F)	1/4	1/3	0/1
Symptom			
Epigastralgia	1	0	1
None	4	4	0
Location			
Adc	4	4	0
Ac	1	0	1
pN			
0	5	4	1
1	0	0	0

Adc: major duodenal papilla and pancreatic duct portion of the papilla of Vater; Ac: portion of the common duct into the duodenal lumen

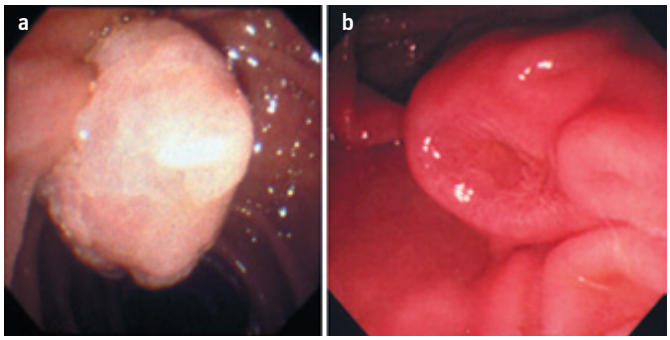

Figure 2. a, b. Superficial type of carcinoma of the ampulla of Vater. The carcinoma shows exophytic growth **(a)**. Luminal type of the ampulla of Vater. The carcinoma is growing on the luminal side **(b)**.

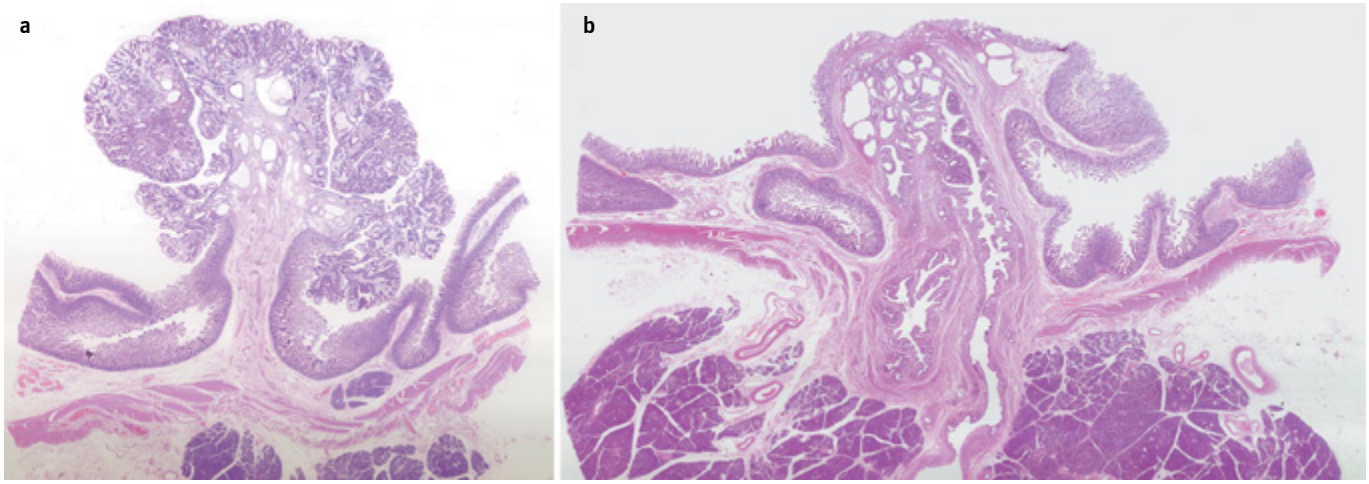

Figure 3. a, b. Superficial type of the ampulla of Vater is predominantly located in the Ad **(a)**. Luminal type of the ampulla of Vater is present in the Ac **(b)**.

patients. For the luminal-type lesion, CK7 staining was positive and CK20 staining was negative. A comparison of the tumor mucous expression patterns and endoscopic findings revealed that all patients with superficial-type lesions were negative for mucin-1 (MUC1), whereas the patient with a luminal-type lesion was positive for MUC1; opposite results were observed for mucin-2 (MUC2) (Table 2).

Table 2. Immunohistochemical results in carcinoma of ampulla of Vater

	n	Superficial	Luminal
Cytokeratin 7			
(+)/(-)	1/4	2/2	1/0
Cytokeratin 20			
(+)/(-)	4/1	4/0	0/1
MUC1			
(+)/(-)	1/4	0/4	1/0
MUC2			
(+)/(-)	4/1	4/0	0/1

DISCUSSION

The morphologic classification of CAV is widely recognized as being useful for the prediction of the pattern tumor of invasion and its prognosis. The classification is based on the endoscopic appearance of the tumor and the intraoperative findings, with a final determination based on the macroscopic type observed after fixation of the resected sample (10-12). However, the classification was originally devised for invasive cancers. The increasing prevalence of early detection of lesions has rendered the classification sometimes unsuitable for borderline lesions and noninvasive cancers. In part, this is due to the morphologic features of noninvasive lesions in the papillary region differing from those of invasive cancers. Lesions in the ampullary region have been shown to shrink by up to 30% after formalin fixation; thus, in mucosal lesions, such as pTis cancer, differences between endoscopic appearance and histological assessment can be expected (13). If the ultimate treatment goal is limited to local excision, rather than traditional invasive surgery, a new morphologic classification, based on preoperative high-precision imaging rather than fixed, post-resection samples, should be established.

Although these means of diagnosis have become increasingly necessary for ampullary tumor treatment selection, they have only limited diagnostic reliability with regard to superficial invasion (horizontal invasion) in the direction of the pancreatic duct/bile duct. The following histopathologic features are specific to the ampullary region: this region does not consist of a single tissue; tumors originating in the region express 2 types of epithelial cells; differences in the primary tumor sites result in differences in their biological malignancy, growth, and invasion patterns; and the deeper the lesion is in the papillary region (i.e., the closer to the pancreatobiliary duct), the higher the degree of cellular atypia (14). Therefore, accurate preoperative prediction of superficial invasion of the mucosal surface, as well as vertical invasion, is required if local excision of the papillary cancer is to be established as a curative treatment.

The morphologic classifications, based on the endoscopic characteristics we investigated, were shown to correlate with the clinical features of the early lesions and with the direction of invasion; the main lesion location can be predicted following a detailed observation of the lesion, viewed from the exposed surface of the papilla. The strength of this correlation is limited by only 1 of the present patients having had a luminal-type lesion. Because superficial-type lesions were mainly located in Ad and exhibited a tendency to grow in the direction of the duodenal lumen, they should have little impact on the outflow of pancreatic juice and bile and, thus, be unlikely to produce pancreatitis. On the other hand, since intraductal tumors grow in the direction of the common channel, the obstruction of bile and pancreatic juice outflow that they produce is likely to cause pancreatitis. Thus, the possibility of intraductal-type pTis cancers, in the papillary region, should always be considered when searching for the cause of

acute pancreatitis. This should involve detailed observations of the frontal view of the mucosal surface, near the ampullary region, using a duodenoscope.

Based on the assumption that the main lesion location is also the primary tumor site, our immunohistochemical investigation showed that the primary site may be predicted based on the morphological features determined from the endoscopic appearance. Recently, CK staining has been widely used to locate the primary cancer site; CKs often reveal the nature of the primary site, even after the lesion has become cancerous, so the identification of the primary cancer site using these traits has been examined (15,16). Based on immunohistochemical staining for CKs, intestinal epithelial and pancreatobiliary duct epithelial origins of papillary cancers have been reported. Based on the primary site of the lesion, Zhou et al. (6) classified papillary cancers into the intestinal and pancreatobiliary types using their expression of a CK subtype (CK7 or CK20). Regrettably, however, their report did not include a description of the primary site. All patients enrolled in the present study had pTis within the papillary region, making them optimal for investigation of the primary site of cancer. A comparison between the immunostaining results and endoscopic classifications suggested that all patients with superficial-type lesions were positive for CK20, an indicator of intestinal epithelial origin. Of note, half of the patients with superficial-type lesions and the patient with an intraductal type lesion were positive for CK7, an indicator of pancreatobiliary epithelial origin. The result for intraductal-type lesion was consistent with the main location of the lesion (Ac), based on the H&E findings. The differences in cytokeratin expression in the superficial type is considered to be because different expressions were observed in samples fixed with formalin than in samples from frozen sections or those fixed with acetone or alcohol (17-21). In any case, our investigation using cytokeratin staining suggested that superficial-type lesions originate in the Ad region, which consists mainly of intestinal epithelium, and in part of the Ac region, in which pancreatobiliary epithelium is also present. Similarly, intraductal-type lesions were suggested to originate in the Ac region, having a pancreatobiliary epithelial origin.

One of the reasons for classifying papillary cancers as either the intestinal or pancreatobiliary type is that each type has a different prognosis (22,23). However, because the morphological classification is based on H&E staining, the classification poorly reflects the nature of the cancer cells. In recent years, a classification, based on mucous characteristics, using apomucin staining, has been developed for various types of cancers to evaluate their malignancy. Matsubayashi et al. (7) classified papillary cancers into intestinal and pancreatobiliary types, based on their expression of MUC1, MUC2, and human gastric mucin. Kitamura et al. (6) reported a positive correlation between MUC2 expression and a more favorable prognosis, and a negative correlation between MUC1 expression and prognosis. These findings are also consistent with the relationship between MUC expression and the prognosis of pancreatic and bile duct cancers (24,25). Kitamura et al. (26) reported that MUC1-positive papillary cancers exhibit a significantly stronger tendency to invade the pancreas and duodenum and have significantly higher incidences of lymph node metastasis, whereas MUC2-positive papillary cancers tend to be less invasive. Ampullary cancers with the superficial-type morphology tend to be confined to a limited area (26), whereas intraductal-type lesions tend to invade surrounding tissues, corresponding to their expression of MUC1.

The EP indications for CAV are quite limited, and the procedure is still performed only in special cases. The primary site of the lesion and the characteristics of the tumor cells should be considered in deciding whether to resect the cancer. Although our investigation included only 5 patients with pTis cancer, multiple immunostaining techniques revealed that differences in morphology, based on endoscopic appearance, are associated with cellular differences. When conducting a preoperative diagnosis of papillary cancer, detailed observations of the mucosal surface, combined with conventional diagnostic modalities, such as EUS and IDUS, will provide useful insight for the evaluation of biological malignancy.

In conclusion, based on their endoscopically observed patterns of growth, CAVs that are localized to the mucosa were classified as superficial or luminal, and histological features were investigated using multiple immunostaining procedures. Assuming that endoscopic treatment is performed, our morphologic classification, based on the lesion's endoscopic appearance, is user-friendly and provides useful information for determining the type of resection; the indications for curative endoscopic resection of CAV will become clearer with more experience.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.Y., M.K.; Design - H.Y.; Supervision - M.K.; Resource - M.K.; Materials - N.Y., H.Y.; Data Collection and/or Processing - H.Y.; Analysis and/or Interpretation - H.Y., M.K., N.Y.; Literature Search - H.Y., M.K., N.Y.; Writing - H.Y., M.K.; Critical Reviews - H.Y., M.K., N.Y.

Acknowledgements: The authors would like to thank K. Yoshinaga, M. Yuhki, M. Ishiguro, H. Kanamaru and C. Fujita for their assistance.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Ponchon T, Berger F, Chavaillon A, Bory R, Lambert R. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of vater. Cancer 1989; 64: 161-7. [CrossRef]

2. Catalano MF, Linder JD, Chak A, et al. Endoscopic management of adenoma of the major duodenal papilla. Gastrointesti Endosc 2004; 59: 225-32. [CrossRef]
3. Moriya T, Kimura W, Hirai I, et al. Total papillectomy for borderline malignant tumor of papilla of vater. Hepatogastroenterology 2004; 51: 859-61.
4. Ito K, Fujita N, Noda Y, et al. Case of early ampullary cancer treated by endoscopic papillectomy. Dig Endosc 2004; 16: 157-61. [CrossRef]
5. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc 1993; 39: 127-31. [CrossRef]
6. Zhou H, Schaefer N, Wolff M, Fischer HP. Carcinoma of the ampulla of Vater: comparative histologic/immunohistochemical classification and follow-up. Am J Surg Pathol 2004; 28: 875-82. [CrossRef]
7. Matsubayashi H, Watanabe H, Yamaguchi T, et al. Differences in mucus and K-ras mutation in relation to phenotypes of tumors of the papilla of Vater. Cancer 1994; 86: 596-607. [CrossRef]
8. Kitamura H, Yonezawa S, Tanaka S, Kim YS, Sato E. Expression of mucin carbohydrates and core proteins in carcinomas of the ampulla of Vater: their relationship to prognosis. Jpn J Cancer Res 1996; 87: 631-40. [CrossRef]
9. Japanese Society of Biliary Surgery. Classification of Biliary Tract Carcinoma. 2nd English Edition. Tokyo: Kanehara & Co, 2004;
10. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of Vater. A clinicopathologic study and pathologic staging of 109 cases of carcinoma and 5 cases of adenoma. Cancer 1987; 59: 506-15. [CrossRef]
11. Cubilla AL, Fitzgerald PJ. Surgical pathology aspects of cancer of the ampulla-head of pancreas region. Monogr Pathol 1980; 21: 67-81.
12. Wise L, Pizzimbono C, Dehner LP. Periampullary cancer. A clinicopathologic study of sixty-two patients. Am J Surg 1976; 131: 141-8. [CrossRef]
13. Rosai J. Gross techniques in surgical pathology. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 9th ed. St. Louis: Mosby; 2004.
14. Rosai J. Gallbladder and extrahepatic bile duct. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology, 9th ed. St. Louis: Mosby; 2004.
15. Tot T. Adenocarcinomas metastatic to the liver: the value of cytokeratins 20 and 7 in the search for unknown primary tumors. Cancer 1999; 85: 171-7. [CrossRef]
16. Alexander J, Krishnamurthy S, Kovacs D, et al. Cytokeratin profile of extrahepatic pancreaticobiliary epithelia and their carcinomas. Appl Immunohistochem 1997; 5: 216-22. [CrossRef]
17. Santini D, Ceccarelli C, Martinelli GN, et al. Expression of intermediate filaments in normal and neoplastic exocrine pancreas. Zentralbl Pathol 1994; 140: 247-58.
18. Sundstrom BE, Nathrath WB, Stigbrand TI. Diversity in immunoreactivity of tumor-derived cytokeratin monoclonal antibodies. J Histochem Cytochem 1989; 37: 1845-54. [CrossRef]
19. Ramaekers F, van Niekerk C, Poels L, et al. Use of monoclonal antibodies to keratin 7 in the differential diagnosis of adenocarcinomas. Am J Pathol 1990; 136: 641-55.
20. Osborn M, van Lessen G, Weber K, Klöppel G, Altmannsberger M. Differential diagnosis of gastrointestinal carcinomas by using monoclonal antibodies specific for individual keratin polypeptides. Lab Invest 1986; 55: 497-504.
21. Schussler MH, Skoudy A, Ramaekers F, Real FX. Intermediate filaments as differentiation markers of normal pancreas and pancreas cancer. Am J Pathol 1992; 140: 559-68.
22. Albores-Saavedra J, Menck HR, Scoazec JC, et al. Carcinoma of the gallbladder and extrahepatic bile ducts. In: Hamilton S, Aaltonen LA, editors. Pathology and Genetics. Tumours of the Digestive System. Lyon: IARC Press; 2000.
23. Albores-Saavedra J, Henson DE, Klimstra DS. Malignant epithelial tumor of the Ampulla. In: Rosai J, editor. Tumors of the Gallbladdr, Extrahepatic bile ducts, and Ampulla of Vater. Atlas of the Tumor Pathology, Washington, DC: Armed Force Institute of Pathology; 1998.p.259-316.
24. Osako M, Yonezawa S, Siddiki B, et al. Immunohistochemical study of mucin carbohydrates and core proteins in human pancreatic tumors. Cancer 1993; 71: 2191-9. [CrossRef]
25. Yamashita K, Yonezawa S, Tanaka S, et al. Immunohistochemical study of mucin carbohydrates and core proteins in hepatolithiasis and cholangiocarcinoma. Int J Cancer 1993; 55: 82-91. [CrossRef]
26. Kitamura H, Yonezawa S, Tanaka S, Kim YS, Sato E. Expression of mucin carbohydrates and core proteins in carcinomas of the ampulla of Vater: their relationship to prognosis. Jpn J Cancer Res 1996; 87: 631-40. [CrossRef]