

Current status of and future issues related to endoscopic papillectomy

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ABSTRACT

Endoscopic papillectomy is widely performed to treat duodenal papillary tumors, particularly at high-volume centers. It is indicated for adenomas without intraductal extension of the bile or pancreatic ducts. However, despite numerous reports of carcinomas that expand the indications to include well-differentiated adenocarcinomas that do not invade the sphincter of Oddi, the low agreement between biopsy and final pathological diagnosis, as well as the current inability of imaging modalities to diagnose sphincter of Oddi invasion, makes it difficult to consider expanding indications. Although complications can be prevented by certain methods, such as pancreatic duct stenting, and the frequency of severe complications has decreased, the safety of the procedure remains unconfirmed. In the future, this technology is expected to progress and enable wider applications, including those in tumors with extensive horizontal spread and those with intraductal extension of the bile and pancreatic ducts. Such technology may also improve the safety and accuracy of diagnosis.

Keywords: endoscopic papillectomy, papilla of Vater, adenoma, guidelines

Abbreviations:

EP: endoscopic papillectomy

EUS: endoscopic ultrasonography

JSGE: Japan Gastroenterological Endoscopy Society

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INTRODUCTION

Since endoscopic papillectomy (EP) for adenoma of the papilla of Vater was first reported by Suzuki et al in 1983,¹ it has become a widely performed treatment for adenomas, particularly at high-volume centers. However, EP still faces challenges, such as low diagnostic accuracy in the biopsy of cancerous lesions, procedural adverse events, and recurrence. In 2021, the Japan

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Gastroenterological Endoscopy Society (JSGE) released clinical practice guidelines for EP,² which summarize the indications, procedures, and short- and long-term outcomes, and identified clear issues to be addressed with respect to EP in Japan. The European Society of Gastrointestinal Endoscopy also published guidelines in the same year,³ which did not differ significantly from those of Japan, thus indicating a global standardization of EP procedures.

INDICATIONS AND CONTRAINDICATIONS

The JSGE guidelines recommend EP for ampullary adenomas.¹ Moreover, the European guidelines strongly recommend EP for ampullary adenomas up to 20–30 mm without bile duct or pancreatic duct invasion based on treatment outcomes.³ This indication is widely accepted in Japan. Meanwhile, for ampullary adenocarcinoma, the Biliary Tract Cancer Treatment Guidelines of Japan (3rd edition) state that EP or local surgical resection for Tis cases may be acceptable, but for T1 cases, which have a 10% incidence of lymph node metastasis and difficulty in accurately diagnosing the depth of invasion, EP or local surgical resection is not recommended.⁴ Therefore, pancreaticoduodenectomy remains the standard treatment option. As the definition of T1 differs between Japan and Western countries, accumulating evidence to expand the indications for EP and local surgical resection for ampullary adenocarcinoma is difficult. In the latest version (7th edition) of the General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract of Japan,⁵ following the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control tumor–node–metastasis staging system, T1 is classified as T1a (invasion up to the mucosal layer (M; T1a(M)) or the Oddi sphincter layer (OD; T1a(OD))) and T1b (invasion beyond the Oddi sphincter (involving the surrounding muscles) or invasion into the submucosal layer of the duodenum). However, in past JSGE rules, T1a was defined as an invasion limited to the mucosal layer of the ampulla, and T1b was defined as an invasion into the Oddi's sphincter. Therefore, caution should be exercised when reviewing the previous studies on this topic.

Yamamoto et al have reported EP cases for ampullary cancer, including 27 cases of Tis–T1a and four cases of T1b (staging according to the old criteria).⁶ According to their report, all cases of Tis–T1a ampullary cancer (ie, all well-differentiated adenocarcinomas without lymphatic invasion) demonstrated no recurrence during an average observation period of 48.5 months, whereas two of four cases of T1b ampullary adenocarcinomas were moderately differentiated adenocarcinomas, and one case indicated lymphatic invasion. No recurrence was observed among T1b cases during a mean observation period of 26.5 months. Although a prospective study with several cases and long-term follow-up is required, the authors concluded that EP is effective in treating ampullary cancers up to T1a. In the results of our facility,⁷ among the cases of EP, including 180 cases of papillary adenoma, 59 cases of T1a (M), 6 cases of T1a (OD), and 1 case of T1b papillary carcinoma (staged according to the latest guidelines, all cases were well-differentiated adenocarcinoma), the presence of cancerous components in pre-EP biopsy ($P = 0.035$, odds ratio [OR] 14.5 (95% confidence interval [CI]: 1.20–167)) was identified as one of the risk factors that could hinder curative resection (defined as no residual lesion 6 months after the final endoscopic treatment). However, once curative resection was achieved, the presence of cancerous components in the pre-EP biopsy or the final pathological diagnosis of adenocarcinoma was not identified as a significant risk factor for subsequent recurrence or additional surgical intervention, and clinical courses similar to those of adenoma cases were observed. In addition, all cases that required additional surgical intervention were in a state where a radical cure was possible. Therefore, even if a well-differentiated adenocarcinoma with adenoma components is

diagnosed by pre-EP biopsy, there is no problem with the indication for EP.

Yoon et al⁸ also stated that adenocarcinoma within the adenoma can also be an indication for EP based on the fact that no recurrence was observed during an average follow-up of 32.2 months. The possibility of lymph node metastasis in well-differentiated adenocarcinomas without invasion of the sphincter of Oddi is considered very low. A possible preoperative diagnosis may be an indication for EP, and further accumulation of cases is expected. On the other hand, the treatment indications for elderly patients as aging progresses can be difficult to identify. Takada et al⁹ investigated the prognostic factors for survival in EP cases, excluding cases of familial adenomatous polyposis, and reported that the only prognostic factor for poor survival was an age-adjusted Charlson Comorbidity Index of 5 points, which included 1 point every 10 years for patients aged 50 years ($P < 0.001$). Therefore, EP should be carefully considered an indication in elderly patients with multiple comorbidities.

The JSGE guidelines state that “cases with bleeding tendencies, acute pancreatitis, and other conditions are considered contraindications for EP, so it should not be performed.”² In actual clinical practice, if the risk of complications (pancreatitis, bleeding, or perforation) expected with EP is high in cases such as liver cirrhosis and ampullary adenoma in the diverticulum, EP should only be performed with appropriate informed consent if it is more beneficial than other treatments such as surgical resections.

PRE-EP EXAMINATION

Considering these indications, a preoperative examination should be performed. Thus, when a tumorous lesion is suspected based on endoscopic findings, a biopsy and other imaging studies are required to determine the presence of bile or pancreatic duct invasion and extension. The JSGE guidelines recommend endoscopic observation and biopsy using duodenoscopy, as well as endoscopic ultrasonography (EUS) or endoscopic retrograde cholangiopancreatography (and intraductal ultrasonography),² whereas the European guidelines recommend limited use of intraductal ultrasonography due to the risk of pancreatitis and strongly recommend observation and biopsy by duodenoscopy, as well as EUS and magnetic resonance cholangiopancreatography.³

The low diagnostic accuracy of preoperative biopsies is a problem in the diagnosis of EP. The reported agreement rate between preoperative biopsy and postoperative diagnosis is 39.7%–70%, with a false-negative rate for adenocarcinoma of 16%–60%.^{10–19} Since a pathological study of surgical specimens reported that ampullary tumors in deeper locations have a higher degree of malignancy,¹³ measures such as biopsy from deeper locations or biopsy of locations that are suspected to have a higher degree of malignancy based on endoscopic findings are necessary. A previous study has also indicated the usefulness of immunostaining with CDX2 and CK20 in determining the indications for EP.²⁰

EUS performance was evaluated in a meta-analysis that included 422 patients from 14 studies.²¹ The pooled sensitivity and specificity of EUS were 77% (95% CI, 69%–83%) and 78% (95% CI, 72%–84%), respectively, for T1 tumors. Additionally, the diagnostic ability of intraductal ultrasonography for the T1 stage was reported to be higher than that of EUS, ranging from 80% to 100%.^{22–24} However, these diagnostic abilities are used to determine whether a tumor has infiltrated beyond the sphincter of Oddi. Diagnosing infiltration into the sphincter of Oddi using the current imaging modalities is theoretically impossible. However, reports have demonstrated that immunostaining of biopsy tissues is useful for diagnosing infiltration of the sphincter of Oddi. We investigated the possibility of diagnosing infiltration into the sphincter of Oddi by immunostaining for insulin-like growth factor II mRNA-binding protein 3 (IMP3) expression,²⁵

which has been reported to be associated with the diagnosis and prognosis of various other organ tumors. We observed a significant difference in the proportion of IMP3-positive cells based on the presence or absence of invasion into the sphincter of Oddi by immunostaining for IMP3 in ampullary tumor specimens resected by EP or surgical excision. By setting the cutoff value to 10% based on the receiver operating characteristic curve, the presence or absence of infiltration into the sphincter of Oddi was diagnosed in the excised specimens with a diagnostic accuracy of 80%, and the distribution of positive cells was uniform (IMP3-positive cells were uniformly present even on the tumor surface that could be biopsied). A preoperative biopsy specimen from the same patient was also diagnosed with a diagnostic accuracy of 75%, using a cutoff value of 10%. Yamamoto et al²⁶ examined the diagnosis of papillary carcinomas suitable for EP based on a combination of subtype classifications using MUC1 and MUC2 immunostaining in 57 cases. They classified papillary carcinomas into three subtypes: intestinal type (I-type; MUC2-positive, MUC1-negative), pancreatobiliary type (PB-type; MUC1-positive, MUC2-negative), and mixed type (M-type; MUC1-positive, MUC2-positive) and reported that the I-type had more cases up to T1a (M) than the PB-type/M-type and a higher proportion of well-differentiated adenocarcinoma (tub1). I-type and tub1 were significantly more frequent in T1a (M) than in T1a (OD). Endoscopic findings of early stage papillary carcinoma with biopsy results of I-type and tub1 can be used as an indication for EP. These methods enable the objective diagnosis of infiltration of the sphincter of Oddi, which cannot be diagnosed by imaging modalities, and are expected to have clinical applications.

RESULTS OF EP AND INCIDENCE OF COMPLICATIONS

According to the JSGE guidelines,² the standard method for EP involves tumor excision using snares with collection of the resected specimen. Figure 1 presents the EP procedure used at Nagoya University Hospital, and Table 1 presents the EP results for >100 cases since 2010.^{6,7,27-31} The JSGE guidelines report complete resection rates for EP ranging from 47% to 93%.² Although a definition of complete resection has not been established, it is often defined as a negative resection margin on pathological examination of an excised specimen. A systematic review with a pooled analysis published in 2020 by Spadaccini et al included 29 studies comprising 1,751 patients who underwent EP.³² The technical success rate for complete endoscopic resection, defined as the absence of any adenomatous remnant from the resection margins at the end of the procedure, was 94.2% (95% CI 90.5–96.5; I₂ = 73%), and the oncologic success rate, defined as the absence of any histological features that predict locoregional persistence, was 87.1% (95% CI 83.0–90.3; I₂ = 70%). En bloc resection was achieved in 82.4% (95% CI 74.7–88.1; I₂ = 84%), which was the only factor affecting curative resection (OR 3.55, 95% CI 1.11–5.99, *P* = 0.004). In one of the largest retrospective series on EP, en bloc resection was significantly associated with a higher complete resection rate than piecemeal resection (OR 4.05, 95% CI 1.71–9.59, *P* < 0.001). Reports indicate the use of both the Endocut and Autocut modes for high-frequency generators. The Endocut mode may reduce postoperative bleeding but increase the risk of postoperative pancreatitis. Iwasaki et al³³ have reported a randomized controlled trial comparing the Endocut mode and Autocut modes in 60 cases of EP. No significant differences in bleeding (13.3% vs 16.7%, *P* = 1.00) and pancreatitis (27% vs 30%, *P* = 0.77) were observed between both modes. However, the proportion of tissue destruction was significantly higher in the Endocut mode than in the Autocut mode based on the histopathological findings of the excised specimen (27% vs 3.3%, *P* = 0.03). This report provides evidence regarding the settings for high-frequency generators.

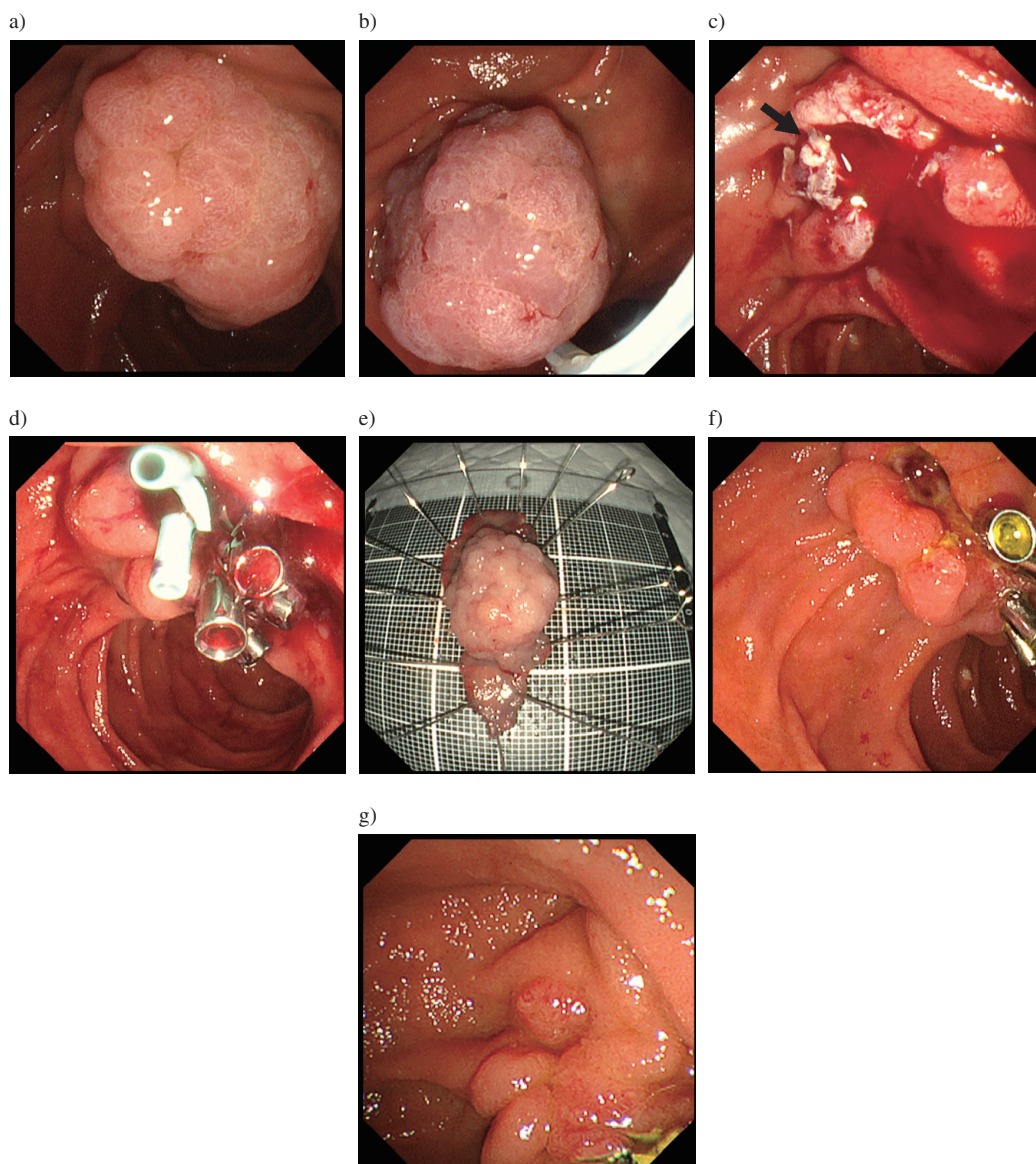


Fig. 1 Endoscopic papillectomy

Fig. 1a: A case of a papillary tumor detected during screening for anemia. Biopsy results revealed adenoma.

Fig. 1b: Although a large tumor was present, it could be resected en bloc.

Fig. 1c: Bleeding was observed in the ulcer after resection, and the opening of the bile duct (arrow) was observed on the oral side of the ulcer.

Fig. 1d: The anal side of the ulcer was sutured with clips, and stents were inserted into the pancreatic and bile ducts to complete the papillectomy.

Fig. 1e: Resected specimen: the final pathological diagnosis was well-differentiated adenocarcinoma, pT1a(M), Ly0, V0, pHM0, and pVM0.

Fig. 1f: Endoscopic findings one week after the procedure indicated no residual tumor or bleeding.

Fig. 1g: Endoscopic findings six months after the procedure revealed a raised area, which may be a flip of the Oddi sphincter. Biopsy results indicated no tumor component.

Table 1 Reports of endoscopic papillectomy (more than 100 cases since 2010)

Year	Source	N*	Complete resection (%)	Adeno-carcinoma cases (%)	FAP cases (%)	Recurrence cases (%)	Observational period (median, month)	Additional surgical cases (%)	Complications				Mortality (%)	Mode**	Pancreatic stent (%)
									Pancr-atitis (%)	Bleed-ing (%)	Perfora-tion (%)	Pancr-atitis (%)			
2014	Riditid et al ²⁷	182	107/151 (71)	12/151 (8)	29/91 (32)	16/107 (15)	22.7 (1–190)	N/A	7/182 (4)	23/182 (13)	3/182 (2)	1/182 (0.5)	Blend	156/182 (86)	
2017	Kang et al ²⁸	104	93/104 (90)	17/104 (16)	N/A	0/93 (0)	44.2 (N/A)	10/104 (9)	16/104 (15)	18/104 (17)	8/104 (8)	2/104 (2)	Blend	60/104 (58)	
2019	Yamamoto et al ⁶	177	132/167 (79)	31/167 (19)	N/A	0/31 (0)	26.5–48.5 (3–60)	N/A	18/167 (11)	36/167 (22)	4/167 (2)	1 or 2/177 (0.6 or 1)	N/A	N/A	
2020	Sahar et al ²⁹	161	106/128 (83)	5/161 (3)	35/161 (22)	8/114 (7)	30 (6–283)	14/161 (8.7)	11/161 (7)	10/161 (6)	2/161 (1)	0/161 (0)	Endocut	142/161 (88)	
2020	Tringali et al ³⁰	135	96/103 (93.2)	21/135 (16)	36/135 (26)	24/103 (23)	40 (3–153)	28/135 (21)	4/135 (3)	16/135 (12)	6/135 (4)	1/135 (1)	Endocut	94/135 (70)	
2021	Kawashima et al ⁷	253	212/221 (96)	65/253 (26)	16/253 (6)	24/212 (11)	46 (0–192.2)	12/253 (5)	19/253 (8)	23/253 (9)	7/253 (3)	0/253 (0)	Autocut	248/253 (98)	
2021	Okano et al ³¹	107	96/107 (90)	27/105 (26)	N/A	N/A	N/A	N/A	21/107 (20)	22/107 (21)	1/107 (1)	0/107 (0)	Autocut	83/107 (78)	

FAP: familial adenomatous polyposis

*Number of cases

** Mode of the high-frequency generator

Takahara et al³⁴ have reported a proof-of-concept study in which they applied the endoscopic submucosal dissection technique, which is also used to treat other gastrointestinal tumors, to achieve negative resection margins. They made a full circumferential incision and mild submucosal dissection, followed by tumor resection using a snare. The procedure was performed in eight cases, and negative horizontal margins were achieved in all the cases, although the vertical margins were unclear in 38% of the cases. The incidence of complications, including pancreatitis and bleeding, was 1 case (13%), which was within the acceptable range. Although the procedure takes longer than the usual method (median, 112 min), it may be a good option for cases where the tumor extends horizontally beyond the size of the snare. For tumors with a broader horizontal spread, completing EP is also possible using the duodenal endoscopic submucosal dissection technique. The differentiation from the usual EP will be discussed in the future. Underwater EP, which is used to treat other small intestinal tumors at some facilities, has also been initiated, although its difference from usual EP remains unknown.³⁵ The application of this endoscopic submucosal dissection technique will be useful for tumors with a horizontal spread in the duodenal direction; however, the development of treatments for tumors that extend in the direction of the biliary and pancreatic ducts is also necessary. Camus et al³⁶ have reported intraductal radiofrequency ablation (RFA) using a catheter-type RFA probe in 20 residual cases after EP in a multicenter prospective study. According to the report, the residual rate after additional ablation by intraductal RFA was 15% at 6 months and 30% at 12 months. Major complications were not observed. If safe and reliable ablation of tumors located in the bile and pancreatic ducts can be achieved with intraductal RFA, the curative rate of EP will increase, and the indications will expand to cases with intraductal progression.

The primary complications of EP include bleeding, pancreatitis, and perforation. A systematic review has reported an overall adverse event rate of 24.9% (95% CI 21.2%–29.0%; I2 = 66%).³² The most common adverse events reported after EP were postprocedural pancreatitis in 11.9% (95% CI 10.4–13.6; I2 = 41%), followed by bleeding in 10.6% (95% CI 5.2–13.6; I2 = 61%) of patients. Perforations and cholangitis were reported in 3.1% (95% CI 2.2–4.2; I2 = 17%) and 2.7% (95% CI 1.9–4.0; I2 = 32%) of patients, respectively. Meanwhile, mortality was reported to be 0.3%.

In a report aimed at preventing bleeding, Okano et al³¹ have reported that although no significant change in postoperative bleeding was observed, intraoperative bleeding decreased significantly ($P = 0.0255$) from 20.5% to 4.8% by injecting 1–2 mL of hypertonic sodium epinephrine locally on the anal side of the tumor. Yang et al³⁷ prospectively evaluated the effect of prophylactic argon plasma coagulation on post-EP ulcers at multiple centers to reduce postoperative bleeding and tumor residue. However, they have reported no significant difference in either outcome with or without argon plasma coagulation. Kagawa et al³⁸ compared the effect of clip closure of ulcers after EP in preventing bleeding in 40 patients with and without clip closure. They have reported that clip closure significantly reduced post-EP bleeding (5% vs 22.5%, $P = 0.026$), regardless of procedure time or post-EP pancreatitis, and significantly shortened length of hospital stay. Although clip closure is a promising technique for reducing post-EP bleeding, the residual tumor lesions may be buried, and long-term follow-up is required to assess the frequency and morphology of recurrence.

Endoscopic pancreatic duct stenting (EPS) is often performed to prevent pancreatitis, and many studies have suggested its usefulness.^{39–43} Harewood et al⁴⁴ have reported the results of a randomized controlled trial on EPS. According to their report, the incidence of pancreatitis was 0% and 33% ($P = 0.02$), and the group treated with EPS had a lower rate. However, a limitation of this study is that although 25 cases were planned to be enrolled in each group, the study was discontinued when the non-stent group reached nine cases with an observed incidence of pancreatitis of 33%; therefore, caution is needed when interpreting the results.

PATHOLOGICAL MARGIN EVALUATION AND LONG-TERM PROGNOSIS OF EP

The major anatomical feature of the duodenal papilla is that it is the site where the bile and pancreatic ducts penetrate and open, making it necessary to perform three-dimensional margin evaluation (including horizontal, vertical, and margin evaluation of the bile and pancreatic ducts) for postoperative pathological margin evaluation of EP, which is often considered indeterminate compared to the pathological margin evaluation of other digestive tract tumors. Therefore, clearly distinguishing between recurrent and residual lesions is difficult, and even reports indicating recurrence rates have inconsistent definitions. Takahashi et al⁴⁵ have reported a recurrence rate of 13.5% in their study of 96 patients, including 34 patients with papillary adenocarcinoma, and identified piecemeal resection as a risk factor. However, in this report, 9 of the 13 cases classified as recurrence were detected within 3 months, and whether they were recurrent or residual lesions was unclear. Tringali et al³⁰ defined residual lesions as those detected during the first postoperative observation within 3 months and recurrence as those detected during subsequent observations in their study of 135 cases, reporting residual lesions in 24.3% and recurrence in 23.3% of cases. Recurrence occurred in cases with negative margins (16.7%), positive margins (20.8%), and indeterminate margins (62.5%).

Sahar et al²⁹ have reported a recurrence rate of 7% in a study of 161 patients, defining recurrence as the detection of lesions at least 6 months after confirming the absence of residual lesions by endoscopy and biopsy during follow-up after endoscopic treatment. Although no significant difference in recurrence rates among tumors with horizontal expansion was identified, a trend toward higher recurrence rates was observed. In our facility, we defined remission as cases in which no residual lesions were detected, including those with additional therapy six months after endoscopic treatment, and defined subsequent lesion detection as recurrence in a study of 253 cases.⁷ The cumulative recurrence rate at 5 years using the Kaplan–Meier method was 16.9%, with the significant risk factors being the female sex ($P = 0.04$), familial adenomatous polyposis ($P < 0.001$), and bile duct and pancreatic duct involvement ($P < 0.001$), whereas negative or positive/indeterminate pathological margins were not significant ($P = 0.58$). Thus, our study may provide evidence of recurrence rates with long-term follow-up of several cases while minimizing residual lesions. These reports suggest that recurrence can occur at a certain frequency even when the pathological margin evaluation is negative, and the fact that recurrence is not always inevitable when the pathological margin evaluation is positive makes evaluating the treatment outcomes of EP difficult. Sakai et al⁴⁶ evaluated the outcomes according to the pathological margin status after endoscopic treatment and observed one case of adenoma recurrence in 21 cases with negative margins and three of 20 cases with positive or indeterminate margins (four of the nine cases of adenocarcinoma required additional surgery), all of which were controlled by additional argon plasma coagulation ablation. These results indicate that long-term follow-up is necessary even with negative pathological margins after EP.

CONCLUSION

We reviewed reports related to EP, including guidelines published in Japan and Europe. EP has demonstrated certain outcomes, including long-term prognosis for papillary adenomas without bile duct or pancreatic duct progression. In the future, the development of safe and reliable treatment methods for cases that can be treated locally and oncologically, such as well-differentiated adenocarcinomas without invasion of the sphincter of Oddi and adenomas with bile duct or pancreatic duct progression, is expected through the accumulation of cases and evaluation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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