Surgical Strategy for T1 Duodenal or Ampullary Carcinoma According to the Depth of Tumor Invasion

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Abstract. *Aim: To investigate the utility of local resection (LR) for T1 duodenal carcinoma and T1 ampullary carcinoma. Patients and Methods: Between June 2002 and November 2014, a total of 64 patients with pathological T1 (pT1) ampullary carcinoma (25 patients) and pT1 duodenal carcinoma (39 patients) were treated. Of these, 33 patients underwent local resection (LR group), while the other 31 patients underwent pancreatoduodenectomy (PD group). Results: The LR group had 31 patients with pT1a and 2 patients with pT1b. PD group had 18 patients with pT1a and 13 patients with pT1b. One patient with pT1b duodenal carcinoma (20.0%) and one patient with pT1b ampullary carcinoma (10.0%) developed lymph node metastasis, while none of the patients with pT1a disease developed metastases. Conclusion: LR may be considered in the patients preoperatively diagnosed with T1a duodenal carcinoma and T1a ampullary carcinoma.*

Tumors of the duodenum or the ampulla of Vater represent a small portion of gastrointestinal tumors, accounting for less than 1% of all gastrointestinal malignancies (1-4). Complete resection is the only potential curative procedure for duodenal or ampullary carcinoma, and various techniques have been proposed for its management ranging from local resection (LR) to pancreatoduodenectomy (PD) (5-8). The method of resection typically depends on the depth of tumor invasion for the treatment of various gastrointestinal tract cancers (9, 10). In the field of duodenal and ampullary carcinomas, PD is standard treatment for advanced invasive

malignancies (5, 6). Recently, LR has been introduced as an alternative, less-invasive procedure for the treatment of early-stage duodenal and ampullary carcinomas in select patients, because PD carries a high risk of morbidity and mortality (11-13). However, its indication for the treatment for early-stage carcinoma remains unclear because duodenal or ampullary carcinoma is an uncommon disease, and the rate of lymph node metastasis, which usually depends on the depth of tumor invasion, also remains unclear. Furthermore, it is difficult to preoperatively assess the accurate depth of invasion in patients with ampullary carcinoma, in particularly whether the sphincter of Oddi is involved (14).

The aim of the present study was to review a cohort of patients with early-stage duodenal and ampullary carcinomas and identify the clinicopathological factors that indicate a possible benefit in LR by comparing the results to those of patients who underwent PD for early-stage duodenal and ampullary carcinomas.

Patients and Methods

Study population. Between June 2002 and November 2014, 76 patients with ampullary carcinoma and 70 patients with duodenal carcinoma underwent macroscopic curative resection at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center. Of these patients, 25 patients had pathological T1 (pT1) ampullary carcinoma and 39 patients had pT1 duodenal carcinoma according to the TNM classification (7th edition) of the American Joint Committee on Cancer (AJCC) (12). Overall, 64 patients with pT1 ampullary and duodenal carcinomas were enrolled in this study. Of these, 31 patients underwent PD (PD group) and 33 patients underwent LR (LR group); 4 patients underwent pancreas-sparing duodenectomy, 1 patient underwent segmental resection of the duodenum, 24 patients underwent partial resection of the duodenum, and 4 patients underwent ampullectomy. Patients with benign lesions, gastrointestinal stromal tumors or neuroendocrine tumors were excluded from this study.

Imaging diagnostic modality. Among 64 patients examined, all patients underwent computed tomography (CT) and esophagogastro-duodenoscopy for diagnostic purposes. Thirty-nine patients

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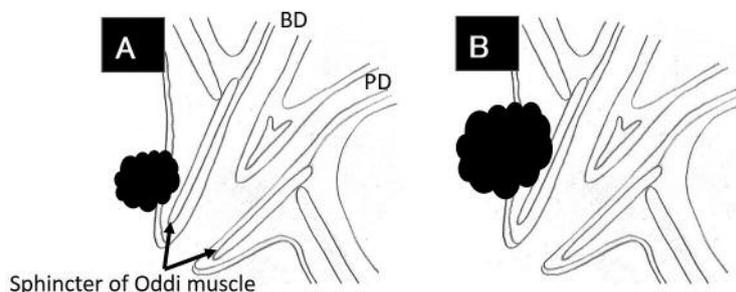*Key Words:* Local resection, duodenal carcinoma, ampullary carcinoma.

Figure 1. *The T1a and T1b defined the patients with ampullary carcinoma as bellow, according to the Japanese classification for biliary tract cancers. A) T1a: invasion to only the mucosa. B) T1b: invasion to the sphincter of Oddi. BD, Bile duct; PD, pancreatic duct.*

underwent preoperative endoscopic ultrasonography (EUS) and 11 patients underwent intraductal ultrasonography (IDUS) in order to diagnose the depth of tumor invasion.

Surgical strategy and surgical procedures for ampullary and duodenal carcinomas. In our institution, PD with regional lymph node dissection was routinely performed for advanced ampullary and duodenal carcinomas. For the patients with clinical T1a duodenal carcinoma, LR was planned. For the patients with clinical T1b duodenal carcinoma, PD with regional lymph node dissection was indicated. In the patients with clinical T1 ampullary carcinoma, PD was initially planned. For the patients with T1 ampullary carcinoma, the following conditions were considered to be candidates for LR: 1) the tumor was located only in the mucosa, 2) there was no apparent lymph node metastasis or distant metastasis, and 3) the tumor was small enough to be completely resected using LR. In the patients with ampullary carcinomas who underwent ampullectomy, frozen sections of the cut end of the specimen were examined. We performed PD when the examination of a frozen section revealed tumor involvement at the resection margin.

Clinicopathological findings. We reviewed the following clinicopathological findings of the patients: demographic parameters (gender and age), preoperative carcinoembryonic antigen (CEA) level and carbohydrate antigen 19-9 (CA19-9) level, pathological factors (tumor size, depth of tumor, histologic grade and lymph node metastasis), perioperative factors (operation time, blood loss, postoperative length of days, postoperative complication), and long-term outcomes (recurrence and survival).

In principle, the T classifications of duodenal and ampullary carcinoma (T1-T4) were defined with reference to the TNM classification (7th edition) of the American Joint Committee on Cancer (AJCC) (15). In addition, for the finer division of T1 ampullary carcinoma, we also referred to the Japanese classification for biliary tract cancers (16), and divided the T1 lesions of ampullary carcinoma into T1a and T1b as follows: T1a, invasion to only the mucosa in both ampullary and duodenal carcinoma; T1b, invasion to the submucosa in patients with duodenal carcinoma or invasion to the sphincter of Oddi in patients with ampullary carcinoma (Figure 1A and B).

Postsurgical management. Complications were classified according to the grading system of Dindo *et al*. (17), and grade III or further

complications were considered to be significant. None of the patients received adjuvant chemotherapy, radiotherapy, or chemoradiotherapy. All patients were examined in the outpatient clinic where abdominal ultrasound, CT, and the measurement of the CEA and CA19-9 levels was performed every 3-6 months after surgery.

Statistical analysis of the surgical outcomes and clinicopathological factors. The clinicopathological factors of the patients treated using LR were compared with those treated using PD.

Pearson's Chi-square test and Fisher's exact test were used to assess nominal variables, and continuous data were compared using the Mann-Whitney *U*-test. All statistical analyses were performed using the Software Package for Social Sciences, version 11.5J for Windows 1 software program (SPSS, Chicago, IL, USA). A *p*-value of <0.05 was considered significant. We performed Yates' correction for calculating the *p*-value using a two-by-two contingency table.

Results

The LR group (n=33) included 31 patients with pT1a lesions (4 ampullary and 27 duodenal carcinoma) and 2 patients with pT1b duodenal cancer. The PD group (n=31) included 18 patients with pT1a lesions (11 ampullary and 7 duodenal carcinoma) and 13 patients with pT1b lesions (10 ampullary and 3 duodenal carcinoma). One patient with pT1b duodenal carcinoma (20.0%) and one patient with pT1b ampullary carcinoma (10%) developed lymph node metastasis (Table I). On the other hand, none of the patients with pT1a developed lymph node metastasis.

Five patients with pT1 ampullary carcinoma were scheduled to undergo LR. Of these patients, two were found to have positive margins according to the findings from frozen section samples. One of the patients converted to PD, while the other could not convert to PD due to old age. Four patients with pT1 ampullary carcinoma were treated by LR alone (Table II). Three patients with pT1a duodenal carcinoma (7.7%) and one patient with pT1a ampullary carcinoma (4%) had previous histories of familial adenomatous polyposis.

Table I. *Clinical characteristics of the patients pathologically diagnosed to have lymph node metastasis.*

Case	Gender/ Age	Disease/ Procedure	No. of Lymph nodes metastasis/dissected	Size (mm)	Depth of invasion	Pathological diagnosis	DFS (month)	OS (month)
1	Male/57	DC/PD	1/28	55	pT1b	Well dif. adenoca.	62	62
2	Female/51	AC/PD	2/36	15	pT1b	Mod. dif. adenoca.	4*	11

DC, Duodenal carcinoma; AC, ampullary carcinoma; PD, pancreatoduodenectomy; Well dif. adenoca., Well differentiated adenocarcinoma; Mod. dif. adenoca., moderately differentiated adenocarcinoma; DFS, disease free survival; OS, overall survival. *Recurrence was occurred in intraabdominal lymph nodes and liver 4 months after operation.

Table II. *Our cases intend to perform local resection for ampullary carcinoma.*

Case	Gender/ Age	Procedure	Operation time (min)/ Blood loss (g)	Tumor size (mm)/ Depth of invasion	Result of frozen section/ Curability	Lymph node dissection	Pathological diagnosis	Observation period (month)
1	Female/59	Ampullectomy	157/103	30/T1a	-/R0	-	Well dif. adenoca.	67
2	Male/55	Ampullectomy→PD	380/885	7/T1a	Positive/R0	present	Well dif. adenoca.	53
3	Male/60	Ampullectomy*	371/1333	20/T1a	Negative/R0	sampling	Well dif. adenoca.	46
4	Male/87	Ampullectomy	175/53	13/T1a	Negative/R0	-	Well dif. adenoca.	15
5	Male/85	Ampullectomy	131/70	9/T1a	Positive/R1	-	Well dif. adenoca.	1

PD, Pancreatoduodenectomy; Well dif. adenoca., Well differentiated adenocarcinoma. *Pancreas-sparing duodenectomy was performed concurrently. All cases have no recurrence during the observation period.

Thirty-nine patients, consisting of 25 patients (64.1%) with duodenal carcinoma and 14 patients (56%) with ampullary carcinoma, underwent preoperative EUS; 11 patients (44%) with ampullary carcinoma underwent IDUS. The preoperative diagnostic sensitivity, specificity, and accuracy of EUS for pT1a duodenal carcinoma were 66.6%, 100%, and 72% respectively, while those for pT1b duodenal carcinoma were 75%, 71.4%, and 72%, respectively. None of 4 patients with pT1b duodenal carcinoma was preoperatively underestimated as clinical T1a disease. On the other hand, the preoperative diagnostic sensitivity, specificity, and accuracy of EUS and/or IDUS for pT1a ampullary carcinoma were 33.3%, 100%, and 57.8%, respectively, and those for pT1b ampullary carcinoma were 28.5%, 66.6%, 52.6%, respectively. None of 7 patients with pT1b ampullary carcinoma was preoperatively underestimated as clinical T1a disease.

Comparison of the clinicopathological factors and the survival between the patients treated with LR and PD. The preoperative CEA in the PD group was significantly higher than that in the LR group (p=0.026) (Table III). In the LR group, 4 patients (12.1%) had a tumor located at the ampulla of Vater, and 27 patients (81.8%) had a tumor located in the 2nd portion of the duodenum (other than ampullary lesions). In contrast, in the PD group 21 patients (67.7%) had a tumor located at the ampulla of Vater, while 6 (19.3%) had a tumor located in the 2nd portion of the duodenum. Tumor size was comparable between both groups. (p=0.861). With regard to surgical results, the operation time (p<0.001) and the amount of blood loss (p<0.001) in the PD group were significantly greater than those in the LR group. Regarding the short-term outcomes, the overall morbidity (p<0.001) and frequency of pancreatic fistula (p<0.001) in the PD group were significantly higher than those in the LR group. The length of hospital stay in the PD group was significantly longer than that in the LR group (p<0.001).

There was no in-hospital mortality observed in both groups. In the PD group, one patient with pathological T1bN1 ampullary carcinoma developed recurrence through intra-abdominal lymph node metastasis and liver metastasis 4 months after surgery and died 11 months after surgery. However, in the LR group, none of the patients showed recurrence during the observation period.

Discussion

The present study analyzed the surgical results of LR and PD for early-stage duodenal and ampullary carcinomas. In this

Table III. *The results of the univariate analyses between clinicopathological factors of LR and PD.*

	LR (n=33)	PD (n=31)	*p*-Value
Gender ; Male/Female	21/12	21/10	0.796
Age (years) (median)	63 (21-87)	68 (48-83)	0.160
CEA (ng/ml) (median)	1.6 (0.5-7.1)	2.7 (0.7-10.4)	0.026↑
CA19-9 (U/ml) (median)	4.5 (2-33)	7.0 (1.9-383)	0.405
Pathological result			0.003↑
pT1aN0	31 (93.9%)	18 (58.0%)	
pT1aN1	0	0	
pT1bN0	2 (6.0%)	11 (35.4%)	
pT1bN1	0	2 (6.4%)	
Location of tumor			<0.001↑
Ampulla of Vater	4 (12.1%)	21 (67.7%)	
1st portion of duodenum	1 (3.0%)	3 (9.6%)	
2nd portion of duodenum	27 (81.8%)	6 (19.3%)	
3rd portion of duodenum	1 (3.0%)	1 (3.2%)	
4th portion of duodenum	0	0	-
Tumor size (mm)	25.4±20.6	23.7±16.6	0.861
Operation time (min)	185±121	412±124	<0.001↑
Blood loss (g)	166±255	957±923	<0.001↑
Postoperative length of stay (day)	13.8±8.0	36.4±22.3	<0.001↑
Lymphatic invasion or venous invasion			0.561
Negative	32	28	
Positive	1	3	
Histological grade			0.055
Well differentiated adenocarcinoma	33	26	
Moderately differentiated adenocarcinoma	0	2	
Papillary adenocarcinoma	0	3	
R0 resection	32 (96.9%)	31 (100%)	>0.999-
Mortality	0	0	-
Incident rate of postoperative complication# (%)	6 (18.1%)	25 (80.6%)	<0.001↑
Pancreatic fistula	1	23	<0.001↑
Bile leakage	0	1	>0.999
Delayed gastric emptying	1	3	0.561
Intraabdominal abscess	1	2	0.561
Others*	3	3	0.727

LR, Local resection including below; 7 ampullectomy, 1 segmental resection, 20 partial resection, 5 pancreas-sparing duodenectomy; PD, pancreatoduodenectomy. #Complications that were regarded as grade 3a or more in the classification of Clavian-Dindo. ↑Statistically significant. *Other complications include below; 1 pancreatitis, 2 intra-abdominal hemorrhage caused by pseudo aneurism, 2 anastomosis leakage, 1 acute myocardial infarction.

study, the rate of postoperative complications in the PD group was significantly higher than that in the LR group. However, there was no in-hospital mortality observed in both groups in this study. Postoperative pancreatic fistula remains a leading cause of morbidity, and the morbidity rate after PD remains high (30-50%) (18-20). In particular, patients with non-pancreatic cancer diseases, such as duodenal or ampullary cancer are reported to have a narrower main pancreatic duct, thicker pancreatic body, and non-fibrotic pancreas; thus, these patients are at greater risks of developing pancreatic fistula (18). However, recent improvements in surgical techniques and perioperative management have reduced surgical mortality and morbidity after PD especially in high-volume centers (18).

Furthermore, other groups have even recommended PD for cases of early duodenal or ampullary cancer in order to avoid tumor recurrence after complete lymphadenectomy (6, 21). Only if a patient has an extremely low probability of lymph node metastases, LR may be an alternative surgical method with lower morbidity and mortality rates.

In the present study, none of the patients with pathological T1a duodenal and ampullary carcinomas developed lymph node metastases, however, one patient with pT1b duodenal carcinoma (20.0%) and one patient with pT1b ampullary carcinoma (10%) developed lymph node metastasis. The consensus of the best operation method for duodenal or ampullary carcinoma has not yet been established, especially in the early stage of the diseases, however, our data suggest

Table IV. *Recent reports associated with local resection for ampullary adenocarcinoma.*

Author	Year	No. of cases	Characteristics of the patients	Procedure	Positive margin (frozen section)	LN dissection	Recurrence rate %	3/5-year OS %
Demetriades (24)	2006	12	pT1, <2 cm, N0[†]	Ampullectomy	0/12 (0.0%)	+	25	75/33.3
Chen (25)	2011	25	pTis or pT1, N0 or N1, M0	PSD	6/31 (19.3%)[#]	+	20	72/–
Feng (11)	2012	25	<2 cm	Ampullectomy	6/25 (24.0%)	+	48	–/48
Zhong (23)	2013	17	*	Ampullectomy	–	–	63	35/21
Zhao (26)	2014	34	12 of pT1, 17 of pT2, 5 of pT3, 0.8~3.5 cm (median 2.0 cm)	Transduodenal or extraduodenal LR	3/34 (8.8%)	5/34	41	69.5/53.7

LN, Lymph node; OS, overall survival; PSD, pancreas-sparing duodenectomy; LR, local resection. [†]Well or moderately differentiated tumors. [#]All 25 patents who underwent PSD were negative. Another 6 patients were found to have positive margins and converted to pancreatoduodenectomy. *LR was performed because of patient's medical comorbidity or patient preference. Including two patients with pT3 lesion.

PD with lymph node dissection may be considered as the standard procedures for T1b duodenal and ampullary carcinomas to achieve curative resection.

As for early-stage duodenal carcinoma, Kato *et al*. suggested that LR could be considered for the patients with pT1a lesions because the patients with pT1a duodenal carcinoma did not develop lymph node metastasis (22). In the present study, none of the 34 patients with pT1a duodenal carcinoma developed lymph node metastasis, whereas 1 of the 5 patients with pT1b duodenal carcinoma developed lymph node metastasis (20%). Moreover, the preoperative diagnostic specificity for pT1a duodenal cancer was 100%. Therefore, our result suggests that LR may be considered only for the patients with duodenal carcinoma preoperatively diagnosed as clinical T1a.

On the other hand, it remains controversial as to whether or not LR is an acceptable treatment for T1 lesions of early stage of ampullary carcinoma. In recent studies, several groups reported the indications of LR for ampullary carcinoma (11, 23-26) (Table IV). You *et al*. reported that none of the ampullary carcinoma patients with tumors limited to within the sphincter of Oddi developed lymph node metastasis, while 4 of 25 patients with tumors beyond the sphincter of Oddi or into the duodenal submucosa developed lymph node metastasis (27). In the present study, all the patients with pT1a ampullary carcinoma did not develop lymph node metastasis or show recurrence. On the other hand, one patient with pT1b ampullary carcinoma (10%) developed lymph node metastasis. Thus, it is plausible that LR could be considered for pT1a ampullary carcinoma if a negative surgical margin is confirmed and if the depth can be correctly diagnosed before surgery. However, the number of patients who met these criteria was insufficient to draw any definitive conclusions.

In our study, one patient with pT1a ampullary carcinoma intending to undergo ampullectomy was converted to PD due to positive results of a frozen section examination of resection margin. Some groups have suggested that frozen section examinations of resection margin are helpful for obtaining free resection margins for the patients with ampullary cancer who underwent LR (24, 28, 29). To confirm the curability, a careful intraoperative frozen section examination may be necessary to achieve curative resection in patients who undergo LR.

Another important issue is how to accurately assess the depth of tumor invasion preoperatively. For the patients with T1 duodenal carcinoma, preoperative EUS is useful to estimate submucosal invasion (30, 31). On the other hand, it is difficult to accurately assess preoperatively the depth of invasion in patients with ampullary carcinoma, in particularly whether the sphincter of Oddi is involved or not (14). However, some authors recently mentioned that the performance of both EUS and IDUS examinations allowed for a high accurate diagnosis of pTis ampullary cancer (32). In the present study, preoperative EUS and IDUS showed low sensitivity (33.3%) and high specificity (100%) for T1a ampullary carcinoma. These results suggested that it is difficult to accurately diagnose the depth of invasion especially in patients with ampullary carcinoma, however it is worthy of attention that none of pT1b disease was preoperatively underestimated as clinical T1a disease. Preoperative EUS and IDUS have the tendency to overestimate the depth of tumor invasion to achieve high curability as much as possible. It also suggested that further improvement of the technology for evaluating the tumor invasion to the sphincter of Oddi will increase selection of LR for patients with T1a ampullary cancer.

In patients with ampullary carcinoma, some of the previous studies showed that patients who underwent LR with regional lymphadenectomy did not show preferable outcomes (Table IV). Demetriades *et al*. reported the results of ampullectomy with routine lymph node dissection for 12 patients with pT1, N0, well or moderately differentiated ampullary carcinoma; 3 patients (25%) recurred, and the 5-year overall survival rate was

33.3% (23). In this study, only one of 25 patients (4%) who underwent PD for pT1b, N1 ampullary carcinoma developed recurrence and died 11 months after surgery. Therefore, it is plausible that LR with regional lymphadenectomy cannot be justified in the patients with T1b ampullary cancer, which had a relatively high risk of lymph node metastasis.

In recent reports, the result of endoscopic resection for superficial duodenal carcinoma or endoscopic papillectomy for T1a ampullary carcinoma were introduced (33-35). Endoscopic resection can lead to en-bloc resection, however, a high perforation rate was reported for the treatment of duodenal tumors (36). Regarding endoscopic papillectomy, several complications such as bleeding, pancreatitis, or papillary stenosis have been reported (37).

Anatomically, the sphincter of Oddi muscle has been reported to correspond to the muscularis mucosa of other gastrointestinal organs including duodenum. Thus, invasion to the sphincter of Oddi may indicate a classification that is closer to pT1a than pT1b (27). On the other hand, overall survival in the patients with invasion beyond the sphincter of Oddi has been reported to be closer to that of T2 patients with invasion to the muscle wall of the duodenum proper (27). In this study, one patient with pT1b ampullary carcinoma (10%) developed lymph node metastasis, while none of the patients with pT1a developed lymph node metastasis. Our results suggest that cases involving invasion to the sphincter of Oddi should be considered separate from pT1a.

There were some limitations associated with this study. Ampullary carcinoma has been reported to be located in both the ampulloduodenal part, which is lined by the intestinal mucosa, and in the deeper parts, which are lined by the pancreatobiliary duct mucosa (35-38). Hence, ampullary carcinoma may have two different tumor origins: the intestinal mucosa and the pancreatobiliary mucosa (38-41). Schiergens *et al*. advocated that the tumor biology and clinical course of pancreatobiliary-type ampullary carcinoma resemble those of pancreatic cancer and differ from intestinal-type ampullary carcinoma (42). In the present study, this difference of ampullary carcinoma was not considered and we could not investigate how the difference of tumor origin impact on the clinical outcomes. In addition, the present study was retrospective in nature and was performed in a single-center. Furthermore, the study population, in particular the number of patients with ampullary cancer who underwent LR, was small. Although previous report also suggested that T1a ampullary carcinoma did not developed lymph node metastasis (27), further study is needed to establish the feasibility of LR for T1a ampullary carcinoma.

In conclusion, it is difficult to accurately diagnose the depth of invasion especially in patients with ampullary carcinoma, however none of pT1b duodenal or ampullary carcinoma was preoperatively underestimated as clinical T1a disease. LR may be considered in patients preoperatively diagnosed with T1a duodenal carcinoma and T1a ampullary carcinoma. Intraoperative frozen-section examination will be necessary, especially for patients with ampullary carcinoma to achieve complete resection. For the patients diagnosed with clinical T1b lesions or worse, PD with lymph node dissection should be considered both in patients with duodenal carcinoma and ampullary carcinomas.

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