

Proposed indications for limited resection of early ampulla of Vater carcinoma: clinico-histopathological criteria to confirm cure

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Abstract

Background Limited resection is reserved for patients with high operative risk or benign adenomas. We aimed to define indications for limited resection of early ampulla of Vater carcinoma with curative intent through detailed pre-operative examinations and histopathological evaluations. **Methods** We performed a retrospective cohort study of all consecutive Japanese patients who underwent resection for ampulla of Vater neoplasms at our hospital from 1986 to 2010.

Results A total of 75 patients were identified. Moderately/poorly differentiated histology, lympho-vascular/perineural invasion, and duodenal/pancreatic invasion were significant risk factors for lymph node metastases. Macroscopically, non-exposed protruded- or ulcerative-type disease did not correlate directly with lymph node metastases; however, these tumor types were associated with other invasive features. In a subset of early carcinomas fulfilling the conditions of exposed protruded adenoma or papillary/well-differentiated adenocarcinoma determined by endoscopic biopsy, negative duodenal invasion determined by endoscopic ultrasonography, no tumor infiltration

into the pancreatic duct determined by intraductal ultrasound, and diameter of the pancreatic duct ≤ 3 mm determined by endoscopic retrograde cholangiopancreatography ($N = 11$), the incidence of lymph node metastasis and tumor infiltration into the pancreatic duct was 0%.

Conclusion Strictly selected patients with early ampulla of Vater carcinomas may benefit from limited resection if the resected specimen is evaluated to confirm all histopathological criteria.

Keywords Ampulla of Vater carcinoma · Limited resection · Local resection · Indication · Criteria

Introduction

Carcinoma of the papilla of Vater (the so-called ampulla of Vater) is relatively uncommon and has been reported to have high resectability rates and favorable overall 5-year survival rates compared with distal cholangiocarcinoma and pancreatic cancer [1–6]. Currently, pancreatoduodenectomy (PD) is considered the curative treatment of choice [3–8]. Although the mortality rate for PD has decreased significantly over the last few decades to less than 5%, it still carries a high morbidity rate. For these reasons, many authors have investigated the possibility of less-invasive procedures for ampullary carcinoma [3, 5–11], and the majority concluded that limited resection should be reserved only for patients with high operative risk or benign adenomas because of the increased likelihood of recurrence due to lymphatic or venous invasion, even for early ampullary carcinomas [3, 5–11]. On the other hand, some investigators have suggested that endoscopic papillectomy (EP) or local resection is potentially curative for a selected population of patients [12, 13]. To achieve the complete

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removal of an ampullary tumor by limited resection, 2 criteria—no lymph node metastasis and a definite tumor-free margin—must be satisfied. The most important consideration is whether these two criteria can be diagnosed before resection. Lymph node metastasis is one of the most significant predictors of poor prognosis for ampulla of Vater carcinoma [2–6, 9, 14], and local resection cannot be associated with the dissection of lymph nodes. That is, no lymph node metastasis is an absolute requirement for limited resection of ampullary cancer. Furthermore, a free surgical margin means that the tumor must be located at the area of the ampulla of Vater within the extent of local resection in the absence of mucosal tumor infiltration into the pancreatic duct, although the presence of tumor extension into the common bile duct does not hinder the limited surgery because of the possibility of complete excision of the extrahepatic portion of the common bile duct en bloc with the ampulla of Vater [15].

In the present study, therefore, our purpose was to clarify the clinico-pathological factors that correlate with lymph node metastasis and local extension, including invasion of the duodenum and tumor infiltration of the pancreatic duct, through a detailed histopathological evaluation of specimens retrieved by standardized radical resection and systematic lymph node dissection, or local resection with curative intent. The findings from this analysis could lead to indications for limited resection of early ampulla of Vater carcinoma.

Patients and methods

A retrospective cohort study was performed for all consecutive Japanese patients at Keio University Hospital, Tokyo, Japan who underwent resection for ampulla of Vater tumors, including adenoma and adenocarcinoma, with curative intent from May 1986 through December 2010. The hospital charts, surgery records, and pathology reports were analyzed. Patients who had tumors without distant organ metastases and/or major vessel invasion by preoperative radiological studies were considered surgical candidates. Whipple resection or pylorus-preserving pancreatoduodenectomy (PPPD) with concurrent lymph node dissection at the anterior and posterior aspect of the pancreatic head, the hepatoduodenal ligament, and the right border of the superior mesenteric artery was the principal procedure. At our institution, transduodenal papillectomy (TDP) and endoscopic papillectomy (since 2000), if applicable, have been the alternative options for benign tumors of the ampulla of Vater, diagnosed as tubular adenoma by endoscopic biopsy without evidence of local extension to the common bile duct or the main pancreatic duct [16, 17]. In some cases, the final histopathological

evaluation of the specimens resected by TDP or EP revealed adenocarcinoma. In addition, complete resection of the extrahepatic portion of the common bile duct and the ampulla of Vater (CRBA) was performed in a high-risk patient with an early stage of ampullary carcinoma extending into the common bile duct without involvement of the pancreatic duct [15]. Two pathologists independently examined all cases to distinguish ampulla of Vater carcinoma from tumors of the pancreas, the distal common bile duct, or the duodenum by microscopic evaluation of the lesion according to the Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery [18]. Positive tumor invasion to the duodenum (\geq Du1) was defined as invasion beyond the sphincter of Oddi. Negative invasion to the duodenum (Du0) was defined as invasion limited to the duodenal mucosa or sphincter of Oddi. Likewise, positive invasion of the pancreas was defined as invasion of the pancreas beyond the sphincter of Oddi or the duodenal wall. The gross appearance of the tumor on the mucosa of the duodenum was categorized as a macroscopic type according to the main macroscopic findings, [18] and was allocated to one of 3 types: an exposed protruded type, a non-exposed protruded type, both of which are without ulceration, and an ulcerative type, including both mixed types of predominant protruded and ulcerative types according to the Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery. Endoscopic ultrasonography (EUS) was performed with mechanical radial endoscopes at a frequency of 5 or 7.5 MHz (GF-UM 2000; Olympus Optical Co., Ltd, Tokyo, Japan) to define the extent of local involvement, especially invasion of the duodenal wall and pancreas, before endoscopic retrograde cholangiopancreatography (ERCP) with intraductal ultrasonography (IDUS) and biliary drainage. After ERCP and before biliary drainage, transpapillary IDUS was performed with an IDUS probe at a frequency of 20 MHz (UM-G20-29R; Olympus), mainly to evaluate tumor extension into the bile duct and pancreatic duct. Tumor infiltration into the bile duct was examined by inserting an IDUS probe into the pancreatic duct. By contrast, tumor infiltration into the pancreatic duct was examined by inserting an IDUS probe into the bile duct.

Statistical analyses

The data are presented as percentages, median (range) and mean \pm standard error. The chi-squared test or Fisher's exact probability test were used when appropriate to determine the correlations between the clinico-pathological variables and lymph node metastases and between the macroscopic type and histopathological differentiation or duodenal invasion. Multivariate analyses by logistic

regression model were performed to identify independent risk factors of nodal spread. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed with SPSS statistical software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

From June 1986 through December 2010, a total of 75 consecutive patients (47 males and 28 females) underwent curative resection for ampulla of Vater carcinoma. The median age (range) was 64 (26–79) years. Precise histopathological evaluation after resection revealed adenocarcinoma in 57 patients and adenoma in 18 patients. Whipple resection or PPPD was performed for 51 patients under the preoperative diagnosis of adenocarcinoma by endoscopic biopsy, and one patient with adenoma underwent PPPD because of the further extent of the tumor along the main pancreatic duct. CRBA was carried out in one patient as described above, and TDP was performed in a total of 4 patients (2 with adenoma, and 2 with adenocarcinoma). A total of 18 patients, 15 with a final diagnosis of adenoma and 3 with a final diagnosis of adenocarcinoma, underwent EP. A total of 23 patients with ampullary tumors (17 adenomas and 6 adenocarcinomas) who received so-called limited resection (EP, TDP or CRBA) did not undergo additional resection and were strictly followed. The median (range) tumor size was 21.0 (8–40) mm (14.7 mm for adenomas, 23.0 mm for adenocarcinomas). With regard to

macroscopic type, 44 cases were classified as the exposed protruded type (17 adenomas, 27 adenocarcinomas), 11 as the non-exposed protruded type (1 adenoma, 10 adenocarcinomas) and 20 as the ulcerative type (adenocarcinomas) (Table 1).

Clinico-pathological findings of the ampullary neoplasms

Overall, 18 cases were diagnosed as adenomas; 9 cases (9/18; 50%) had adenoma with low-grade dysplasia, and 9 (9/18; 50%) had adenoma with components of high-grade dysplasia, including one case with tubulovillous adenoma. A total of 57 cases had adenocarcinoma diagnosed by final histological examination. Papillary or well-differentiated tubular adenocarcinoma was the predominant histological feature in 28 cases (28/57; 49%), moderately differentiated adenocarcinoma in 18 (18/57; 32%), and poorly differentiated adenocarcinoma in 11 (11/57; 19%). Lympho-vascular and perineural invasion were found in 34 (34/57; 60%) and 10 (10/57; 17%) cases, respectively. Tumor invasion of the duodenal wall and the pancreas was confirmed in 40 (40/57; 70%) and 25 (25/57; 44%) cases, respectively. A common bile duct size of 10 mm or less at ERCP was found in only 3 cases (3/45; 7%). A pancreatic duct size of 3 mm or less at ERCP was found in 10 cases (10/43; 23%). Histopathological examination revealed positive tumor infiltration into the bile duct in 13 cases (13/57; 23%), and positive tumor infiltration into the pancreatic duct in 31 cases (31/57; 54%). Regional lymph node metastases were found in 23 patients (23/57; 40%), including 6 patients (6/57; 10%) with distant lymph node

Table 1 Demographic characteristics of the patients with adenoma or adenocarcinoma of the ampulla of Vater

	Adenoma	Adenocarcinoma	Total
No. of patients	18	57	75
Gender			
Male	12	35	47
Female	6	22	28
Age (years) mean ± SD (range)	59 ± 11.1 (26–73)	65 ± 9.1 (43–79)	64 ± 10.1 (26–79)
Operative procedure			
PD/PPPD	1	51	52
CRBA	0	1	1
TDP	2	2	4
EP	15	3	18
Tumor size (mm) mean ± SD (range)	14.7 ± 5.2 (8–30)	23.0 ± 11.3 (11–40)	21.0 ± 10.8 (8–40)
Macroscopic tumor type			
Exposed protruded type	17	27	44
Non-exposed protruded type	1	10	11
Ulcerative type	0	20	20

PD pancreatoduodenectomy, PPPD pylorus-preserving pancreatoduodenectomy, CRBA complete resection of the extrahepatic portion of the common bile duct and the ampulla of Vater, TDP transduodenal papillectomy, EP endoscopic papillectomy

metastases (around the common hepatic artery in 1 patient, distal mesenteric artery in 1 patient, and para-aortic in 4 patients).

Relationship of clinico-histopathological factors with lymph node metastases

The following data were collected from 57 patients with adenocarcinoma of the ampulla of Vater to determine the relationship between clinico-histopathological factors and lymph-node metastases: age, gender, macroscopic type, final histopathological differentiation, tumor size, lympho-vascular invasion, perineural invasion, duodenal invasion, pancreatic invasion, diameter of the bile duct or main pancreatic duct, and extension to the bile duct (Ab) or main pancreatic duct (Ap). The chi-squared univariate analyses revealed that histopathological differentiation (moderately or poorly differentiated histology), lympho-vascular/perineural invasion, and local extension to the duodenal wall or the pancreas correlated significantly with lymph node metastases (Table 2), although these 5 factors did not remain as independent predictors of lymph node metastasis on multivariate analysis.

Relationship of macroscopic type with histopathological differentiation and duodenal invasion

The relationship of macroscopic type with histopathological differentiation and duodenal invasion was investigated in a total of 75 patients with ampullary tumors. Of the exposed protruded-type tumors, 81.8% (36/44) had histopathology ranging from adenoma to papillary/well-differentiated adenocarcinoma. Furthermore, 54.5% (6/11) of the non-exposed protruded type tumors had a histopathology ranging from adenoma to papillary/well-differentiated adenocarcinoma. In contrast, 80% (16/20) of ulcerative-type tumors corresponded to moderately/poorly differentiated adenocarcinomas. Among the ulcerative-type tumors, there was a significantly higher rate of moderately or poorly differentiated adenocarcinomas compared with exposed protruded-type tumors ($p < 0.001$) (Table 3). Association of macroscopic type with duodenal invasion diagnosed by final histological examination was likewise observed. Of the exposed protruded-type tumors, 72.7% (32/44) were negative for duodenal invasion, while only 9.1% (1/11) of the non-exposed protruded-type tumors and 10% (2/20) of the ulcerative-type tumors were negative for duodenal invasion. The non-exposed protruded-type and ulcerative-type tumors had significantly higher rates of positive duodenal invasion compared with the exposed-protruded type ($p < 0.001$ and $p < 0.001$, respectively) (Table 4).

Table 2 Relationship of clinico-histopathological factors to lymph node metastases

Variable	Lymph node metastases (%)	P value
Age		
≤65 years	9/25 (36)	0.749
>65 years	14/32 (44)	
Gender		
Male	14/35 (40)	0.834
Female	9/22 (41)	
Macroscopic type		
Exposed protruded type	8/27 (30)	0.179
Non-exposed protruded type	3/10 (30)	
Ulcerative type	12/20 (60)	
Histopathological differentiation		
pap/wel	5/28 (17.9)	0.002
mod/por	18/29 (62.1)	
Tumor size (mm)		
1–10	2/4 (50)	0.996
11–20	8/22 (36)	
21–30	8/22 (36)	
31–40	3/6 (50)	
41+	2/3 (67)	
Lympho-vascular invasion		
Negative	0/23 (0)	<0.001
Positive	23/34 (68)	
Perineural invasion		
Negative	14/47 (30)	0.001
Positive	9/10 (90)	
Duodenal invasion		
Negative	0/17 (0)	0.004
Positive	23/40 (57)	
Pancreatic invasion		
Negative	5/32 (16)	<0.001
Positive	18/25 (72)	
CBD size in ERCP		
≤10 mm	0/3 (0)	0.354
>10 mm	19/42 (45)	
P-duct size in ERCP		
≤3 mm	2/10 (20)	0.362
>3 mm	14/33 (42)	
Ab		
Negative	18/44 (41)	0.87
Positive	5/13 (38)	
Ap		
Negative	8/26 (31)	0.28
Positive	15/31 (48)	

pap papillary, *wel* well-differentiated, *mod* moderately, *por* poorly differentiated, *CBD* common bile duct, *P-duct* main pancreatic duct, *ERCP* endoscopic retrograde cholangio-pancreatography, *Ab* ductal infiltration into the bile duct, *Ap* ductal infiltration into the pancreatic duct

Table 3 Relationship of macroscopic type with histopathological differentiation type

Macroscopic type	Adenoma No. (%)	Adenocarcinoma		Total No. (%)
		pap/wel No. (%)	mod/por No. (%)	
Exposed protruded	17 (38.6)	19 (43.2)	8 (18.2)	44 (100)
Non-exposed protruded	1 (9.1)	5 (45.4)	5 (45.4)	11 (100)
Ulcerative ^a	0	4 (20)	16 (80)	20 (100)

pap papillary, *wel* well-differentiated, *mod* moderately, *por* poorly differentiated

^a Ulcerative type tumors had a significantly higher rate of mod/por adenocarcinoma compared with exposed protruded type tumors ($P < 0.001$)

Table 4 Relationship of macroscopic type with duodenal invasion

Macroscopic type	Du0	≥Du1	Total
	No. (%)	No. (%)	
Exposed protruded	32 (72.7)	12 (27.3)	44 (100)
Non-exposed protruded ^a	1 (9.1)	10 (90.9)	11 (100)
Ulcerative ^a	2 (10)	18 (90)	20 (100)

Du0 invasion limited to the duodenal mucosa or sphincter of Oddi, *≥Du1* invasion beyond the sphincter of Oddi

^a The non-exposed protruded type and ulcerative type tumors had a significantly higher rate of *≥Du1* compared with the exposed protruded type ($P < 0.001$ and $P < 0.001$, respectively)

Predictability of endoscopic biopsies for histopathological differentiation

Among the 75 cases with adenoma or adenocarcinoma, 71 underwent preoperative endoscopic forceps biopsy of the ampullary tumor. The number of preoperative biopsies taken from each ampullary tumor in our series ranged from 1 to 13 with a mean of 4.7. Agreement of pathological diagnoses between preoperative endoscopic biopsies and resected specimens was investigated (Table 5). The diagnostic accuracy of endoscopic biopsy in the discrimination of benign and malignant tumors of the ampulla of Vater was 84% (60/71). On the other hand, when the pathological diagnosis of preoperative endoscopic biopsies and resected specimens was combined with the diagnosis of histopathological differentiation, the diagnostic accuracy was 62% (44/71). With regard to underestimation (i.e. false-negative cases), which would more likely affect the indications for limited treatment, no patient had moderately/poorly differentiated adenocarcinoma in resected specimens from adenomas with low-grade dysplasia in biopsied specimens. Only one out of 13 patients with adenoma with high-grade dysplasia in biopsied specimens had moderately/poorly differentiated adenocarcinoma in resected specimens. This

Table 5 Histological agreement between preoperative biopsies and resected specimens

Histology of preoperative biopsies	Final diagnosis of resected specimens			
	Adenoma		Adenocarcinoma	
	Low-grade	High-grade	pap/wel	mod/por
Chronic inflammation			2	
Adenoma				
Low-grade	7	3	4	
High-grade	2	6	4	
Adenocarcinoma				
pap/wel			16	9
mod/por			2	15

Data are number of patients

Low-grade low-grade dysplasia, *High-grade* high-grade dysplasia, *pap papillary*, *wel* well-differentiated, *por* poorly differentiated

one case appeared to have the non-exposed protruded-type tumor and positive duodenal invasion beyond the sphincter of Oddi. Eight of 9 patients with adenocarcinoma on final analysis who were thought to have adenoma on preoperative biopsy samples were found to have adenocarcinomas on resected specimens, consisting of papillary/well-differentiated adenocarcinomas. Among these 8 patients, 2 were Ap (+) on histopathology; in both patients, the pancreatic ducts were found to be dilated more than 3 mm in diameter by ERCP. These 2 patients underwent Whipple/PPPD procedures. With regard to duodenal invasion, five of 8 patients showed tumor invasion limited to mucosa, 1 showed tumor invasion limited to the sphincter of Oddi, and 2 showed positive duodenal invasion on final histopathological analysis. The patient with tumor invasion limited to the sphincter of Oddi was diagnosed with exposed protruded-type tumor, that was Du0 and Ap (–), and underwent EP. One of 2 patients positive for duodenal invasion had a non-exposed protruded-type tumor, with the main pancreatic duct measuring 5 mm in diameter. The other patient positive for duodenal invasion underwent PPPD because obvious duodenal invasion was diagnosed before resection. Finally, five of the 8 patients underwent limited resection and the other 3 patients underwent Whipple/PPPD procedures. None of the 8 patients developed recurrence during the follow-up period. Furthermore, 9 (36%) patients had moderately/poorly differentiated adenocarcinoma in resected specimens among 25 patients with papillary/well-differentiated adenocarcinoma in biopsied specimens. Among these 9 cases, 6 appeared to have the ulcerative-type tumor, 6 had positive duodenal invasion, and 5 had positive tumor infiltration into the pancreatic duct. All of these 9 patients had at least one of the following preoperatively:

ulcerative type, positive duodenal invasion, and positive tumor infiltration into the pancreatic duct, despite a mismatch of histopathological differentiation between endoscopic biopsies and resected specimens.

Diagnostic accuracy of EUS for duodenal invasion

The correlation of EUS for duodenal invasion between the preoperative diagnosis and final histological analysis was investigated (Table 6). EUS was used to diagnose 33 patients with Du0 and 18 patients with \geq Du1. A mismatch of duodenal invasion between EUS and pathology occurred in 9 of 51 (18%) patients. Overestimation (i.e. false positive) was observed in 2 of 51 (4%) patients, and underestimation (i.e. false negative) was observed in 7 of 51 (14%) patients examined with EUS. The overall accuracy of duodenal invasion by EUS was 82% (42/51). Investigation of the characteristics of the 7 patients who were underestimated on duodenal invasion with EUS found that 4 patients appeared to have the exposed protruded type and 3 appeared to have the non-exposed protruded type. With regard to the pathology with histopathological differentiation of preoperative endoscopic biopsies, adenoma with high-grade dysplasia was seen in one patient, well-

Table 6 Diagnostic agreement of endoscopic ultrasonography for duodenal invasion

EUS	Pathology		Total
	Du0	\geq Du1	
Du0	26	7	33
\geq Du1	2	16	18
Total	28	23	51

Data are number of patients

EUS endoscopic ultrasonography, Du0 invasion limited to the duodenal mucosa or sphincter of Oddi, \geq Du1 invasion beyond the sphincter of Oddi

differentiated adenocarcinoma was seen in 3 patients, and moderately/poorly differentiated adenocarcinoma was seen in 3 patients. There were 3 patients who had a tumor of both the exposed protruded type and well-differentiated adenocarcinoma by endoscopic biopsy. In all 3 of these patients, the pancreatic duct was clearly dilated at ERCP (7, 10, and 12 mm in diameter) (Table 7).

Diagnosis of tumor infiltration into the pancreatic duct

Intraductal ultrasonography was performed for the diagnosis of tumor infiltration into the pancreatic duct in 45 of 75 patients with adenoma or adenocarcinoma. IDUS diagnosed 30 patients with Ap (–) and 15 patients with Ap (+) tumors (Table 8). Tumor infiltration with IDUS was correct in 26 of 27 (96%) patients with pathological Ap (–) and 14 of 18 (78%) patients with pathological Ap (+) tumors. With IDUS, 4 of 45 (9%) patients with pathological Ap (+) tumors were underestimated as Ap (–). The overall accuracy of IDUS for tumor infiltration into the pancreatic duct was 89% (40/45). On the other hand, pancreatography at ERCP was performed in 59 of 75 patients. A pancreatic duct diameter of 3 mm or less was seen in 17 patients and of 4 mm or more was seen in 42 patients (Table 9). Of the 17 patients with a pancreatic duct diameter of 3 mm or less, only one showed pathological Ap (+). By contrast, more than half of the patients with a pancreatic duct diameter of 4 mm or more showed pathological Ap (+). Then, we examined the diagnostic ability of tumor infiltration into the pancreatic duct by the combination of IDUS findings and the pancreatic duct diameter on ERCP. None of the patients who had both Ap (–) with IDUS and a pancreatic duct diameter of 3 mm or less at ERCP had pathological Ap (+), although 15 of 27 (55%) patients who had Ap (+) with IDUS and/or a pancreatic duct diameter of 4 mm or more had pathological Ap (+) (Table 10).

Table 7 Characteristics of patients with underestimation (Du0) of endoscopic ultrasonography for duodenal invasion

Patient no.	Pathological Du	Macroscopic type	Histological type		PD diameter on ERCP (mm)
			Preoperative	Final	
1	1	NEP	por	wel	5
2	1	NEP	High-grade	wel	5
3	1	EP	wel	mod	7
4	1	EP	wel	wel	12
5	1	EP	wel	wel	10
6	1	NEP	mod	mod	5
7	1	EP	por	por	10

Du duodenum, NEP non-exposed protruded, EP exposed protruded, High-grade adenoma with high-grade dysplasia, wel well-differentiated adenocarcinoma, mod moderately differentiated adenocarcinoma, por poorly differentiated adenocarcinoma, PD pancreatic duct, ERCP endoscopic retrograde cholangiopancreatography

Table 8 Diagnostic agreement of intraductal ultrasonography for ductal infiltration into PD

IDUS	Pathology		Total
	Ap (–)	Ap (+)	
Ap (–)	26	4	30
Ap (+)	1	14	15
Total	27	18	45

Data are number of patients

PD pancreatic duct, Ap ductal infiltration into the pancreatic duct

Table 9 Diagnostic agreement of PD diameter found by ERCP for ductal infiltration into the PD

PD diameter (mm) from ERCP	Pathology		Total
	Ap (–)	Ap (+)	
≤3	16	1	17
4–5	8	11	19
6–10	7	14	21
≥11	0	2	2
Total	31	28	59

Data are number of patients

ERCP endoscopic retrograde cholangiopancreatography, PD pancreatic duct, Ap ductal infiltration into the pancreatic duct

Table 10 Diagnostic agreement of combination of IDUS and PD diameter in ERCP for ductal infiltration into PD

IDUS and PD diameter (mm)	Pathology		Total
	Ap (–)	Ap (+)	
Ap (–) and ≤3	13	0	13
Ap (+) and/or ≥4	12	15	27
Total	25	15	40

Data are number of patients

ERCP endoscopic retrograde cholangiography, IDUS intraductal ultrasonography, PD pancreatic duct, Ap ductal infiltration into the pancreatic duct

Criteria capable of predicting an indication for limited resection of ampullary carcinoma

The patients with ampullary carcinoma who met the following 5 requirements were investigated: (1) exposed protruding macroscopic type, (2) adenoma or papillary/well-differentiated adenocarcinoma by endoscopic biopsy preoperatively, (3) negative duodenal invasion (Du0) with EUS, (4) no tumor infiltration into the pancreatic duct with IDUS, (5) pancreatic duct diameter of 3 mm or less at ERCP (Table 11). There were 11 patients among the 75 patients with neoplasms of the ampulla of Vater who fulfilled all of the above 5 requirements simultaneously (Table 12). Furthermore, 4 of those 11 patients had

Table 11 Proposed indications for limited resection

Requirements	Diagnostic work-up
Exposed protruding macroscopic type	Endoscopy
Adenoma or papillary/well-differentiated adenocarcinoma	Biopsy
Negative duodenal invasion	EUS
No tumor infiltration into the pancreatic duct	IDUS
Pancreatic duct diameter of 3 mm or less	ERCP

EUS endoscopic ultrasonography, IDUS intraductal ultrasonography, ERCP endoscopic retrograde cholangiography

adenocarcinoma as their final histological analysis with negative duodenal invasion and lympho-vascular/perineural invasion pathologically and with no lymph node metastasis. Finally, all 11 patients have remained alive without recurrence during the follow-up period.

Discussion

This is the first study to propose indications for limited resection of early ampulla of Vater carcinoma based on preoperative information and to provide detailed histopathological criteria to confirm complete resection. We must predict a successful local resection of ampullary carcinoma with preoperative information, that is, endoscopic findings of macroscopic type, pathological findings of endoscopic forceps biopsy, depth of duodenal invasion by EUS, and extent of tumor infiltration into the pancreatic duct by IDUS or ERCP. In early ampulla of Vater carcinomas (deepest invasion limited to the sphincter of Oddi), a strictly selected subset of tumors fulfilling the following conditions: an exposed protruding macroscopic type, adenoma or papillary/well-differentiated adenocarcinoma by preoperative endoscopic biopsy, negative duodenal invasion (Du0) with EUS, no tumor infiltration into the pancreatic duct with IDUS, and pancreatic duct diameter of 3 mm or less at ERCP were not associated with lymph node metastasis and were resectable with tumor-free margins achieved by local resection, suggesting potential cure. Determining whether or not tumor invasion is limited to mucosa before resection is very important, because patients with tumor invasion limited to the sphincter of Oddi may have nodal involvement. There have been some reports that patients with tumor invasion limited to the sphincter of Oddi did have nodal involvement [5, 9, 28, 29]. However, with regard to the extent of tumor invasion of the duodenum, it is impossible to completely discriminate between mucosa and the sphincter of Oddi even using EUS and IDUS preoperatively [20, 23, 25]. We need to elucidate the characteristics of the subset of patients with tumor invasion

Table 12 Characteristics and outcome of 11 patients who satisfied the 5 factors indicating suitability for limited resection of ampullary tumors

Patient no.	Surgery	Final histological type	Lympho-vascular/perineural invasion	Pathological Du	Lymph node metastases	Outcome (follow-up period, months)
1	TDP	wel	Negative	m	None	Alive (161)
2	TDP	wel	Negative	m	None	Alive (40)
3	CRBA	wel	Negative	m	None	Alive (18)
4	EP	wel	Negative	od	NA	Alive (49)
5	EP	Low-grade	Negative	m	NA	Alive (19)
6	EP	Low-grade	Negative	m	NA	Alive (14)
7	EP	High-grade	Negative	m	NA	Alive (51)
8	TDP	High-grade	Negative	m	Nonee	Alive (84)
9	EP	High-grade	Negative	m	NA	Alive (82)
10	EP	Low-grade	Negative	m	NA	Alive (113)
11	EP	Low-grade	Negative	m	NA	Alive (101)

Du duodenum, *TDP* transduodenal papillectomy, *CRBA* complete resection of the extrahepatic portion of the common bile duct and the ampulla of Vater, *EP* endoscopic papillectomy, *wel* well-differentiated adenocarcinoma, *Low-grade* adenoma with low-grade dysplasia, *High-grade* adenoma with high-grade dysplasia, *m* invasion limited to the duodenal mucosa, *od* invasion limited to the sphincter of Oddi, *NA* not available

limited to the sphincter of Oddi who do not have nodal involvement. Furthermore, since we could not preoperatively diagnose lympho-vascular invasion and perineural invasion of ampullary tumors, which were significant risk factors for lymph node metastases, we tried to narrow down the characteristics of Du0 ampullary tumors without nodal involvement using preoperative findings from the endoscopy, endoscopic biopsy, and combined findings from examinations such as EUS, IDUS, and ERCP. The most important concept is that local resection could be accomplished after the resected specimens were confirmed pathologically to be not moderately/poorly differentiated adenocarcinoma and to show negative invasion of the lympho-vasculature, perineural, duodenum, and pancreas as well as to have negative surgical margins. In our series, 11 patients who met our limited resection criteria were identified. All patients actually underwent limited resection of the tumor in our institution, and 4 of these patients had well-differentiated adenocarcinoma. During a median (range) follow-up of 49 (14–161) months, none of the 11 patients experienced disease recurrence (5-year overall and disease-free survival, 100%). However, the duration of follow-up was not sufficient, because only five of the 11 patients were followed for more than 5 years. In addition, although our data satisfy the assumptions stated above, this study is a retrospective analysis, and the number of patients was small.

The diagnostic accuracy of EUS and T1 staging for ampulla of Vater carcinoma is reported to be 60–90 and 80–100%, respectively [19–25]. In particular, whether EUS can correctly assess the depth of invasion within or beyond the sphincter of Oddi is still controversial [20, 23, 25]. Our study also showed that it was impossible to identify 100% of duodenal invasion by preoperative EUS (our diagnostic

accuracy rate was 82%). Therefore, we referred to other tumor findings, such as endoscopic findings and the pathology of the endoscopic biopsy to predict no lymph node metastases.

Likewise, a single IDUS examination for tumor infiltration into the pancreatic duct was limited in diagnostic accuracy [20, 23]. Therefore, we needed to make a more precise diagnosis by combining several examinations. Our data indicated that the combination of IDUS with ERCP could make up for the diagnostic drawbacks of each for tumor infiltration into the pancreatic duct. Since this study was a retrospective study, we analyzed all patients with ampullary tumor from 1986 to 2010. EUS and IDUS were not performed during the early part of this period. However, 37 (72.5%) of 51 patients who were treated in our institution after January 2000 received comprehensive preoperative examinations that consisted of EUS, IDUS, and ERCP. Furthermore, 19 of 23 patients (82.6%) who underwent limited resection received comprehensive preoperative examinations. Therefore, we believe that these proposed clinical criteria may be realistic. The major reason for failure of comprehensive examinations was the inability to insert a catheter into the main pancreatic duct during ERCP. Determining the diameter of the pancreatic duct using magnetic resonance cholangiopancreatography may be an appropriate avenue for future investigation.

Two critical factors must be considered: the curability of the disease by limited resection and its technical feasibility. Regarding curability, the operative mortality rate of Whipple resection or PPPD is reported to be 1–5% in high-volume centers, and the overall 5-year survival rates for pT1 tumors ranged from 70 to 90% in recent studies [3, 5, 6, 9]. Limited resection would be an acceptable alternative for early ampulla of Vater carcinoma if the risk of lymph

node recurrence is estimated to be less than 1%. Meanwhile, there is currently no definition for “limited resection”. Advocated procedures include EP, TDP, segmental resection of the duodenum, resection of the head of the pancreas with segmental duodenectomy, pancreas-preserving biliary amputation with pancreatic diversion, and CRBA, and their indications have yet to be defined, which leaves the door open for “tailored” limited resection according to tumor size and location within the papilla of Vater and possibly the inferior bile duct [12, 13, 15, 26, 27]. Our surgical strategy for ampullary tumors is as follows: EP is indicated for patients who fulfill the 5 requirements described above and have a tumor diameter 2 cm or less (that is, the diameter of a snare) without involvement of the bile duct; TDP is indicated for patients who fulfill the 5 requirements with tumor diameter more than 2 cm or with small tumor infiltration of the bile duct; CRBA is indicated for patients who fulfill the 5 requirements with the tumor extending into the bile duct to a high degree; and PPPD is indicated for patients who have a tumor infiltrating into the pancreatic duct despite adenoma or adenocarcinoma. Naturally, after limited resection, precise pathological examination and close follow-up are inevitable. Obviously, the worst scenario is that those cases that should have been subjected to radical surgery undergo inappropriate follow-up after limited resection, directly affecting long-term survival. Taking the viewpoints of both curability and technical feasibility together, limited resection must allow thorough histopathological evaluation.

This study has certain limitations: the number of cases was small, the length of follow-up period was not satisfactory, and the analysis was retrospective. Accordingly, we should not rush to conclusions. More histopathological data is needed from patients, especially from those with tumor invasion limited to the sphincter of Oddi, before a multicenter, randomized trial that assigns patients to a limited resection arm and a PPPD arm is planned.

In conclusion, ampulla of Vater carcinomas meeting the following criteria may benefit from limited resection for potential cure: (1) an exposed protruding macroscopic type, (2) adenoma or papillary/well-differentiated adenocarcinoma detected by endoscopic biopsy preoperatively, (3) negative duodenal invasion with EUS, (4) no tumor infiltration into the pancreatic duct with IDUS, (5) a pancreatic duct diameter of 3 mm or less at ERCP. Furthermore, confirmation of no moderately/poorly differentiated adenocarcinoma and negative invasion of the lympho-vasculature, perineural, duodenum, and pancreas, as well as negative surgical margins by precise histopathological examination of resected specimens is very important to accomplish the limited procedure. Further improvements in diagnostic accuracy and accumulation of cases for justification of our proposed indications are warranted.

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Conflict of interest None.

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