

Endoscopic Papillectomy in Vater Papilla Adenomas with Focal Carcinoma in Cuban Patients

Julián Francisco Ruiz Torres^{1*}, Raúl Antonio Brizuela Quintanilla², Jorge Luis García Menocal³, Felipe Neri Pinol Jiménez⁴ and Patricia Ruiz Rodríguez³

¹International Member of the American College of Gastroenterology, President of the Cuban Society for Surgical Endoscopy, Member of the Cuban Society of Gastroenterology, National Center for Minimum Access Surgery, Cuba

²Member of the Cuban Society of Gastroenterology, National Center for Minimum Invasive Surgery, Cuba

³National Center for Minimum Invasive Surgery, Cuba

⁴International member of the American Society of Gastroenterology and Endoscopy and the American College of Gastroenterology, Member of the Cuban Society of Gastroenterology, National Center for Minimum Invasive Surgery, Cuba

***Corresponding author:** Julián Francisco Ruiz Torres, Specialist in Gastroenterology, Professor and assistant researcher, Academic, International Member of the American College of Gastroenterology, President of the Cuban Society for Surgical Endoscopy. Member of the Cuban Society of Gastroenterology, National Center for Minimum Access Surgery, Cuba, E-mail: julian@infomed.sld.cu

Abstract

Background: The ampullary adenomas are infrequent lesions, being the pancreatoduodenectomy the standard therapeutic method. Currently, endoscopic papillectomy is a therapeutic alternative in ampullary adenomas. There is evidence that it can also be performed in those adenomas with focal carcinoma, with minimal risk of complications.

Method: To describe the experience of endoscopic papillectomy in Cuban patients with adenomas with focal carcinoma, at the National Center of Minimally Invasive Surgery in Havana, Cuba. Retrospective study of several cases, in endoscopic service, from January 2009 to December 2017.

Results: A total of 123 ampullary lesions were diagnosed, classified from the clinical-endoscopic, imaging and histopathological point of view. Twenty-three ampullary lesions (19.0%) were resected endoscopically. Histologically, 30.4% were adenomas with focal carcinoma, (57.2% in stage T1 and 42.8% in stage T2) and the highest proportion were well-differentiated adenocarcinomas. The estimate of the overall survival time after treatment was 51.1 months after five years. The maximum follow-up time of the patients in the series was 77.0 months. Eighty-three percent (83%) did not present complications, only 13% presented bleeding and 4% stenosis of the sphincterotomy.

Conclusions: Endoscopic papillectomy is an alternative curative, effective and safe treatment for the resection of ampullary adenomas with T1 stage focal carcinoma.

Keywords: *Ampullary adenoma; Endoscopic papillectomy; Focal carcinoma*

Received Date: September 14, 2019; **Accepted Date:** September 30, 2019; **Published Date:** October 07, 2019

Citation: Julián Francisco Ruiz Torres, Endoscopic Papillectomy in Vater Papilla Adenomas with Focal Carcinoma in Cuban Patients. Clin Surg J 3(1): 6-16.

Introduction

In Cuba, ampullary, malignant or benign lesions are infrequent, difficult to diagnose and manage [1]. Worldwide, it is reported that they represent 0.2% of gastrointestinal cancers, and 6% of periampullary tumors. Pancreatoduodenectomy is the standard surgical method for radical resection, with a high rate of complications, mortality and a five-year survival of 50%-85% [2].

The development of video endoscopy and biliopancreatic endoscopic ultrasonography has not only allowed the diagnosis of these lesions to be regenerated, but also their therapeutics, a fact that is evidenced in several studies of series of cases performed worldwide, with encouraging results in terms of minimum risk of complications and high survival rate, which justifies that endoscopic papillectomy be considered an alternative-curative, safe and effective therapeutic method for the resection of adenomas with focal carcinoma in stage T1 [3-5].

Historical, epidemiological, clinical and experimental evidences allow defining the adenomas of the Vater papilla as infrequent and slow-growing proliferative glandular lesions. Generally, they occur at an average age of 54 years, more frequent in males and correspond to the periampullary tumors with the best prognosis [4].

Clinically, they are characterized by an obstructive cholestatic picture, identified by ultrasonography and classified according to the presence of dilatations of the intrahepatic and extrahepatic biliary tract. It is reported that these lesions can infiltrate neighboring structures slowly, offering a good prognosis at an early stage. In this sense, its late diagnosis overshadows the patient's survival [6].

Histologically, the most frequent ampullary lesions reported are adenomas and adenocarcinomas. The advance of endoscopic techniques (endoscopic ultrasound and endoscopic retrograde cholangiopancreatography: ERCP), and imaging (computerized axial tomography) have increased their diagnosis, offering a detailed and magnified visualization of the mucous pattern of the ampullary lesion, thus defining their therapeutic behavior, either through radical or local resection (endoscopic papillectomy) or open surgery [4,6,7].

In this sense, endoscopic papillectomy is a minimally invasive treatment method, currently proposed by the scientific community to resect superficial lesions of well-staged Vater ampulla. It constitutes a safe and effective therapeutic procedure, which can evade a radical resection (pancreatoduodenectomy) [8].

This research aims to describe the experience of performing endoscopic papillectomy in Cuban patient's diagnosed adenomas with focal carcinoma in T1 and T2 stages, as an alternative to conservative treatment and for those who refuse to undergo radical surgery.

Patients and Methods

Data collection: patients included

An observational, descriptive and retrospective study of series of cases was carried out. From a total of 3634 patients registered in the database of the endoscopic service of the National Center for Minimally Invasive Surgery of Havana (Cuba), between the period of January 2009 and December 2017, 123 patients were identified with clinical diagnosis-endoscopic,

imaging of ampullary lesions, from different regions of the country. Of these, 100 had advanced tumor lesions diagnosed by endoscopy and ERCP. On the other hand, 23 patients received local resection (endoscopic papillectomy) of their lesions that histologically corresponded to adenomas.

Patients

The data of interest such as age, sex, histological results, lesions staging, complications and follow-up, were obtained from the medical record and endoscopic reports of each of the patients.

Classification of the clinical phase

All patients were diagnosed and classified according to their stages through abdominal ultrasound, computerized axial tomography, upper video endoscopy (Olympus, 260 y 190), endoscopic ultrasonography (EUS Olympus GF-UE 260, GF-UCT 240), ERCP, and by histology of the lesions.

Histological evaluation was performed by specialized pathologists of the center, who reported the presence or absence of adenomas with or without focal carcinoma (well, poorly, moderately differentiated adenocarcinoma), lymphovascular invasion, lymph node metastasis, as well as infiltration of the mucosa of the common bile duct and/or pancreatic duct.

The classification of the International Union against Cancer (UICC) was considered for the staging of tumors of the Vater ampulla, which allowed classifying them according to the degree of tumor extension with the T staging (Table 1) [9,10].

Classification of the tumor stage (T) *	
Tx	Primary tumor cannot be determined
T0	There is no evidence of a primary tumor
Tis	Carcinoma in situ
T1	Limited: in Vater ampulla or sphincter of Oddi
T2	Invades: duodenal Wall
T3	Invades: pancreas <2 cm Long
T4	Invades: pancreas > 2 cm long (peripancreatic tissues and adjacent organs)

Table 1: Staging according to the Union for International Cancer Control (UICC).

Note: *Union for International Cancer Control (UICC).

All patients who had criteria for endoscopic and histological malignancy were informed that standard treatment was pancreatoduodenectomy. In those with T1 and T2 lesions, with complete exeresis of the lesion, due to various comorbidities, age, and denial of surgery, it was decided to perform endoscopic treatment.

Complications from post papillectomy were classified in minors (they happened during the endoscopic procedure, were solved with the same procedure and they did not require surgical intervention) and majors when they required a surgical intervention for their solution. The survival rate was estimated in the followed-up patients during months post papillectomy, and among these, the survival of each one was determined separately according to the histopathological diagnosis.

Description of therapeutic endoscopy

During the ERCP, a thickened, prominent and adenomatous Vater papilla was found, with an approximate size of less than 2 cm. Endoscopic papillectomy was indicated, previously marking the area to be resected and infiltrating the submucosa with

epinephrine 1x 20000, according to the following endoscopic criteria: lesions without evidence of malignancy (well defined, with regular borders, not ulcerated, or friable, no spontaneous bleeding and mild consistency), and histological findings of benignity of biopsy samples and absence of intraductal extension of the lesion demonstrated by ERCP. When it was observed that the malignant aspect was not more than ¼ of the lesion, resection was also carried out.

Endoscopic resection was performed or block when it was possible or fragmented if not. All the specimens were collected and sent for biopsy. Subsequently, biliary and pancreatic sphincterotomy was performed; the biliary and pancreatic ducts were canalized, placing a biliary plastic prosthesis and a pancreatic one when possible. In the cases that bleeding occurred during the procedure, argon plasma was applied using ERBE equipment and topical washing with adrenaline diluted in physiological saline for its control (Figure 1 & Figure 2).

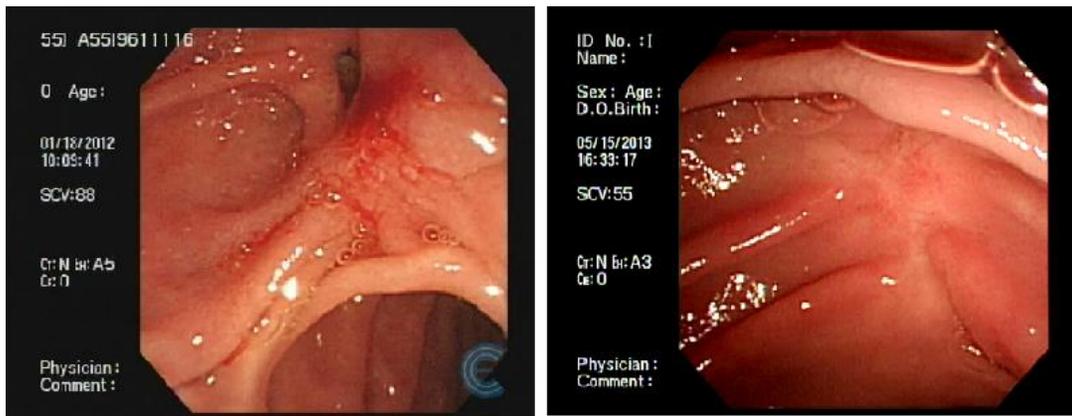


Figure 1 & Figure 2: In the cases that bleeding occurred during the procedure, argon plasma was applied using ERBE equipment and topical washing with adrenaline diluted in physiological saline for its control.

Statistical analysis and ethics

The statistical program SPSS version 21 was used to process the data. The variables were summarized using absolute and relative frequencies (percentages). The Kaplan-Meier method was used to estimate overall survival. The survival curves were compared for the different categories of the same variable through the Log-Rank test. Patients without event (death) at the end of the follow-up period (December 31, 2017) were considered censored on the right. A value of statistical significance of 0.05 was taken. The results are presented graphically for better analysis and understanding.

The study design was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Scientific Council and the Ethics Committee of the National Center for Minimally Invasive Surgery. The consent was obtained for the review of the patients' data, maintaining their confidentiality and their exclusive use for scientific research.

Results

Demographic evaluation of patients

When evaluating the demographic data of the patients, the average age of the 123 patients was 59.8 years and men prevailed (57.2%) with respect to women (42.8%).

Patients with lesions of the Vater ampulla

After evaluating the distribution of 123 patients with lesions of the Vater ampulla, in 23 of them (19.0%) these were resected by endoscopic papillectomy when not presenting evidence of endoscopic malignancy and 100 (81.0%) received radical surgery or palliative endoscopic treatment (placement of prosthesis or sphincterotomy only) for showing evidence of endoscopic malignancy.

Histology of resected lesions

The histological study of the lesions resected in 23 patients showed that 16 of them (69.6%) presented adenomas alone and 7 (30.4%) had adenomas with focal carcinoma (Figure 3).

Staging according to the Union for International Cancer Control (UICC)

After evaluation according to classification and staging, four (57.2%) corresponded to stage T1 located in the Vater ampulla mucosa without involving the sphincter of Oddi and three (42.8%) to stage T2 invading the duodenal wall (Figure 4).

It is noteworthy that in those patients classified as T1 who preferred surgery, no metastatic lesions or lymphovascular infiltration of the surgical specimen were found.

After analyzing the distribution of the histological findings of these carcinomas according to staging (Table 2), four (57.2%) were well differentiated adenocarcinomas (three in stage T1 and one in stage T2); two (28.5%) poorly differentiated adenocarcinomas (one in stage T1 and another in stage T2), and only one (14.3%) was a moderately differentiated adenocarcinoma in stage T2.

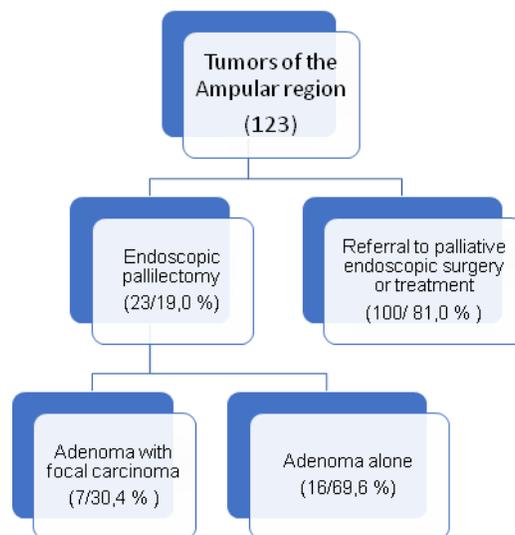


Figure 3: Distribution of patients with clinical-endoscopic and histological diagnosis of tumor in the ampullary region.

National Center for Minimally Invasive Surgery, 2009-2017.

The mean time of clinical-endoscopic follow-up of the patients presenting adenomas

The mean time of clinical-endoscopic follow-up of the seven patients presenting adenomas with focal carcinoma was 38 months. The maximum follow-up time of the patients in the series was 77.0 months.

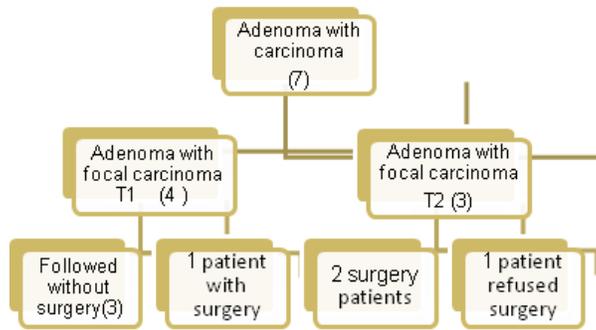


Figure 4: Distribution of patients presenting adenomas with focal carcinoma. National Center for Minimally Invasive Surgery, 2009-2017.

Adenoma with focal carcinoma	Staging (T)	
	T1	T2
Adenocarcinoma		
Well differentiated N= 4 (57.2 %)	1	1
Poorly differentiated N= 2 (28.5 %)	3	1
Moderately differentiated N= 1 (14.3 %)	0	1

Table 2: Distribution of patients presenting adenomas with focal carcinoma, according to histological findings and staging (T), National Center for Minimally Invasive Surgery, 2009-2017.

The overall survival after endoscopic post papillectomy

The overall survival estimated at 12 months after endoscopic post papillectomy was 85.7%, it decreased to 71.4% at 24 months, 57.1% at 36, 48 and 60 months respectively. The estimated overall survival time after treatment was 51.1 months, CI: 95%; 28.7-73.6 months (Figure 5).

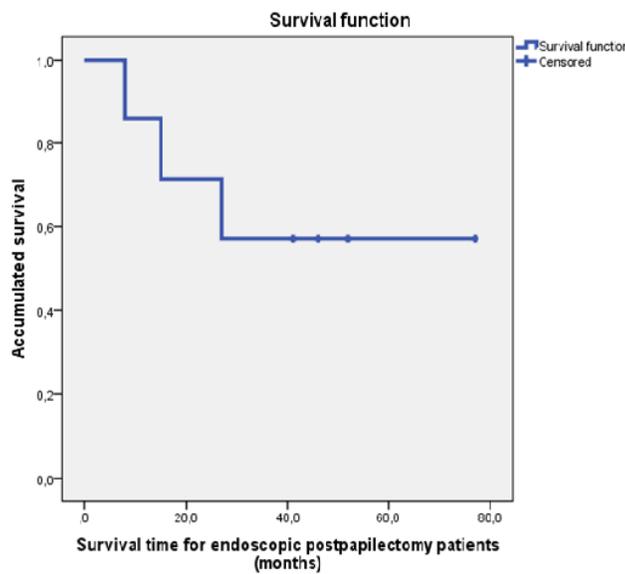


Figure 5: Overall survival in months of patients presenting adenoma with focal carcinoma after endoscopic papillectomy. National Center for Minimally Invasive Surgery, 2009-2017.

The overall survival was lower in patients with T2 stage compared to those who were in stage T1 (21.3 months vs. 64.5, respectively). These differences were not significant ($\chi^2 = 1.718$ 1 chi-square) (1gl df degrees of freedom) ($p = 0.190$); (Figure 6).

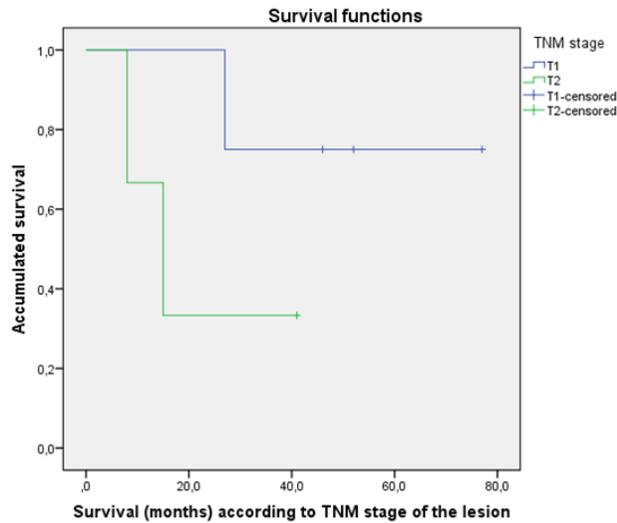


Figure 6: Overall survival in months of patients presenting adenoma with focal carcinoma after endoscopic papillectomy according to the TNM stage. National Center for Minimally Invasive Surgery, 2009-2017.

Complications presented in patients after endoscopic papillectomy

When studying the distribution of complications presented in patients after endoscopic papillectomy (Figure 7), it was observed that 19 patients (83%) did not present complications. A total of seven patients (17%) presented complications, of which there were three minors (13%) that corresponded to bleeding. Stenosis of the sphincterotomy of the bile duct was the major complication that occurred in one patient (4%).

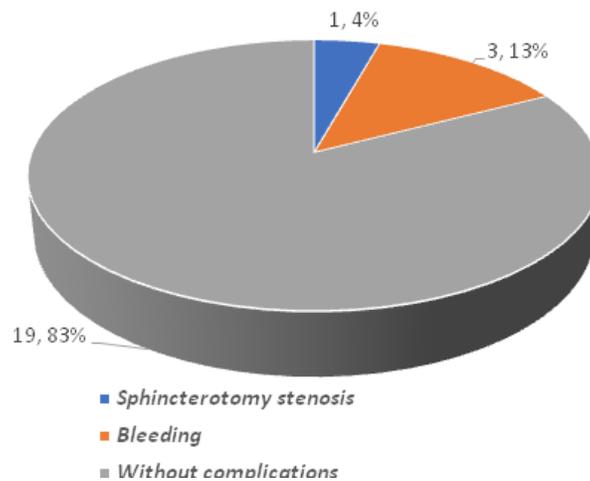


Figure 5: Distribution of complications presented in patients after endoscopic papillectomy. National Center for Minimally Invasive Surgery, 2009-2017.

Discussion

According to international reports, ampullary adenomas are infrequent lesions, being less frequent in females (rate of 0.36/100000) than in males (0.56/100000, $p < 0.05$) and after 50 years of age [11], a fact which is reinforced by the results of this research, where the highest proportion of patients were on average 59.8 years of age and corresponded to the male sex.

A point of current controversy in the management of these lesions continues to be their treatment, where the great unknown is the type of suitable resection for each tumor and each patient [12]. In this sense, the therapeutic alternative proposed by the scientific community is radical resection, as a standard technique. However, with the development of endoscopy and imaging, local resection (endoscopic papillectomy) is currently proposed, considering the results of several case series studies, which qualify it as a safe and effective method applied in early stages of the injuries.

Currently, there is no agreement on which lesions to resect endoscopically, their size, diameter, or the frequency of follow-up. However, in the studies by Baillie J, and De Palma GD, endoscopic resection is recommended when the size of the lesions oscillate between 4 cm and 5 cm, there is no intraductal growth, evidence of malignancy or endoscopic finding of ulceration, friability or spontaneous bleeding [13,14].

Considering these criteria, endoscopic papillectomy was performed in patients with a diagnosis of ampullary lesion when there were no endoscopic findings of malignancy or histological lymphovascular invasion or lymph node metastases, while radical surgery or palliative endoscopic treatment (placement of prosthesis or sphincterotomy only) was only performed in those who, from the endoscopic point of view, had morphological characteristics compatible with advanced tumors.

However, the systematic review conducted on the subject does not report randomized prospective studies that currently allow direct decision-making between radical or local resection. This depends on the preference of the doctor and the patient, the experience in its execution, the comorbidity and the technical-anatomical elements, being the justification for resection of the ampullary adenoma, treatment of the symptoms and prevention of malignant degeneration [15].

When performing the endoscopic diagnosis of an ampullary lesion, it is important to determine the presence or absence of carcinoma, the type and extent of dysplasia, to establish the need for resection, which is difficult, since the presence of carcinoma *in situ* or infiltrating carcinoma in the adenomas cannot be assessed without their complete resection.

The adenomas are considered premalignant lesions with a risk of development to carcinoma between 25% to 50%, with 40% of these located *in situ* [16]. In the present study, the highest proportion of ampullary lesions diagnosed by endoscopy and resected by endoscopic papillectomy, corresponded histologically to adenomas only and in smaller proportion with focal carcinoma. Of these, the highest histological proportions were well differentiated adenocarcinomas and T1 staging. These results reinforce what was reported by Yoon SM et al. [17], who performed endoscopic polypectomy as a curative treatment in a high proportion of patients with ampullary adenomas with focal carcinoma (well differentiated adenocarcinoma, T1 stage).

Regardless of the histological characteristics of focal carcinoma, endoscopic papillectomy was performed in the T2-staged patients with an acceptable margin of resection; no lymph node involvement was found after echo endoscopy. No lymphovascular involvement was found in the histological findings; only the duodenal mucosa was affected.

Studies on the follow-up of patients with ampullary lesions resected by endoscopic papillectomy are controversial. According to a report by Ridditid W et al. [18] who evaluated the risk factors for incomplete resection and recurrence in patients followed for a long time who received an endoscopic papillectomy, a greater number of patients is required to define the follow-up time, and this must be leveled in the long term in order to be able to standardize surveillance periods.

However, the fact that the endoscopic and histological findings of the resected lesions offer characteristics of advanced malignancy absence, only follow-up at short periods is justified; in cases of not obtaining a complete resection, and therefore it is proposed to execute other treatment options [19-21]. In this sense, in our study the mean time of clinical-endoscopic follow-up of patients with focal carcinoma was 38 months, and the maximum follow-up time was 77 months, during which no clinical or endoscopic recurrence was reported.

Survival rates in patients with periampullary tumors are markedly superior to those of pancreatic cancer. Therefore, early diagnosis and adequate staging of this particular group of neoplasms will make possible an important therapeutic success [22,23]. This is reflected when evaluating the estimated overall survival according to the years of follow-up in patients with an overall survival rate of 85.7% at 12 months post endoscopic papillectomy and 57.1% at 60 months, the latter maintained from 36 months of follow-up. Although overall survival was lower in patients with stage T2 compared to those who were in stage T1, the differences were not significant.

Endoscopic papillectomy is considered a "high risk" procedure for complications, ranging from 8% to 35%. The most frequent early complications reported in series of cases are pancreatitis (5%-15%) and bleeding (2%-16%), followed in a lesser proportion by perforation and cholangitis, while in late cases, stenosis, pancreatic as well as biliary range between 0 to 8%. Mortality after endoscopic papillectomy is rare, and 0.4% is reported (range 0% -7%) [24-26].

The results of the investigation reinforce what was described previously, and those reported by Galandiuk in 1988, since the highest proportion of patients who received endoscopic papillectomy did not present complications. The complications presented were mostly minor, that is, they appeared during the procedure and were resolved during the procedure (bleeding). Only one patient presented a major complication that required sphincterotomy and placement of a prosthesis, but no mortality was reported related to the procedure.

Finally, we can conclude that endoscopic papillectomy is a valid, safe technique with acceptable oncological results for the resection of premalignant and malignant lesions early in the ampulla of Vater.

Acknowledgement

We thank Dr. Maricela Perez for her assistance with Biostatistics and Ms. Barbara Ontivero for searching and organizing the Bibliography.

Financial

No sponsorship of any kind was received to carry out this article.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Supplementary Information

What is known?

In Cuba the standard treatment for patients with benign or malign tumors of the Vater papilla is Pancreatoduodenectomy

Endoscopic papillectomy is an alternative treatment for patients with adenomas in Vater papilla.

Endoscopic papillectomy has been performed with acceptable results in patients with adenomas with *in situ* carcinomas and with T1 stage focal carcinoma.

What is new here?

The practicality of performing endoscopic papillectomy with acceptable results in patients with focal carcinoma in T2 stage Vater papilla.

Endoscopic papillectomy is used in patients with adenomas with T1 and T2 focal carcinomas for the first time in Cuba.

References

1. Alonso Soto J, Martínez Piti A, Díaz Rondón B, et al. (2016) Characterization of patients with bile duct tumors by endoscopic retrograde cholangiopancreatography. *Revista Cubana de Medicina* 55(2): 141-149.
2. Martin JA, Haber GB (2003) Ampullary adenoma: Clinical manifestations, diagnosis, and treatment. *Gastrointestinal Endoscopy Clinics of North America* 13(4): 649-669.
3. Sharma M, Somani P, Sunkara T, et al. (2018) Endoscopic ultrasound-guided management of bleeding periampullary tumor. *Endoscopy* 50(07): e192-e193.
4. Solano J, Cabrera LF, Pinto R, et al. (2016) Current management of adenomas of the ampulla of vater. *Revista Colombiana de Cirugía* 31(3): 212-218.
5. Will U, Müller AK, Fueledner F, et al. (2013) Endoscopic papillectomy: Data of a prospective observational study. *World Journal of Gastroenterology* 19(27): 4316-4324.
6. Nguyen N, Shah JN, Binmoeller KF (2010) Outcomes of endoscopic papillectomy in elderly patients with ampullary adenoma or early carcinoma. *Endoscopy* 42(11): 975-977.
7. Moon JH, Choi HJ, Lee YN (2014) Current status of endoscopic papillectomy for ampullary tumors. *Gut and Liver* 8(6): 598-604.
8. Ceppa EP, Burbridge RA, Rialon KL, et al. (2013) Endoscopic versus surgical ampullectomy: An algorithm to treat disease of the ampulla of Vater. *Annals of Surgery* 257(2): 315-322.

9. Greene FL, Page DL, Fleming ID, et al. (2002) Ampulla of Vater. In: AJCC cancer staging manual (6th Edn.) New York: Springer-Verlag: 151-156.
10. Chun YS, Pawlik TM, Vauthey JN (2018) (8th Edn.) of the AJCC Cancer Staging Manual: Pancreas and hepatobiliary cancers. *Annals of Surgical Oncology* 25(4): 845-847.
11. Albores-Saavedra J, Schwartz AM, Batich K, et al. (2009) Cancers of the ampulla of vater: Demographics, morphology, and survival based on 5,625 cases from the SEER program. *Journal of Surgical Oncology* 100(7): 598-605.
12. Schneider L, Contin P, Fritz S, et al. (2016) Surgical ampullectomy: An underestimated operation in the era of endoscopy. *HPB* 18(1): 65-71.
13. Baillie J (2006) Endoscopic Ampullectomy. *Gastroenterology & Hepatology* 2(5): 315-316.
14. De Palma GD (2014) Endoscopic papillectomy: Indications, techniques, and results. *World Journal of Gastroenterology* 20(6): 1537-1543.
15. Tran TC, Vitale GC (2004) Ampullary tumors: Endoscopic versus operative management. *Surgical Innovation* 11(4): 255-263.
16. Deichler F, Fuentes M, Cárcamo C, et al. (2018) Periapular tumors. Findings and results in 21 consecutive cases resected. *Cuadernos de Cirugía* 20(1): 21-27.
17. Yoon SM, Kim MH, Kim MJ, et al. (2007) Focal early stage cancer in ampullary adenoma: Surgery or endoscopic papillectomy?. *Gastrointestinal Endoscopy* 66(4): 701-707.
18. Riditid W, Tan D, Schmidt SE, et al. (2014) Endoscopic papillectomy: Risk factors for incomplete resection and recurrence during long-term follow-up. *Gastrointestinal Endoscopy* 79(2): 289-296.
19. Palomo Hoil RA, FarcaBelsaguy A, Salceda Otero JC, et al. (2016) Endoscopic management of ampullary adenocarcinoma of Vater. *Medical Annals of the Medical Association of the ABC Medical Center* 61(3): 221-224.
20. Solano J, Cabrera LF, Pinto R, et al. (2016) Current management of adenomas of the ampulla of vater. *Colombian Journal of Surgery* 31(3): 212-218.
21. Espinel J, Pinedo E, Ojeda V, et al. (2016) Endoscopic ampullectomy: A technical review. *Revista Española de Enfermedades Digestivas* 108(5): 271-278.
22. Napoleon B, Gincul R, Ponchon T, et al. (2014) Endoscopic papillectomy for early ampullary tumors: Long-term results from a large multicenter prospective study. *Endoscopy* 46(02): 127-134.
23. Ismail S, Marianne U, Heikki J, et al. (2014) Endoscopic papillectomy, Single-centre experience. *Surgical Endoscopy* 28(11): 3234-3239.
24. Ardengh JC, Kemp R, Lima-Filho ÉR, et al. (2015) Endoscopic papillectomy: The limits of the indication, technique and results. *World Journal of Gastrointestinal Endoscopy* 7(10): 987-994.
25. Adler DG, Qureshi W, Davila R, et al. (2006) The role of endoscopy in ampullary and duodenal adenomas. *Gastrointestinal Endoscopy* 64(6): 849-854.
26. Heinzow HS, Lenz P, Lenze F, et al. (2012) Feasibility of snare papillectomy in ampulla of vater tumors: Meta-analysis and study results from a tertiary referral center. *Hepato-gastroenterology* 59(114): 332-335.