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【 ORIGINAL ARTICLE 】

Clinical Impact of Piecemeal Resection Concerning the Lateral Spread of Ampullary Adenomas

Kenjiro Yamamoto[1], Atsushi Sofuni[1], Takayoshi Tsuchiya[1], Kentaro Ishii[1], Shujiro Tsuji[1], Reina Tanaka[1], Ryosuke Tonozuka[1], Mitsuyoshi Honjo[1], Shuntaro Mukai[1], Mitsuru Fujita[1], Yasutsugu Asai[1], Yukitoshi Matsunami[1], Yuichi Nagakawa[2], Hiroshi Yamaguchi[3] and Takao Itoi[1]

Abstract:

Objective Endoscopic papillectomy (EP) has been recognized to be a safe and reliable treatment modality for ampullary adenomas. The purpose of this study was to determine the safety and efficacy of endoscopic piecemeal resection for laterally spreading ampullary adenomas and to compare these findings with a control population of smaller conventional ampullary tumors treated in the same time period.

Methods Between May 1999 and September 2015, 136 patients underwent EP at Tokyo Medical University hospital. A total of 125 patients underwent en bloc resection, and 11 patients underwent piecemeal resection.

Results The final pathological diagnoses were 103 adenomas, 14 carcinomas in adenomas, 4 carcinomas, and 4 hyperplasia in the en bloc resection group, versus 7 adenomas, 3 carcinomas in adenoma, and 1 carcinomas in the piecemeal resection group. A single treatment session was possible in 104 (83.2%) of the 125 patients in the en bloc resection group and in 8 (72.7%) of the 11 in the piecemeal resection group. The total resection rate including additional treatments was 98.4% in the en bloc resection group and 100% in the piecemeal resection group.

Conclusion Piecemeal resection for laterally spreading ampullary adenomas was sufficiently performed compared with en bloc resection.

Key words: endoscopic papillectomy, laterally spreading ampullary adenomas, piecemeal resection

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Introduction

Adenomas of the papilla of Vater, also known as ampullary adenomas, can emerge sporadically or in the context of genetic syndromes such as familial adenomatous polyposis. These lesions have the potential to undergo malignant transformation to ampullary carcinoma and should be considered for resection (1, 2).

Ampullary adenomas have historically been treated surgically. Although surgical management often allows complete removal, it is associated with morbidity, including postoperative anastomotic dehiscence and fistula in up to 9% and 14% of patients, respectively, and mortality rates ranging from 1% to 9% (3-5).

Endoscopic papillectomy (EP) has been recognized to be a safe and reliable treatment modality for ampullary adenomas (6-10). Therefore, EP appears to be useful as a method for performing a total biopsy and as an alternative procedure to surgical resection for the treatment of ampullary adenomas. However, many authors recommend surgical resection for larger lesions (>30 mm) and those with significant extrapapillary extension (11-15).

The aim of this study was to determine the safety and efficacy of endoscopic piecemeal resection of laterally spreading ampullary adenomas and compare these findings with a

[1]Department of Gastroenterology and Hepatology, Tokyo Medical University, Japan, [2]Third Department of Surgery, Tokyo Medical University, Japan and [3]Department of Pathology, Tokyo Medical University, Japan
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Correspondence to Dr. Takao Itoi, itoi@tokyo-med.ac.jp

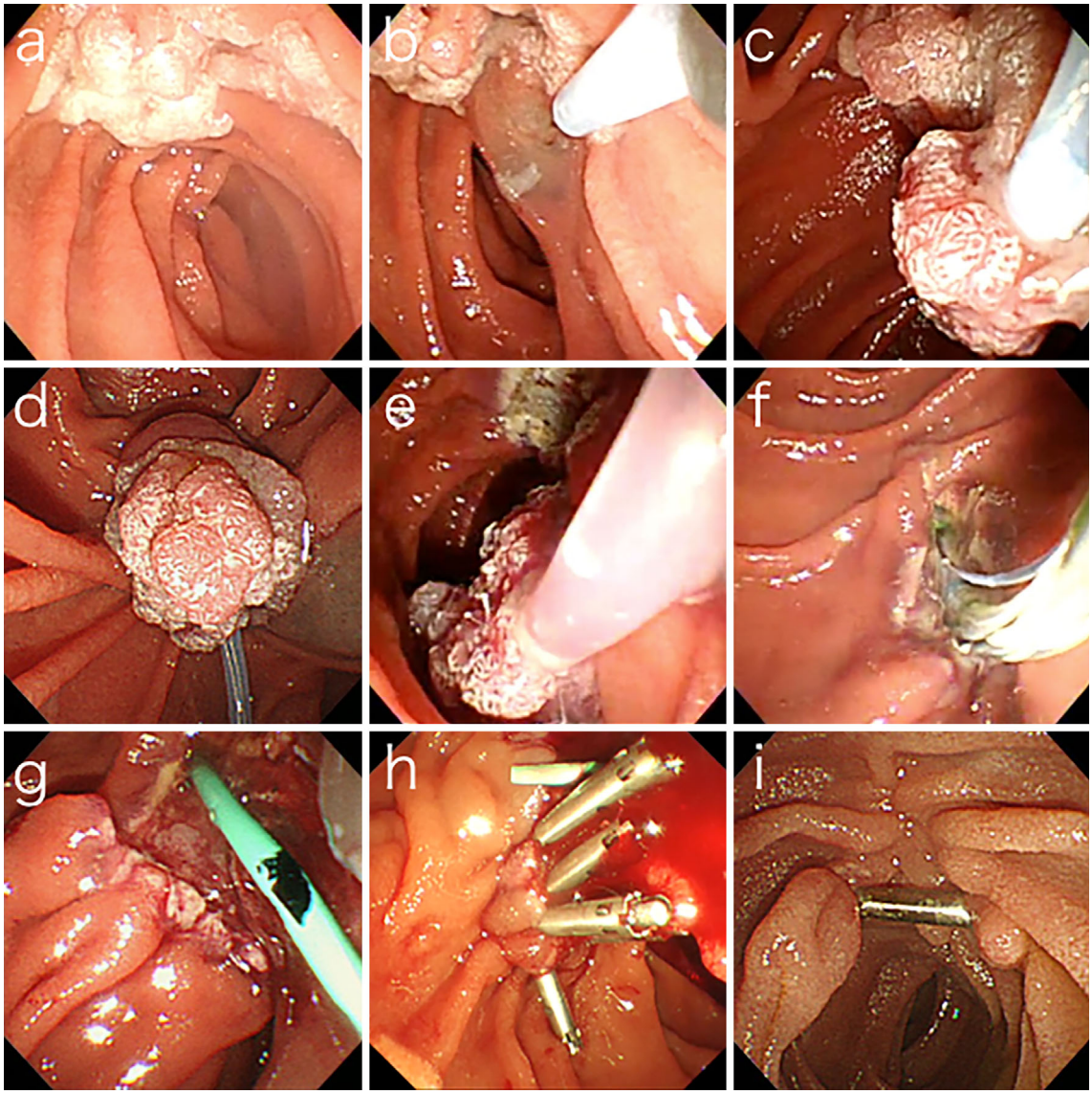

Figure **(a) Endoscopic features of laterally spreading ampullary adenomas. (b) Submucosal injection with indigo carmine dye was performed to elevate the extrapapillary lesions. (c) First, the extrapapillary lesions were removed using a spiral snare. (d) Finally, the main lesion of ampullary adenoma was removed using the standard en bloc technique without submucosal injection. (e) The specimens were grasped using net forceps. (f) Endoscopic biliary sphincterotomy was performed. (g) A pancreatic duct stent was placed. (h) Endoscopic closure of the mucosal defect, particularly at the anal side of cutting, was performed after EP using an endoscopic hemoclip. (i) Follow-up at three months revealed no residual adenoma and clean scar with a hemoclip.**

control population of smaller conventional ampullary adenomas treated in the same time period.

Materials and Methods

Between May 1999 and September 2015, 136 patients underwent EP at Tokyo Medical University Hospital. Our indications for EP were follows: 1) lesions <4 cm in size (mostly ≤3 cm), 2) no evidence of malignancy based on endoscopic appearance (no ulceration, no excessive friability) and soft consistency, 3) benign histologic findings on a forceps biopsy, and 4) the absence of extension into the pancreatic duct or biliary duct. For laterally spreading ampullary adenomas, we proposed endoscopic piecemeal resection for patients who refused surgical resection.

This study was approved by our Institutional Review Board (No. 3521), and informed consent was obtained from all individual participants included in this study.

Piecemeal resection technique for laterally spreading ampullary adenomas (Figure)

EP was performed with a duodenoscope with a large working channel (4.2 mm in diameter) and a spiral snare (20 mm, Spiral Snare; Olympus Medical Systems, Tokyo, Japan) with a microprocessor-controlled electrosurgical generator (ICC200; ERBE ElektromedizinL, Tubingen, Ger-

Table 1. The Characteristics of the Patients and Technical Results.

	En block	Piecemeal
Number of patients	125	11
Mean age, years, ±SD (range)	62.7±13.1 (20-86)	61.3±11.5 (35-77)
Sex, men/women	77/48	5/6
Mean tumor size, mm, ±SD (range)	15.6±6.4 (6-35)	26.8±6.6 (15-35)
A single treatment session, n (%)	104 (83.2)	8 (72.7)
Total resection rate	98.4%	100%
Final histology, n (%)		
Adenoma	103 (82.4)	7 (63.6)
Carcinoma in adenoma	14 (11.2)	3 (27.3)
Carcinoma	4 (3.2)	1 (9)
Hyperplasia	4 (3.2)	0

SD: standard deviation

many). The output was set for Endocut mode, effect 3 (output limit 120 W), and soft coagulation (output limit 30 W).

The en bloc removal of laterally spreading ampullary adenomas appeared to be difficult or impossible (Figure a). Before piecemeal resection, submucosal injection of indigo carmine dye was usually performed to elevate the extrapapillary lesions (Figure b). These lesions were then removed using a spiral snare from the anal side to the oral side (Figure c). Finally, the main lesion of ampullary adenoma was removed using the standard en bloc technique without submucosal injection (Figure d). To avoid the loss of the resected specimen, we grasped the specimen using net forceps (Figure e) and removed the endoscope immediately to prevent any damage to the specimen and thereby allow for a more accurate pathological diagnosis. We did not place a biliary stent and instead performed endoscopic biliary sphincterotomy (Figure f). We did place a pancreatic duct stent to avoid obstructive pancreatitis due to EP (Figure g). Usually, straight-type 5-Fr diameter and 5- to 7-cm-long pancreatic duct stents with double flanges were used. We then intentionally performed sufficient endoscopic closure of the mucosal defect, particularly at the anal side of cutting, after EP using an endoscopic hemoclip (Resolution™; Boston Scientific Japan, Tokyo, Japan) to prevent hemorrhaging (Figure h).

After EP, all resected specimens were recovered for a histological evaluation, and the tumor size was determined using the endoscopic specimens before formalin fixation (in piecemeal resection cases, the size was determined using endoscope field-of-view measurement).

Follow-up

Follow-up duodenoscopy was performed one to three months later. Potential areas of adenoma recurrence underwent a biopsy followed by endoscopic resection preferentially or ablation with argon plasma coagulation if resection was not possible.

Statistical analyses

Statistical analyses were performed using the StatMate III software program (ATMS, Tokyo, Japan). Normally distributed data were presented as the means±standard deviation (SD). A p value <0.05 was considered to indicate a statistically significant difference.

Results

One-hundred and thirty-six patients with papillary adenomas were referred for consideration of endoscopic papillectomy. Of these patients, 125 underwent en bloc resection, and 11 underwent piecemeal resection. The characteristics of the patients and the technical results are shown in Table 1.

En bloc resection

The man-to-woman ratio with en bloc resection was 77: 48, the mean age was 62.7±13.1 years (range, 20-86 years), and the mean tumor diameter was 15.6±6.4 (range, 6-35) mm. The final pathological diagnoses were 103 adenomas, 14 carcinomas in adenoma, 4 carcinomas, and 4 hyperplasia. A single session of treatment was possible in 104 (83.2%) of the 125 patients. Additional treatment was required for the remaining 21 (16.8%) patients. For these 21 patients, the post-resection pathological diagnoses were 19 adenomas, 1 carcinoma in adenoma, and 1 carcinoma. Both the carcinoma in adenoma and carcinoma had vein insults that required surgical operation. Pancreaticoduodenectomy was performed in one patient, while the remaining patient was not indicated for surgery due to comorbidity.

The total resection rate including additional treatments was 98.4%.

Piecemeal resection

The man-to-woman ratio with piecemeal resection was 5: 6, the mean age was 61.3±11.5 years (range, 35-77 years), and the mean tumor diameter was 26.8±6.6 (range, 15-35) mm. The final pathological diagnoses were seven adenomas, three carcinomas in adenoma, and one carcinomas. A single session of treatment was possible in 8 (72.7%) of the 11 patients. Additional treatment was required for the remaining 3 (27.3%) patients. None required additional surgical operations. The total resection rate including additional treatments

Table 2. Patients Undergoing Piecemeal Resection.

Patient	Age, years/ sex	size (mm)	Number of piecemeal resections	Single treatment session	Additional treatments	Complete resection	Final pathological diagnosis	Complications
1	55/F	15	2	Yes	-	Yes	Carcinoma in adenoma	No
2	57/M	18	2	Yes	-	Yes	Carcinoma in adenoma	Hemorrhaging
3	63/M	19	2	Yes	-	Yes	Adenoma	No
4	72/M	25	2	Yes	-	Yes	Adenoma	No
5	35/M	30	2	No	Snare + APC	Yes	Adenoma	No
6	66/F	30	2	Yes	-	Yes	Adenoma	Papillary stenosis
7	77/F	25	3	Yes	-	Yes	Carcinoma	No
8	67/F	30	3	Yes	-	Yes	Adenoma	No
9	71/F	32	3	No	APC	Yes	Adenoma	Pancreatitis
10	63/M	35	3	Yes	-	Yes	Carcinoma in adenoma	Hemorrhaging
11	48/F	35	4	No	APC	Yes	Adenoma	No

APC: argon plasma coagulation

Table 3. Procedure-related Complications.

	En bloc (n=125)	Piecemeal (n=11)	p value
Complications n (%)			
Hemorrhaging	21 (16.8)	2 (18.2)	NS
Pancreatitis	11 (8.8)	1 (9.1)	NS
Cholangitis/Cholecystitis	3 (2.4)	0	NS
Perforation	5 (4)	0	NS
Papillary stenosis	5 (4)	1 (9.1)	NS

NS: not significant

was 100%. The summary of patients undergoing piecemeal resection is shown in Table 2.

Complications

The procedure-related complications are described in Table 3. In en bloc resection, we found 21 cases of hemorrhaging (16.8%), 11 cases of acute pancreatitis (8.8%), 3 cases of acute cholangitis/cholecystitis (2.4%), and 5 cases of perforation (4%) as early complications, along with 5 cases of papillary stenosis resulting from biliary and/or pancreatic duct obstruction caused by fibrosis after endoscopic resection (4%) as a late complication among the 125 cases. In piecemeal resection, we found 2 cases of hemorrhaging (18.2%) and 1 cases of acute pancreatitis (9.1%) as early complications, along with 1 cases of papillary stenosis (9.1%) as a late complication among the 11 cases. Perforation and cholangitis/cholecystitis were not observed.

Discussion

The results of this study clearly show that piecemeal resection of laterally spreading ampullary adenomas is as safe and effective as en bloc resection. Therefore, piecemeal resection is a viable alternative to en bloc resection for laterally spreading ampullary adenomas. Most ampullary adenomas can be successfully removed in a single session using the combination technique of endoscopic mucosal resection and papillectomy.

In terms of residual tumor, complete endoscopic resection of the ampullary tumor is defined as the absence of an endoscopically visible and histologically proven residual tumor for a follow-up of three to six months (16, 17). In this study, we treated lesions that were detected during one to three months of follow-up as a residual tumor. In the piecemeal resection group, all residual tumors were able to be treated with snare resection, removal with biopsy forceps, or thermal ablation by argon plasma coagulation. Although there was no significant difference in the rate of residual tumors between the two groups, the rate in the piecemeal resection group (27.3%) was higher than in the en bloc resection group (16.8%) in the present study. Furthermore, the residual mucosa tended to be found in proportion to the number of piecemeal resections in a single procedure, as shown in Table 2. As such, the number of resections should be reduced as much as possible, and careful follow-up by endoscopic observation and a tissue biopsy is necessary for patients who undergo many piecemeal resections in a single procedure.

Regarding complications, bleeding, pancreatitis, and perforation carry a higher risk of a fatal outcome than cholangitis/cholecystitis or papillary stenosis, which can be easily managed with endoscopic drainage (18, 19). Bleeding is the most common complication, with rates of 0% to 25% reported in previously published studies (17). One of those reports described the rate of bleeding after endoscopic removal of large ampullary adenomas (>30 mm) as 10.3% (20). In the present study, bleeding occurred in 16.8% of patients undergoing en bloc resection and in 18.2% of patients undergoing piecemeal resection, with no marked difference between them. In piecemeal resection, the resection area is larger and the exposure to digestive juice greater than with en bloc resection, making bleeding more likely to occur. Therefore sufficient endoscopic closure of the mucosal defect might prevent bleeding in cases with a large resection area.

However, pancreatitis is the most problematic complication. Placement of a prophylactic pancreatic duct stent is highly recommended in order to reduce the risk of pancreatitis (21, 22). The rate of pancreatitis after EP was 8.8% in the en bloc resection group and 9.1% in the piecemeal resection group in this study. Most cases of pancreatitis were mild to moderate and were able to be managed by conservative therapy. Serious pancreatitis was observed in one patient in the en bloc resection group in whom a pancreatic stent was placed. Piecemeal resection seems not to be associated to pancreatitis.

Perforation was observed in 5 (4%) patients in the en bloc resection group, including 1 with serious pancreatitis as described above. All of these cases were retroperitoneal perforation, and the four aside from the serious pancreatitis case were improved solely by temporary endoscopic nasobiliary drainage tube placement. In contrast, there were no cases of perforation in the piecemeal resection group. Before piecemeal resection, submucosal injection was usually performed to elevate the extrapapillary lesions, which may have helped prevent perforation even if large lesions were being resected.

In general, the treatment of laterally spreading ampullary tumors requires a high endoscopic resection technique. However, in the current study, the piecemeal resection group developed no perforation, and the outcomes were not inferior to those in the en bloc resection group. Two reasons are suggested for this: 1) many cases underwent piecemeal resection in the later years after EP induction, and 2) experienced endoscopists tended to perform piecemeal resection more frequently than inexperienced endoscopists. For these reasons, piecemeal resection for laterally spreading ampullary adenomas should be performed at high-volume centers.

An important point to consider is whether or not to perform endoscopic closure of the mucosal defect using an endoscopic hemoclip after piecemeal resection. The present study showed that piecemeal resection tends to require additional endoscopic treatment more frequently than en bloc resection because of the high residual tissue rate. In addition, some ampullary tumors are identified as carcinoma only after endoscopic resection. Therefore, as measures against hemorrhaging after piecemeal resection, it might be safer to perform careful follow-up by endoscopic observation without endoscopic closure of the mucosal defect until the long-term recurrence rate after piecemeal resection is clarified.

The limitations of this study were its retrospective nature, the lack of a control group, the small case series, and the single-center nature of the experience.

In conclusion, the present study showed that piecemeal resection for laterally spreading ampullary adenomas was not inferior to en bloc resection in the short-term complication rate or short-term recurrence rate. However, although we were able to achieve complete resection of the residual tumor with additional endoscopic treatment, the medium- and long-term recurrence rate remains unclear. These later outcomes will need to be determined in the near future in order to establish piecemeal resection for laterally spreading ampullary adenomas as a viable alternative procedure to surgical resection.

Institutional review board statement: This study was approved by our institutional review board (Tokyo Medical University No. 3521).

Informed consent statement: Informed consent was obtained from all of the patients.

The authors state that they have no Conflict of Interest (COI).

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References

1. Chathadi KV, Khashab MA, Acosta RD, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc **82**: 773-781, 2015.

2. Scarpa A, Capelli P, Zamboni G, et al. Neoplasia of the ampulla of Vater. Ki-ras and p53 mutations. Am J Pathol **142**: 1163-1172, 1993.

3. Cahen DL, Fockens P, de Wit LT, Offerhaus GJ, Obertop H, Gouma DJ. Local resection or pancreaticoduodenectomy for villous adenoma of the ampulla of Vater diagnosed before operation. Brit J Surg **84**: 948-951, 1997.

4. Jordan PH Jr, Ayala G, Rosenberg WR, Kinner BM. Treatment of ampullary villous adenomas thatmay harbor carcinoma. J Gastrointest Surg **6**: 770-775, 2002.

5. Tran TC, Vitale GC. Ampullary tumors: endoscopic versus operative management. Surg Innov **11**: 255-263, 2004.

6. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc **39**: 127-131, 1993.

7. Norton ID, Gostout CJ, Baron TH, Geller A, Peterson BT, Wiesema MJ. Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc **56**: 239-243, 2002.

8. Maguchi H, Takahashi K, Katanuma A, Hayashi T, Yoshida A. Indication of endoscopic papillectomy for tumors of the papilla of Vater and its problem. Dig Endosc **15**: S33-S35, 2003.

9. Itoi T, Tsuji S, Sofuni A, et al. A novel approach emphasizing pre-

operative margin enhancement of tumor of the major duodenal papilla using narrow-band imaging in comparison to indigo carmine chromoendoscopy (with video). Gastrointest Endosc **69**: 136-141, 2009.

10. Tsuji S, Itoi T, Sofuni A, Mukai S, Tonozuka R, Moriyasu F. Tips and tricks in endoscopic papillectomy of ampullary tumors: single-center experience with large case series (with videos). J Hepatobiliary Pancreat Sci **22**: E22-E27, 2015.

11. Chathadi KV, Khashab MA, Acosta RD, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc **82**: 773-781, 2015.

12. Cheng CL, Sherman S, Fogel EL, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc **60**: 757-764, 2004.

13. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc **39**: 127-131, 1993.

14. Beger HG, Staib L, Schoenberg MH. Ampullectomy for adenoma of the papilla and ampulla of Vater. Langenbecks Arch Surg **383**: 190-193, 1998.

15. Han J, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla (with video). Gastrointest Endosc **63**: 292-301, 2006.

16. Cheng CL, Sherman S, Fogel EL, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc **60**: 757-764, 2004.

17. Han J, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla. Gastrointest Endosc **63**: 292-301, 2006.

18. Mukai S, Itoi T, Baron TH, et al. Indications and techniques of biliary drainage for acute cholangitis in updated Tokyo Guidelines 2018. J Hepatobiliary Pancreat Sci **24**: 539-549, 2017 (Epub ahead of print).

19. Umeda J, Itoi T. Current status of preoperative biliary drainage. J Gastroenterol **50**: 940-954, 2015.

20. Eswaran SL, Sanders M, Bernadino KP, et al. Success and complications of endoscopic removal of giant duodenal and ampullary polyps: a comparative series. Gastrointest Endosc **64**: 925-932, 2006.

21. Fazel A, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc **57**: 291-294, 2003.

22. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc **62**: 367-370, 2005.