

Endoscopic papillectomy for early ampullary neoplastic lesions – a case series analysis

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ABSTRACT – **Background** – Endoscopic papillectomy has been conceived as a less invasive therapeutic option for treatment of early neoplastic lesions located at the major duodenal papilla. **Objective** – Evaluating patients with early ampullary lesions who underwent curative intent endoscopic papillectomy related to technical success (histopathological tumor margin assessment) and safety (adverse event rate). **Methods** – A retrospective study including consecutive patients who underwent curative intent endoscopic papillectomy for demographic, histopathological and pre-/post-procedural clinical assessment. Endpoints were technical success (histopathological residual tumor assessment) and adverse events rates. **Results** – A total of 21 medical records patients with a female predominance (13 cases, 61.9%) were included. The tumor was incidental in 8 (38%) cases. Negative residual tumor resection margin rate was 72% (15 cases); three of these cases confirmed high-grade dysplasia in the resected specimen, and six cases were invasive neoplasia. Tumoral recurrence was seen in two cases, and median follow-up time was 12 months, with a 23% loss rate (five patients). Six (28.5%) patients had adverse events, all of them early (bleeding and pancreatitis); none of them required surgical intervention and there was no mortality. **Conclusion** – Endoscopic papillectomy allowed for technical successful procedure with complete removal of ampullary neoplastic lesions in the majority of cases with acceptable adverse event rates. Recurrence rate should be carefully assessed in further studies. There was a recent increase in the number of procedures. There was also a low correlation between pre- and post-histopathological assessment regarding the presence of invasive carcinoma and adenoma with high grade dysplasia, with a predominance of superficial neoplastic adenomatous lesions.

HEADINGS – Ampulla of Vater. Adenoma. Endoscopic mucosal resection.

INTRODUCTION

Tumors arising at the major duodenal papilla, or ampullary tumors, are a group of neoplasms uncommon in the gastrointestinal tract. However there has been an increase in their annual incidence up to 3000 cases/year in the United States⁽¹⁾. Such lesions can be benign, pre-neoplastic (e.g. adenomas) and malignant in nature⁽¹⁻³⁾. Although adenocarcinoma of the ampulla of Vater is reportedly the most prevalent lesion, the emergence of cases of incidental neoplastic adenomas (for example, during a routine gastroduodenal endoscopic examination) is changing this trend⁽⁴⁾.

The therapeutic approach of ampullary tumors has been traditionally surgical and technically challenging due to the confluence of biliary, duodenal and pancreatic drainage. Duodenopancreatectomy (Whipple procedure) has been advised for ampullary tumors with adenocarcinoma confirmed at biopsy and suspicion of invasion of the duodenal muscular layer wall at imaging, and macroscopic signs of ulceration, infiltration, friability and hardening at endoscopy⁽⁵⁾. Although allowing for complete removal of the entire anatomic region, it is associated with considerable rates of morbidity and mortality⁽⁵⁾. Local excision encompassing either surgical ampullectomy or endoscopic papillectomy (EP) may be used for early neoplastic lesions, that is, tumors (usually adenomas) with superficial neoplastic involvement at biopsy (high-grade dysplasia)

without macroscopic signs of ulceration or friability at endoscopy and without invasion of the duodenal muscular layer wall at imaging (preoperative clinical oncological staging: T0/T1aN0M0). Incidental and early neoplastic ampullary lesions represent a challenge for surgeons and endoscopists for appropriate selection of patients who will benefit from a less invasive approach.

Although EP has gained popularity worldwide as a less invasive therapeutic option in the treatment of early ampullary lesions, there are scarce reports of this procedure in the South American continent^(6,7). The present study aims to present a multicenter case series in Southern Brazil about the use of EP with curative intent in patients with early ampullary lesions.

The aim of this study was to retrospectively evaluate patients with early ampullary neoplastic lesions subjected to curative intent endoscopic papillectomy, in relation to technical success (histopathological tumor margin assessment) and safety (adverse events).

METHODS

This retrospective study was designed to identify medical records of patients who underwent EP with curative intent for ampullary neoplastic lesions, from January 2006 to February 2017 in three tertiary hospitals in Curitiba, Paraná, Brazil (*Hospital de Clínicas-Universidade Federal do Paraná* [UFPR], *Hospital São*

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Vicente and Hospital Nossa Senhora das Graças). We did not aim to obtain records of patients with early ampullary neoplastic lesions either sent to surgery or watchful waiting as a primary treatment.

This present study was approved by the participating institutions and by the Research Ethics Committee of the Hospital de Clínicas-UFPR and *Plataforma Brasil* (<http://plataformabrasil.saude.gov.br>) under the protocol number 76456717.9.0000.0096. It was performed according to resolution 466/2012 from the *Conselho Nacional de Saúde do Ministério da Saúde* (Brazil).

For each patient, at least one lateral viewing duodenoscopy was performed, specifically aimed at evaluating morphological aspects of the major duodenal papilla and endoscopic biopsy sampling for histological analysis. The histological diagnosis, considered as a “gold standard” for decision making, was made from multiple endoscopic biopsies (at least six fragments). In some cases more than one procedure was needed for proving the presence of adenoma fragments with high grade dysplasia (HGD) confirmed by a pathologist experienced in gastrointestinal pathology.

EP was indicated only for curative intent, therefore no patient with endoscopic suspicion or histopathological diagnosis of invasive adenocarcinoma was considered for endoscopic treatment. The EP technique was standardized according to previous reports⁽⁷⁾, and similar to a procedure of endoscopic mucosectomy, in which a diathermic loop (13 mm polypectomy loop) was used to involve the entire tumoral tissue and section the major duodenal papilla in its insertion along the duodenal wall, with the aim of specimen removal in a single piece (enblock). As a prophylaxis for acute pancreatitis, rectal Indometacin was used in all patients. Placement of a biliary and/or pancreatic stent was at the discretion of the physician, however, prophylactic pancreatic stenting was always attempted and performed when the insertion of guidewire into the main pancreatic duct was technically possible.

Magnetic resonance cholangiogram (CholangioMR) and computed tomography of the abdomen (AbdominalCT) were advocated for biliopancreatic locoregional evaluation, detection of distant metastases (M) and lymph node involvement (N). Endoscopic ultrasound (EUS) was advocated for local staging (T), and endoscopic retrograde cholangiopancreatography (ERCP) was performed in the occurrence of obstructive jaundice in obstructive lesions.

Demographic and clinical data such as age, gender, current or previous morbidity (including genetic syndromes [familial adenomatous polyposis] and neoplasms), clinical presentation, diagnosis and size of the lesion (as described in the histopathological report) were obtained.

Also, we obtained information on the endoscopic technique employed (type of resection, use of biliary and/or pancreatic stents), the occurrence of adverse events (AEs) regarded as early or late when later than 30 days, histopathological analysis of the resected specimen and follow-up with endoscopic examination with or without biopsies. The resection margin of the resected specimen was evaluated according to the TNM classification for residual tumor⁽⁸⁾ (R0: without residual tumor, R1: microscopic tumor, R2: macroscopic tumor), evaluated by histopathological examination (lateral and deep margins). Complete endoscopic resection was regarded as R0, and incomplete endoscopic resection was regarded as R1 or R2. A technical successful EP was regarded as a procedure allowing complete resection without residual tumor (R0) at resection margin.

Exclusion criteria were patients with duodenal papilla lesions under 18 years old, inconsistent medical records and patients who

underwent other endoscopic treatment than endoscopic papillectomy with curative intent (endoscopic suspicion or histopathological diagnosis of invasive adenocarcinoma).

For statistical analysis, data was described in terms of frequency and percentage, and analyzed using the Excel software (Microsoft, NM, EUA).

RESULTS

We obtained 21 medical records of patients who underwent endoscopic papillectomy. Fourteen cases were obtained from Hospital São Vicente, six from *Hospital Nossa Senhora das Graças* and one from *Hospital de Clínicas-UFPR*. Of these 21 patients, nearly half of the procedures (12 cases, 57%) were performed less than 5 years ago, with only one case of a known genetic syndrome (PAF). In this population, predominantly female (13 cases, 61%), the diagnosis of neoplastic lesions was incidental in eight (38%) cases; in 13 (61.9%) of them there was a sign or symptom, with jaundice and acute pancreatitis being the most common, corresponding to 8 (38%) and 5 (23.8%) cases, respectively (TABLE 1). No medical records met the exclusion criteria.

TABLE 1. Demographic data of patients who underwent endoscopic papillectomy for early ampullary lesions.

	Gender	Associated diseases	Clinical presentation	Age	Staging method	Size of the lesion (cm)
1	M		J	75	CTA, RM	3
2	M		J	73	CTA, EUS	2.5
3	F		J	90	RM	2.5
4	F		P	70	CTA, RM	2.5
5	F		IF	57	CTA, RM	1
6	M		P	39	CTA, RM	1
7	F		P	30	CTA, RM	1
8	F		J	47	CTA, RM	1
9	M		J	79	CTA, RM	3
10	F		J	66	CTA, RM	1.5
11	F		J	79	CTA, RM	1.5
12	M		P	69	CTA, RM	1
13	F		IF	42	CTA, RM	1
14	F		J	54	CTA, RM, EUS	3
15	F	FAP	IF	67	RM, EUS	1.6
16	F		Dilatation BT	75	RM, EUS	1
17	F		P	35	CTA, RM	3.6
18	M		P	68	RM, EUS	2.5
19	M		IF	66	RM, EUS	1
20	F	CRC	IF	67	RM, EUS	1.2
21	M	PEC	IF	31	RM, EUS	1

IF: incidental finding; J: jaundice; P: pancreatitis; BT: biliary tract; CTA: computed tomography of the abdomen; MR: magnetic resonance; EUS: endoscopic ultrasound; CRC: previous colorectal cancer; PEC: primary sclerosing cholangitis; FAP: familial adenomatous polyposis.

CholangioRM was the most widely used staging method, followed by AbdominalCT in 19 (90.4%) and 15 (71.4%) cases, respectively, with both being requested concomitantly in some cases. EUS was performed in 8 patients as a complementary imaging method. ERCP was not performed for staging in any case (TABLE 1).

The resected lesions measured in average less than 2 cm in 13 (61.9%) cases. There were lesions up to 3.5 cm resected with curative intent. Also regarding the EP technique, biliary or pancreatic stents were not necessary in 8 patients, the latter being used solely as prophylaxis in 9 patients (42.8%) (TABLE 2). There were 2 confirmed cases of acute pancreatitis.

TABLE 2. Clinical and histopathological results of patients who underwent endoscopic papillectomy for early neoplastic ampullary lesions.

	Use of stent	Adverse events (treatment)	Histopathology
1	BS		R1, invasive adenocarcinoma
2	BS		R0, TA
3			R0, TA
4		postop bleeding (e. injection)	R0, TA
5		AP	R0, TA
6			R1, invasiveadenocarcinoma
7			R1, invasiveadenocarcinoma
8		intraop bleeding (e. cauterization)	R0, TVA+ DAG
9			R1, invasiveintraductal tumor
10	PS		R0, TA
11	PS	intraopbleeding (e. clip)	R0, TA
12	BS		R1, invasiveadenocarcinoma
13	BS e PS		R0, TA
14	BS e PS		R0, AT + DAG
15	PS		R0, ATV + DAG
16	BS e PS		R0,TA
17			R0, TA
18	PS		R0, TA
19	PS		R0, TA
20	BS e PS	intraop bleeding (e. clip), perf., AP	R0, TVA
21	BS	postop bleeding (e. injection)	R1, invasive adenocarcinoma

BS: biliary stent; PS: pancreatic stent; AP: acute pancreatitis; perf: perforation; intra op: intraoperative; postop: postoperative; e. injection: endoscopic injection; e. cauterization: endoscopic cauterization; e. clip: endoscopic clipping; R0: complete histopatological resection; R1: incomplete histopatological resection; TA: tubular adenoma; TVA: tubulo-villous adenoma; HGD: high grade dysplasia.

A complete endoscopic resection, (R0, without histopathological residual tumor) was obtained in 72% (15 cases), all adenomatous lesions. Regarding the concordance of the histopathologic findings before and after the procedure, all 15 cases had HGD in the pre-procedure and there were only three cases with HGD confirmed in the resected specimen (14.3% of pre- and post-histopathological concordance).

There were 6 cases of invasive neoplasia and all of them were referred to complementary surgical treatment (TABLE 2). Of the 15 remaining patients, the median follow-up was 12 months (3 were followed up for 6 months, 2 for 12 months, 1 patient for 24, 36 and

60 months). There was a loss of follow-up of 5 patients (23% of the total of 21 patients). Two cases showed signs of recurrence of local neoplastic tissue, confirmed histologically, after 6 and 12 months of follow-up.

Six (28.5%) patients presented adverse events (TABLE 2), one of them with more than one complication, with immediate complications such as bleeding (five cases) and acute pancreatitis (two cases) being the most frequent ones. There was one case of retroperitoneal duodenal perforation (FIGURE 1 AND FIGURE 2). All complications were treated endoscopically and with clinical support, with no need for surgical intervention. There was no mortality related to the procedure.



FIGURE 1. An ampullary adenoma with high-grade dysplasia in a 67-year-old, female patient with familial adenomatous polyposis, asymptomatic. This lesion was resected endoscopically in a piece-meal fashion until there were no signs of macroscopic residual tissue after resection.

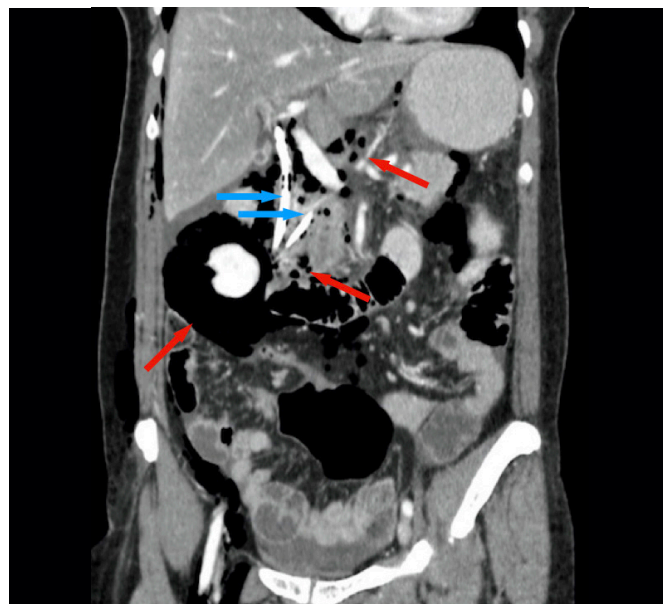


FIGURE 2. Abdominal CT obtained 1 day after endoscopic papillectomy (same patient as Figure 1). This patient had intraoperative bleeding, treated endoscopically. There is a duodenal perforation with retroperitoneum without liquid collection (red arrows). A biliary and a pancreatic plastic stent were placed, which were removed later (blue arrows). This patient underwent conservative treatment and discharge from hospital 9 days after the procedure. There were no signs of recurrence after 18 months at endoscopic follow-up.

DISCUSSION

Tumors of the Ampulla of Vater are neoplasms that, although rare, are increasing in prevalence; Adenocarcinoma and adenoma represent more than 95% of histological diagnosis⁽⁴⁾. The adenoma of the major duodenal papilla is considered a pre-cancerous condition, as it tends to follow the adenoma-adenocarcinoma sequence in a similar way to colorectal cancer, with transformation rates for adenocarcinoma varying between 25%–85%⁽⁹⁾. Adenomas may be sporadic or occur in the context of genetic syndromes, such as non-polypoid hereditary colorectal cancer and familial adenomatous polyposis (PAF), where up to 80% of patients will develop this condition during their lifetime⁽⁹⁾. Symptoms, when present, are usually nonspecific, such as abdominal pain, malaise, nausea, vomiting and weight loss⁽¹⁰⁾; Jaundice is more frequently associated with invasive lesions⁽⁸⁾. In our series, although nearly half of patients had symptoms at presentation (60%), there was an increase in the incidental diagnosis of upper digestive endoscopy in the last 5 years, with predominance of adenomas with HGD.

Because they are often diagnosed incidentally and do not present symptoms, adenomas in this region represent a diagnostic and therapeutic dilemma today. Although there is no consensus on which adenomas should be monitored or resected by surgical or endoscopic approach, EP is recommended in tubular, tubule-villous or villous adenomas in the presence of HGD⁽⁴⁾. Local surgical excision (surgical ampullectomy) is associated with higher rates of complete resection, clinical success and lower recurrence when compared to endoscopic resection⁽¹¹⁾. In the largest comparative series (case-control) published so far, involving 180 patients undergoing endoscopic technique (130 patients) versus surgery for local excision of adenomas of the Vater papilla, the clinical results were similar. The surgery group which had the highest rate of AE and EP had the highest chance of recurrence when there was a need for more than one endoscopic treatment session⁽¹²⁾. The typical unfavorable lesion for endoscopic treatment was regarded as a lesion greater than 3.5 cm and with extension to the bile duct. Therefore, EP is recommended as the main option of local excision for adenomas smaller than 4 cm, invasion depth confined to the mucosa and submucosa and with ductal extension not surpassing 1cm^(12,13).

The biopsy of the major duodenal papilla remains the gold standard diagnostic method for therapeutic decision, with the recommendation to obtain at least six specimens overall during lateral-viewing duodenoscopy and/or collection of fragments after 10 days of a sphincterotomy after biliary drainage of obstructive ampullary tumor, as well as an evaluation by an experienced pathologist in biliopancreatic diseases⁽⁴⁾. However, the biopsy alone offers low sensitivity for the diagnosis of adenoma and carcinoma, in which the lesion can be underestimated in up to 23% of the cases, where as in the suspicion of neoplasia it is recommended to perform a complete resection of the lesion⁽¹⁴⁾. Conversely, multiple histopathologic and endoscopic morphological variations of a normal major duodenal papilla may be erroneously interpreted as adenomas. These diagnostic dilemmas are evidenced when studying the population of patients undergoing EP, where currently only 13% to 36% of them present histopathological correlation with the resected surgical specimen^(15,16). In our sample, approximately one-fourth of the cases (six patients) presented invasive adenocarcinoma in the resected specimen, which were referred to complementary surgical treatment. All of these cases, the previous biopsies indicated only

adenoma with HGD. Otherwise, in 15 of the resected adenomas only three (about 20%) confirmed HGD as a finding in the surgical specimen. We found there was, therefore, a low correlation between the pre- and post-EP diagnosis for invasive adenocarcinoma and the presence of HGD. With the increasing experience of the team in addressing these lesions, it is expected that this correlation will be balanced over time.

EP has been widely used to remove early neoplastic lesions of the major duodenal papilla, including adenomas. The main advantage of this procedure compared to the surgical ampullectomy is to avoid an abdominal incision and a duodenotomy, with their implications⁽¹⁷⁾. Currently, complete endoscopic resection of ampullary neoplastic lesions of up to 4–5cm lateral extension has been described, provided that the lesions are restricted to the submucosa and with intraductal infiltration of less than 1cm, maintaining technical success rates as high as those of surgical series with lower morbidity. In a recent systematic review with pooled analysis of 29 studies and 1751 patients who underwent EP, the complete resection and recurrence rates were 94.2% and 11.8% (follow-up: 9.6–84.5 months), respectively, and the overall AEs rate was 24.9% (acute pancreatitis 11.9%)⁽¹⁸⁾. EP is performed for selected patients with T1 adenocarcinoma in the surgical specimen and high surgical risk. Patients with intraductal biliary recurrence (adenoma) can be treated with endoscopic ablation with radiofrequency⁽¹⁹⁾.

Improvement in the therapeutic approach of these lesions in recent decades has been possible through the improvement of endoscopic staging techniques, such as endoscopic ultrasound (EUS). The use of EUS seems to be a useful method for staging early lesions, with a detection rate of 82% for suspected malignancy⁽²⁰⁾.

The EP technique aims to remove the entire lesion using a diathermic snare, similar to a procedure of endoscopic mucosectomy for colonic adenomas. Regarding the technique used, its main controversies involve the use of submucosal injection preceding the resection, and the use of prophylactic pancreatic stents after resection of the lesion. The arguments for the use of submucosal injection are a reduction in the risk of bleeding when associated with adrenaline, besides the creation of a cushion with separation of the superficial and deep layers. However, this has been abolished by many centers because it increases the difficulty of grasping the lesion and the risk of pancreatitis⁽²¹⁾. In our series, submucosal injection with a saline solution containing adrenaline was used in only two procedures. The benefit of the use of pancreatic stents as prophylaxis for pancreatitis, currently recommended in this context for patients at high risk for pancreatitis^(4,22), has been questioned in more recent series^(23,24). In the present study, the placement of a pancreatic stent was used in under half of the cases (when it was possible to access the pancreatic duct), and the rate of pancreatitis was not above that described in the literature. The use of biliary stents is not encouraged on routinely⁽⁶⁾; these were inserted in nearly a third (38%) of our cases.

Because there is a predominance of lesions smaller than 2 cm, the enblock resection technique was the most used; However, two 3 cm-lesions already had signs of incomplete resection at the end of the procedure, showing macroscopic invasive adenocarcinoma, with local infiltration, hindering a complete endoscopic resection (R2 resection). About one third of the patients had adverse events and when they occurred, the most frequent were bleeding and acute pancreatitis, all treated without the need for surgery, with similar rates as described in the literature. There was no mortality.

As outcome parameters, technical success can be defined as a complete endoscopic resection, or resection without residual tumor at histopathological evaluation (R0 resection). The clinical success rate is defined as absence of remaining neoplastic lesions in subsequent biopsies up to 6 months. The finding of a lesion after this initial 6-month period is called tumor recurrence⁽²⁵⁾. Therefore, our series had 72% technically successful (complete endoscopic resection rate (R0)) within the variation demonstrated by current studies, which ranges between 46 and 97%^(4,24). Two recurrences were observed, with one case of a remnant tumor (sclerosing cholangitis with papillary extension) and another case of recurrent tumor (pancreatic intraductal neoplasia).

As a limitation of the present study, we can mention an information bias, typical in retrospective studies, where there is the inherent risk of data from inconsistent medical records and loss of follow-up. The follow-up was limited to a median of 12 months, with loss of follow-up of approximately one quarter of the cases, making it impossible to adequately assess tumor recurrence and clinical success rate. The present series does not have a number of patients with statistical power for a statistical comparative analysis, being useful, therefore, only as a descriptive study. It was not possible to evaluate early ampullary neoplastic lesions sent directly to surgical treatment or watchful waiting, therefore this study was restricted only to those who underwent endoscopic papillectomy (selection bias). As the procedures were performed by three different physicians (RCAS, EAB, RWN) from three different institutions, there is a natural technical variation.

In summary, the present study is one of the few Brazilian and Latin American series to address this subject, demonstrating that the population of patients undergoing PE was composed mostly of cases of superficial neoplastic adenomas, with acceptable technical success and morbimortality similar of other reports. There was a low correlation between the pre- and post-procedural histopathological diagnosis, thus it would be interesting to adopt an interdisciplinary clinical and pathological interaction strategy.

CONCLUSION

Endoscopic papillectomy was technically successful, allowing for complete tumor removal of early ampullary lesions in most cases, with an acceptable adverse event rate. Recurrence rate should be carefully assessed in further studies. There was a recent increase in the number of procedures performed. In addition, there was a low correlation between the pre- and post-procedure histological diagnosis for the presence of invasive adenocarcinoma and adenoma with high-grade dysplasia, with a predominance of adenomatous ampullary lesions.

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Authors' contribution

Cathcart Jr NS: study design, data assembly, data analysis, manuscript crafting, manuscript review. Souza RCA – study design, study coordination, data assembly, manuscript review. Noda RW: data assembly, manuscript review. Taglieri E, Ardengh JC: manuscript review. Bonin EA: study design, study coordination, data analysis, manuscript crafting, manuscript review.

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RESUMO – Contexto – A papilectomia endoscópica tem sido a opção terapêutica menos invasiva no tratamento de tumores precoces que acometem a papila duodenal maior. **Objetivo** – Avaliar pacientes com tumores ampulares precoces submetidos a papilectomia endoscópica com finalidade curativa, com relação ao sucesso técnico (avaliação histopatológica da margem tumoral) e sua segurança (taxa de eventos adversos [EAs]). **Métodos** – Foram avaliados retrospectivamente dados demográficos, exame histopatológico e evolução clínica pré e pós-procedimento de pacientes consecutivos submetidos a papilectomia endoscópica. Os desfechos avaliados foram o sucesso técnico (avaliação histopatológica de tumor residual) e taxa de EAs. **Resultados** – Um total de 21 prontuários de pacientes com predominância feminina (13 casos, 61,9%) foi incluído no estudo. O diagnóstico tumoral foi incidental em 8 (38%) casos. A taxa de margem de ressecção negativa foi 72% (15 casos); três destas lesões confirmaram displasia de alto grau (DAG) no espécime ressecado e seis casos de neoplasia invasora. Houve recorrência tumoral em dois casos e a mediana de seguimento foi de 12 meses, com 23% de taxa de perda de seguimento (cinco casos). Seis (28,5%) pacientes apresentaram EAs, todos precoces (hemorragia e pancreatite aguda); nenhum destes necessitou de intervenção cirúrgica e não houve mortalidade. **Conclusão** – A papilectomia endoscópica permitiu sucesso técnico, com a completa remoção de lesões neoplásicas ampulares na maioria dos casos com taxa de EAs aceitáveis. A taxa de recorrência tumoral deve ser cuidadosamente avaliada em estudos futuros. Houve um aumento recente do número de procedimentos realizados. Também houve baixa correlação entre o diagnóstico histológico pré e pós-procedimento para a presença de adenocarcinoma invasor e adenoma com DAG, com predomínio de lesões adenomatosas superficiais.

DESCRITORES – Ampola hepatopancreática. Adenoma. Ressecção endoscópica de mucosa.

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