Asian Journal of Surgery 44 (2021) 723–729

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Transduodenal ampullectomy for ampullary tumor

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ARTICLE INFO

Article history:
Received 21 September 2020
Received in revised form
11 December 2020
Accepted 15 December 2020
Available online 21 January 2021

Keywords:
Ampullary tumor
Ampullectomy
Transduodenal ampullectomy

SUMMARY

Background: Transduodenal ampullectiomy (TDA) is a surgical local excision method that can be performed in patients with ampullary tumors, but it has not been widely used clinically. Recently, TDA is considered as a good alternative surgical technique in patients who are unable to perform the endoscopic ampullectomy (EA) or pancreaticoduodenectomy (PD) for various reasons. The purpose of this study is to evaluate the surgical outcomes of TDA and the clinicopathological significance of pathologic findings in TDA.

Methods: We reviewed the medical records of 31 patients diagnosed as ampullary tumor and underwent TDA from March 2004 to December 2019 in a single center.

Results: All 31 patients were planned to perform TDA, and 4 of them were converted to PPPD due to the marginal status results of frozen biopsy. Of the 31 patients, 19 were diagnosed with malignancy and 12 were diagnosed with benign. Of the 18 patients who were diagnosed as malignancy in final biopsy, only 9 patients (50%) were diagnosed with malignancy on the preoperative endoscopic biopsy. In 15 patients who underwent only TDA for malignancy, there was no recurrence during the follow-up period (mean: 51.1 months, range: 19–137).

Conclusions: In benign ampullary tumor, TDA is a choice of treatment for patients who are unsuitable for endoscopic ampullectomy. TDA may be considered as an alternative operation in highly selective patients with early ampullary cancer (Tis and T1). Further studies on consensus of TDA indication for ampullary tumor will be needed in the future.

1. Introduction

Ampullary tumor has a low incidence, accounting for about 0.5% of gastrointestinal tumors.[1] However, as the health examination and endoscopic approach have become more common, the discovery rate of ampullary tumor is increasing.

For ampullary tumor, excision is generally recommended as a therapeutic principle for the following reasons. First, the ampullary mass is known to follow the adenoma-carcinoma sequence, similar to colorectal cancer.[2,3] Second, there is high probability of false negative results in endoscopic biopsy and the possibility of hidden malignancy cannot be completely ruled out by endoscopic biopsy.[4,5]

There are two main methods for excision of the ampullary tumor. One is local excision, such as endoscopic ampullectomy (EA) and transduodenal ampullectomy (TDA), and the other is radical excision, such as pancreaticoduodenectomy (PD). There are currently no guidelines for selecting these treatment methods. In general, however, for benign ampullary mass, EA is recognized as the primary treatment choice.[6] In addition, when EA is incomplete or impossible, or when malignancy is suspected, PD is accepted as a treatment of choice.[7] Between these two options, the area of TDA without accurate indications and guidelines is very narrow and ambiguous.

TDA has a long history as a first operation in Halsted in 1899.[8] TDA, which has not been noticed in comparison with this long history, has recently been attracting attention as an alternative treatment option that can be applied to the following patients. First, TDA can be performed when EA is inadequate due to the patient's anatomical factors and previous surgical history, among patients suspected of benign ampullary tumor. Second, among patients suspected of malignancy, TDA can be performed if the risk of PD is

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https://doi.org/10.1016/j.asjsur.2020.12.021

remarkably high considering the patient's age and general conditions. In addition, studies have been reported recently that patients with TDA in early ampullary cancer have a similar prognosis as those with PD.[4,9,10] As a result, interest in TDA indications in ampullary tumor has increased.

This study retrospectively analyzed the TDAs performed in a single center and confirmed the safety of the TDA through the perioperative surgical outcomes. In addition, we compare the results of endoscopic biopsy, frozen section biopsy, and final biopsy to confirm the efficacy and importance of each test.

2. Methods

We retrospectively analyzed the clinical data of 31 patients who underwent TDA from 2004 to 2019 at Hanyang University Hospital, Seoul, Republic of Korea. Among these 31 patients, 4 patients who had positive marginal status in intraoperative frozen biopsy switched to PD (Fig. 1). Clinical data were obtained by reviewing the electronic medical records of hospital. General characteristics such as patient's age, sex, height and weight and clinicopathologic data such as patient's biopsy, perioperative hospital days, and perioperative complications were extracted.

This retrospective study was approved by the Institutional Review Board (IRB) of Hanyang University Hospital, Seoul, Republic of Korea, and all research conducted adhered to the tenets of the Declaration of Helsinki (IRB No. 2018-09-022).

2.1. Preoperative evaluation and operative indications for TDA

When we select patients for TDA, we make a careful decision by evaluating all the patient's medical records and the general condition of the patient. Contrast enhanced abdominal computed tomography (CT) and endoscopy were performed routinely for preoperative evaluation of patients, and endoscopic ultrasonography (EUS) and endoscopic biopsy were performed routinely. Magnetic resonance cholangiopancreatography (MRCP) was performed when EUS and endoscopic biopsy were not available due to the medical history of the patient (e.g. history of gastric bypass, severe duodenal deformity).

A brief summary of the indications applied by our institution is as follows: First, TDA was performed in patients who were not confirmed with cancer in endoscopic biopsy and whose endoscopic resection was impossible to resect clearly (e.g. large size, ulcerative lesion and previous operation history). Second, patients with abnormal laboratory findings such as jaundice or those with suspicious lymph node metastasis in preoperative evaluations were excluded. Third, of the patients with malignancy diagnosed by preoperative biopsy, those with Tis or T1 stage and without invasion or metastasis to other organ, TDA was performed only when the general condition of patient was poor for PD, or when patient or guardian rejected PD for various reasons.

2.2. Operative technique

Under general anesthesia, the operation was performed through

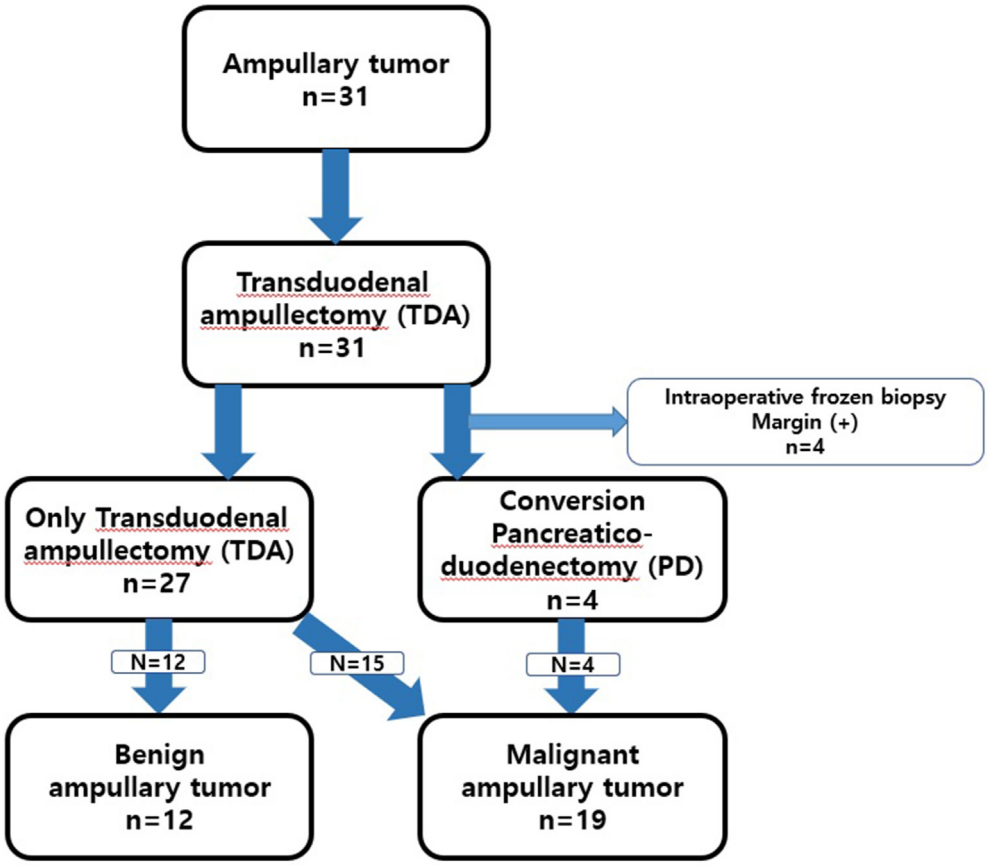

Fig. 1. Treatment algorithm for ampullary tumors. According to the indications, a total of 31 patients were included in this study. In 4 patients, transduodenal ampullectomy was converted to pancreaticoduodenectomy according to intraoperative biopsy results. Of the 27 patients who underwent transduodenal ampullectomy alone, 15 patients were diagnosed with malignancy at the final diagnosis.

the subcostal incision at supine position. After approaching the abdominal cavity, it was necessary to confirm there are no abnormal findings in the abdominal cavity such as seeding nodules as a whole. All patients with gallbladder underwent cholecystectomy. Prior to performing a duodenostomy, hepatic flexure of colon was mobilized inferiorly and a wide Kocher maneuver was performed to mobilize the duodenum. While fully mobilizing duodenum, the presence of peripancreatic lymph node was confirmed to perform frozen biopsy if necessary. After confirming the location of the ampullary mass with palpation, duodenostomy of about 4–5 cm was performed around it (Figs. 2A and 3A). After the ampullary mass was tracted efficiently using suture, ampullary mass was resected using "needle-point" electrocautery with "cutting mode" to secure clear margin for frozen biopsy (Figs. 2B and 3B). During this resection, the pancreatic duct and bile duct were identified and guiding sutures were performed if necessary. The removed mass was delivered directly to a pathologist for frozen biopsy, and the operator performed reconstruction of the bile duct and pancreatic duct. Regardless of the results of frozen biopsy, surgery is performed continuosly because bowel edema progresses over time, increasing the likelihood of complications. Bile duct and pancreatic duct were reconstructed through interrupted sutures using 5-0 polydioxanone suture (PDS II®, Ethicon) on the mucosa of adjacent duodenum (Figs. 2C and 3C). Duodenostomy site was closed with interrupted double layer sutures by 4-0 polyglactin suture (Vicryl®, Ethicon) to prevent duodenal stenosis (Figs. 2D and 3D). Before the end of the operation, frozen biopsy was checked and if the malignancy was suspected in the peripancreatic lymph node or margin of ampullary mass, it was converted to pancreaticoduodenectomy immediately. Secondary resection was not performed because of the high risk of complications and difficulty of margin evaluation. After confirming that there were no acute complications, the abdominal wall was closed as usual after insertion of the drain tube. If malignancy was detected in preoperative or frozen section biopsy, regional lymph node dissection was also performed.[11]

2.3. Postoperative management and follow up

Patients who underwent operation did not usually insert nasogastric tube and started dieting step in 2–3 days after surgery. If no specific complications were found, drain was removed and

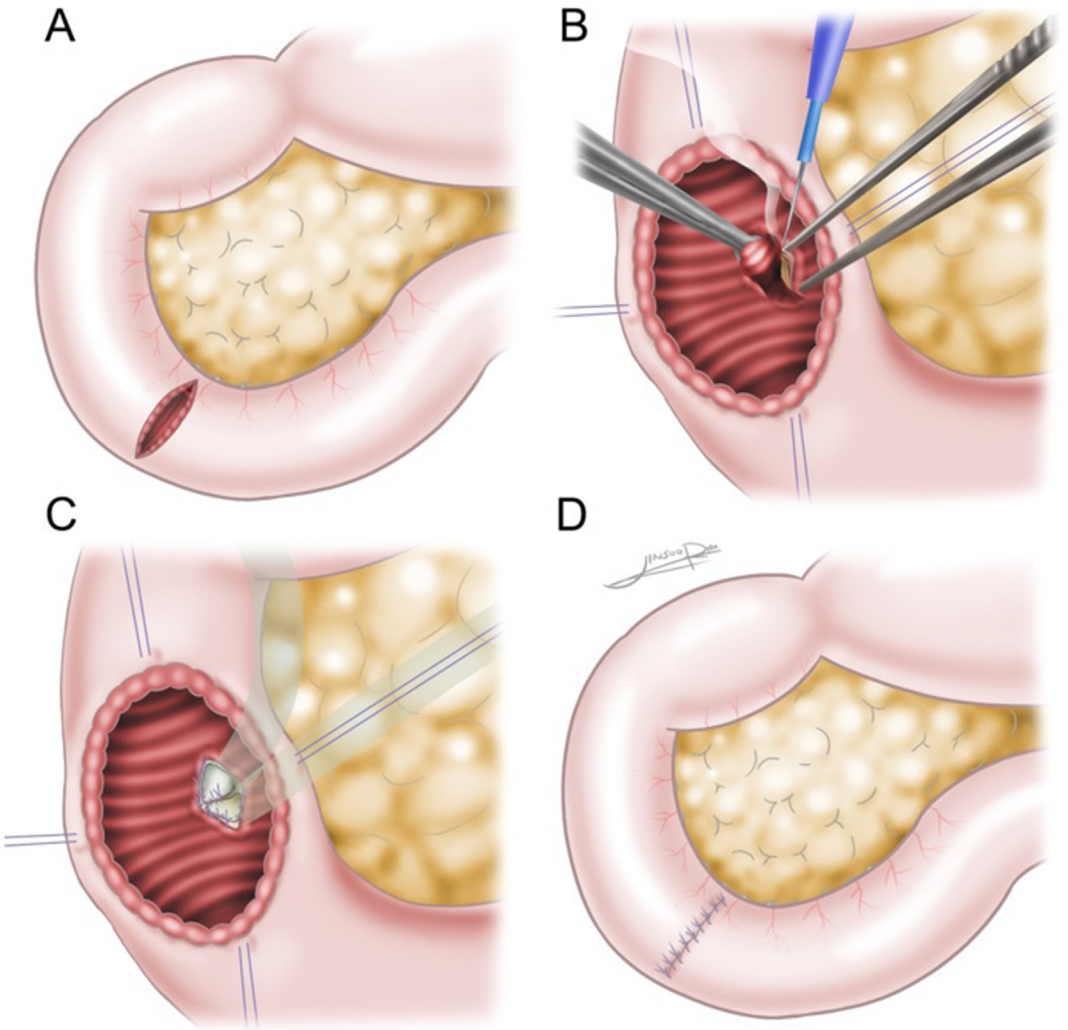

Fig. 2. Operative technique for trasnduodenal ampullectomy (illustration). (a) After intraperitoneal exploration and sufficient mobilization of the duodenum, duodenostomy is performed around the lesion. (b) After obtaining a sufficient surgical field of view using traction sutures, the ampullary tumor is resected by securing a clear margin using "needle-point" electrocautery in the "cutting mode". (c) After the resection, the pancreatic duct and bile duct are identified and reconstructed using interrupted sutures on the mucosa of the adjacent duodenum. (d) The duodenostomy site is closed using double-layer interrupted sutures.

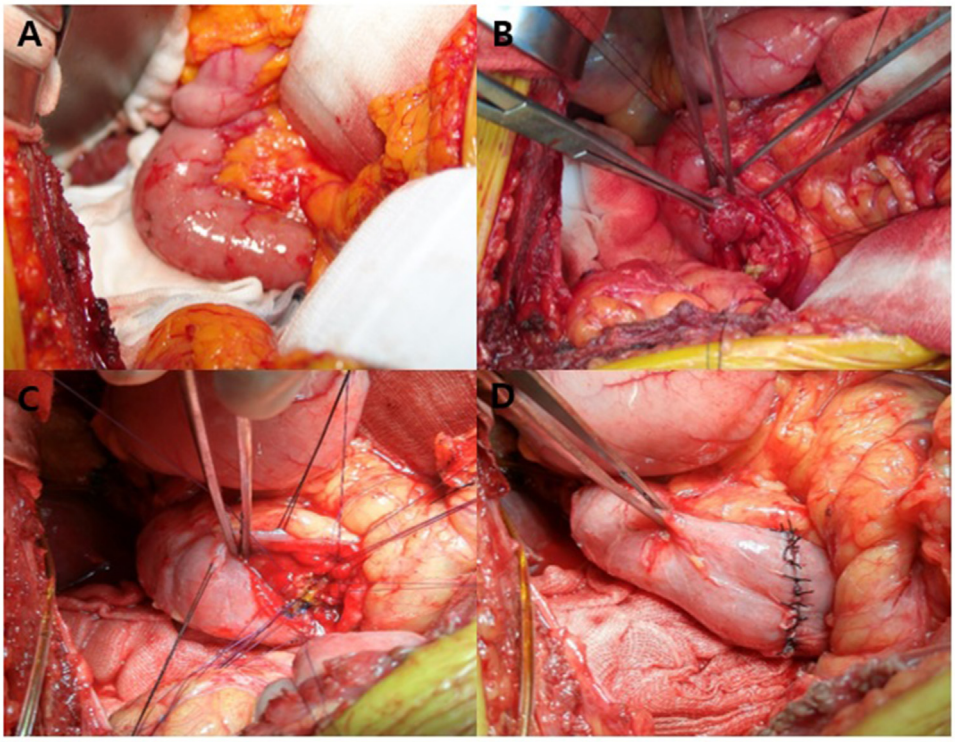

Fig. 3. Operative technique for transduodenal ampullectomy (surgical fields). The figure legend is the same as that of Fig. 2.

discharged within 7 days after surgery. During the hospital stay, no special imaging tests were performed except for abdominal X-ray. The lesions were finally evaluated by pathologist according to the World Health Organization(WHO) classification. When the lesion is classified as malignancy, the TNM stage was reported according to the 8th American Joint Committee on Cancer (AJCC) staging system.[12] After confirming the biopsy, in the outpatient department, multidisciplinary team was conducted to determine future follow-up treatment and follow-up periods.

2.4. Statistical analysis

All statistical analyzes were performed with SPSS (24.0 software, Chicago, IL, USA). Data were expressed as mean ± standard deviation. Pearson chi-square test, Fisher's exact test and linear by linear association test were used to compare categorical variables. Independent t-test and Mann–Whitney test was used to compare continuous variables. A p-value less than 0.05 was defined as statistically significant in all analyzes.

3. Results

According to the indications of our center, a total of 31 patients underwent surgery for TDA. Among 31 patients who underwent TDA, whether to convert to PD was determined according to intraoperative biopsy, especially margin status. As a result, 4 patients were converted to PD. Of the 27 patients who underwent only TDA, 15 patients were classified as malignancy at the final diagnosis (Fig. 1).

3.1. General characteristics of patients

The average age of the patients was 66.23 years, and the male was 61.3%, which was higher than female. The average body mass index (BMI) was 23.81, and the American society of anesthesiologists (ASA) score of I was 12.9%, II was 71.0%, and III was 16.1%, retrospectively, with the highest percentage of patients with ASA score II. There was no statistically significant difference between the two groups when compared by classifying benign and malignant patients (Table 1).

3.2. Perioperative outcomes

In the analysis of perioperative outcome, the malignant group included all patients who switched to PD (5 cases, 38.5%). Operative time took an average of 212.26 min (range: 115–505), and when comparing benign and malignant patients, the time required for surgery for malignant patients was longer than that for benign patients (benign: 172.97, malignant: 237.11). However, there was no statistically significant difference between them ($p = 0.060$). Complications were classified by Clavien-Dindo (CD) classification, and wound complications classified as CD score I was the most common among all patients, and severe complications of CD score III or higher were identified only in malignant patients undergoing PD.[13] Reoperation was absent in both benign and malignant patients, and the average postoperative hospital days were 14.29 days. Postoperative hospital day was 15.89 days in malignant patients, which was higher than 11.75 days in benign patients, though there was no statistically significant difference ($p = 0.496$). (Table 1).

The average follow-up period of patients after surgery was 39.26 months (range: 4–137), and within 90 days after surgery, there was no mortality in both benign and malignant groups. One cases of recurrence were found in benign patients. Recurred patient showed tubular adenoma in gastroscopy performed 6 months after surgery. However, since the biopsy result at the time of surgery was tubular adenoma with low grade dysplasia, follow-up performed without additional treatment with informed consent, and there was no significant change for about 9 years (Table 1).

Table 1
General characteristics and surgical outcomes of patients.

		Total (n = 31)	Benign (n = 12)	Malignant (n = 19)	p-value
Age (year)		66.23±11.61	67.25±8.09	65.58±13.55	0.703
Sex	**Male**	19 (61.3%)	8 (66.7%)	11 (57.9%)	0.717
	Female	12 (38.7%)	4 (33.3%)	8 (42.1%)	
Height (cm)		162.65±9.90	162.97±8.61	162.44±10.86	0.889
Weight (kg)		63.41±12.08	59.92±13.84	65.61±10.62	0.206
BMI		23.81±3.03	22.26±3.28	24.79±2.47	0.033
ASA	**I**	4 (12.9%)	2 (16.7%)	2 (10.5%)	0.679
	II	22 (71.0%)	7 (58.3%)	15 (78.9%)	
	III	5 (16.1%)	3 (25.0%)	2 (10.5%)	
Operative time (min)		212.26±107.90	172.97±50.47	237.11±127.14	0.060
Conversion rate		4 (12.9%)	0 (0.0%)	4 (21.05%)	0.139
Complications (CD score)	**I**	3 (9.7%)	2 (16.7%)	1 (5.3%)	0.510
	II	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	IIIa	2 (6.5%)	0 (0.0%)	2 (10.5%)	
	IIIb	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Reoperation		0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Postop HD		14.29±16.15	11.75±5.28	15.89±20.27	0.496
Mean f/u		39.26±31.26	31.50±22.65	44.16±35.35	0.279
Mortality (90days)		0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Recurrence		1 (%)	1 (8.3%)	0 (0%)	0.387

3.3. Histologic findings of ampullary tumor

Table 2 shows the results of preoperative, frozen, and final biopsy of all patients included in this study. Two patients, one in each of the benign and malignant patients, were unable to perform preoperative biopsy because endoscopic approach was not possible due to the previous surgical history.

Table 3 shows the diagnostic accuracy of each stage of biopsy. First, compared to the final biopsy in 29 patients who underwent preoperative biopsy, only 9 patients (50.0%) were diagnosed as

Table 2
Comparison of pathologic results in ampullary tumor.

Benign ampullary tumor (n = 12)				
Case no.	Preoperative biopsy	Intraoperative biopsy	Final biopsy	
1	TA LGD	TA LGD	TA LGD	
2	TA LGD	TA LGD	TA LGD	
3	TA LGD	TA LGD	TA LGD	
4	TA LGD	TA HGD	TA LGD	
5	TA LGD	No evidence of malignancy	TA LGD	Incomplete EP
6	Not checkable	Rule out adenocarcinoma	TA LGD	
7	TA LGD	TA	TA LGD	
8	Rule out adenocarcinoma	No evidence of malignancy	No evidence of malignancy	
9	Hyperplastic polyp	No evidence of malignancy	No evidence of malignancy	
10	Rule out adenocarcinoma	Rule out adenocarcinoma	Chronic inflammation	
11	TA LGD	TA LGD	TA LGD	
12	TA LGD	TA	TA LGD	
Malignant ampullary tumor (n = 19)				
Case no.	**Preoperative biopsy**	**Intraoperative biopsy**	**Final biopsy**	
1	TVA HGD	Adenocarcinoma	Adenocarcinoma/pT1	
2	TVA LGD	TVA LGD	TVA HGD	
3	TVA LGD	TVA HGD	TVA HGD	
4	VA HGD	Dysplastic gland	Adenocarcinoma/pTis	Incomplete EP
5	TVA HGD	TA LGD	Carcinoma in situ/pTis	
6	Chronic inflammation	Adenocarcinoma	Adenocarcinoma/pT1	
7	TA HGD	TA LGD	TA HGD	
8	TVA LGD	TVA LGD	Carcinoma in situ/pTis	
9	VA HGD	TVA HGD	Adenocarcinoma/pT1	
10	VA LGD	Carcinoma in situ	Carcinoma in situ/pTis	
11	TA HGD	TA	TA HGD	
12	Not checkable	Adenocarcinoma	Adenocarcinoma/pT1	Convert to PD
13	TA LGD	TA HGD	TA HGD	
14	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma/pT1	
15	TA LGD	Adenocarcinoma	Adenocarcinoma/pT1	Convert to PD
16	TA HGD	TA LGD	TVA HGD	
17	TA LGD	TA HGD	TA HGD	
18	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma/pT2	Convert to PD
19	Chronic inflammation	Adenocarcinoma	Adenocarcinoma/pT3	Convert to PD

*TA: Tubular adenoma; TVA: Tubulo-villous adenoma; VA: Villous adenoma; LGD: Low grade dysplasia; HGD: High grade dysplasia; EP: Endoscopic papillectomy; PD: Pancreaticoduodenectomy.

Table 3
Diagnostic accuracy of biopsy.

Preoperative biopsy		**Final diagnosis**			
		Malignant (n = 18)	**Benign (n = 11)**		
Preoperative biopsy (n = 29)	**Malignant (n = 11)**	9	2	11	**Sensitivity**
	Benign (n = 18)	9	9	18	= 50%
		18	11	29	**Specificity**
					= 82.82%
Intraoperative biopsy		**Final diagnosis**			
		Malignant (n = 19)	**Benign (n = 12)**		
Intraoperative biopsy (n = 31)	**Malignant (n = 15)**	12	1 + 2	15	**Sensitivity**
	Benign (n = 16)	7	9	16	= 63.16%
		19	12	31	**Specificity**
					= 75%

malignant tumor in preoperative biopsy among 18 patients who were diagnosed as malignant in final biopsy. In addition, a total of 18 patients (62.07%) had a diagnosis consistent with the result of final biopsy. Based on this, it was found that the sensitivity of preoperative biopsy in diagnosis for malignancy was 50.0% and the specificity of that was 82.82%. Second, when the frozen biopsy was analyzed by the same method as above, the sensitivity of the frozen biopsy in diagnosis for malignancy was 63.16% and the specificity of that was 75.0%. In addition, if the frozen biopsy indicated that the possibility of cancer malignancy could not be excluded, it was classified as malignancy because the treatment corresponding to malignancy was performed such as lymph node dissection.

Finally, the marginal status obtained through frozen biopsy and that obtained from final biopsy after surgery were compared and analyzed. Since this is a test for evaluating margin status rather than diagnosis, sensitivity and specificity were not obtained, and only the agreement rate of the test was considered. Through this, it was found that the agreement rate of margin status evaluation during and after surgery was 100%.

4. Discussion

TDA has a long history since it was first started by Halsted in 1899.[8] However, it is true that TDA has not received much attention compared to its long history. This is because, in benign ampullary tumors, EA is recognized as the primary choice for treatment, and for malignant ampullary tumors, PD is known as treatment of choice.[6,7,14] As a result, TDA only had an ambiguous treatment area between EA and PD. However, recently, the TDA is drawing attention again. This is because the number of patients who have difficulty in performing EA or PD has increased due to patient's multiple surgical history or aging.[10,15] In addition, for ampullary tumors, doubts on the accuracy of diagnosis from preoperative biopsy also contributed. Therefore, we retrospectively analyzed the 31 cases of TDA conducted at this center to find out the safety of TDA and the accuracy and importance of histologic findings.

Although it is true that the mortality and morbidity of PD decreased significantly as patient management and surgical techniques developed, PD still shows high mortality and morbidity.[16] In particular, the risk is higher for older patients and patients with many underlying diseases. In contrast, TDA is known to have a relatively simple surgical procedure and low complication rates.[4,9] In the result of this study, the average operation time of patients who received only TDA was 176.48 min (range: 115–360), and complications with CD score II or higher were not seen in patients who received only TDA. Gao et al also reported that TDA showed statistically short operation time and low surgical morbidity when compared to PD.[10] In addition, many studies reported that TDA was superior to PD in perioperative outcomes.[4,9]

Recently, many studies have reported that TDA has shown good results in long term surgical outcomes in early malignant ampullary tumors as well as in these perioperative outcomes.[4,9,10,17–19] Song et al reported that there were no statistically significant differences between the groups of patients who underwent PD and TDA when survival was analyzed for a total of 89 patients diagnosed with pT1 ampullary cancer.[17] In our study, fifteen patients who received TDA alone for malignant ampullary tumor showed no recurrence during the follow-up period. Through this, PD is still a standard treatment in malignant ampullary tumors, but it has been shown that TDA may be an excellent alternative for PD in patients with early ampullary cancer for which PD is unfit for various reasons.

For benign ampullary tumor, EA is the best option if possible.[6] However, EA is generally not recommended in patients with suspected malignant or malignant ampullary tumors. This is because it is difficult to evaluate margin status and to secure a negative

Table 4
Surgical outcomes and accuracy of pathology for transduodenal ampullectomy

Author	Year	Patients	Period	Surgical outcomes	Accuracy of pathology
Nappo et al.[4]	2020	Benign 13 patients Malignant 23 patients	2010–2018	Severe morbidity (Clavien-Dindo > IIIa): 13.9% 90-day mortality: 0%	Preoperative biopsy: Sensitivity 60.9% Frozen biopsy: Sensitivity 78.3%
Liu et al.[24]	2019	Benign 7 patients Malignant 3 patients	2011–2017	Complication rate: 10%	Preoperative biopsy false negative rate: 30% Accuracy of frozen biopsy: 100%
Hong et al.[18]	2018	Benign 23 patients Malignant 3 patients	2004–2016	Major in-hospital complication: 3.8% 90-day mortality: 0%	Preoperative biopsy: Sensitivity 21.4%
Kim et al.[25]	2017	Benign 21 patients	2001–2016	Complication rate: 23.8%	Accuracy or preop Bx: 81% Accuracy of frozen Bx: 81%
Mansukhani et al.[26]	2017	Benign 7 patients Malignant 4 patients	2009–2015	Complication rate: 9.1%	Preoperative Bx: Sensitivity 25% Preoperative Bx: Specificity 100%
Lee et al.[9]	2016	Malignant 18 patients	1994–2013	Complication rate (Clavien-Dindo≥2): 33%	Preoperative Bx: Sensitivity 44.4%
Gao et al.[10]	2016	Malignant 22 patients	2001–2014	Surgical mortality: 0% Surgical morbidity: 13.6%	Preoperative biopsy: Sensitivity 74.4% Intraoperative biopsy: Sensitivity 95.3%

margin through full thickness EA.[20–23] For these reasons, it is ideal to determine the treatment plan after accurately checking whether it is benign or malignant, but it is true that the accuracy of the preoperative biopsy is low. The accuracy of preoperative biopsy in this study was 62.07%, which was very low. This is also why excision is generally recommended in ampullary tumors. In conclusion, it can be seen that TDA can be a good alternative for patients who suspected malignancy or who are unfit for EA.

As mentioned earlier, preoperative histologic findings are less accurate, and there are doubts about their efficacy. On the contrary, intraoperative histologic finding, that is, evaluating margin status or lymph node metastasis through frozen biopsy, is one of the most important process in performing TDA.[24] It also shows remarkably high accuracy in close cooperation between surgeon and pathologist. In this study, the diagnosis through intraoperative biopsy also showed a slightly low level of 67.74%, but it was 100% consistent with the final biopsy in evaluating margin status or lymph node metastasis. Gao et al also reported a 100% match with intraoperative margin status and final pathology in all 43 patients undergoing TDA.[10] This accurate evaluation of margin status or lymph node metastasis can serve as an accurate evaluation tool in judging the treatment plan, such as the conversion to PD, which determines the success or failure of TDA.

Table 4 summarizes the surgical outcomes and accuracy of pathology for TDA reported in other studies.

This study has some limitations. First, this study was conducted retrospectively on TDA performed in a single center. The second is that, like other studies on the subject of TDA, it was based on a small group of 31 patients. However, considering that the incidence of the ampullary tumor itself is very low and TDA is currently not a widely performed operation, the group of 31 patients seems to have never been small. This could be a good foundational study for conducting large-scale multicenter studies and randomized controlled studies to be performed in the future.

In conclusion, TDA can be appropriately performed in patients with benign ampullary tumors where EA is not possible and in patients with suspected malignant ampullary tumors. Furthermore, even in patients with early ampullary cancer, TDA is a relatively safe and reliable surgical technique in highly selective patients, such as those who were unfit to PD. In addition, in order to perform TDA successfully, intraoperative histological evaluation of marginal status and lymph node metastasis are essential through frozen biopsy. Finally, the most important prerequisite for defining the treatment area of TDA is establishing accurate indications and treatment guidelines. To this end, more studies such as large-scale multicenter studies or randomized controlled studies should be conducted in the future.

Declaration of competing interest

Yun Kyung Jung, Seung Sam Paik, Dongho Choi and Kyeong Geun Lee have no conflicts of interest or financial ties to disclose.

Acknowledgements

The authors thank Jinsoo Rhu, surgeon and medical illustrator, for help with illustration.

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