

[CASE REPORT]

Endoscopic Mucosal Resection of Adenocarcinoma at the Minor Duodenal Papilla: A Case Report and Suggestions for the Optimal Treatment Strategy

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Abstract:

We herein report an extremely rare case of adenocarcinoma of the minor duodenal papilla (MiDP) which was successfully treated by endoscopic mucosal resection (EMR). An asymptomatic 84-year-old man underwent upper gastrointestinal endoscopy, which revealed a slightly elevated lesion at the MiDP. The biopsy findings were suggestive of adenocarcinoma. Computed tomography, magnetic resonance images and endoscopic ultrasonography did not reveal pancreatic tumor infiltration nor any apparent distant metastases. Therefore, we treated the lesion using EMR with complete resection. No recurrence or metastasis has been detected at 13 months after EMR. Total resection of the MiDP can thus serve as a relatively safe and simple treatment.

Key words: adenocarcinoma, endoscopic mucosal resection, major duodenal papilla, minor duodenal papilla

(Intern Med 60: 2593-2599, 2021)

(DOI: 10.2169/internalmedicine.6404-20)

Introduction

The minor duodenal papilla (MiDP) is typically located in the second portion of the duodenum, proximal to the major duodenal papilla (MaDP) (1). It is an orifice to the accessory pancreatic duct from the dorsal pancreas and is recognized as a small elevation. Since the first case of MiDP adenocarcinoma was reported in 1998 (2), tumors of the MiDP have only rarely been reported. Most have been treated by surgical resection, however, a few cases were treated by endoscopic resection (3, 4). Endoscopic resection of MaDP tumors, via papillectomy, has already been established to some extent (5-7). However, there is no consensus on the optimal treatment for MiDP tumors. Recently, endoscopic resection of early-stage MiDP tumors has been considered an easy, minimally invasive, and diagnostic primary treatment prior to surgical resection. We herein report a case of MiDP adenocarcinoma which was completely resected endo-

scopically in order to provide suggestions for the optimal endoscopic treatment of MiDP tumors with support from a literature review.

Case Report

An asymptomatic 84-year-old Japanese man underwent upper gastrointestinal endoscopy for the follow-up of varices secondary to cirrhosis. The MiDP was reddish, slightly elevated, and measured 5 mm in diameter. It was located 2 cm proximal to the normal MaDP (Fig. 1). The biopsy specimen histopathologically indicated adenocarcinoma. All laboratory data, including tumor markers and pancreatic enzymes, were within the normal ranges. This lesion was not detected by any other imaging modality. Distant metastasis, dilatation of main pancreatic duct, and pancreatic divisum were not noted by abdominal computed tomography (CT) and magnetic resonance images. The tumor was considered to be a non-invasive lesion because of the image of a hy-

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Received: September 29, 2020; Accepted: December 22, 2020; Advance Publication by J-STAGE: March 15, 2021

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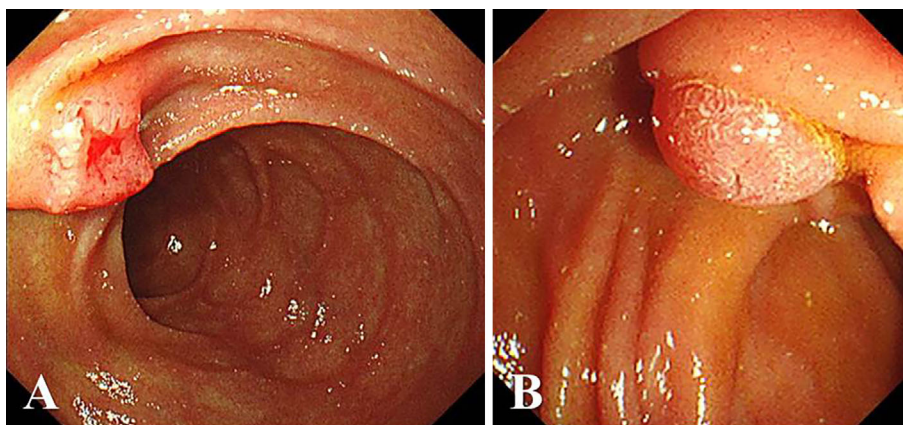


Figure 1. Imaging of the minor and major duodenal papilla. A: Upper gastrointestinal endoscopy revealed a reddish, slightly elevated lesion measuring 5 mm in diameter at the minor duodenal papilla. B: The major papilla of Vater was normal.

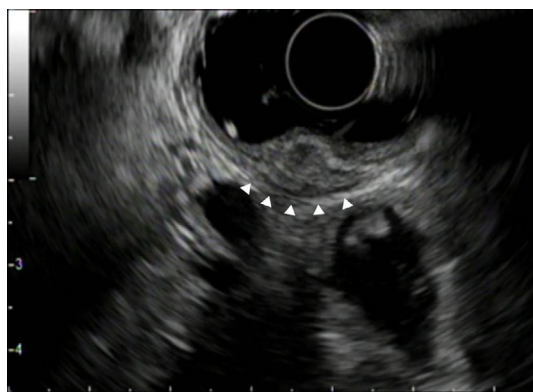


Figure 2. EUS detected a 14×9 mm homogeneous, hypoechoic lesion in the submucosal layer with preservation of the muscularis propria (arrowheads).

poechoic lesion in the submucosal layer without invasion of the muscularis layer by endoscopic ultrasonography (EUS); a convex type EUS (UCT-260; Olympus Medical Systems, Tokyo, Japan) combining with a transabdominal US (Pro-sound F75; Aloka, Tokyo, Japan) (Fig. 2). The patient and his family provided their informed consent and did not request surgical treatment due to the risk of his old age and underlying cirrhosis. Hence, the patient underwent endoscopic mucosal resection (EMR) using a side-viewing instrument (TJF-260 V; Olympus, Tokyo, Japan) (Fig. 3). Dilute epinephrine was injected into the submucosa to separate it from the muscularis propria, and the lesion was resected en-bloc using an electric snare (SD-6 L-1; Olympus, Tokyo, Japan). After resection, the ulcer was closed with clips to prevent any late adverse events of bleeding and perforation. Considering the possibility of pancreatic juice outflow from the accessory pancreatic duct, the excision cite was not closed completely. Lastly, endoscopic nasobiliary and nasopancreatic drainage (ENBPD) tubes were inserted from the MaDP to prevent exposing the ulcer to bile and pancreatic juices. A proton-pump inhibitor was also given for pro-

phylaxis of exposing the ulcer to gastric acid. The ENBPD tubes were removed after second-look endoscopy. The patient was discharged 10 days after EMR without any adverse events.

Histopathologically, the MiDP specimen (measuring 7×6 mm in diameter) had an atypical epithelium on the surface of the mucosa, continuously elevated from the duodenal epithelium with increased chromatin and enlarged nuclei (Fig. 4). There was a proliferation of the atypical epithelium with formed solid parts, irregular gland duct structures, and conspicuous structural heteromorphism. The lesion was diagnosed to be moderately differentiated tubular adenocarcinoma measuring 4×4 mm in diameter which was limited to the mucosa, without invasion of the submucosa, accessory pancreatic duct, vascular or lymphovascular structures with negative margins of the vertical and lateral sides. An immunohistochemical examination revealed limited positive staining for MUC-2 and MUC-5AC, and negative staining for MUC-1 and MUC-6. Unfortunately, there were too few positive cells to discuss MUC expression. No local recurrence or metastasis has been detected by upper gastrointestinal endoscopy or CT 13 months after EMR.

Discussion

Characteristics of MiDP adenocarcinoma

Most MiDP tumors are reported to be adenomas (8-12), neuroendocrine tumors (13, 14), or rarely, ganglionic paragangliomas (15, 16). MiDP adenocarcinoma is extremely rare. We reviewed the PubMed database for articles written in English and published between 1998 and 2019 with the keywords adenocarcinoma and minor duodenal papilla. Thirteen reports about MiDP adenocarcinoma were found (2-4, 17-26). One of the reasons for so few reports on MiDP adenocarcinoma is the difficulty in early diagnosis (2, 25). MiDP is not carefully observed during upper gastrointestinal screening endoscopy and an MiDP tumor

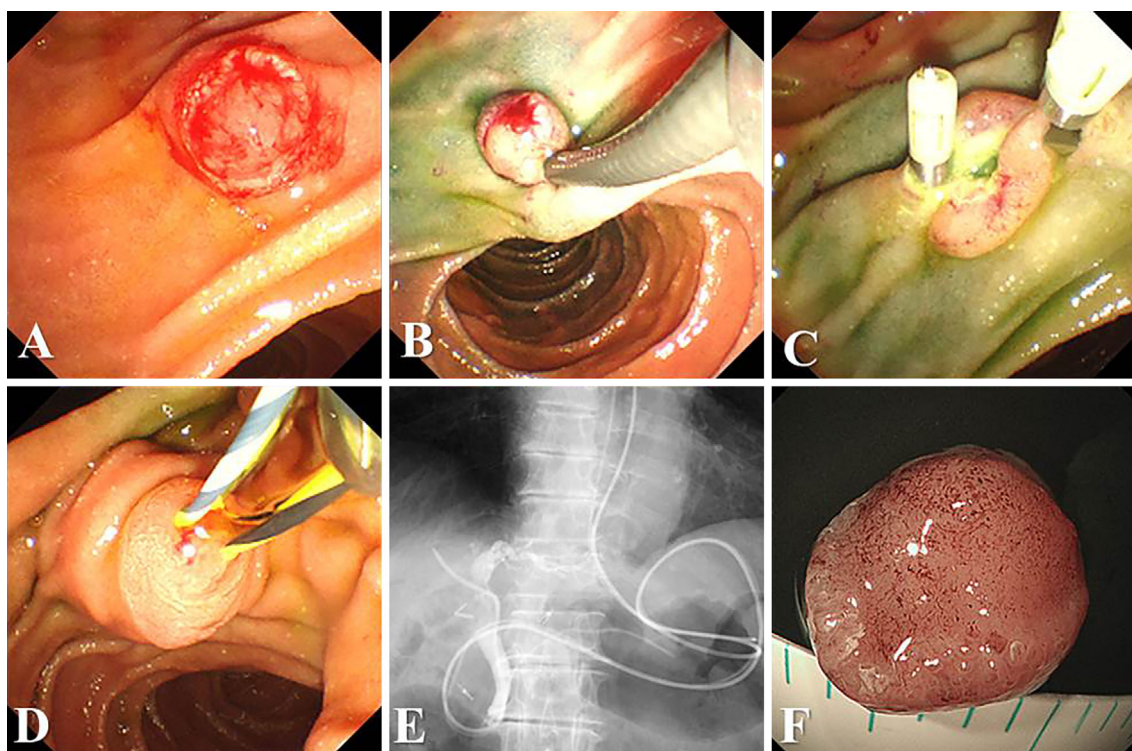


Figure 3. Endoscopic treatment of the lesion of minor duodenal papilla. A: Side-view of the tumor. B: Snare polypectomy (EMR) of the tumor. C: Closure by clips after resection. D/E: Both endoscopic nasobiliary drainage tube (5Fr) and nasopancreatic drainage tube (4Fr) were inserted from the major duodenal papilla. F: Resected specimen.

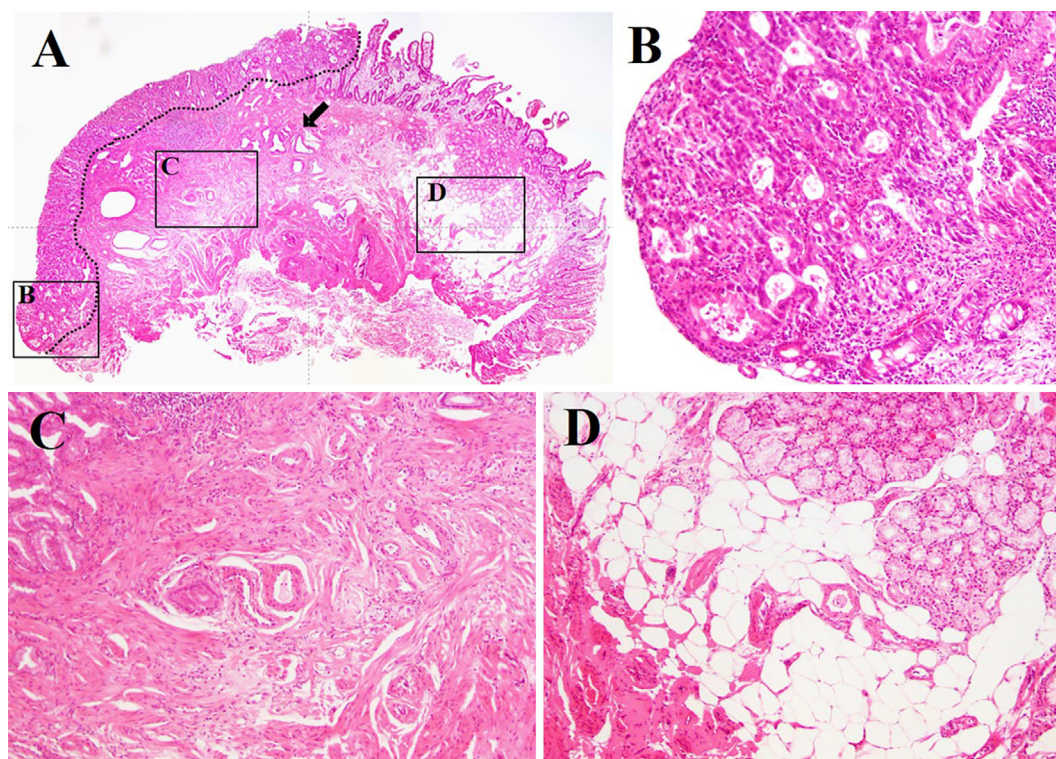


Figure 4. The histopathological examination of the resected specimen (Hematoxylin and Eosin staining). There was moderately differentiated tubular adenocarcinoma within the mucosa of the minor duodenal papilla without infiltration submucosa, accessory pancreatic duct (arrow), vascular, or lymphovascular structures (magnification, A: $\times 4$, B-D: $\times 20$). Mild inflammatory cell infiltration with fibrosis (C) and fatty replacement (D) are seen in the submucosa.

has few clinical symptoms unless it obstructs the pancreatic duct flow with pancreas divisum, in which the drainage route of pancreatic juice generally becomes the MiDP and may cause pancreatitis-related symptoms at a relatively early stage when a tumor develops. Therefore, tumors are typically detected only in advanced stages when the origin of the tumor cannot be determined (2). In our case, the patient had neither any symptoms nor pancreas divisum. However, an abnormal MiDP was incidentally detected due to the observation of the duodenum in detail during varices screening.

Twenty-two cases of MiDP adenocarcinomas in 13 reports, as well as our case, are summarized in Table. The mean age was 69 years (range 50 to 84) and 13 patients were men. Mean tumor size was 21 mm (range 4 to 50). Eight patients (61.5%) were asymptomatic, whereas the remainder had either abdominal pain and/or jaundice. Four non-invasive carcinomas were incidentally identified by screening upper gastrointestinal endoscopy. There were no patients with familial adenomatous polyposis (FAP). Patients with FAP invariably develop duodenal adenomas and have a risk of papillary carcinoma (27), however, there have been no cases of MiDP carcinoma with FAP and the difference between FAP-complicated MiDP adenomas and sporadic adenomas has not been clarified (28). Most tumors were resected surgically, and only 3 cases with non-invasive carcinoma were managed using EMR. Additionally, 2 cases involved synchronous carcinomas of the MaDP and MiDP. Non-invasive carcinomas were smaller in diameter compared to invasive carcinoma at 10.5 vs. 23.8 mm, respectively ($p=0.003$). Lymph node metastasis was observed in only 2 cases with larger tumors. During the follow-up period (average, 42 months; range, 8-85 months), thirteen cases (68.4%) had no evidence of recurrence, and 3 cases died due to tumor recurrence.

On immunostaining in the previously reported cases of MiDP carcinomas, intestinal-type tumors tended to be positive for CK20, CDX2 and MUC-2, whereas the pancreatobiliary-type tumors tended to stain with CK7, MUC-1 (25, 29). Only one case of gastric-type carcinoma in adenoma of MiDP was reported to be stained with MUC-5 AC in the surface layer and MUC-6 in the deep layer (4).

Diagnosis and treatment for MiDP adenocarcinoma

A biopsy is necessary to make a preoperative diagnosis of adenocarcinoma. However, an endoscopic biopsy has limited accuracy in the diagnosis of MaDP tumors because it is difficult to rule out the presence of cancer in deeper layers (30, 31). Differentiating benign tumors from malignant ones, based on the size or endoscopic findings, is also difficult (24). The same may be expected in MiDP tumors. On the other hand, an accurate assessment of invasion depth is important to determine the optimal therapy.

Some reports suggested that evaluations of invasion by EUS had an accuracy rate of 63% to 92% in local extent of MaDP tumor progression (32-35), and similar results are ob-

tained in MiDP tumors (4). In the present case, a 14×9 mm hypoechoic lesion was found in the submucosa by EUS, the cause of which was unclear from the resected specimen as well as previously reported case (4). In our case, fibrosis, mild inflammatory cell infiltration and fatty replacement may be induced by accessory pancreatic duct obstruction in submucosa histopathologically, and they may appear as a hypoechoic lesion in EUS. EUS is a highly accurate modality for staging ampullary tumors and for evaluating ductal involvement (34), however, there is also an opinion that a single layer of neoplastic cell extension is <20 μ m thick and cannot be distinguished with clinical imaging (3). On the other hand, the EUS image obtained by the miniature ultrasonic probe with a high frequency (20 MHz) was reported to visualize more faithfully the histological findings of the excised specimen than the normal EUS image (36). Therefore, the ultrasonic diagnosis with a 20 MHz microprobe may be more effective and useful in diagnosing the progression of MiDP tumors. In clinical practice, however, there is no consensus regarding the preoperative diagnosis of MiDP tumors.

Recently, with the development of endoscopic tools and techniques, the indications for endoscopic papillectomy have been expanding and en block endoscopic resection for suspicious lesions of adenoma or non-invasive adenocarcinoma at MaDP is recommended as a diagnostic treatment (5-7), and that may apply to MiDP. However, in our review, surgical resection was selected as the primary therapy in most cases. Although a pancreaticoduodenectomy allows for the complete resection of the tumor, it is associated with a risk of various adverse events, including bleeding, pancreatic fistula, pulmonary complications, or delayed gastric emptying (37). Therefore, surgical treatment of the MiDP adenocarcinoma has been avoided in elderly patients, as well as those with various underlying diseases, such as in our case. However, many EMR procedures were performed for MiDP tumors without adenocarcinoma with good results (8, 11-14, 16, 38). If there are no apparent imaging findings of invasive cancer, total biopsy by EMR as a diagnostic treatment for MiDP tumors will be the good option prior to surgery. At our institutions, when MiDP or MaDP tumors have no apparent infiltration to the muscular layer or deeper site, we propose diagnostic treatment with EMR only in cases with a high risk for performing pancreaticoduodenectomy; nevertheless the careful selection of patients with appropriate criteria for EMR or surgery is required.

Endoscopic resection for MiDP tumors

In the endoscopic resection of MaDP tumors, local injection prior to resection or closure by clip after resection is not generally recommended. Meanwhile, pancreatic stent placement is recommended to prevent postoperative pancreatitis (39-42). Per our review, local injection was performed in most MiDP cases treated by EMR using glycerol (3), diluted epinephrine, or saline (4). In cases without pancreas divisum, local injection at the MiDP may not cause pancrea-

Table. Previously Reported Cases of a Minor Papillary Adenocarcinoma.

Case	Ref	Author	Year	Age	Sex	Symptom	Treatment	Macroscopic-type	Size (mm)	Major papilla	Pancreas divisum	Extent of Invasion	LN meta	Follow up (M)	Outcome
1	2	Yamao	1998	77	M	Transient abdominal pain	PPPD	Elevated, central ulcer	25	Normal	-	Pancreas	ND	42	DOO
2	17	Kajiwara	2007	60	M	Transient abdominal pain	SSPPD	Like villous adenoma with a stalk	50	Normal	+	Pancreatic duct	-	ND	NED
3	18	Wakatsuki	2008	70	M	None	PPPD	Elevated, central ulcer	11	Normal	-	Duodenal submucosa	-	32	NED
4	19	Parthasarathy	2008	60	F	Fever, jaundice	PD	Elevated, central ulcer	15	Carcinoma	-	Unclear	-	8	NED
5	20	Matheus	2008	50	F	Abdominal pain, jaundice	PPPD	Elevated	15	Carcinoma	ND	Duodenal wall	-	24	NED
6	21	Takami	2011	81	M	None	SSPPD	Elevated	20	Normal	-	Pancreas	-	ND	NED
7	22	Okuma	2011	76	M	None	PPPD	Elevated	12	Normal	-	Duodenal submucosa	-	16	NED
8	23	Zutiki	2011	69	M	Abdominal pain	PSSD	Elevated	18	Normal	-	Sphincter muscle	-	32	NED
9	24	Hoshino	2013	64	F	None	TP	Elevated	15	Normal	-	Intramucosa	-	48	NED
10	25	Shia	2014	66	M	ND	Surgical resection	ND	30	ND	ND	Pancreas	-	75	DOD
11	"	"	"	75	F	ND	Surgical resection	ND	18	ND	ND	Duodenal wall	-	17	DOU
12	"	"	"	76	M	ND	Surgical resection	ND	12	ND	ND	Duodenal wall	-	60	DOD
13	"	"	"	72	F	ND	Surgical resection	ND	40	ND	ND	Pancreas	-	85	DOD
14	"	"	"	66	F	ND	Surgical resection	ND	22	ND	ND	Pancreas	-	84	DOD
15	"	"	"	50	M	ND	Surgical resection	ND	12	ND	ND	Pancreas	-	ND	ND
16	"	"	"	75	F	ND	Surgical resection	ND	35	ND	ND	Duodenal serosa	-	ND	ND
17	"	"	"	59	M	ND	Surgical resection	ND	37	ND	ND	Pancreas	-	ND	ND
18	"	"	"	76	M	ND	Surgical resection	ND	44	ND	ND	Pancreas	+	51	NED
19	26	Suzumura	2015	70	M	None	PPPD	Elevated	12	Normal	-	Pancreas	-	17	NED
20	3	Matsui	2016	69	F	None	EMR	Elevated	11	Normal	-	Intramucosa	-	80	NED
21	4	Kawashima	2019	67	F	None	EMR	Elevated	12	Normal	-	Intramucosa	-	36	NED
22	Our	Our	2020	84	M	None	EMR	Elevated	4	Normal	-	Intramucosa	-	13	NED

ND: not described, DOO: died of other cause, NED: no evidence of disease, DOD: died of unknown cause, PPDP: pylorus-preserving pancreaticoduodenectomy, PD: pancreaticoduodenectomy, SSPPD: subtotal stomach-preserving pancreaticoduodenectomy, PSSD: pancreas sparing segmental duodenectomy, TP: transduodenal papillectomy, EMR: endoscopic mucosal resection

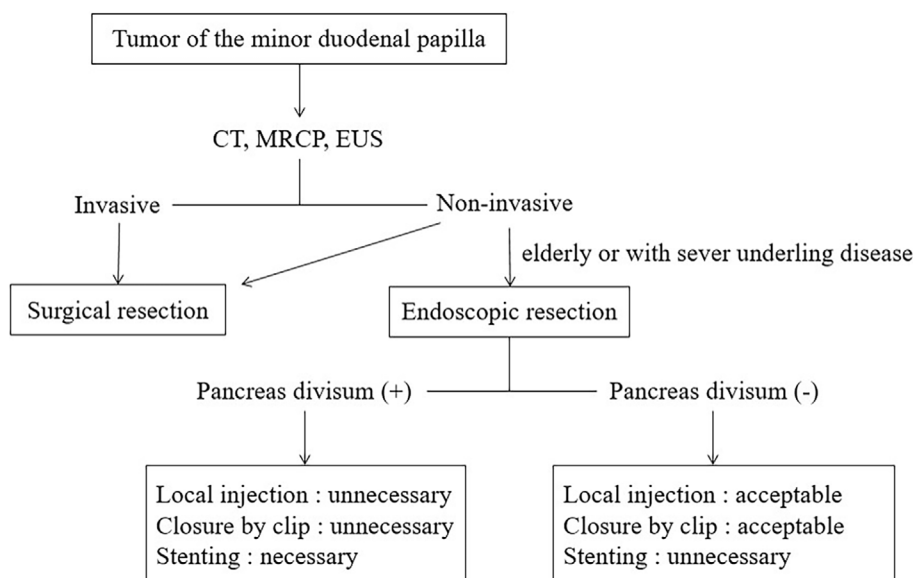


Figure 5. The established strategy for tumors at the minor duodenal papilla.

titis. In previous reports, underwater EMR for superficial non-ampullary duodenal epithelial tumor was reported to be safe, even without the use of submucosal injection (43), however, the optimal treatment strategies for MaDP and MiDP tumors are unclear. The surrounding muscular construction of MiDP is less massive compared to that of the MaDP (44). In addition, the area lined by the pancreatic tissue under the MiDP may not be wide compared to that of the MaDP. Therefore, the risk of perforation after resection of MiDP tumor may increase if the tumor is resected without submucosal injection (3). Although there is no consensus on whether local injection is needed, excessive local injection interfering the resection with sufficient vertical and horizontal margins by snaring should be avoided.

There are few reports which describe successfully treating the MiDP with pancreas divisum combined with pancreatic stenting (12, 45), therefore, it is difficult to discuss the usefulness of pancreatic stenting after resection of MiDP with pancreas divisum. In our case, ENBPD tubes were placed through the MaDP into the pancreatic and bile ducts after EMR. The insertion of ENBPD tubes was reported to be useful for the prevention of perforation when complete closure of the post- endoscopic submucosal dissection (ESD) mucosal defect was impossible (46). The MiDP can be structurally weaker than the MaDP as mentioned above, hence we considered that the post-EMR ulcers should be prevented from exposure to pancreatic and bile juice, which may cause delayed perforation or bleeding.

We recommend EMR for the management of MiDP adenocarcinomas (Fig. 5). If there is no pancreas divisum, then the tumors are expected to have a relatively low risk of pancreatitis due to EMR combined with submucosal injection. Additionally, closure of the ulcer by clips after EMR may be acceptable. If there is pancreas divisum, the tumors might be detected relatively secondary to pancreatic obstruction symptoms (3). In such cases, the occurrence of post-EMR

pancreatitis should be carefully monitored, and accessory pancreatic duct stenting should be considered. Submucosal injection prior to EMR requires careful judgment because while it may reduce delayed bleeding or perforation (3), it may complicate snaring or stent placement through MiDP. We believe that endoscopic resection of MiDP tumors can be performed to treat not only benign tumors, but also early adenocarcinomas whose abdominal CT and EUS do not show any metastasis or infiltration to the dorsal pancreatic duct.

In conclusion, we herein described a rare case of MiDP adenocarcinoma which was successfully and safely resected by EMR. Endoscopic resection as a diagnostic treatment, as well as total biopsy, is a minimally invasive treatment alternative to surgery for non-invasive MiDP adenocarcinoma. Further research is needed to obtain consensus regarding the primary method for the diagnosis and treatment of MiDP tumors.

The authors state that they have no Conflict of Interest (COI).

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