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Cumulative detection and clinical outcomes of ampullary tumors in patients with familial adenomatous polyposis undergoing endoscopic surveillance

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Abstract

Background

Patients with familial adenomatous polyposis (FAP) are at an increased risk of ampullary tumors. This study aimed to evaluate their cumulative detection rate and clinical outcomes.

Methods

We retrospectively identified consecutive patients with FAP who first visited our hospital in 2007–2023 without a known ampullary tumor. The primary outcome was the cumulative detection of ampullary tumors. The secondary outcomes included the therapeutic outcomes of endoscopic papillectomy (EP) and clinical course of ampullary tumors managed by watchful waiting.

Results

Among 124 patients with FAP, ampullary tumors were found in 33 (pTis-T1a adenocarcinoma, n = 5; adenoma, n = 28). The median lesion size was significantly larger in the adenocarcinoma group than in the adenoma group (25 mm vs. 10 mm; $p = 0.001$). The cumulative detection of ampullary tumors linearly increased with age, reaching 33% by 50 years, and was significantly higher in patients with Spigelman stage II–IV disease than in those with stage 0–I ($p = 0.003$). EP was performed after the initial detection in 19 patients; 14 patients underwent watchful waiting. 2 (14%) of these subsequently required EP due to lesion growth. Thus, 21 patients underwent EP. Adverse events of EP included pancreatitis (14%), delayed bleeding (38%), and intraprocedural bleeding (5%). Local recurrence occurred in 38%.

Conclusions

Careful ampullary evaluation is required in older patients with FAP and those with an advanced Spigelman stage. EP was a reasonable therapeutic option, although adverse events and local recurrence require attention. Watchful waiting might be considered under appropriate surveillance.

INTRODUCTION

Familial adenomatous polyposis (FAP) is an autosomal-dominant hereditary disorder caused by pathogenic germline variants of the *adenomatous polyposis coli* (*APC*) gene [1]. It is characterized by colorectal adenomatous polyposis. Without treatment, approximately half of the patients develop colorectal cancer by the age of 40 years; approximately all develop it by the age of 60 [2]. In recent years, avoiding death from colorectal cancer has become possible through therapeutic interventions such as prophylactic colectomy [3] and intensive downstaging polypectomy, a strategy involving thorough endoscopic removal of numerous colorectal polyps [4–6]. Consequently, the management of duodenal

cancer, which is the third leading cause of death in patients with FAP [7], has become an important issue. Previous studies have indicated that duodenal tumors most commonly arise in the ampulla of Vater and its surrounding areas; moreover, periodic endoscopic surveillance is recommended for early detecting tumors in that area [7–11]. However, data regarding the cumulative detection rate, lesion characteristics, treatment outcomes, and natural history of ampullary tumors in patients with FAP remain scarce.

Therefore, the aims of this study were to assess the cumulative detection rate of ampullary tumors in patients with FAP who underwent regular endoscopic surveillance at our institution and evaluate the clinical outcomes in patients endoscopically treated and those managed by observation without immediate intervention.

METHODS

Patients

This single-center retrospective study was approved by the Ethics Committee of Osaka International Cancer Institute (approval number: 23243; approval date: March 19, 2024) and conducted in accordance with the principles of the Declaration of Helsinki. The study information was published on the hospital website and patient consent was obtained using an opt-out approach.

We evaluated consecutive patients who first visited our institution between April 2007 and October 2023 and were diagnosed with FAP. We excluded patients who had already been diagnosed with ampullary tumors at their initial visit, who underwent fewer than two esophagogastroduodenoscopies (EGD) during follow-up, who had a history of duodenal surgery before the first visit, whose follow-up period was shorter than 6 months, or who declined study participation via the institutional opt-out process.

Since genetic testing for *APC* mutations was not covered by the Japanese public insurance system, not all patients in this study underwent APC mutation analysis. Therefore, the diagnosis of FAP was based on clinical findings. The criteria for the clinical diagnosis of FAP were: The presence of more than 100 colorectal adenomas and having approximately 10 to fewer than 100 adenomas with a family history of FAP [7].

Data collection

The following patient demographics were collected: Date of birth, age at first visit, sex, FAP phenotype (profuse, non-profuse, or attenuated type), results of *APC* genetic testing, history of colorectal cancer, history of extracolonic manifestations (i.e., thyroid cancer, gastric cancer, desmoid tumor), Spigelman stage at the initial EGD at our institution, and presence of an ampullary tumor. Ampullary tumors were histologically confirmed in specimens collected via biopsy or endoscopic papillectomy (EP). When discrepancies existed between biopsy and resected specimens, the diagnosis based on analysis of resected specimens was prioritized. The Spigelman stage included the number of polyps, maximum

diameter, tissue structure, and degree of dysplasia. Stages 0–IV were determined based on the total score (Table 1) [12].

Table 1
Modified Spigelman's score and stage

Factor	Score		
	1 Point	2 Points	3 Points
Number of polyps	1–4	5–20	> 20
Polyp size, mm	1–4	5–10	> 10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	—	High grade
Stage 0: 0 points, stage I: 1–4 points, stage II: 5–6 points, stage III: 7–8 points, and stage IV: 9–12 points.			

In patients with ampullary tumors, we collected data on the date of detection, lesion size, and whether EP was performed. Lesion size was estimated visually by each endoscopist. Data on the therapeutic outcomes of EP, such as rates of *en bloc* resection, R0 resection, adverse events (intraoperative bleeding, delayed bleeding, perforation, and pancreatitis), and recurrence, were also collected. Intraoperative bleeding was defined as any bleeding necessitating endoscopic intervention immediately after snare resection. Delayed bleeding was defined as endoscopically confirmed bleeding from the resection site that occurred after completing the initial procedure. Postprocedural pancreatitis was defined according to the criteria of Cotton *et al.*, the presence of abdominal pain consistent with pancreatitis and a serum amylase level exceeding three times the upper limit of normal range at 24 h after the procedure [13].

Endoscopic surveillance

Endoscopic examination of the upper gastrointestinal tract was performed using a forward-viewing gastroscope (GIF-H290Z, GIF-XZ1200, or GIF-EZ1500; Olympus, Tokyo, Japan) or pediatric colonoscope (PCF-Q260JI, PCF-PQ260I, or PCF-H290TI; Olympus) with a plastic cap at the distal end [9–11]. If the ampulla could not be completely visualized despite using a cap, a side-viewing endoscope (JF-260V, Olympus) was used. A biopsy of the papilla was performed if it appeared suspicious for tumor. Routine biopsy of the papilla was not included in the surveillance protocol given the potential risk of pancreatitis. Endoscopic examinations were performed at intervals not exceeding one year.

Indications for EP

In general, indications for EP in patients with FAP were ampullary adenoma > 10 mm in the absence of intraductal extension into the pancreatic and/or bile ducts, as assessed by endoscopic ultrasonography

(EUS) [9, 10]. However, treatment was occasionally performed for lesions < 10 mm at the patient's strong request; conversely, even for lesions ≥ 10 mm, watchful waiting was sometimes selected based on patient preference and clinical condition.

Regarding ampullary adenocarcinoma preoperatively confirmed by biopsy, the guidelines for EP remain controversial [14–17]. At our institution, EP was selected when EUS suggested ≤ T1 stage disease and cross-sectional imaging, including computed tomography and magnetic resonance imaging, demonstrated no evidence of lymph node metastasis.

EP

EP was performed jointly by gastrointestinal and pancreatobiliary endoscopists. All procedures were performed under fluoroscopic guidance using a therapeutic duodenoscope (TJF-260V or TJF-290V; Olympus). Gastrointestinal endoscopists captured lesions using a snare and performed electrocautery resection using a high-frequency generator (ICC-200, VIO300D, or VIO3; ERBE, Tubingen, Germany). Subsequently, clip closure was performed on the anal side of the resected ulcer at the discretion of the endoscopist to prevent delayed bleeding. Finally, pancreatic and biliary stents were placed to prevent pancreatitis and biliary obstruction, respectively. At our institution, pancreatic and biliary drainage is generally performed primarily by stenting. The procedures were performed under deep sedation with midazolam and opioid-pethidine. Patients fasted on the day of treatment and following day; oral intake was resumed on postoperative day 2.

Measured outcomes

The primary outcome measure was the cumulative detection rate of ampullary tumors in patients with FAP. In addition, the cumulative detection rate of ampullary tumors was compared by stratifying patients according to Spigelman stage at the initial EGD.

The secondary outcome measures comprised the therapeutic outcomes of EP, comparison of clinical characteristics between patients with ampullary adenocarcinoma and those with adenoma and the clinical outcomes of ampullary adenomas in patients who were initially managed by watchful waiting.

Statistical analysis

Comparisons of continuous variables between the two groups were performed using the Mann–Whitney U test, while comparisons of categorical variables were conducted using Fisher's exact test or the chi-square test, as appropriate. The cumulative detection rate of ampullary tumors was plotted using the Kaplan-Meier method; the difference between Spigelman stages 0–I and II–IV was evaluated by the log-rank test. The cumulative incidence of local tumor recurrence after EP was plotted using the Kaplan-Meier method. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A *P* value < 0.05 was considered statistically significant.

RESULTS

Study flow and patient characteristics

Table 2
Patient characteristics

	Total	Ampullary tumor positive	Ampullary tumor negative	*p*-value
	N = 124	**n = 33**	**n = 91**	
Age at the first visit, y	40 (30–50)	44 (31–50)	38 (30–49)	0.06
Sex				1.00
Male	50 (40%)	13 (39%)	37 (41%)	
Female	74 (60%)	20 (61%)	54 (59%)	
FAP phenotype				N/A[b]
Profuse	3 (2%)	0 (0%)	3 (3%)	
Non-profuse	68 (55%)	13 (39%)	55 (60%)	
Attenuated	6 (5%)	3 (9%)	3 (3%)	
Unknown[a]	47 (38%)	17 (52%)	30 (33%)	
APC mutation				N/A[b]
Positive	34 (27%)	9 (27%)	25 (27%)	
Negative	3 (2%)	0 (0%)	3 (3%)	
Not tested	87 (70%)	24 (73%)	63 (69%)	
History of colorectal cancer	26 (21%)	4 (12%)	22 (24%)	0.21
History of thyroid cancer	7 (6%)	4 (12%)	3 (3%)	0.08
History of gastric cancer	27 (22%)	9 (27%)	18 (20%)	0.61
History of desmoid tumor	12 (10%)	5 (15%)	7 (8%)	0.30
Spigelman stage at the initial EGD				**0.04**
Stage 0	12 (10%)	0 (0%)	12 (13%)	
Stage I	7 (5%)	0 (0%)	7 (8%)	
Stage II	26 (21%)	10 (29%)	16 (18%)	
Stage III	60 (48%)	17 (48%)	43 (47%)	
Stage IV	19 (15%)	6 (20%)	13 (14%)	

	Total	Ampullary tumor positive	Ampullary tumor negative	*p*-value
	N = 124	n = 33	n = 91	
Data are expressed as the median (interquartile range) or number (%).				
FAP, familial adenomatous polyposis; *APC*, adenomatous polyposis coli; EGD, esophagogastroduodenoscopy.				
[a] The primary reason was the inability to evaluate adenoma density due to prior colorectal surgery.				
[b] As many cases were classified as 'Unknown or Not tested' we did not perform a *p*-value calculation.				

Cumulative detection of ampullary tumors

The cumulative detection rate of ampullary tumors linearly increased with age: 4% at 30 years, 12% at 40 years, 23% at 50 years, and 43% at 60 years (Fig. 2). Compared with patients classified as Spigelman stages 0–I at the initial EGD, the cumulative detection rate of ampullary tumors was significantly higher in those classified as Spigelman stages II–IV at the initial EGD. At age 50, the cumulative detection rate was 0% in the Spigelman stage 0–I group and 27% in the stage II–IV group ($p = 0.003$) (Fig. 3).

Therapeutic outcomes of endoscopic papillectomy

Among the 33 patients with ampullary tumors, EP was performed at the initial detection in 19 patients, and the remaining 14 underwent watchful waiting. Among 14 patients undergoing watchful waiting, 2 (14%) required EP due to lesion growth. Thus, 21 patients underwent EP.

Table 3 presents the treatment outcomes and histopathological results. The median lesion size was 10 mm (IQR, 9–17). *En bloc* resection was achieved in 11 of 21 patients (52%) and R0 resection in 4 of 21 patients (19%).

Table 3
Treatment outcomes of endoscopic papillectomy and histopathologic results.

Lesion size, mm	**10 (9–17)**
En bloc resection	11 (52)
Resection Margin	
HM 0/X/1	6 (30) / 10 (50) / 4 (20)
VM 0/X/1	13 (65) / 3 (15) / 4 (20)
R0 resection	4 (19)
Final histology[a]	
Adenoma	15 (71)
Adenocarcinoma	5 (24)[b]
Adverse events	
Intraoperative bleeding	1 (5)
Delayed bleeding	8 (38)
Perforation	0 (0)
Pancreatitis	3 (14)
Recurrence	8 (38)
Data are expressed as the median (interquartile range) or number (%).	
[a]The specimen was lost in 1 case.	
[b]pTis: 1 case; pT1a: 4 cases.	

On final pathological diagnosis, 15 lesions (71%) were adenomas and 5 (24%) were adenocarcinomas (pTis, 1 case; pT1a, 4 cases); the specimen was lost in 1 case. Adverse events included bleeding [intraoperative, 1 case (5%); delayed, 8 cases (38%)], pancreatitis in 3 cases (14%), and no perforations.

During the median follow-up period of 29 months (IQR, 13–53), local recurrence was found in 8 cases (38%, 8/21), with cumulative recurrence rates of 1, 2, and 3 years at 11%, 39%, and 46%, respectively (Fig. 4). Among the 8 patients with local recurrence, 4 were retreated with EP, 1 with cold snare polypectomy, 1 with cold forceps polypectomy, and 2 with surveillance. No metastatic recurrences were observed in any patient.

Differences of clinical characteristics between ampullary adenocarcinomas and adenomas

Univariate analyses were performed to compare the clinical backgrounds of the 5 patients whose final pathological diagnosis after EP was adenocarcinoma and 15 patients who were diagnosed with adenoma (Table 4). The median lesion size was significantly larger in patients with adenocarcinomas (25 mm [IQR, 13–35 mm]) than in those with adenomas (10 mm [IQR, 8–13 mm]; $p = 0.001$). Additionally, the proportion of patients classified as Spigelman stage IV at the initial EGD was significantly higher in patients with adenocarcinoma (80%, 4/5) than that in patients with adenoma (0%, 0/16; $p = 0.001$). There were no significant differences in age or sex between the patients with adenocarcinomas and those with adenomas. The proportion (95% confidence intervals) of adenocarcinoma according to lesion size was 0% (0%–52%) for lesions < 10 mm, 13% (0.3%–53%) for 10– < 15 mm, 33% (0.8%–91%) for 15– < 20 mm, and 75% (19%–99%) for ≥ 20 mm, demonstrating an increasing trend in adenocarcinoma proportion with larger lesion size (Fig. 5).

Table 4
Differences in clinical characteristics between ampullary adenocarcinomas and adenomas resected by endoscopic papillectomy

	Ampullary adenocarcinoma	**Ampullary adenoma**	***p*-value**
	n = 5	**n = 16**	
Age at endoscopic papillectomy, y	50 (38–59)	46(34–56)	0.64
Sex			1.00
Male	2 (40)	5 (31)	
Female	3 (60)	11 (69)	
Lesion size, mm	25 (13–35)	10 (8–13)	**0.001**
Spigelman stage IV at the initial EGD	4 (80)	0 (0)	**< 0.001**
History of colorectal cancer	1 (20)	2 (13)	1.00
History of thyroid cancer	0 (0)	2 (13)	1.00
History of gastric cancer	1 (20)	5 (31)	1.00
History of desmoid tumor	0 (0)	3 (19)	0.55
Data are expressed as the median (interquartile range) or number (%).			
EGD, esophagogastroduodenoscopy.			

Clinical course of duodenal ampullary tumor managed by watchful waiting

Among 33 patients with ampullary tumors, 14 patients with ampullary adenoma (42%, 14/33) were managed by watchful waiting. During the median follow-up period of 32 months (IQR, 4–93), 2 lesions (14%, 2/14) showed enlargement and subsequently underwent EP. Regarding these 2 lesions, the interval from detection to EP was 34 and 86 months; these were pathologically diagnosed as adenomas after EP. The remaining 12 lesions showed no progression during the follow-up.

DISCUSSION

Our findings revealed that the cumulative detection rate of ampullary tumors linearly increased with age, reaching 33% at 50 years. Furthermore, the cumulative detection rate of ampullary tumors was significantly higher in the Spigelman stage II–IV group than that in the stage 0–I group, suggesting an association between Spigelman stage severity and the development of ampullary tumors. Our findings indicated that the ampulla should be periodically and carefully examined, particularly in patients with FAP of advanced age and those with higher Spigelman stages.

Among a total of 124 patients included in this study, ampullary adenocarcinoma was confirmed only in 5 patients (4%), indicating a low prevalence. This rate was comparable to that reported in previous studies. A European multicenter surveillance study including 261 participants with FAP reported ampullary cancer in 13 patients (5%) [18]. Another report from Japan indicated ampullary cancer in 2 of 130 FAP patients (2%) [19]. Malignant transformation of ampullary adenomas in patients with FAP is reportedly rare [20, 21]. Accordingly, not all ampullary tumors should be treated; furthermore, careful selection of lesions that truly require therapeutic intervention is essential. Therefore, we performed univariate analysis, compared with the characteristics of ampullary adenoma, ampullary adenocarcinoma and showed a significantly larger median lesion size (25 mm vs. 10 mm, $p = 0.001$). Additionally, the proportion of patients with Spigelman stage IV was significantly higher in the adenocarcinoma group (80% vs. 0%, $p = 0.001$). These results could provide important guidance for determining indications for the treatment of ampullary tumors in patients with FAP.

However, whether ampullary adenocarcinoma could be included as an indication for EP remains controversial. In this study, EP was performed in 5 cases of ampullary adenocarcinoma. Since all were confirmed by final pathology to be Tis-T1a lesions, suggesting a low risk of lymph node metastasis, no surgical intervention was attempted. Although pancreaticoduodenectomy (PD) is generally recommended by the existing guidelines for ampullary cancer [14–17], necessitating discussions about the expansion of EP indications in the context of FAP-associated lesions. This is attributable not only to the highly invasive nature of PD, but also to the fact that patients with FAP often have a history of prophylactic colectomy. Furthermore, these patients are at an increased risk of developing postoperative desmoid tumors, which could occasionally be life-threatening [7].

We performed EP in 21 patients; regarding adverse events, pancreatitis occurred in 3 (14%), delayed bleeding in 8 (38%), and intraprocedural bleeding in 1 (5%) patients. In addition, local recurrence occurred in 8 patients (38%). These findings were comparable to the results in a recent meta-analysis of the outcomes of EP in patients with FAP (99 cases), which reported a pooled recurrence rate of 25%, a pancreatitis rate of 15%, and a bleeding rate of 9% [22]. Given the higher morbidity and mortality associated with surgical interventions in patients with ampullary tumors [23, 24], EP is considered a feasible option. However, of note, both the adverse event and recurrence rates were higher than those associated with other gastrointestinal endoscopic resections.

Considering the procedural risks of EP and low rate of cancerous transformation of ampullary adenomas, a watchful waiting approach might be an option for managing ampullary adenomas in patients with FAP. Among the 14 patients managed by watchful waiting in our cohort, 2 subsequently required EP due to lesion growth, whereas no progression was observed in the remaining 12 patients. All 2 lesions resected using the watchful-waiting approach were adenomas without evidence of malignant transformation. Given that, in our cohort, no adenocarcinoma was identified in lesions < 10 mm treated with EP, immediate intervention might not be required for managing such small lesions; a watchful-waiting approach could be an acceptable option. Therefore, careful and regular endoscopic surveillance is required in such situations. A key aspect of surveillance endoscopy involves thorough examination of the ampulla via cap-assisted endoscopy, with a low threshold for switching to a side-viewing endoscope if optimal visualization cannot be achieved [9–11]. We have consistently followed this approach in clinical practice.

The present study has some limitations. First, it was limited by its retrospective single-center design. However, restricting the study population to patients followed up at our institution allowed for standardized endoscopic surveillance quality. Second, the limited number of patients undergoing watchful waiting and insufficient follow-up duration precluded definitive conclusions on the validity of this approach. Third, a biopsy of an endoscopically normal-appearing duodenal papilla was not routinely performed at our institution. Therefore, our estimates reflect the detection of endoscopically recognizable ampullary tumors and may underestimate the frequency of histologically confirmed ampullary adenomas. Previous reports have suggested that adenomatous histological changes can exist in an endoscopically normal-appearing papilla and might not be identifiable without tissue sampling [25, 26]. These findings suggest that some adenomas were missed by visual assessment in our cohort. The natural history and clinical implications of adenomas detected only by biopsy remain to be clarified. Future prospective studies should assess whether routine or risk-adapted papillary biopsy improves clinically relevant outcomes.

In conclusion, we demonstrated an age-related increase in the detection of ampullary tumors in patients with FAP. Careful ampullary evaluation is required in older patients with FAP and in those with an advanced Spigelman stage. Given the low incidence of adenocarcinoma, watchful waiting might be acceptable for selected small lesions, particularly those < 10 mm. EP was a reasonable therapeutic option; however, attention should be paid to the possibility of local recurrence.

Declarations

Statement of Ethics

The study protocol was approved by the Institutional Review Board of Osaka International Cancer Institute (No. 23243), date of decision (March 19, 2024).

Opt-out informed consent protocol was used for use or collection of participant data for research purposes.

Conflict of Interest Statement

Takashi Kanesaka received honoraria from Olympus, AstraZeneca, and AI Medical Service. Satoki Shichijo received honoraria from FUJIFILM Medical, Olympus, Boston Scientific, EA Pharma, Daiichi-Sankyo, and Zeria Pharmaceutical. Sachiko Yamamoto received honoraria from Ono Pharmaceutical and MSD. Noriya Uedo received honoraria from Olympus, FUJIFILM Medical, Boston Scientific, Daiichi-Sankyo, Takeda Pharmaceutical, EA Pharma, Otsuka Pharmaceutical, AstraZeneca, Miyarisan Pharmaceutical, AI Medical Service, and MC Medical. Ryu Ishihara received honoraria from Olympus, FUJIFILM Medical, Daiichi-Sankyo, Miyarisan Pharmaceutical, AI Medical Service, Astra Zeneca, MSD, and Ono Pharmaceutical. Yugo Kai received honoraria from Kaneka Medix, Piolax Medical Devices, and Medico's Hirata. Ryoji Takada received honoraria from AstraZeneca, Novartis, Teijin Pharma, Myriad Genetics, Taiho Pharmaceutical, MSD, Century Medical, Guardant Health Japan, and SB-Kawasumi. The other authors declare no financial relationships.

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Author Contribution

M.K. and H.M. conceptualized the study, developed the methodology, performed the formal analysis, administered the project, developed the software, and prepared the visualizations. M.K., H.M., Ya.T., S.Yo., S.S., Yo.T., T.K., S.Ya., K.H., N.U., Y.K., R.T., and M.S. curated the data. M.K., H.M., Ya.T., S.Yo., S.S., T.K., K.H., N.U., R.I., and T.M. conducted the investigation. H.M. provided resources and wrote the original manuscript draft. M.K., S.Yo., R.I., T.M., Y.K., R.T., M.S., and H.Y. supervised the study. All authors reviewed and edited the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because they contain information that could compromise participant privacy but are available from the corresponding author on reasonable request.

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Figures

Figure 1

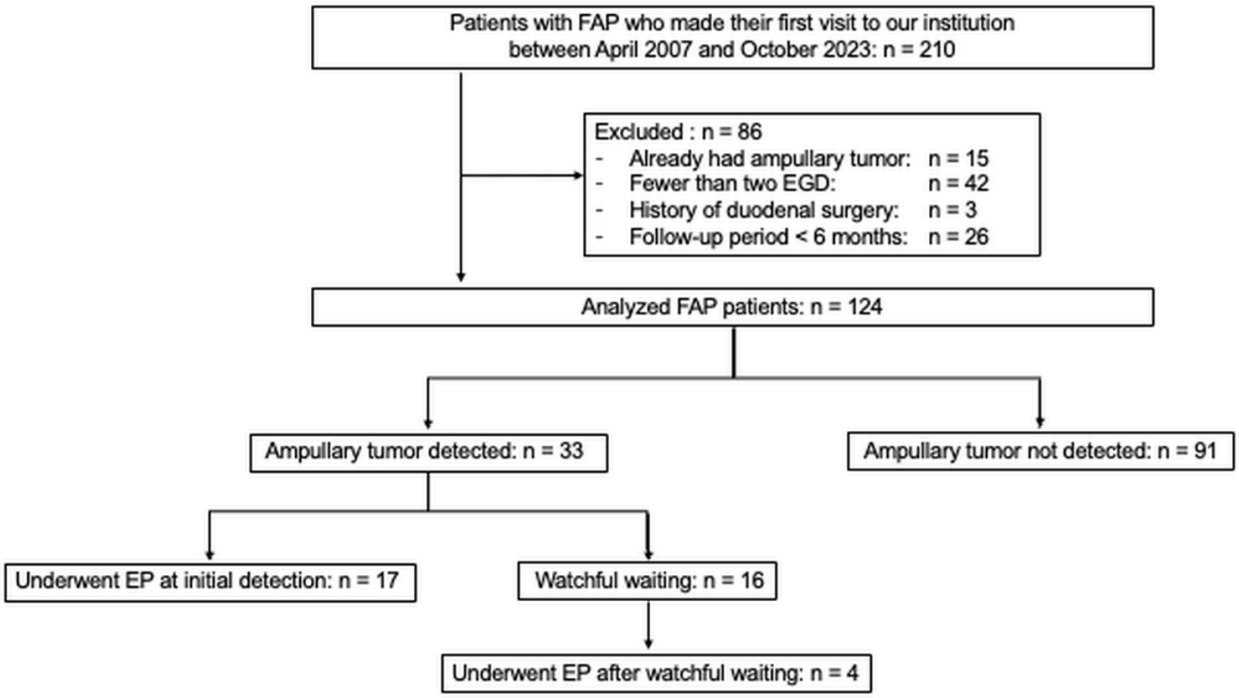


Figure 1

Patient flow diagram.

FAP, familial adenomatous polyposis; EGD, esophagogastroduodenoscopy; EP, endoscopic papillectomy.

Figure 2

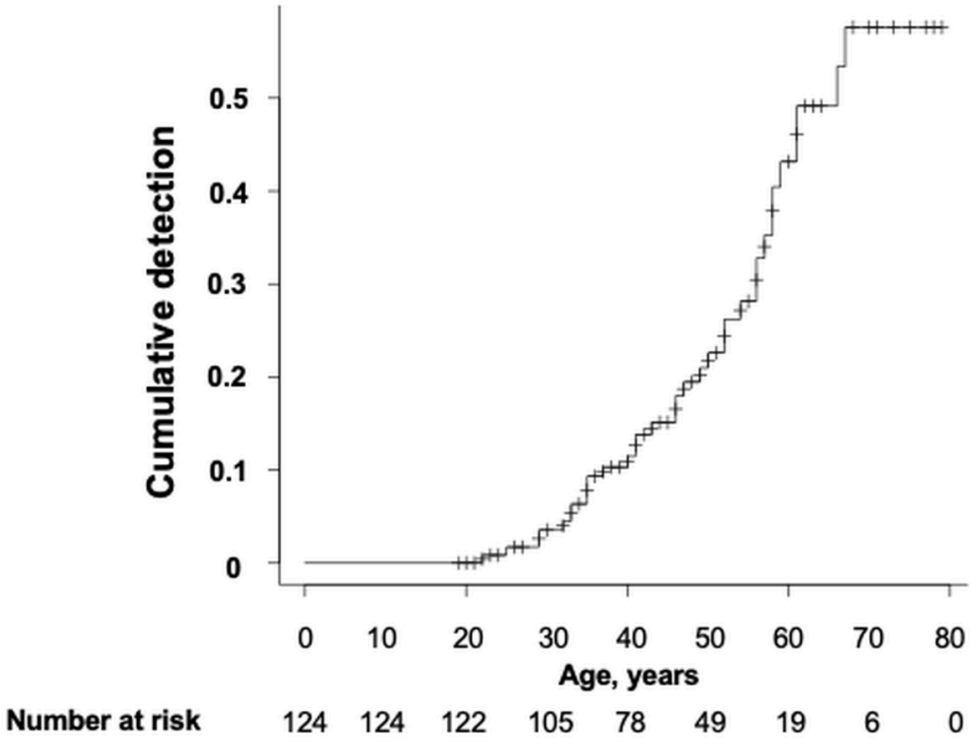


Figure 2

Cumulative detection rate of ampullary tumor in patients with familial adenomatous polyposis.

Figure 3

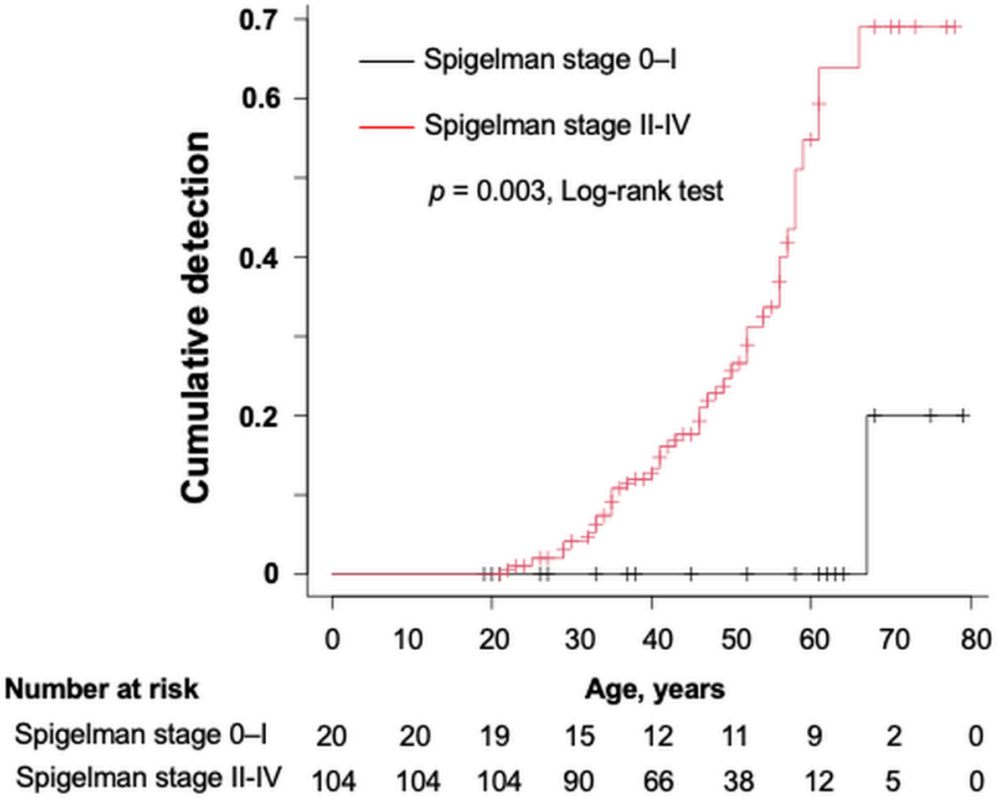


Figure 3

Cumulative detection rate of ampullary tumor between patients in Spigelman stage 0–I and Spigelman stage II-IV.

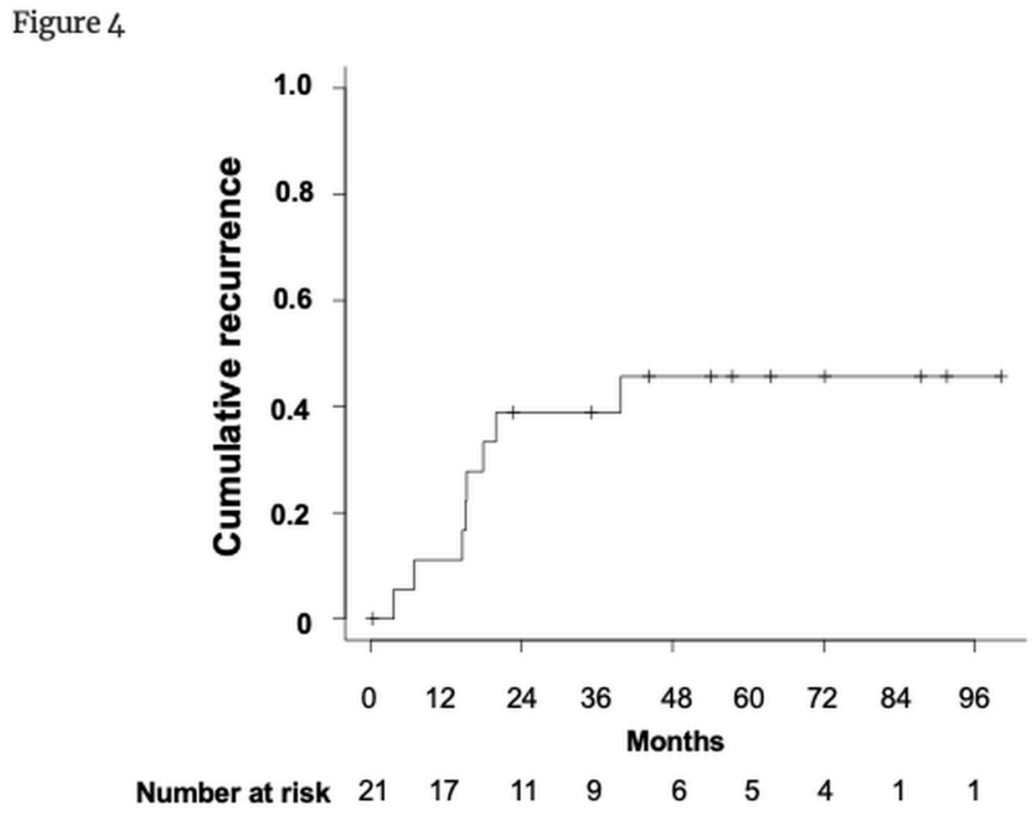


Figure 4

Cumulative local recurrence rate after endoscopic papillectomy for ampullary tumors.

Figure 5

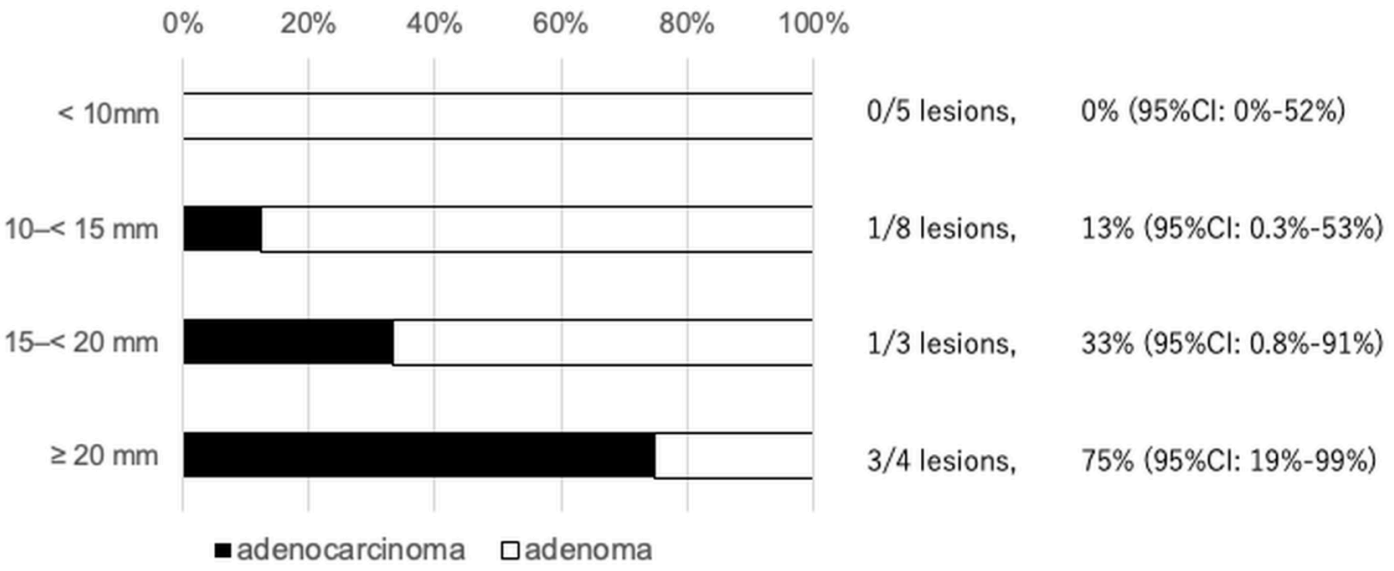


Figure 5

Proportion of adenocarcinoma according to lesion size (Analysis of lesions resected by endoscopic papillectomy).