Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4102-24
Intern Med 64: 1151-1159, 2025
http://internmed.jp

【 ORIGINAL ARTICLE 】

Endoscopic Papillectomy for Ampullary Gangliocytic Paraganglioma: A Case Series and Literature Review

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Abstract:

Objective Gangliocytic paraganglioma (GP) significantly affects patients' quality of life. However, studies on endoscopic papillectomy (EP) for ampullary GP are limited. We therefore evaluated the safety and efficacy of EP for treating ampullary GP.

Methods We retrospectively reviewed the clinicopathological characteristics of patients with GP who underwent EP at Nagoya University Hospital and conducted a literature survey.

Results We enrolled six patients with a median tumor diameter of 17 mm. Complications related to EP were observed in three patients: two experienced bleeding, one had mild acute pancreatitis, and one had perforation (duplicate patients included), all of whom improved conservatively. Five resected specimens were confined to the submucosal layer, and one was beyond the submucosal layer. All patients were monitored without surgery, and no disease recurrence was observed after a median follow-up of 73 months. A literature review identified 14 patients, and additional surgery due to a positive vertical margin after EP revealed lymph node metastasis in 2 patients. There was no disease recurrence or death.

Conclusion EP led to good long-term outcomes and effectively treated ampullary GP. Considering the potential for lymph node metastasis, additional surgery is recommended if the tumor exceeds the submucosal layer.

Key words: endoscopic papillectomy, gangliocytic paraganglioma, neuroendocrine tumor, complication, lymphatic metastasis

(Intern Med 64: 1151-1159, 2025)
(DOI: 10.2169/internalmedicine.4102-24)

Introduction

Gangliocytic paraganglioma (GP) is a rare cancer typically arising in the second portion of the duodenum. Common symptoms include gastrointestinal bleeding and abdominal pain, which can be detected asymptomatically using endoscopy (1). GP is considered to have a slow progression and good prognosis; however, 10% of patients develop lymph node metastases, and 1% develop liver metastases (2).

Notably, a fatal case has been previously reported (3). Thus, GP has malignant potential and requires further treatment. The standard treatment is pancreaticoduodenectomy (PD); however, its associated high morbidity and mortality rates have led to a preference for less-invasive treatments. Barret et al. (4) recommended endoscopic treatment or surgical local excision for duodenal GPs less than 2 cm duodenal GP without obvious lymph node metastasis.

The endoscopic treatment of GP depends on tumor localization. If the GP is a non-ampullary lesion, endoscopic mucosal resection or snare polypectomy is performed; if it is an ampullary lesion, however, endoscopic papillectomy (EP) is required. EP has been established as a minimally invasive

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Received: May 7, 2024; Accepted: August 10, 2024; Advance Publication by J-STAGE: September 27, 2024
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and highly effective treatment for ampullary adenomas (5, 6) and has been reported to be useful for managing early-stage ampullary carcinomas limited to the mucosa (7). Favorable long-term outcomes have been reported in several ampullary neuroendocrine neoplasms (NENs) (8). EP can also be a curative treatment for ampullary GP; however, studies of EP for ampullary GP are limited.

In the present study, we investigated the utility of EP for ampullary GP and reviewed the literature to evaluate its safety and efficacy. The findings of this study may help develop strategies for improving GP treatment.

Materials and Methods

Study design and patient selection

This retrospective observational study focused on patients who underwent EP for submucosal tumors of the papilla of Vater at the Nagoya University Hospital between June 2010 and November 2012. This study was approved by the Nagoya University Ethics Committee (approval number: 2016-00328296) and was conducted in accordance with the Declaration of Helsinki.

Indications and procedures of EP

The indications for EP for submucosal tumors at our hospital were as follows: the tumor was confined to the submucosal layer and did not extend into the bile or pancreatic duct or invaded the duodenal muscularis propria; en bloc resection was possible using a snare; and there was no lymph node or distant metastasis on computed tomography (CT).

Before EP, the tumor was observed using a duodenoscope, and endoscopic retrograde cholangiopancreatography (ERCP), intraductal ultrasonography (IDUS), or endoscopic ultrasonography (EUS) was performed to confirm the localization of the tumor. A biopsy was performed for the histopathological diagnosis. If the tumor was amenable to EP, a 15- or 20-mm hard single snare (SD-Y-0001; Olympus, Tokyo, Japan) was used for en bloc resection, followed by clip closure, and a 5-French stent was placed in the bile and pancreatic ducts. Two or more pathologists performed pathological evaluations of the biopsy and post-EP specimens. Complete resection was defined as the absence of tumor components in both the horizontal and vertical margins. Endoscopy and CT were performed six months after EP, and the patient was deemed to be in remission if there was no residual recurrence of the tumor. Subsequently, annual follow-ups with endoscopy and CT were recommended for five years.

Complications

Complications were evaluated according to the guidelines of the American Society for Gastrointestinal Endoscopy, as follows:

•**Bleeding**: Symptoms of gastrointestinal bleeding that appeared after EP and a decrease in the serum hemoglobin level by >2 g/dL.

•**Pancreatitis**: New onset of abdominal pain after EP and increased serum amylase levels more than three times higher than the baseline level.

•**Perforation**: Leakage of gastrointestinal contents from the intestinal tract on CT after EP.

Literature sources and search strategies

Relevant published reports were found in PubMed, Web of Science, and Cochrane Library databases using the following terms: ("non-chromaffin" OR "paraganglioma" OR "paraganglioneuroma" OR "gangliocytoma") AND ("ampulla of Vater" OR "duodenal"). Additional searches were conducted for the Igaku Chuo Zasshi database using the Japanese words for "gangliocytic paraganglioma" and "ampulla of Vater." The last search date was March 31, 2024. We screened all abstracts of the selected publications and extracted those describing the GP of the duodenum. Subsequently, the full text was reviewed, and articles in which EP was performed for ampullary GP were selected. Reviews, conference abstracts, letters to the editor, and articles without full texts were excluded.

Results

Six patients were enrolled at our hospital, and all were diagnosed with GP based on the resected pathological specimens obtained after EP. The patients' background characteristics are listed in Table 1. In brief, the median age was 48 years old; 2 patients were men, and 4 were women. Three cases were incidentally detected during upper gastrointestinal endoscopy at a medical checkup, and two were detected during a careful examination of gastrointestinal symptoms; one was discovered due to gastrointestinal bleeding and was subsequently referred for endoscopic treatment. None of the patients had hypertension or received antihypertensive drugs. Contrast-enhanced CT (CE-CT) showed that all tumors in the ampullary region were hypervascularized with no obvious metastasis. Each patient underwent a forceps biopsy, and three or more specimens were obtained. A pretreatment diagnosis of GP was made in three cases, while two cases lacked sufficient tumor components for a definitive diagnosis, and one case required differentiation between GP and NEN. The median procedure time was 42 min, with a median tumor diameter of 17 (range, 7-38) mm. All patients underwent en bloc snare resection. No cases of severe blood pressure fluctuations required vasopressors or antihypertensive drugs during the procedure. Complications were observed in three patients: two experienced bleeding, one had mild acute pancreatitis, and one had perforation (duplicate patients included). All patients improved with conservative treatment. A histopathological evaluation of the resected specimens revealed complete resection in five cases, with a positive vertical margin in one case. The median follow-up period was 73 (range, 17-147) months, and all patients were free of residual tumor, recurrence, or death. Two representa-

Table 1. **Six Patients Who Underwent Endoscopic Papillectomy for Gangliocytic Paraganglioma of the Papilla of Vater.**

Case	Age (y) / Sex	Symptom	Pre-treatment biopsy result	Number of biopsies	Tumor size (mm)	Procedure time (min)	Complication	Exceeding the submucosal layer	Resected margins HM/VM	Follow-up period (month)	Residual/ Recurrence
1	50/F	Melena	GP	5	38	40	Breeding	Yes	−/+	76	No
2	41/M	None	GP or NET	4	20	49	Perforation	No	−/−	147	No
3	51/F	Epigastric pain	Atypical epithelium	9	20	34	Pancreatitis/ breeding	No	−/−	19	No
4	46/F	None	No tumor seen	3	14	44	No	No	−/−	17	No
5	72/F	None	GP	3	13	50	No	No	−/−	146	No
6	38/M	Epigastric discomfort	GP	3	7	32	No	No	−/−	70	No

GP: gangliocytic paraganglioma, NET: neuroendocrine tumor, HM: horizontal margin, VM: vertical margin, F: woman, M: man

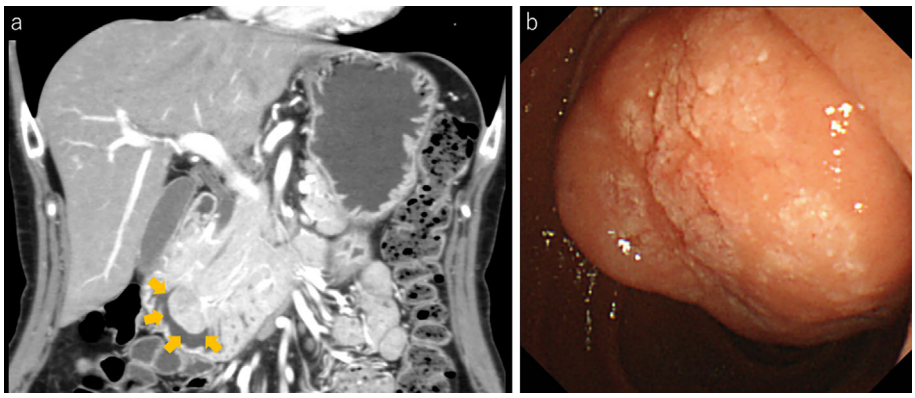

Figure 1. **(a) Contrast-enhanced computed tomography image showing a hypervascularized tumor in the ampullary region (yellow arrow). No bile or pancreatic duct dilatation was observed. (b) Duodenoscopy revealed a markedly enlarged papilla of Vater.**

tive cases are presented below.

Representative case presentation

• **Case 1**

A 50-year-old woman was diagnosed with ampullary GP 8 years before she visited our hospital. She was hospitalized twice for gastrointestinal bleeding and required a transfusion at the referral center. The patient was referred to our hospital because of a strong request for endoscopic treatment, although surgical treatment was recommended at the referral center. CE-CT revealed a hypervascularized tumor in the ampullary region (Fig. 1a). Dilatation of the bile or pancreatic duct was not observed. Duodenoscopy revealed a markedly enlarged papilla of Vater (Fig. 1b). IDUS revealed no invasion of the bile or pancreatic duct, and tumor invasion into the duodenal muscularis propria was unclear. Hematoxylin and eosin staining of biopsy specimens revealed proliferation of epithelioid cells, spindle-shaped cells in the stroma, and ganglion cell-like cells (Fig. 2a). Immunostaining showed that epithelioid cell nests stained positive for pan-cytokeratin (Fig. 2b), and spindle-shaped cells and ganglion cell-like cells stained positive for the S-100 protein (Fig. 2c) and chromogranin A (Fig. 2d), leading to a diagnosis of GP. Surgery was recommended again because of the possibility of lymph node metastasis. However, the patient refused surgery and underwent EP.

Hypertonic saline epinephrine solution (HSE) was localized to the anal side of the tumor, followed by en bloc snare resection using the auto-cut mode to prevent perforation. Gushing bleeding was observed immediately after resection. HSE administration and clip closure were performed using a QuickClip 2 (Olympus), and plastic stents were placed in the bile and pancreatic ducts. Blood samples collected on postoperative day (POD) 1 showed a decrease in the hemoglobin level by 1 g/dL. Endoscopy was performed on POD 2 to confirm the absence of wound bleeding, and the stents were removed. On POD 3, the appearance of melena, decreased blood pressure, and a hemoglobin level of 3.5 g/dL from baseline were observed. Emergency endoscopy was performed while red blood cell transfusions were administered; however, no bleeding from the wound was observed. The patient was conservatively monitored and did not experience any bleeding. The pathological specimen comprised mixed clusters of epithelioid, spindle-shaped, and ganglion-

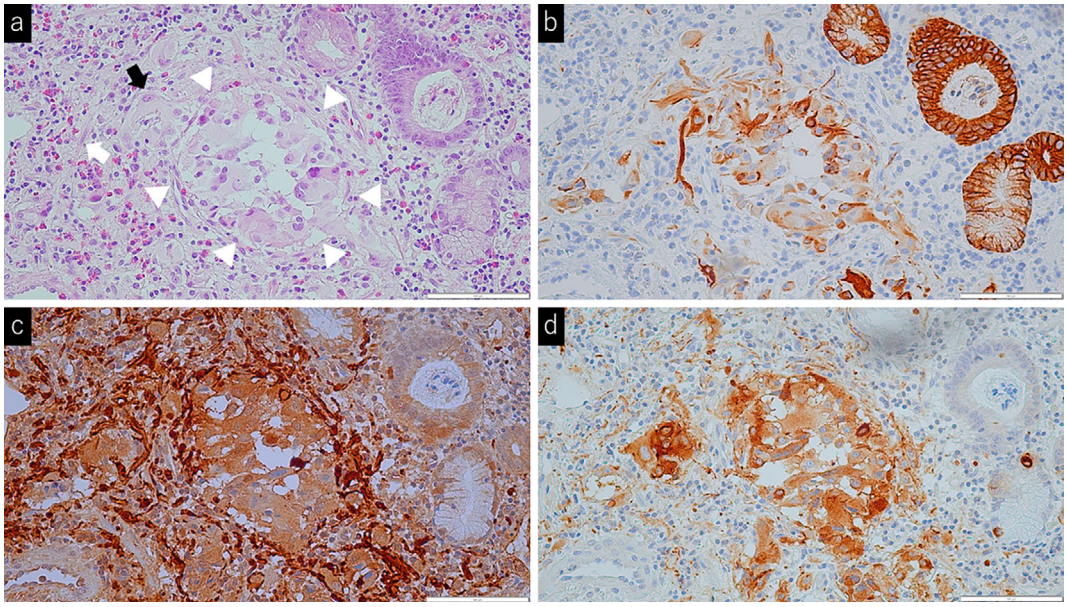

Figure 2. **(a) Hematoxylin and Eosin staining (×400) of the biopsy tissue showed epithelioid cell nests (white arrowhead), spindle-shaped cells (white arrow), and ganglion cell-like cells (black arrow). (b) Epithelioid cell nests were stained positive for pan-cytokeratin (×400). (c) Spindle-shaped and ganglion cell-like cells stained positive for S-100 protein (×400). (d) Spindle-shaped and ganglion cell-like cells stained positive for chromogranin A (×400).**

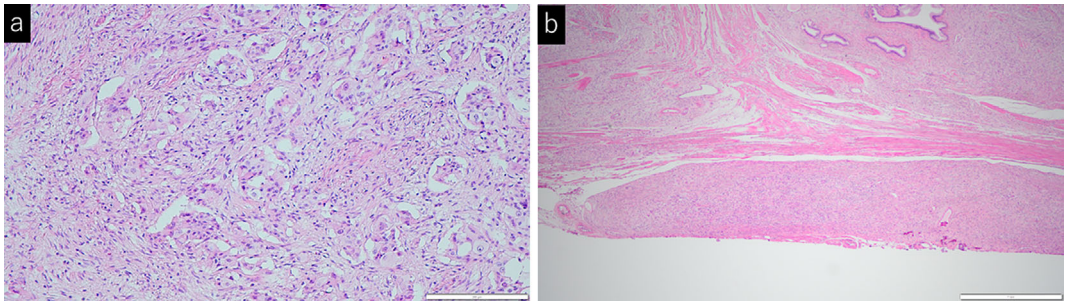

Figure 3. **(a) Pathological specimens obtained after endoscopic papillectomy comprise mixed clusters of epithelioid, spindle-shaped, and ganglion-like cells. (b) A tumor mass was observed beyond the submucosa, which was exposed on the resected surface.**

like cells (Fig. 3a). The horizontal margins were negative; however, tumor cells were found under the muscularis propria, suggesting positive deep margins (Fig. 3b). Since there was no obvious tumor remnant endoscopically on POD 7, we decided to carefully follow-up with the patient, fully informing her of the possibility of lymph node metastasis. Six months after EP, endoscopy and CE-CT revealed no residual tumor recurrence. No recurrence was observed after 76 months.

• **Case 2**

A 41-year-old man with no medical history or comorbidities was referred to our hospital for a careful examination after upper gastrointestinal endoscopy revealed an enlarged papilla of Vater. ERCP showed an elevated mass with a central depressed lesion in the papilla of Vater (Fig. 4a) but no extension into the bile or pancreatic duct on subsequent IDUS. EUS revealed a 13-mm hypoechoic mass confined to the submucosal layer (Fig. 4b). CE-EUS using perflubutane (GE Healthcare Japan, Tokyo, Japan) showed enhancement within 20 seconds (Fig. 4c), and the contrast effect persisted for up to 60 seconds. A biopsy revealed neuroendocrine cell-like cells exhibiting proliferation (Fig. 4d), suggesting NEN or GP. We considered surgery or endoscopic resection because of the frequency of lymph node metastasis in both diseases, and EP was performed as diagnostic treatment. The tumor was resected en bloc using a snare (Fig. 5a), and spurting bleeding was observed immediately after the resection (Fig. 5b). Hemostatic treatment with clips and HSE was performed. During stenting of the bile and pancreatic ducts, free air was found on the subhepatic surface, which was diagnosed as a perforation (Fig. 5c). Endoscopy revealed no perforation. Endoscopic nasopancreatic drainage and nasogastric tube placement were also performed. CT after EP indicated leakage of the digestive tract contents into the

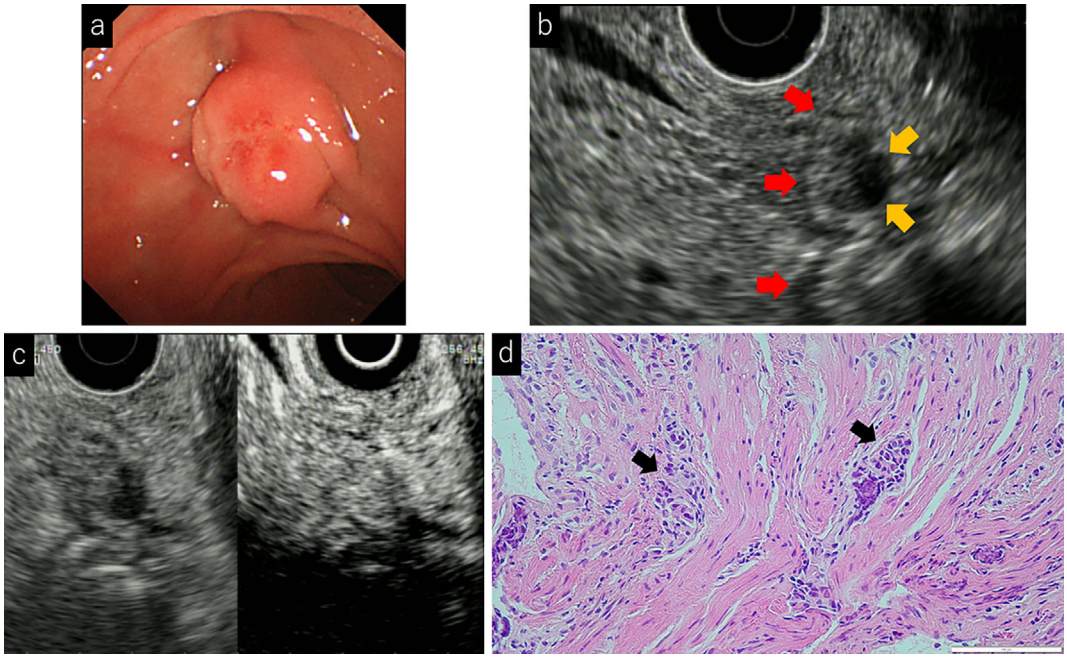

Figure 4. **(a) Duodenoscopy showed an elevated mass with a central depressed area in the papilla of Vater. (b) Endoscopic ultrasonography showed a hypoechoic mass (yellow arrow) confined to the submucosal layer (red arrow). (c) Contrast-enhanced endoscopic ultrasonography showed an inflow of contrast medium into the mass within 20 seconds. (d) Hematoxylin and Eosin staining (×400) of biopsy tissue showed nests of neuroendocrine cell-like cells (black arrow).**

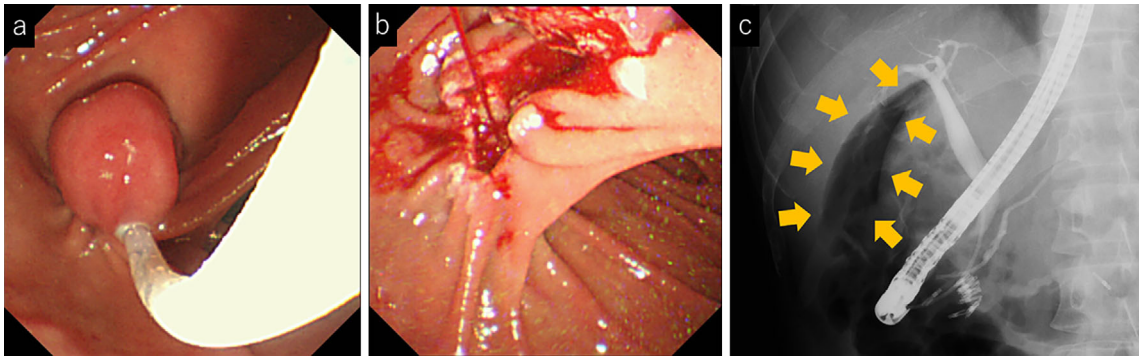

Figure 5. **(a) The submucosal tumor in the papilla of Vater was grasped with a snare. (b) Spurting bleeding was observed from the wound after resection. (c) Free air spreading the subhepatic surface (yellow arrow) was observed during endoscopic papillectomy.**

retroperitoneum. However, the patient did not experience abdominal pain or a fever and was treated conservatively. In the resected specimen, the epithelial cells were densely proliferating and surrounded by blood vessels in a Zellbaren pattern (Fig. 6a). Immunostaining showed that epithelioid and ganglion-like cells were positive for synaptophysin (Fig. 6b) and chromogranin A (Fig. 6c). Spindle-shaped cells stained positive for S-100 protein and surrounded the nests of the epithelioid cells (Fig. 6d). These findings led to the diagnosis of GP. Approximately two years after EP, the patient was hospitalized for deep vein thrombosis and pulmonary embolism. Genetic tests revealed protein S deficiency. Endoscopic follow-up was completed five years after EP, but the patient continued to undergo follow-up with CE-CT. No recurrence was observed after 147 months of treatment.

Results of the literature review

The literature search identified 423 articles. After title and abstract review, 209 articles on duodenal GP were identified. Subsequently, the full text was reviewed, and 13 articles in which 14 patients underwent EP were extracted (Fig. 7). The background characteristics of the included patients are presented in Table 2 (9-21). In brief, the median age was 52.5 years old; 6 patients were men, 8 were women, and 10 were symptomatic. Of the eight cases in which a pretreatment diagnosis was mentioned, GP was diagnosed in two cases: one with endoscopic sphincterotomy plus forceps bi-

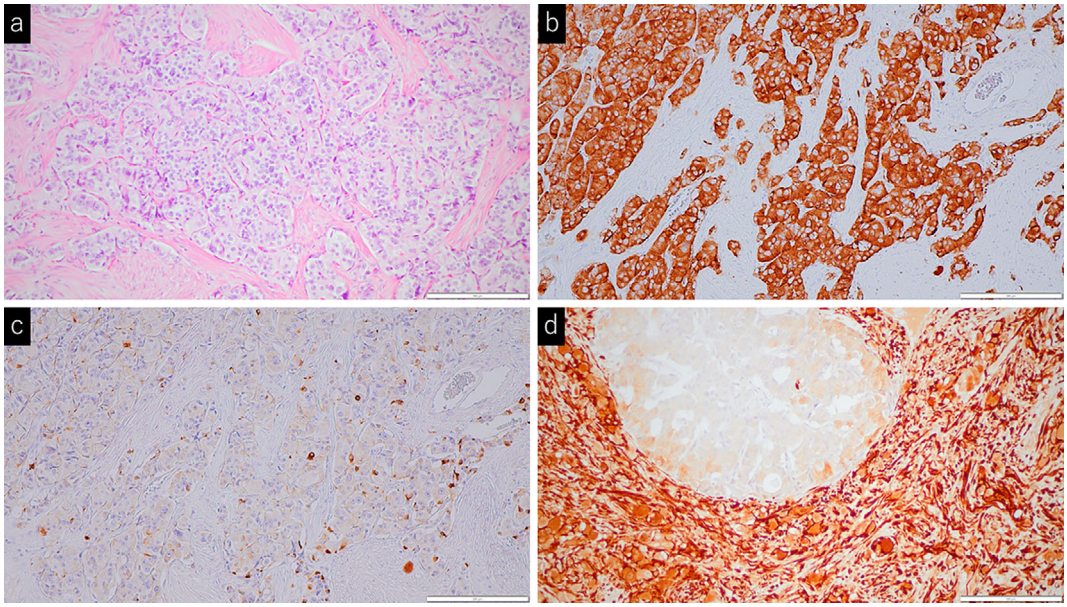

Figure 6. **(a) In Hematoxylin and Eosin staining (×400) of the resection specimen after endoscopic papillectomy, the epithelioid cells were densely proliferating, a so-called Zellbaren pattern.(b) Epithelioid cells and ganglion cell-like cells were stained positive for synaptophysin (×200).(c) Epithelioid cells and ganglion cell-like cells were stained positive for chromogranin A (×200).(d) Spindle-shaped cells were stained positive for the S-100 protein (×200) and surrounded the nests of epithelioid cells.**

opsy and the other with a deep subepithelial forceps biopsy. The median tumor size was 16.5 mm. Sekine et al. (15) reported a 3-mm GP discovered incidentally at a deep location after EP for ampullary carcinoma. Complications were noted in four patients: two experienced bleeding, one had mild acute pancreatitis, and one had hypotension requiring the administration of a vasopressor. Complete resection was performed in 12 patients; two patients did not undergo follow-up, and the remaining ten had no recurrence after a median follow-up of 13 (range: 2-36) months. Two patients had positive vertical margins after EP, and additional surgery was performed, which revealed lymph node metastasis. In one case, the tumor was confined to the submucosa, and imaging studies before EP did not reveal lymph node metastasis. While it exceeded the submucosa to the muscularis propria, lymph node metastasis was not detected before EP.

Discussion

GP was first reported in 1957 by Dahl and is pathologically characterized by epithelioid, spindle-shaped, and ganglion-like cells. Although the identification of these three components is necessary for the diagnosis, the tumor grows submucosally and is usually difficult to diagnose using a forceps biopsy. Okubo et al. (22) reported that the diagnostic rate of a forceps biopsy for GP was 11.4%, with 20% of cases misdiagnosed as another NEN. Another report found that a pretreatment forceps biopsy of ampullary NENs provided a correct diagnosis in only 15% of cases (23). In our literature search, no cases of GP were diagnosed by a forceps biopsy. However, in our hospital, a forceps biopsy resulted in the collection of tumor tissue in four cases, with a diagnosis of GP in three cases. This is a higher diagnostic rate than that previously reported; however, no clear features, such as tumor size or number of biopsies, were found between cases where the diagnosis was made by a forceps biopsy and those where it was not. If a forceps biopsy fails to provide a diagnosis, it is necessary to use endoscopic techniques that allow deep-tissue sampling from the submucosa.

EUS-guided fine-needle aspiration (FNA) is one useful technique for diagnosing ampullary NEN (24). Ogura et al. (25) reported that EUS-FNA increases the diagnostic yield for ampullary tumors and should be performed, especially when a histopathological diagnosis cannot be confirmed by a forceps biopsy. In the present study, for the two cases in which the pre-treatment biopsy was negative, EUS-FNA was not performed, and EP was performed as a diagnostic treatment at the discretion of the attending physician. Since EP is more difficult to perform and has a greater risk of complications than EUS-FNA, it would have been preferable to first obtain a histopathological diagnosis with EUS-FNA to determine whether or not endoscopic treatment was indeed appropriate. GP may cause massive release of catecholamines, as in pheochromocytoma, leading to blood pressure fluctuations or arrhythmias. Nikas et al. (26) reviewed EUS-FNA for abdominal extra-adrenal paragangliomas and reported transient hypertension in 5.6% of the patients. Katayama et al. (19) reported that endoscopic GP resection could be associated with hypotension. Blood pressure fluctuations are unique to GPs and should be carefully noted when performing invasive endoscopic procedures,

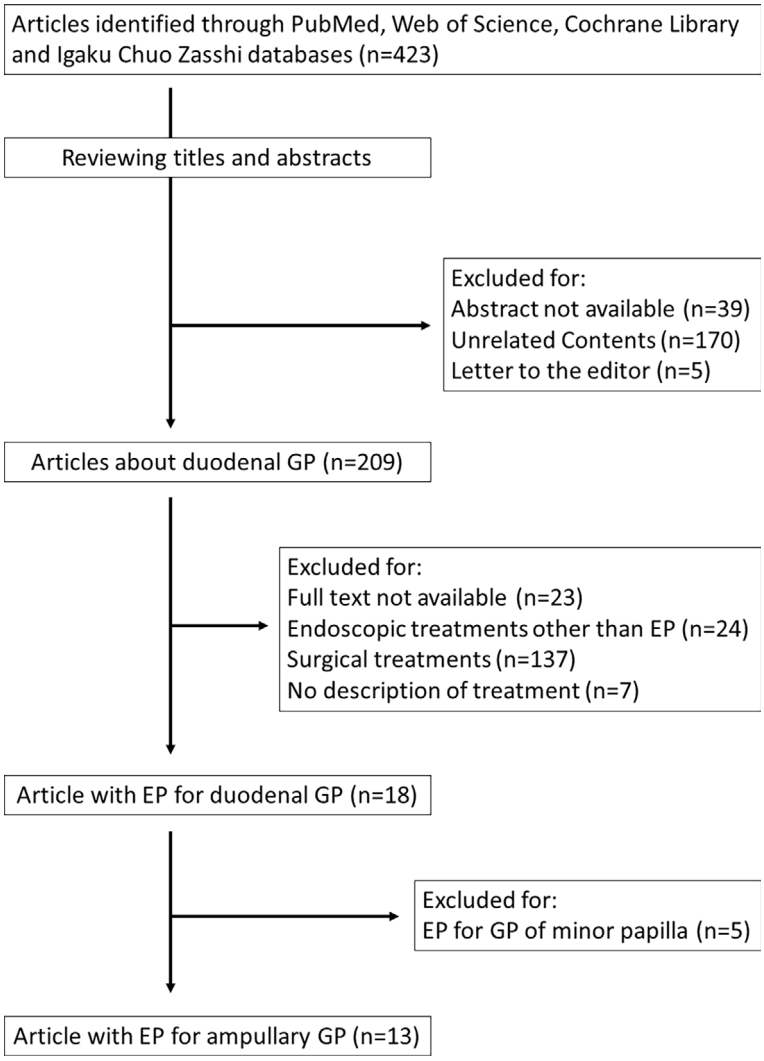

Figure 7. Flowchart of the literature selection.

such as EUS-FNA and EP. In the present study, serum catecholamines were not measured in any of the patients, but none of them experienced blood pressure fluctuations during pretreatment biopsy or EP. During surgical treatment, a high preoperative blood pressure and large tumor size are considered risk factors for intraoperative hypertensive crisis (27). However, GPs eligible for endoscopic treatment were generally smaller than those requiring surgery, and there were no patients with hypertension in this study. Therefore, the patients in this study were considered to have a low risk of experiencing blood pressure fluctuations.

As no reports have indicated hypertensive crises resulting from a forceps biopsy, the measurement of serum catecholamine levels before a forceps biopsy may be unnecessary. However, because GP can cause sudden intraoperative changes in blood pressure, serum catecholamine levels should be measured before EUS-FNA or EP is performed for ampullary submucosal tumors.

GP is recognized on CE-CT as a hypervascularized tumor, with gastrointestinal bleeding being the most common symptom (22). Therefore, post-EP bleeding was a common complication in this study. In a report of 20 EPs for ampullary NENs (28), 5 patients (25%) experienced bleeding, with 3 requiring re-intervention. Kawashima et al. (29) reviewed ampullary adenomas and adenocarcinomas in 2023 and reported a post-EP bleeding frequency of 10.6%.

Considering these findings, submucosal tumors may carry a high risk of bleeding. Recent advances in hemostatic devices have allowed the use of SureClips (Micro-Tech, Nanjing, China) since 2018, and self-assembling peptide hydrogels (PureStat gel; 3-D Matrix Europe SAS, France) since 2022. The suture clip can be easily manipulated and potentially reduce post-EP bleeding with prophylactic closure (30). In addition, PureStat gel is valuable for treating post-EP bleeding (31). In our study, EP was performed before 2018, and such devices were not available, which may have led to a higher frequency of bleeding than might otherwise be expected. When performing EP for submucosal tumors, these devices should be used to control the bleeding.

GP is generally considered to have a good prognosis, although a few cases of recurrences, lymph node metastases, and distant metastases have been reported in surgically treated GPs (21). Some of these cases occurred 11 years after surgery (32) and required long-term follow-up. In our re-

Table 2. Summary of Reports of Endoscopic Papillectomy for Ampullary Gangliocytic Paraganglioma.

Author	Age (y)/ Sex	Symptoms	Diagnosis method	Pre-treatment diagnosis	Size (mm)	Complication	Exceeding the submucosal layer	Follow-up period (month)	Residual/ Recurrence
(9)	76/M	Abdominal pain	EST+forceps biopsy	GP	15	NA	No	12	No
(11)	51/M	Anemia	NA	NA	14	Bleeding	No	14	No
(13)	41/F	Abdominal pain	Deep subepithelial forceps biopsy	GP	20	NA	No	6	No
(14)	46/F	Absent	Forceps biopsy	No tumor cells observed	18	NA	No	23	No
(16)	65/F	Abdominal pain	NA	NA	21	Mild pancreatitis	No	24	No
(10)	42/F	Abdominal pain	Forceps biopsy	No tumor cells observed	25	NA	No	3	No
(10)	46/M	Abdominal pain	NA	NA	13	NA	No	24	No
(18)	54/M	None	Forceps biopsy	NET	11	Bleeding	No	2	No
(19)	37/M	None	Tunnel biopsy	NET	13	Hypotension	No	36	No
(20)	54/F	Melena	Forceps biopsy	No tumor cells observed	30	NA	No	2	No
(15)	73/F	Weight loss	NA	NA	3	NA	No	NA	NA
(17)	54/M	None	NA	NA	24	NA	No	NA	NA
(12)	62/F	Gastrointestinal bleeding	NA	NA	20	NA	No	12	Residual
(21)	38/F	Abdominal pain	Forceps biopsy	No tumor cells observed	15	NA	Yes	NA	Residual

EST: endoscopic sphincterotomy, NA: not applicable, GP: gangliocytic paraganglioma, NET: neuroendocrine tumor, F: woman, M: man

view, two cases of lymph node metastasis were identified after additional surgery. Local resection cannot detect potential lymph node metastases, which may lead to a lower malignancy estimate. Okubo et al. (22) compared the clinicopathological findings of GP within and exceeding the submucosal layer and reported significantly more lymph node metastases in GP exceeding the submucosal layer than within and exceeding the submucosal layer (2.4% vs. 16.7%; $p = 0.03$). Ghassemi et al. (12) concluded that local resection is not recommended because lymph node metastasis occurs even when GP is localized in the submucosa. In one of our cases with a tumor exceeding the submucosal layer, no recurrence was observed after approximately 6.5 years of follow-up. However, considering the slow growth of the tumor, the follow-up period may have been insufficient. If a pathological evaluation after EP shows a positive vertical margin or exceeds the submucosal layer, long-term follow-up may reveal lymph node metastasis, and additional surgery is recommended. However, the indications for additional surgery for GP confined to the submucosal layer remain controversial because of the low lymph node metastasis or mortality rate and invasiveness of PD.

Several limitations associated with the present study warrant mention. This was a single-center retrospective observational study with a small number of cases. However, the follow-up period was longer than that reported in previous studies. We believe that we were able to provide important information that allowed us to evaluate the effectiveness of the EP. Future studies should focus on larger sample sizes, prospective study designs, and longer follow-up periods to provide more robust evidence regarding the safety and efficacy of endoscopic papillectomy for ampullary GP.

In conclusion, EP is a useful treatment for ampullary GP, with favorable long-term outcomes. Complications such as blood pressure fluctuations and bleeding should be noted. If the tumor exceeds the submucosal layer, additional surgery is recommended owing to the risk of lymph node metastasis. These findings may provide insights into strategies likely to benefit EP treatment.

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

Acknowledgement

We thank Dr. Yoshie Shimoyama, Department of Pathology and Laboratory Medicine, Nagoya University Graduate School of Medicine, for assisting us with the pathology findings.

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