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Original Article

Ampullectomy versus pancreaticoduodenectomy for ampullary tumors

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Abstract

Background: Considerable controversy surrounds the treatment of ampullary neoplasms. This report describes the authors' experiences regarding the choice of either ampullectomy or pancreaticoduodenectomy for treatment of ampullary tumors.
Methods: Demographics, statistical findings concerning diagnosis, surgical risks including morbidity and mortality, and outcomes were evaluated and compared between the ampullectomy and pancreaticoduodenectomy groups for ampullary tumors retrieved from a prospectively collected computer database of 992 periampullary tumors resected during the period from 1965 to 2013.
Results: A total of 377 patients with ampullary tumors were included; 15 underwent ampullectomy and 362 underwent pancreaticoduodenectomy. The overall false-negative rate for diagnosis of ampullary malignancy was 11.2%, specificity was 50.0%, positive predictive value was 98.3%, negative predictive value was 12.2%, and the overall accuracy was 87.6% (77.5% by preoperative endoscopic biopsy and 83.9% by intraoperative frozen-section biopsy). Ampullectomy was associated with shorter postoperative stays and lower surgical morbidity. There was no statistical difference observed between the two groups regarding surgical mortality, pancreatic leakage, or gastric atonia. The tumor recurrence rate was lower after pancreaticoduodenectomy, but the difference between the groups was not significant. Overall, there was no difference in survival observed between the two groups.
Conclusion: Because biopsy is not routinely reliable, pancreaticoduodenectomy is preferable to ampullectomy for an ampullary tumor of uncertain diagnosis. Ampullectomy is associated with lower surgical morbidity and should therefore remain in the armamentarium of the pancreatic surgeon when comorbidity precludes major surgery.

Keywords: ampullary tumor; ampullectomy; pancreaticoduodenectomy

1. Introduction

Two surgical procedures have historically been used in the treatment of ampullary tumors: ampullectomy, a local resection of the ampulla of Vater, was described in 1899 by Halsted,[1] and pancreaticoduodenectomy was introduced by Whipple et al in 1935.[2] However, ampullectomy has not achieved widespread acceptance because of its lesser radicality and the higher rates of tumor recurrence associated with it (range, 20–100%).[3–6] By contrast, pancreaticoduodenectomy (also known as the Whipple procedure) is a more radical form of surgery and has long been considered the only alternative for patients with malignant periampullary diseases.[7–10] In addition, many centers have developed the expertise for reducing the surgical risks associated with pancreaticoduodenectomy, which is currently considered the superior treatment option for benign or premalignant diseases of the ampulla of Vater.[7,9,10] Nonetheless, pancreaticoduodenectomy is clearly associated with high perioperative morbidity, and the quality of life of patients after undergoing this radical surgery is much poorer than that following local resection with ampullectomy.[8–10]

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Because it is characterized by more limited resection, lesser morbidity, and lower surgical risk as compared with pancreaticoduodenectomy, ampullectomy represents a potentially attractive alternative for removal of certain benign ampullary lesions and may be more appropriate for those rare patients with a malignancy and who are unfit for major surgery.[7,8,10–12] A recent review of the literature revealed that the number of patients undergoing ampullectomy is relatively small. Consequently, the clinical features and outcomes for these patients have not been well-described, indications for this procedure remain controversial, and the limitations of this form of resection remain unclear.[6,8,11]

This report presents the experiences of members of the Department of Surgery, Taipei Veterans General Hospital regarding ampullectomy and pancreaticoduodenectomy in the treatment of ampullary tumors. The two surgical procedures were evaluated and compared with respect to demographics, clinical presentations, diagnostic accuracy, associated surgical risks, and patient outcome.

2. Methods

Data on two series of consecutive patients, those who underwent ampullectomy and those who underwent pancreaticoduodenectomy, were retrieved from a prospectively collected computer database of 992 periampullary tumors resected during the period from 1965 to 2013 at the Taipei Veterans General Hospital. Informed consent was obtained from each patient. The study protocol was approved by our Institutional Review Board. We did not improperly disclose any personal data of the patients, and furthermore there was no safety concern for the patients in this study. Pancreaticoduodenectomy for radical tumor removal has been the treatment of choice at this institution for ampullary tumors, with ampullectomy reserved for patients at high surgical risk or who refuse a more radical surgery.

Demographics, clinical presentations, statistical findings concerning diagnosis, surgical risks including morbidity and mortality, follow-up periods, and survival outcomes were evaluated and then compared between these two surgical groups. Based on the definitions of the International Study Group on Pancreatic Fistula,[13] pancreatic leakage was defined as grade B or C postoperative pancreatic fistula, and gastric atonia was defined as grade B or C delayed gastric emptying according to the definition by the International Study Group of Pancreatic Surgery.[14] Surgical mortality was defined as death occurring perioperatively and within 30 days following surgery or during the initial hospital stay if 30 or more days had elapsed.

Ampullectomy was performed to achieve a wide excision, which included a portion of the duodenal wall, distal segments of the distal common bile and pancreatic ducts, and a wedge of pancreatic parenchyma. Resection margins of the biliary and pancreatic ducts (frozen section) were sent for pathological analysis to confirm that surgical resection was complete. To reconstruct the defect, the pancreatic and common bile ducts were sutured together in a common septum (common wall) fashion, and the surrounding duodenal wall was then reapproximated to the joined pancreatic and common duct openings.

Pancreaticoduodenectomy was performed at this institution with a standard resection and without extensive retroperitoneal lymph node dissection. Whether the classic pancreaticoduodenectomy procedure would utilize either a distal gastrectomy or a pylorus-preserving resection was generally left to the discretion of the surgeon. A pancreaticogastrostomy or pancreaticojejunostomy was chosen for pancreatic reconstruction; vagotomy was not routinely performed.

Statistical analyses were performed using Statistical Product and Service Solutions (SPSS) version 21.0 software (SPSS Inc., IBM, Armonk, NY, USA). All continuous data are presented as median and mean ± standard deviation, and frequencies are presented when appropriate to the type of data. The mean values of continuous variables were compared using a two-tailed Student *t* test. Nonparametric statistical tests were used if the variables did not follow normal distribution. Categorical variables are presented as numbers and percentages, and were compared using Pearson χ^2 test or Fisher exact test contingency tables. The Kaplan–Meier method was used for the calculation of median survival and survival analysis. For all analyses, a p value less than 0.050 was considered statistically significant.

3. Results

Of the 992 patients in the database who underwent periampullary tumor resection, 377 with ampullary lesions were enrolled in this study; of this total, 15 underwent ampullectomy (Table 1) and 362 underwent pancreaticoduodenectomy. Therefore, ampullectomy was performed in 1.5% (15/992) of cases of resected periampullary tumors and 4.0% (15/377) of cases of resected ampullary tumors. Reasons for selection of ampullectomy included high surgical risk due to severe comorbidity in eight patients, obesity in two patients, and patient preference due to the small size and unclear characteristics of the tumor in five patients. Among the ampullectomy group, eight cases were malignant and in two (25%) of these cases death occurred due to tumor recurrence; the latter involved carcinomatosis at 67 months following ampullectomy for a pT2 ampullary adenocarcinoma in one patient and liver metastasis at 88 months following ampullectomy for a carcinoma *in situ* tumor (pTis) in the other. The cut margins for the resected specimens were all proved to be free from malignancy in the ampullectomy patients. No statistical difference was observed between the ampullectomy and pancreaticoduodenectomy groups with respect to sex, age, duration of symptoms, tumor size, and serum tumor markers including carbohydrate antigen 19-9 and carcinoembryonic antigen. Regarding clinical presentation, more patients without symptoms (20.0% vs. 3.6%, $p = 0.021$) and fewer patients with jaundice (33.3% vs. 76.0%, $p = 0.001$) were observed in the ampullectomy group as compared with the pancreaticoduodenectomy group (Table 2).

Table 3 presents the statistical parameters for diagnosis of ampullary malignancy before resection. Forty-six (12.2%)

Table 1
Ampullectomy for ampullary lesions.

Case	Age (y)	Sex	Tumor size (cm)	Pathology [a]	Complication	Tumor recurrence	Survival time (mo)	Outcome
1	73	M	2.5	4	No	No	86	Alive
2	83	F	3.5	1 (pT2)	No	No	31	Died of other cause
3	51	M	2	1 (pT2)	No	Yes (carcinomatosis)	67	Died of disease
4	61	M	1.5	1 (pTis)	No	Yes (liver metastasis)	88	Died of disease
5	70	M	1.5	5	No	No	108	Alive
6	63	M	4	6	No	No	195	Died of other cause
7	73	M	3	2	Yes (intra-abdominal bleeding)	No	133	Died of other cause
8	64	M	2	2	Yes (wound infection)	No	136	Died of other cause
9	85	M	3	2	No	No	148	Alive
10	29	M	0.5	3	No	No	95	Alive
11	72	M	3	1 (pT2)	No	No	40	Alive
12	80	M	2.5	1 (pTis)	No	No	38	Alive
13	69	M	3.5	1 (pT1)	No	No	18	Alive
14	69	F	1.5	1 (pTis)	No	No	6	Alive
15	79	F	3.5	1 (pT2)	No	No	6	Alive

[a] *Pathology:* 1 = adenocarcinoma; 2 = tubulovillous adenoma; 3 = dysplasia; 4 = leiomyoma; 5 = ectopic pancreas; 6 = adenomatous polyp; pTis = pathological carcinoma *in situ*.

patients underwent resection without biopsy for pathological diagnosis in this study. The overall false-negative rate for diagnosis was 11.2%; for diagnosis by preoperative endoscopic biopsy, the false-negative rate was 21.1% and for diagnosis by intraoperative frozen-section biopsy, the false-negative rate was 14.4%. The overall sensitivity for diagnosis before resection, therefore, was 88.8%; sensitivity by preoperative endoscopic biopsy was 77.9% and by

Table 2
Demographics and clinical presentations of ampullary lesions undergoing resection.

	Total (n = 377)	Ampullectomy (n = 15)	Pancreaticoduodenectomy (n = 362)	p
Sex				0.404
Male	256 (67.9%)	12 (80.0%)	244 (67.4%)	
Female	121 (32.1%)	3 (30.0%)	118 (32.6%)	
Age (y)				0.345
Median	66	69	66	
Range	29–90	29–83	31–90	
Mean ± SD	64.9 ± 11.6	66.7 ± 13.2	64.9 ± 11.6	
Duration of symptoms (mo)				0.430
Median	1	1	1	
Range	0–120	0–96	0–120	
Mean ± SD	2.6 ± 8.4	8.9 ± 25.3	2.4 ± 7.0	
Symptoms				
No symptoms	16 (4.2%)	3 (20.0%)	13 (3.6%)	0.021
Jaundice	280 (74.3%)	5 (33.3%)	275 (76.0%)	0.001
Epigastric pain	167 (44.3%)	7 (46.7%)	160 (44.2%)	> 0.99
Fever	134 (35.5%)	3 (20.0%)	131 (36.2%)	0.274
Body weight loss	128 (34.0%)	2 (13.3%)	126 (34.8%)	0.100
Nausea/vomiting	43 (11.4%)	3 (20.0%)	40 (11.0%)	0.395
Size (cm)				0.857
Median	2.0	2.8	2.0	
Range	0.4–10.0	0.5–3.5	0.4–10	
Mean ± SD	2.4 ± 1.4	2.5 ± 1.1	2.4 ± 1.4	
Serum CA 19-9 (U/mL)				
Median	53.7	16.3	53.8	0.421
Range	0.6–64,562.0	4.9–73.9	0.6–64,562.0	
Mean ± SD	695.2 ± 4511.3	27.8 ± 31.4	706.7 ± 4549.3	
Serum CEA (ng/mL)				0.522
Median	3.2	1.4	3.3	
Range	0.4–143.0	1.1–2.0	0.4–143.0	
Mean ± SD	4.9 ± 10.7	1.5 ± 0.4	4.9 ± 10.7	

CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; SD = standard deviation.

Table 3
Diagnosis of ampullary malignancy before resection.

Diagnosis of malignancy	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
1. Preoperative endoscopic biopsy ($n = 275$)	77.9%	62.5%	98.6%	7.8%	77.5%
2. Intraoperative frozen section ($n = 93$)	85.6%	33.3%	97.5%	7.1%	83.9%
3. Overall before resection (1 + 2) [a] ($n = 331$)	88.8%	50.0%	98.3%	12.2%	87.6%

[a] Forty-six (12.2%) patients underwent resection without biopsy for pathological diagnosis.

intraoperative frozen-section biopsy was 85.6%. The overall specificity was only 50.0%. The positive predictive value reached as high as 98.3% but the negative predictive value was only 12.2%. The overall accuracy was 87.6%; accuracy by preoperative endoscopic biopsy was 77.5% and by intraoperative frozen-section biopsy was 83.9%.

The length of the postoperative stay was significantly shorter for the ampullectomy group as compared with the pancreaticoduodenectomy group (median, 13 vs. 27 days, $p = 0.021$). Surgical morbidity was also lower for the ampullectomy group as compared with the pancreaticoduodenectomy group (20.0% vs. 50.6%, $p = 0.032$; Table 4). No statistical differences were observed between the two surgical groups with respect to surgical mortality, pancreatic leakage, or gastric atonia. Although the tumor recurrence rate was lower after pancreaticoduodenectomy, the difference between the groups did not reach statistical significance for either overall (25.0% vs. 21.6%, $p = 0.671$) or early (pTis-2: 25.0% vs. 16.6%, $p = 0.608$) ampullary adenocarcinoma. No difference in survival was observed between the two surgical techniques.

4. Discussion

Ampullectomy is seldom considered the best treatment for an ampullary tumor. In the present series, ampullectomy was performed in only 4.0% of cases of ampullary tumor resection and 1.5% of cases of periampullary tumor resection. Furthermore, there is no clear consensus for performing ampullectomy. Surgical ampullectomy, as a method of local resection, is generally considered acceptable for: (1) a benign or premalignant ampullary tumor, (2) a carcinoma that is small in size (<2 cm), pTis/pT1, well or moderately differentiated, not extending more than 1 cm into the pancreatic or bile ducts, and without nodal involvement, and (3) a small neuroendocrine tumor.[1,5,10,15,16] For the ampullectomy to be successful, however, the biopsy should prove reliable, the surgical risk(s) should be minimal, and the surgery should be curative.

A prominent concern of surgeons considering ampullectomy is the accuracy of biopsy. Distinguishing between ampullary adenoma and adenocarcinoma before resection of the tumor represents a considerable challenge. Because most preoperative biopsies and biopsies of frozen sections obtained

Table 4
Surgical outcomes of resection for ampullary tumors.

	Total ($n = 377$)	Ampullectomy ($n = 15$)	Pancreaticoduodenectomy ($n = 362$)	p
Length of stay (d)				
Median	27	13	27	
Range	7–383	7–60	8–383	
Mean ± SD	34.5 ± 29.1	17.5 ± 13.3	35.3 ± 29.4	<0.001
Surgical mortality	35 (9.3%)	0	35 (9.7%)	0.379
Surgical morbidity	186 (49.3%)	3 (20.0%)	183 (50.6%)	0.032
Pancreatic leakage	66 (17.5%)	1 (6.7%)	65 (18.0%)	0.458
Gastric atonia	19 (5.0%)	1 (6.7%)	18 (5.0%)	0.547
Recurrence after resection[a]				
Total ($n = 332$)	72 (21.7%)	2 (25.0%)	70 (21.6%)	0.671
pTis-2 ($n = 261$)	42 (16.7%)	2 (25.0%)	42 (16.6%)	0.608
Survival for all [a] (mo)	$n = 332$	$n = 8$	$n = 324$	0.563
Median	29.0	34.2	28.9	
Range	0.9–364.9	4.7–88.6	0.9–364.9	
Mean ± SD	56.5 ± 65.2	36.3 ± 28.4	57.0 ± 65.9	
5-y survival (%)	39.1	80.0	40.1	
Survival for pTis-2 (mo)	$n = 261$	$n = 8$	$n = 253$	0.745
Median	32.1	34.2	32.1	
Range	0.9–364.9	4.7–88.6	0.9–364.9	
Mean ± SD	62.1 ± 69.8	36.3 ± 28.4	65.9 ± 70.6	
5-y survival (%)	47.2	80.0	46.5	

pTis-2 = pathological carcinoma *in situ* to T2 ampullary adenocarcinoma; SD = standard deviation.
[a] For adenocarcinoma only.

intraoperatively involve removal of small samples from the superficial part of a larger ampullary tumor, the presence of invasive disease could be missed.[8,17] Recent findings reveal that the accuracy of preoperative biopsy ranges from 62% to 81%, highlighting the insufficiency of preoperative biopsy alone in the diagnosis of malignancy.[6–8,10,17–22] Furthermore, frozen-section analyses of resected specimens are thought to fail to detect malignancy in 14% of cases.[10,15] Therefore, it is not routinely possible to exclude malignancy before resection.[10] In the present study, the false-negative rate of biopsy in the diagnosis of ampullary malignancy before resection was 11.2%, with a 21.1% false-negative rate obtained by preoperative endoscopic biopsy and 14.4% false-negative rate obtained by intraoperative frozen-section biopsy. However, the positive predictive value was found to be as high as 98.3%, the negative predictive value was only 12.2%, and the overall accuracy was 87.6%. Given that preoperative and intraoperative biopsy findings cannot fully exclude the possibility that an ampullary tumor is malignant, most surgeons are reluctant to choose ampullectomy in preference to pancreaticoduodenectomy.

Alternatively, ampullectomy as a method of local resection is simpler to perform, has fewer long-term digestive sequelae, and is associated with shorter hospitalization times and lower surgical morbidity and mortality as compared with pancreaticoduodenectomy.[6,7,15,23] The mortality and morbidity of pancreaticoduodenectomy are a little bit higher than those for pancreatic head cancer in experienced centers. The reasons for that might be the pancreatic parenchyma of ampullary cancer is softer (one of the risk factors for pancreatic leakage) than that of pancreatic head cancer, and multiple surgeons are involved in pancreaticoduodenectomy. The present study confirms that ampullectomy is associated with lower surgical morbidity and shorter hospital stays; in addition, ampullectomy was not associated with surgical mortality in this study. Therefore, ampullectomy should be more appropriate for patients with comorbid conditions precluding a major, more radical operation such as pancreaticoduodenectomy.

When a potentially malignant mass is to be treated, adequate tumor excision and accurate staging are paramount. Therefore, if ampullectomy guarantees curability, this procedure is preferable to pancreaticoduodenectomy in treatment of early ampullary cancer. For the treatment of invasive cancer, however, ampullectomy is clearly limited by its inabilities to achieve a wide negative margin and to address lymph node metastasis.[3,22] Although some experts have advocated ampullectomy for early stage (T1) invasive ampullary cancers, most still believe that this procedure is inadequate for invasive malignancy.[10,16] In this regard, the lymph node positivity rate is reported to be 28–42% in patients undergoing pancreaticoduodenectomy for T1 ampullary malignancies.[7,10,19] In addition, 33% of patients are reported to have at least one risk factor for failure after receiving ampullectomy for early ampullary cancer; these factors include perineural invasion, lymphovascular invasion, and extensive common bile duct or pancreatic duct mucosal involvement.[16] For those with pTis-2 ampullary adenocarcinoma, the case number in the ampullectomy group is too small to reach any solid conclusions, but the 5-year survival was 80% in the ampullectomy group and 46.5% in the pancreaticoduodenectomy group. In the present study, tumor recurrence was observed in two patients (25%) with ampullary malignancy: in one case, carcinomatosis was present at 67 months after ampullectomy for a pT2 ampullary adenocarcinoma and in the other case, liver metastasis was present at 88 months after ampullectomy for a carcinoma *in situ* tumor (pTis). The clinical course for these two patients with tumor recurrence was relatively indolent after ampullectomy but both eventually died of the disease, consistent with inadequate resection. In general, because ampullectomy is associated with a greater risk of recurrence as compared with pancreaticoduodenectomy, careful follow-up is recommended for all patients who have been treated for ampullary malignancy.[8,17]

In conclusion, because preoperative and intraoperative frozen-section biopsies are not always reliable enough to exclude ampullary malignancy, pancreaticoduodenectomy is preferable to ampullectomy for a tumor with an uncertain diagnosis. As a local resection, ampullectomy is associated with a high recurrence rate and questionable curability. However, ampullectomy is a relatively simple and safe procedure with lower surgical risks as compared with pancreaticoduodenectomy. Ampullectomy should therefore remain a viable alternative in the armamentarium of the pancreatic surgeon for patients with comorbidities precluding a major operation.

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