Clinical and histopathological characteristics of patients with duodenal papillary tumors treated at Kitasato University East Hospital

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Objectives and Background

Endoscopic mucosal resection is now widely used as a minimally invasive curative treatment for early cancer of the esophagus, stomach, and colorectum. Its indication range is now being broadened. In patients with duodenal papillary tumors, however, pancreaticoduodenectomy is generally considered necessary for cure even when the diagnosis is adenoma. Whether this highly invasive procedure is needed has been questioned. Recently, less invasive techniques, such as endoscopic resection, have been used to manage duodenal papillary tumors¹⁻⁴, but the indications remain a matter of debate. To curatively treat duodenal papillary tumors by endoscopic papillectomy in patients without lymph-node metastasis or distant metastasis, the conditions required for successful outcomes should be defined, similar to the indications for tumors arising in other organs. To collect data that could serve as a basis for defining the indications for endoscopic papillectomy, we studied the natural history and clinical and histopathological features of duodenal papillary tumors. We also studied differences in clinical characteristics between patients whose tumors were associated with familial polyposis and those who had sporadic lesions.

Subjects and Methods

The study group comprised 110 patients (67 men and 43 women) with duodenal papillary tumors treated between October 1986 and September 2009 (mean follow-up, 7.8 years). Their mean age was 62.4 years (**Table 1**). Tumors were associated with familial polyposis in 11 patients (2 carcinoma and 9 adenomas). The other 99 patients had sporadic (solitary) lesions (86 carcinomas and 13 adenomas). There was a significantly higher prevalence of carcinoma ($p < 0.01$) (**Table 2**). Before 2001 when we started papillectomy, we had followed up papillary adenoma once or twice a year with patient's consensus in principle, then totally sixteen patients with adenomas were followed up for at least 6 months (mean follow-

up, 7.8 years) and underwent endoscopic examination with biopsy 2 or more times. In these patients, we studied the time course of the diagnosis on biopsy. Histopathological findings were recorded according to the Japanese General Rules of Cancer of the Biliary Tract (Second Edition).⁵

As for treatment, tumor resection was performed in 89 patients (80.9%) and not performed in 13 (11.8%). 8 patients (7.3%) were followed up and received no treatment because of operation risk and rejection. Statistical analysis statistical evaluation was performed by using the χ^2 test or the Mann-Whitney's U test. Data expressed as $\pm$ SE of the mean, A p value of less than 5% was considered statistically significant.

Results

Follow-up observations

A total of 16 patients with adenomas (10 with familial polyposis and 6 with sporadic tumors) were followed up for at least 6 months. During follow-up, the adenomas became carcinomas in 1 patient with familial polyposis and 3 patients with sporadic tumors. This difference was not significant. Mean follow-up tended to be longer in the patients with familial polyposis (3945 days) than in those with sporadic lesions (978 days). After follow-up, tumors were resected surgically (4 patients) or endoscopically (5 patients) in 9 patients (**Table 2**).

We examined changes in the histopathological diagnosis of biopsy specimens obtained from 13 patients who underwent endoscopy with biopsy at least 2 times during follow-up and remaining 3 patients had only one time biopsy. Overall, adenomas showed a trend toward a gradual transition in the grade of atypia from mild to moderate and severe, culminating in the development of carcinoma during long-term follow-up. Tumors were subsequently resected in 9 patients. One of these patients died of other diseases, and the other 3 continue to be followed up (**Fig. 1**).

Preoperative diagnosis on biopsy

We compared the preoperative diagnosis on biopsy with the postoperative histopathological diagnosis in 89 patients whose tumors were resected surgically or endoscopically. Of the 69 patients with a preoperative diagnosis of carcinoma, 71 had a postoperative histopathological diagnosis of carcinoma, and the

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Table 1. Demographic characteristics and histopathological diagnoses of 110 patients with duodenal papillary tumors treated at Our Hospital between October 1986 and September 2009

Characteristics			
Sex (male/female)	67/43		
Mean age $\pm$ SD (yr)	62.0 $\pm$ 12.5		
Familial polyposis	11		
Sporadic lesions	99		
	Familial Polyposis	Sporadic Lesions	p value
	n=11 (%)	n=99 (%)	
Carcinoma	2 (18.2)	86 (86.9)	
Adenoma	9 (81.8)	13 (13.1)	p<0.01

Table 2. Follow-up observations of 16 patients who had adenoma associated with familial polyposis or sporadic lesions

	Familial Polyposis	Sporadic Lesions	p value
No. of patients	10	6	
No. of patients whose adenomas became carcinomas (%)	1 (10.0%)	3 (50.0%)	p=0.074
Mean follow-up period (days)	3945	798	p=0.0067
Range	1949-7976	188-5714	

Table 3. Comparison of preoperative diagnosis on biopsy and postoperative histopathological diagnosis in 81 patients whose tumors were resected surgically or endoscopically

Figure 1. Histological changes of papillary tumors (followed up cases)

other had carcinoma in adenoma. Of the 20 patients with a preoperative diagnosis of adenoma (all with severe atypia), 5 had a different postoperative histopathological diagnosis: carcinoma was diagnosed in 3 patients, and carcinoma in adenoma was diagnosed in 2 (Table 3).

Characteristics of resected specimens

Of the 74 patients whose tumors were surgically resected in our hospital, we studied the characteristics of resected specimens from 15 patients with carcinomas that invaded the mucosa or sphincter

Table 4. Clinical characteristics of 15 patients with pathological pT1 tumors that invaded the mucosa or sphincter of oddi

No.	Depth of Tumor Invasion	ly	v	Involvement of bile duct	Involvement of pancreatic duct	Tumor Location	Panc	Du	N	EM	Survival time (months)	Tumor size (mm)	Macroscopic appearance	Outcomes
1	m	0	0	No	No	Ab	0	0	0	0	141	15		Death from other disease
2	m	0	0	No	No	Ac	0	0	0	0	117	19	Exposed mass type	Alive
3	m	0	0	No	No	Ac	0	0	0	0	203	21	Exposed mass type	Alive
4	m	0	0	No	No	Ab	0	0	0	0	82	22		Alive
5	m	0	0	No	Yes	Ad	0	0	0	0	15	45		Alive
6	od	0	0	Yes	Yes	Abcd	0	0	0	0	118	39		Alive
7	od	0	0	No	No	Ad	0	0	0	0	82	30	Exposed mass type	Alive
8	od	0	0	No	No	Ac	0	0	0	0	51	14	Exposed mass type	Alive
9	od	0	0	No	No	Ad	0	0	0	0	56	20		Alive
10	od	0	0	Yes	No	Ab	0	0	0	0	249	20	Exposed mass type	Alive
11	od	0	0	Yes	No	Ac	0	0	0	0	57	30	Exposed mass type	Alive
12	od	0	1	No	No	Ac	0	0	0	0	47	12	Exposed mass type	Death from lung metastasis
13	od	0	0	No	Yes	Ac	0	0	0	1	45	10	Non-exposed mass type	Death from liver metastasis
14	od	2	1	No	No	Ac	0	0	0	0	55	15	Non-exposed mass type	Death from liver metastasis
15	od	1	0	Yes	No	Abc	0	0	0	0	27	11	Exposed mass type	Death from liver metastasis

m, Invasion limited to mucosa; od, Invasion limited to Oddi's sphincter; ly, lymphatic invasion; v, venous invasion; Ab, bile duct of ampulla of Vater; Ac, common duct and bile duct of Ampulla of Vater; Ad, common duct and duodenum of Ampulla of Vater; Abcd, bile duct, common duct and duodenum of Ampulla of Vater; Ac, common duct and duodenum of Ampulla of Vater; Abc, bile duct and common duct of Ampulla of Vater; Panc, Pancreas; Du, Duodenum; N, Lymph Node Metastasis; EM, cancer-free-margin from the tumor edge.

of Oddi. 5 patients had pathological T1 tumors that invaded the mucosa; none of them had lymphovascular invasion or involvement of the bile duct or pancreatic duct except for one patient had involvement of the pancreatic duct. One patient died of another disease, and the other 4 are alive at the time of this writing. Ten patients had pathological T1 tumors that invaded the sphincter of Oddi. Seven of these patients had lymphovascular invasion with involvement of the bile duct or pancreatic duct. Four patients died of their tumors: all had lymphovascular invasion with involvement of the bile duct or pancreatic duct, and all 3 had liver metastasis and one had lung metastasis and carcinomatous peritonitis (Table 4).

Discussion

Endoscopic mucosal resection and endoscopic submucosal dissection are now widely used for the curative treatment of early carcinomas of the esophagus, stomach, and colorectum. The indications for these minimally invasive procedures have been established for carcinomas arising in these organs. The feasibility of broader indications is now being studied.⁶⁻⁸

The clinical and histopathological characteristics of duodenal papillary tumors were previously studied by Yoon et al. In their series, 23 patients underwent papillectomy, and 60 underwent surgical resection. Patients who had adenomas with high-grade intraepithelial neoplasia/tumor in situ (category 4 of the Vienna classification⁹) had no lymphovascular invasion, whereas 10.7% of patients with focal T1 cancer in ampullary adenomas had lymphovascular invasion or lymph-node metastasis.¹⁰ Lee et al. studied 159 patients with duodenal papillary tumors that were resected surgically. Lymphovascular invasion was not found in any of the 6 patients with tumors in situ, but was present in 17 (56.7%) of 30 patients with T1-stage disease.¹¹

From our results, the indication for papillectomy should be limited to adenoma and maybe T1 carcinoma limited to the mucosa, not to T1 carcinoma invaded to the sphincter of oddi. The adenoma-carcinoma sequence may play an important role in carcinogenesis in patients with duodenal papillary tumors.¹² Our study showed a trend toward progressively higher grades of atypia on long-term follow-up of adenomas in 13 patients who underwent endoscopic biopsy at least 2 times. Carcinomas developed in 4 of these patients. These findings indicate that even adenomas should be resected.

Forceps biopsy can sample only very small amounts of tissue. Its reliability for the histopathologic diagnosis of duodenal papillary tumors has therefore been criticized.^{13,14} In our series, there was lack of agreement between the preoperative and postoperative histopathological diagnosis in 5 of the 89 patients whose tumors were resected surgically or endoscopically. Our results thus showed that duodenal papillary tumors can be associated with the adenoma-carcinoma sequence, as well as false negative results on biopsy. Duodenal papillary tumors should therefore be

completely resected, and the entire tumor should be evaluated histopathologically. Most adenomas can be curatively treated by endoscopic papillectomy and T1 carcinoma limited to the mucosa may also be cured.

Pancreaticoduodenectomy has been used as standard treatment even in patients with duodenal adenomas, but this procedure carries one of the highest risks among all gastrointestinal operations.¹⁵ Endoscopic papillectomy is minimally invasive and reduces psychological and physical stress on patients, even though it has complications such as pancreatitis, bleeding, and perforation etc, which can mostly be treated without surgery. This procedure may thus be useful for the treatment of duodenal papillary tumors in the future. Endoscopic mucosal resection can also be recommended for elderly patients and those in whom pancreaticoduodenectomy is contraindicated because of complications such as heart disease etc.

An important limitation of our study was the small sample size. Larger groups of patients should be studied in the future to better define the clinical and histopathological characteristics of duodenal papillary tumors and establish indications for endoscopic papillectomy.

Conclusions

Our experience with this series of patients who underwent surgical or endoscopic resection of duodenal papillary tumors suggests that endoscopic papillectomy can be indicated for the management of papillary adenomas and maybe pathological T1 carcinomas invading the mucosa. Because this was a small study performed at a single hospital further studies are needed to better understand the clinical implications of the adenoma-carcinoma sequence and

the risks of false-negative results on biopsy.

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