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**Endoscopic papillectomy: The limits of the indication, technique and results** Ardengh JC *et al*. Endoscopic Papillectomy in Papillary Tumor

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**Abstract (no less than 200 words)**

In the majority of cases, duodenal papillary tumors are adenomas or adenocarcinomas, but the endoscopy biopsy shows low accuracy to make the correct differentiation. Endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) are important tools for the diagnosis, staging and management of ampullary lesions. Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The authors review the epidemiology and discuss the current evidence for the use of endoscopic procedures for resection, the selection of the patient and the preventive maneuvers that can minimize the probability of persistent or recurrent lesions and to avoid complications after the procedure.The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas. EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas.

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**Key words:** Epidemiology; Ampullary tumors, endoscopic resection, Endoscopic ultrasound, Staging, Endoscopic papillectomy, surgical ampullectomy

**Core tip: (Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.)**

**Ardengh JC, Kemp R, Lima-Filho ER, Santos JS. A Current Appraisal of Endoscopic Papillectomy in Patients with Papillary tumor. World J Gastroenterol 2014; In press**

Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The accurate staging of ampullary tumors is important for selecting patients to endoscopic papillectomy (EP) or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas. EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas.

**INTRODUCTION**

Ampullomas represent an uncommon group of gastrointestinal malignancies. Advances in endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) have significantly impacted the clinical approach to patients with suspected premalignant or malignant lesions of the duodenal papilla [[1](#_ENREF_1)]. The present review leads us to the discussion of numerous current issues related to the epidemiology of ampullary tumors, the role of the endoscopy biopsy, EUS, and ERCP, as well as indications, optimal technique, complications and outcomes in patients with benign or malignant tumor.

The term "endoscopic papillectomy” refers to the duodenal mucosa and submucosa resection, including all the anatomic attachments of the ampulla of Vater, and the tissues around the bile and pancreatic ducts. In turn, the term ampullectomy should be used to define this surgical procedure, which consists in the resection of the ampulla of Vater, through a duodenotomy including the cephalic pancreatic tissue resection, followed by separate reinsertion of common bile duct (CBD) and main pancreatic duct (MPD) in the duodenal wall [[2](#_ENREF_2)].

The endoscopic papillectomy (EP) was first reported as a route of access to the biliary tract [[3](#_ENREF_3)]. Years later, it was used as a treatment modality for two cases of duodenal papilla cancer [[4](#_ENREF_4)], and today it is accepted as a viable alternative therapy to surgery in patients with sporadic adenoma of the major or minor duodenal papilla due to its high success rate and low recurrence [[2](#_ENREF_2)].

**EPIDEMIOLOGY**

Tumors of the duodenal papila may be classified as benign, premalignant, and malignant [[5](#_ENREF_5)]. The annual incidence of ampullary lesions in the United States is 3,000, with reported prevalence rates of 0.04%–0.12% in autopsy series [[6](#_ENREF_6), [7](#_ENREF_7)]. Ampullary adenomas may occur sporadically or in the setting of hereditary polyposis syndromes, including familial adenomatous polyposis (FAP) with adenomatous polyposis coli gene mutations. In patients with FAP, ampullary adenomas occur in up to 80% of individuals during their lifetime and progress to malignancy in 4% [[8](#_ENREF_8)]. Ampullary adenomas are likely to follow an adenoma-to-carcinoma sequence similar to colorectal adenocarcinoma [[9](#_ENREF_9)]. These lesions are considered premalignant, with an incidence of transformation to carcinoma ranging from 25%–85% for sporadic adenomas. As with all neoplasms, tumor stage dictates the appropriate therapy [[10](#_ENREF_10)].

***DETERMINANT FACTORS IN THE RESECTION OF NON-INVASIVE NEOPLASMS OF THE VATER´S AMPULLA***

It seems that the knowledge of the histological and immunohistochemical characteristics is useful for precisely indicate an EP. In this context, the study of such characteristics is useful for selecting the appropriate surgical or endoscopic procedure. To corroborate this fact, japanese authors reported the results of this analysis in 56 noninvasive ampullary tumors. They demonstrated that the intestinal type cancer of intra-ampullary location shows lower CK20 expression than tumors of the periampullary location, and besides that, the intestinal type tumors without CDX2 expression, that included extended and intra-ampullary location types, tend to show a compromised vertical margin after EP. This suggests that periampullary tumors, intestinal histology and high CK20-positive rate can be regarded as good indications for the EP procedure. On the other hand, this study shows that tumors that are either pancreatobiliary or intestinal type without CDX2 expression have a higher chance of involvement of the common channel inside duodenal papilla, CBD and MPD.[[11](file:///C:\Users\usuario\Desktop\PAPER%20WJG\PAPER%20PAPILECTOMY\The%20endoscopic%20papillectomy.docx#_ENREF_11)]

**INDICATIONS**

The indications for EP are based on features that can predict a complete tumor removal, while minimizing complications related to the procedure [[1](#_ENREF_1)]. Currently the indications are not fully established and are far from a consensus.

The main criteria for EP include the lesion size (up to 5 cm), no evidence of intraductal tumor growth or malignancy in endoscopic findings, such as ulceration, spontaneous bleeding and friability [[1](#_ENREF_1), [11-17](#_ENREF_11)]. However, the indications for EP are expanding [[10](#_ENREF_10), [18-23](#_ENREF_18)]. For example, the endoscopic piecemeal resection technique, is used to removing tumors that can´t be removed “en bloc”, and provided increasing resections, when properly performed [[24](#_ENREF_24)]. The clinical results of this technique are very good, but the chance of recurrence is higher when this technique is used.

The ductal invasion in an extension less than 1 cm does not seem to be an absolute contraindication for EP, because the tumor can be exposed by endoscopic maneuvers, such as the use of an extractor balloon into the lumen, and thus it can be completely resected with a polypectomy snare [[25-27](#_ENREF_25)].

The cancer arising within an adenoma without invasion of duodenal muscularis propria and pancreas, or CBD and MPD invasion, are liable to resection by EP [[28-32](#_ENREF_28)]. However, in some situations, EP can be used as a macrobiopsy procedure for a simple local tumoral staging, if the resection margins are compromised [[33](#_ENREF_33)].

**PREOPERATIVE ENDOSCOPIC EVALUATION**

The most common preoperative concern is to define if a papillary tumor is benign or malignant. The endoscopic aspect alone cannot always distinguish adenomas from carcinomas and even from adenomatous polyps, carcinoids, gangliocytic paraganglioma, and other tumors that may occur in this region [[34](#_ENREF_34), [35](#_ENREF_35)]. Some endoscopic aspects like ulceration, friability, spontaneous bleeding are usually relate to malignant lesions. The use of endoscopic tools such as NBI, FICE and magnifying endoscopy are useful to select patients for EP (Figure 1) [[36](#_ENREF_36)].

A definitive histological diagnosis is a basic pre-requisite for adequate management of these patients, but we must remember that endoscopic biopsy of the duodenal papilla misses 30% of malignant tumors [[37](#_ENREF_37)]. Moreover, the coexistence of carcinoma and adenoma cannot be excluded by endoscopic biopsy. Some authors advocate deep biopsy after sphincterotomy, to increase diagnostic accuracy of endoscopic biopsy [[38](#_ENREF_38)]. We do not recommend this procedure, because endoscopic sphincterotomy eliminates the possibility of endoscopic en bloc resection of ampullary tumors, impeding a possible curative resection.

Favoring our impression, a prospective study showed that endoscopic biopsy is not reliable for preoperative diagnosis of tumors of the duodenal papilla (sensitivity of 21% before and 37% after sphincterotomy) [40]. Thus, in some cases, EP can be recommended as a technique for preoperative diagnosis because a high false negative rate of endoscopic biopsy [[33](#_ENREF_33)].

**PREOPERATIVE STAGING**

Endoscopic ultrasound (EUS) is the imaging modality of choice for local staging (T). EUS is superior to helical computed tomography (CT) for preoperative evaluation of tumor size, detection of regional lymph node metastasis, vascular invasion in patients with periampullary neoplasms and also to detect tumor infiltration of biliary and pancreatic ducts (Figure 2a) [[39](#_ENREF_39)].

Many experts believe that EUS is not useful in lesions less than 1 cm in diameter, with no suspicious signs of malignancy (ulceration, induration, bleeding and/or biopsies with high-grade dysplasia or carcinoma) [[11](#_ENREF_11)]. Our experience shows that, when EUS is performed for staging ampullary tumor prior to EP, it allows deciding for EP, because it shows the relationship between CBD and MPD, as well their diameter. EUS allows the verification of the relationship of the borders of the tumor in the duodenal wall, CBD and MPD, regardless of the size of the tumor. However, prospective studies are needed to evaluate the accuracy of these findings.

The use of intraductal ultrasound (IDUS), with a 20 MHz probe can be more accurate in visualizing mucosa layers compared to conventional EUS [[40](#_ENREF_40)]. According to literature, EUS and IDUS accuracy before surgical resection or diagnostic EP was 97% and 94% for pTis, 73% and 73% for pT1, 50% and 50% for pT2 and 50% and 100% for pT3-4 respectively. The overall EUS and IDUS accuracy was 85% and 80% for T stage [[41](#_ENREF_41)]. In our experience with this type of technology, the interpretation is more difficult, especially when the mini-probe is placed within the biliary or pancreatic ducts. If this is not done, the sensitivity is lower when compared with the conventional EUS [41].

From a technical standpoint, EUS and IDUS are able to detect, with high precision, tumoral infiltration of the common bile duct and main pancreatic duct (Figure 2b and c). Despite endoscopic retrograde cholangiopancreatography (ERCP) can detect CBD invasion, we believe that it should only be performed after EUS, if EP is indicated. EUS and IDUS can provide high precision diagnostic information for staging ampullary tumors, and are useful in identifying lesions selected for EP. However, these tools have limitations, because the occurrence of super and understating and the difficulty in assessing focal infiltration are relevant. The improvement of endoscopic procedures is necessary for an accurate assessment of ampullary tumors [[42](#_ENREF_42)].

From a practical standpoint, ERCP should be performed before EP, if EUS is not available or inconclusive as to ductal involvement. Although intraductal invasion is usually an indication for surgery, it has been demonstrated that, when tumoral infiltration reaches ± 1 cm into CBD and MPD, tumor is amenable to endoscopic resection [[25](#_ENREF_25), [26](#_ENREF_26), [43](#_ENREF_43)].

Positron computerized tomography (PET / CT) and magnetic resonance imaging (MRI) are highly sensitive for detection of distant metastases. MRI and CT was superior to EUS for assessment of nodal involvement [[44](#_ENREF_44)].

**ENDOSCOPIC PAPILLECTOMY TECHNIQUE**

EP is performed after EUS staging confirming a less than 5,0 cm tumor confined to mucosa and/or submucosal (uT1), with intraductal tumoral infiltration less than 1 cm. It can be performed using the EUS device itself or a duodenoscope. With the duodenoscope rectified, a preferable monofilament polypectomy snare is used for grasping the tumor, always in the craniocaudal direction, i.e. the snare tip is positioned on cranial tumor apex.

The snare is widely opened, duodenoscope is pushed in a craniocaudal direction, and tumor is grasped for en bloc resection (Figure 3). The papillary tumor is grasped at its base, always respecting a limit, up to 0,5 cm below the lesion border identified by FICE. Thereafter a constant tension is applied to the ring handle while using an electrocautery until tumor en bloc resection is completed. There are no specific equipment or a standard technique for EP.

There is also no guidance on the potency and mode of electronic current (cutting or coagulation). The authors prefer to use only cutting current (40 to 50J) and the endocutter. Some authors recommend performing submucosal injection, ablative therapy after EP, and placement of a prophylactic pancreatic stent. The use of antibiotic prophylaxis before EP is not established [[45](#_ENREF_45)]. The authors do not advocate its use.

Some experts use injection of contrast with methylene blue into MPD to identify the pancreatic orifice after tumor resection. This is not our practice. After complete removal of the lesion, which sometimes takes a few minutes, depending on its size and extension, a whitish rough area can be seen, which in some cases reveals the muscular layer of duodenal wall, as well two holes (biliary and pancreatic ducts).

Efforts should be exhaustive and mandatory to recover all resected tissue in all patients, for histopathological evaluation. Then CBD and MPD catheterization is performed, with contrast injection, to ensure easy recanalization after ampullary resection.

When en bloc resection is not feasible, a  piecemeal resection is recommended. However, it should be noted that the en bloc resection is essential for the treatment of preneoplastic and/or malignant lesions, because this allows accurate histopathologic evaluation after tumoral resection [[25](#_ENREF_25)].

The submucosal injection of diluted epinephrine is suggested as a means to lift the tumor from the wall, which at least theoretically may reduce the risk of bleeding. However, it is uncertain and questionable whether injection of adrenaline reduces the risk of bleeding and/or perforation [[19](#_ENREF_19), [26](#_ENREF_26), [46](#_ENREF_46)]. The authors dismiss the submucosal injection of pharmacological agents, due to distortion of tumoral anatomy and its periphery, hindering an adequate grasping by the polypectomy snare. Moreover, a perforation following tumor resection may occur, due to a short distance between duodenal wall and pancreas, as seen by EUS.

If residual tumor tissue remains after resection, it should be destroyed! The use of coagulation with argon gas is the most widely used modality; it is safe because it is a non-contact technique, acting in tumor surface [[11](#_ENREF_11), [45-47](#_ENREF_45)].

The use of stent in MPD, in order to reduce the risk of acute pancreatitis (AP) associated to EP, seems to be a consensus because it minimizes the risk of MPD stenosis, allowing the use of safer coagulation therapies. Anyway we must emphasize that this theory is unproven. Others advocate pancreatic stent placement only if MPD drainage is not sufficient after EP [[48-51](#_ENREF_48)]. The only prospective, randomized, controlled study, to evaluate the role of prophylactic stent in MPD, to reduce AP after EP, showed a statistically significant decrease in the rate of AP after stent procedure [[52](#_ENREF_52)].

Otherwise, the adequate MPD diameter and length for stenting are uncertain. In other work, for example, the authors suggests that routine use of prophylactic pancreatic stent in all patients is unnecessary and efforts should be directed to know which groups of patients actually benefit from its insertion [[53](#_ENREF_53)]. Most pancreatic stents migrate spontaneously from MPD within 2 weeks after insertion. Abdominal X-ray after 2 weeks can confirm this finding. A stent, which remains "in situ" for more than 2 weeks, should be removed endoscopically.

The placement of a prophylactic plastic biliary stent, to reduce the risk of cholangitis, has not been widely performed and cannot be uniformly recommended at the present moment, unless there is concern about inadequate biliary drainage after EP.

**Complications**

The EP is a 'high risk’ procedure, due to complications inherent to the method. They can be classified as early: Acute pancreatitis (AP), bleeding, perforation and cholangitis or late: papillary stenosis. The overall complication rate reported by major centers of tertiary care varies between 8% and 35%, and the most common complications are AP (5-15%) and bleeding (2-16%) [[10](#_ENREF_10), [24](#_ENREF_24), [47](#_ENREF_47), [54](#_ENREF_54)]. Most episodes of bleeding can be controlled immediately by conservative treatment and endoscopic hemostasis and most episodes of AP are mild and resolve with conservative treatment only. The rate of pancreatic and/or biliary ductal stenosis varies between 0-8%, and can be treated by sphincterotomy, stent placement, and balloon dilation.

The use of pancreatic stent can prevent an episode of AP and papillary stenosis [[48-53](#_ENREF_48)]. Another interesting fact reported by a recent randomized study showed that prophylactic rectal indomethacin significantly reduced the incidence and severity of AP post-ERCP, providing an additional benefit in pancreatic temporary stenting [[55](#_ENREF_55)]. The mortality after-EP is rare, but it has been reported to be 0.4% (range 0% to 7%) [[56](#_ENREF_56)].

**Results**

The results of the endoscopic treatment of ampullary tumors reported in the literature are shown in Table 1. The EP results are based on retrospective case series studies with heterogeneous groups. As there is no consensus on the definition of 'success' after EP, it is difficult to compare the results of the reported studies. Conventionally, '' success' can be defined as a complete tumor resection (as the proven absence of visible residual adenoma by endoscopy and histological analysis during a 3-6 months follow up). In the literature the rate of the success varies between 46 to 92% in the different series. The complication rate after EP varies between 8 to 42% and the major problems are acute pancreatitis, perforation and bleeding. The most important complication after EP is the acute pancreatitis that could be solved with the insertion of the plastic pancreatic stent. This is a controversial point, because in our experience if you have a dilated main pancreatic duct the use of the PPS is unnecessary [[57](#_ENREF_57)].

Recurrence of benign lesions occur in up to 33% of patients depending on the tumor size, final histology, presence of intraductal tumor, coexistence of FAP and endoscopist experience [[20](#_ENREF_20), [56](#_ENREF_56), [58-63](#_ENREF_58)]. If you use the endoscopic ultrasound before the EP you could find with precision the presence of intraductal tumor. In this case there are contraindication to submitted the patient to EP. Recurrent lesions are usually benign and most can be removed endoscopically.

**Conclusion**

EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas.

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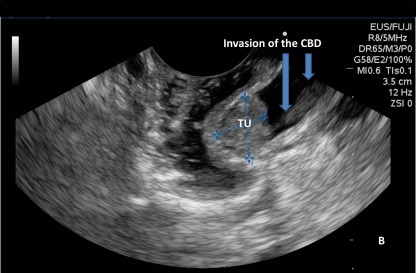
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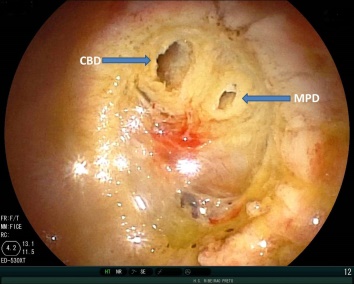
**Figure 1:** Endoscopic view of neuroendocrine tumor of the papilla with FICE (Fujinon Intelligent Chromo Endoscopy). This picture show the depression in the center of the lesion. The other picture shows the aspect of the papillary region after the “en bloc “ resection.

** **

**Figure 2: (A)** Patient of the figure 1. EUS staging shows the regular and hypoechoic nodule (1.93 cm) in the papilla without infiltration of the duodenal wall and pancreatic gland. The staging was uT1N0Mx. **(B)** This picture shows the papillary tumor with 1.72 cm with invasion of the common bile duct wall (blue arrows).

**Figure 3**: En bloc resection of the tumor, after the snare is widely opened, duodenoscope is pushed in a craniocaudal direction (A). (B) the endoscopic view of the CBD (Common bile duct) and MPD (Main Pancreatic Duct) [blue arrows] after a complete en bloc resection of the papillary tumor.

Table

**Table 1**: Result after Endoscopic Papilectomy (EP).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Patients | Success/(%) | Complications/(%) | Mortality/(%) | Recidive/(%) | Surgery/(%) |
| Binmoeller et al [[12](#_ENREF_12)] | 25 | 23/92 | 5/20 | 0/0 | 6/24 | 3/12 |
| Vogt et al [[63](#_ENREF_63)] | 18 | 12/67 | 4/22 | 0/0 | 6/33 | NA |
| Zádorová et al[[17](#_ENREF_17)] | 16 | 13/81 | 4/25 | 0/0 | 3/19 | 1/6.2 |
| Desilets et al [[46](#_ENREF_46)] | 13 | 12/92 | 1/7.7 | 0/0 | 0/0 | 1/7.7 |
| Norton et al[[47](#_ENREF_47)] | 26 | 12/46 | 5/19 | 0/0 | 2/7.7 | 1/3.8 |
| Bohnacker et al[[19](#_ENREF_19)] | 87 | 74/85 | 29/33 | 0/0 | 15/17 | 17/19 |
| Catalano et al[[13](#_ENREF_13)] | 103 | 83/80 | 10/9.7 | 0/0 | 10/9.7 | 16/15.5 |
| Cheng et al[[14](#_ENREF_14)] | 55 | 39/71 | 12/22 | 0/0 | 9/16.3 | 4/7.2 |
| Han et al [[20](#_ENREF_20)] | 33 | 20/60.6 | 11/33.3 | 0/0 | 2/6 | 2/6 |
| Ismail et al. [[64](#_ENREF_64)] | 61 | 56/92 | 15/24.5 | 0/0 | 12/19.6 | 9/14.7 |
| Napoleon et al. [[65](#_ENREF_65)] | 93 | 84/90 | 39/42 | 1/1 | 5/5.3 | NA |
| Ridtitid et al. [[66](#_ENREF_66)] | 182 | 134/73.6 | 34/18.6 | 0/0 | 16/8.7 | NA |
| Ardengh et al. [[67](#_ENREF_67)] | 41 | 38/92 | 11/26.8 | 0/0 | 3/7.3 | 4/9.7 |

**Not available = NA**