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## **Endoscopic and surgical ampullectomy for intramucosal ampullary tumor: the patient populations are not the same**

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**Key words:** ampullomas, surgical ampullectomy, endoscopic ampullectomy

## **Endoscopic and surgical ampullectomy for intramucosal ampullary tumor: the patient populations are not the same**

### **Abstract**

**Purpose:** To evaluate and compare the results of endoscopic ampullectomy (EA) and surgical ampullectomy (SA) for benign tumors.

### **Material and method:**

From 2005 to 2018, 66 patients were eligible for ampullectomy (adenoma, ultrasound grading  $\leq$  T1, N0). The principal endpoint was the rate of complete resection: R0 resection without local recurrence and no recurrence after a single operative procedure and with final pathology confirming the operative indications. Secondary endpoints were: morbidity, mean length of stay (LOS), pre-operative and final pathology results, complete (or incomplete) resection, mean duration of follow-up, local recurrence rate and late complications (biliary stricture).

### **Results:**

Among the 41 patients eligible for EA, 36 ampullectomies were performed, while five were referred for SA because of intracanalicular invasion that had not been diagnosed initially. The rate of complete treatment was 48% (13/27), the morbidity was 10%; the LOS was 3.3 days; no adenomatous lesion was found on the definitive pathology in 9 patients (25%). The resection was R1 in 30% but there were no R2 resections. The median duration of follow-up was 20 months, the rate of local recurrence was 22% and the rate of late biliary stricture was 2%. Among the 30 patients who were eligible for SA, (25 plus the five referred by endoscopists after intracanalicular invasion was found), SA was eventually performed in 24: five patients were converted to pancreatoduodenectomy, one patient was found to have metastatic disease and had no resection. An extemporaneous frozen-section pathology examination was performed in 22 of the 24 SA patients and confirmed healthy margins on the bile ducts and pancreatic ducts. The rate of complete treatment was 71% (17/24), morbidity was 35%; LOS was 10 days; seven patients (29%) were found to have invasive adenocarcinoma, and six of these (86%) underwent subsequent pancreatoduodenectomy. None of the resections were R1 or R2; median follow-up was 21 months; there was no local recurrence; biliary stricture rate was 8%.

### **Conclusion:**

The short-term and long-term results of patients undergoing endoscopic or surgical ampullectomy are different. The lesions resected by EA were less advanced, with simpler post-operative course. The lesions for which SA was performed were more advanced, and had more morbid sequelae, but with a better rate of complete treatment and better long-term results.

## Introduction

For most physicians, ampullectomy consists of the endoscopic excision of the Ampulla of Vater, (AV), usually for a benign lesion. The results of endoscopic ampullectomy (EA) are often compared to those of cephalic pancreatoduodenectomy (CPD) and not to surgical ampullectomy (SA).

However, some elements are worth recalling: The Ampulla of Vater (AV) (Figure 1) is an anatomical entity defined by the junction of the main (Wirsung's) pancreatic duct and the common bile duct (CBD) to form a common channel that takes the form of a fusiform terminal dilation or saccular reservoir in two-thirds of cases [1]. Tumors of the AV, commonly called ampullomas, represent 0.2% to 5% of digestive tumors with an incidence in autopsy series of 1/100,000 inhabitants [1-5]. Ten to 30% of these tumors are benign [4-6]. Among these benign lesions, the most common are adenomas [7,8], similar to colonic adenomas in that the adenoma-to-adenocarcinoma progression has been demonstrated [5-9] Therefore, the discovery of an adenoma of the ampulla implies the need for resection of a pre-cancerous lesion.

There are several modalities for treatment of ampullary lesions. Local excision, *i.e.*, ampullectomy, is indicated for intramucosal lesions (adenoma with low- or high-grade dysplasia, carcinoma-in-situ, non-ulcerated, less than 3 cm, uT1) and is correlated with absence of lymph node extension. Ampullectomy can be performed by either an endoscopic or surgical approach. Radical excision, *i.e.*, CPD, is reserved for invasive lesions at risk of nodal or distant metastasis.

The assessment of an ampullary lesion comprises three stages that determine the type of treatment.

The first corresponds to the description of the lesion during the loco-regional assessment (size, ulceration, exo- or endo-sphincteric location, intracanalicular invasion, duodenal extension, presence of lymphadenopathy). This is based on an endoscopic assessment that includes both duodenoscopy and endoscopic ultrasound (EU), which has a sensitivity and specificity for the positive diagnosis of ampulloma of about 90% [10-11]. The ability of EU to determine local extension (T stage) has shown a sensitivity of 74-84.4%, while detection of nodal metastasis (N stage) varies from 53.1% to 100% in various series [10-17]. Conventional EU makes it possible to determine the presence or absence of intraductal extension, but cannot appreciate involvement of the *muscularis mucosae*, but only of the duodenal *muscularis propria*. Moreover, the negative predictive value of EU for lymph node extension is low (it does not rule out nodal spread), and it does not allow classification of T1m and T1sm lesions. Nevertheless EU makes it possible to select T1 lesions that are potentially treatable by ampullectomy.

The second step is the pathological study of the biopsied lesion, which must confirm the adenomatous nature of the lesion, its non-invasive character, and the presence or absence of submucosal invasion when possible. If submucosal invasion is present, the risk of lymph node invasion is 30%, (Figure 2) [18-20].

Finally, the third step is imaging assessment of distant extension to either secondary nodal groups or to other organs

The purpose of this study was to evaluate and compare the results of EA and SA for supposedly superficial tumors of the AV (adenoma, <sub>us</sub> T $\leq$ 1, N0).

## **Patients and Method**

### Study population, study design.

The study population consisted of all patients treated for ampulloma at the Amiens University Hospital Center from 2005 to 2018. The data were collected retrospectively from DIM codes (Department of Medical Informatics) (code C24.1). From January 2005 to December 2018, 92 patients were treated for ampulloma. The inclusion criterion for this study was eligibility for treatment by ampullectomy, *i.e.*, 66 patients. Twenty-six patients were excluded because of the need for CPD from the outset for T $>$ 1 or N+ lesions or because distant metastasis at the outset contraindicated resection. Patients were included if they underwent ampullectomy or at least an exploratory duodenotomy. The average age of the population was 69 years and 48% of the patients were men. Patients eligible for local treatment were divided into two groups, the EA group and the SA group. Initially the choice between EA *versus* SA was not made in a multi-disciplinary conference but according to the choice of the patient's physician. Subsequently, in order to improve patient management, the choice of whether to perform EA or SA was made within CAPENDOS, a multidisciplinary consultative meeting. CAPENDOS meets weekly and brings together endoscopists, surgeons, and radiologists

### Choice of the technical modality for ampullectomy

The indication for a local resection (EA or SA) or radical resection (CPD) depended on the invasiveness of the lesion, the risk of nodal involvement, and the presence of intracanal invasion. Criteria favoring radical resection from the outset included jaundice, tumor ulceration, stages  $>$  <sub>us</sub> T1 and/or N+, and submucosal invasion. On the whole, indications for a local resection in our series were intramucosal lesions, classified <sub>us</sub> T1, N0.

A lesion larger than 4 cm, a lesion with significant duodenal extension (sessile lesion), or a lesion with intracanal extension, were contraindications to EA and favored SA. Previous sphincterotomy complicated the decision but was not an absolute contraindication to EA. Intraluminal extension into the CBD is resectable by SA if the lesion remains limited to the intrapancreatic portion of the duct. Extension into the pancreatic duct is resectable by SA if the lesion is limited to 1 cm. A larger extension should be treated by CPD.

### Surgical ampullectomy (SA) technique (Figure 3)

SA is performed according to the standard technique [7]. After midline laparotomy overlying the second portion of the duodenum (D2), the abdominal

cavity is explored in search of findings that would contra-indicate the procedure. D2 is then mobilized medially by detachment of the greater omentum from the transverse colon, mobilization of the root of the transverse mesocolon, takedown of the hepatic flexure, and a Kocher maneuver. The location of the papilla must then be identified (this gesture can be facilitated by introduction of a probe via the cystic duct). A longitudinal duodenotomy overlying the papilla then exposes the papilla, and traction sutures are placed around the edges of the duodenotomy to facilitate exposure. The submucosa is then injected with 0.1% epinephrine solution starting at the bottom in order to identify the main pancreatic duct first. The submucosal injection is performed in analogous fashion to endoscopic resection of colonic polyps, allowing elevation of the lesion around the ducto-duodenal junction and facilitating dissection. The use of an epinephrine solution decreases local bleeding that would hinder the gesture. The duodenal wall is incised with a "cold" scalpel or scissors at least 5 mm from the tumor edges. Then the entire ampullary mass is pedicled on the CBD and Wirsung's duct. We first identify the main pancreatic duct that will be divided, then the CBD is identified and divided as low as possible within the pancreas. The biliary and pancreatic ducts are re-implanted into the duodenum and then the anterior duodenotomy is closed in one or two layers (Figure 3). The cystic duct drain is removed, but an abdominal drainage can be put in place. The resected specimen is oriented on a corkboard to facilitate pathology examination. In our center, we no longer request a systematic extemporaneous frozen-section examination of the bile duct and pancreatic duct margins, since the gesture is pushed as far as possible along the ducts to obtain an R0 resection, until no further resection is possible. If frozen-section examination shows positive margins, a CPD would be indicated, but this procedure is no longer performed at the same time. Moreover, these lesions are difficult to interpret on extemporaneous frozen-section examination with risks of false positives and false negatives, so we prefer a maximalist local gesture, followed by classical pathological analysis; if pathology findings indicate the need for CPD, this is performed after a two-month interval.

#### Endoscopic ampullectomy (EA) technique (Figure 4).

The EA technique is similar to the mucosectomy resection of polypoid lesions by electrocautery loop. blended or pure cutting mode (not preceded by submucosal injection of saline since the AV is fixed by the bilio-pancreatic ducts). Sphincterotomy should not be performed, since it may complicate the pathologic analysis and compromise definitive conclusions about the R0 character of the resected specimen. If previous endoscopic sphincterotomy has been performed, the ampullectomy is performed in two pieces (anterior and posterior). At the end of the procedure, rigorous hemostasis of the mucosectomy scar is performed. Pancreatic and biliary ductal prosthetic stents are inserted whenever this is possible and easy to perform in order to reduce, respectively, the risk of acute pancreatitis and to prevent delayed bleeding. An NSAID suppository is always placed at the end of the procedure to prevent pancreatitis.

#### Purpose of the study and endpoint

The purpose of this study was to evaluate and compare the results of EA and SA for treatment of intramucosal tumors of the AV (adenoma, carcinoma –in- situ, ultrasound grade  $\leq$  T1, N0).

The composite primary endpoint was the rate of complete treatment: 1) an R0 resection (clear lateral and deep margins), after a single procedure whose indication was validated by definitive pathology, that is, resection of an adenomatous lesion or carcinoma-in-situ not invading the *muscularis mucosae*, and 2) no recurrence.

The secondary endpoints were: morbidity (any complication occurring during hospitalization), mortality, mean length of stay (LOS), definitive histology, complete or incomplete resection, a specimen with indeterminate margins that were therefore considered R1, recurrence rate, and remote complications of the gesture (biliary stricture).

### Statistical analysis

Statistical analysis was performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics, version 22.0, 2013: IBM Corp., Armonk, NY).

Quantitative variables were expressed in numbers (percent) and compared by a Student test. The qualitative variables were compared by a  $\chi^2$  test (Chi 2).

The threshold of significance was  $p < 0.05$ .

### **Results**

Sixty-six patients were eligible for treatment by ampullectomy. Thirty-one patients were treated prior to the creation of the CAPENDOS meeting. Of these, 13 underwent SA and 20 underwent EA. Of the 35 patients who were evaluated following the institution of the CAPENDOS meeting, 12 patients were eligible for SA and 21 for EA (Figure 5).

#### Endoscopic treatment (EA):

In group EA (Table 1): among these 36 patients, the lesions were exophytic in 10 (27%), and intracanalicular in five (13%) who were eligible for SA after re-evaluation.

These five patients were therefore referred to the surgeons for SA. In eight patients (22%), the specimen was fragmented mainly due to efforts at ductal canalization. For prophylaxis against pancreatitis, 36 (100%) patients were treated with NSAID suppositories, while placement of a pancreatic endostent was possible in 20 (55%) patients. Of the 36 patients who underwent ampullectomy, the lesion proved to be adenoma with low-grade dysplasia in 10 (28%), high-grade dysplasia in 11 (30%), adenocarcinoma-in-situ in six (17%), while no adenomatous lesion was found by definitive histology in nine (25%).

Of the 27 patients with adenomatous lesions, 19 (70%) patients had an R0 resection that was considered curative, while eight patients (30%) had an R1 resection. All of these eight patients had undergone a previous sphincterotomy and in five of them, the R1 resection classification was based on an Rx status due to fragmentation of the lesion. These five patients were followed with an

endoscopy at six months and then annual endoscopy for five years and none showed evidence of recurrence. The median follow-up of these patients was 70 (65-120) months. Two of the other R1 resections underwent a second endoscopic resection that was R0 and they showed no signs of late recurrence. The last of the eight was lost to follow-up.

Six patients who had an initial R0 resection (22%) developed local recurrence that was treated by a second endoscopic resection and they had no further recurrence.

The rate of complete treatment with the initial procedure was 48% (13 complete treatment for 27 confirmed indications).

Post-operative morbidity for EA was 10%. The specific morbidity for ampullectomy consisted of Grade D acute pancreatitis in two patients (6%), while no patients had bleeding or duodenal perforation. Mortality was 0%. The mean LOS was 3.3 days. The median follow-up after EA for adenoma was 20 (1-120) months and the rate of biliary stricture at one year was 2%.

### Surgical treatment (SA):

In the SA group (Table 1), 30 patients were eligible for surgical treatment (25 initially plus five referred secondarily by the endoscopists). All of these patients had intracanalicular extension by the morphological assessment. An SA was performed in 24, while five (different from the five patients referred by our endoscopists) had more advanced lesions than expected and therefore underwent CPD immediately after duodenotomy confirmed the extent of the lesion. One patient with metastases did not undergo resection. Of the 24 SA's, 1 (4%) had an adenoma with low-grade dysplasia, 13 (54%) had high-grade dysplasia, three (13%) had adenocarcinoma-in-situ, and seven (29%) had invasive adenocarcinoma that therefore required secondary CPD. Of these seven patients, six eventually underwent secondary CPD, while one patient whose general condition did not allow CPD was simply observed.

Although this is no longer a systematic practice, extemporaneous frozen-section pathology was performed in 22 of the 24 SAs and confirmed tumor-free CBD and pancreatic duct margins. In 17 patients whose indication was validated by pathology, there were no R1 or R2 resections. There was no local recurrence. The complete treatment rate was therefore 71% (17 complete treatments for 24 confirmed indications).

Post-operative morbidity was 35% (excluding CPD) specific morbidity consisted of a peri-duodenal collection without fistula in two (8%) patients. The mortality was 0%. The LOS was 10 days. The median follow-up was 21 (1-118] months, and the 1-year biliary stricture rate was 8%.

## **Discussion**



The type of treatment differed according to the specific nature of the lesion. Fifty-three percent of the lesions in the EA group were low-grade lesions (25% non-adenomatous, 28% low-grade dysplasia), while 67% in the SA group were high-grade lesions (54% with high-grade dysplasia and 13% with in-situ carcinoma). The rate of complete treatment was higher in the SA group: 71% (17 complete treatments for 24 confirmed indications) vs. 48% in the EA group (13 complete treatments for 27 confirmed indications). Mean LOS and morbidity were lower in the EA group. The rate of R1 resection was higher in the EA group, 30% versus 0% in the SA group. Median follow-up was 120 [1-120] months in the EA group, and 118 [1-118] months in the SA group.

The main difference between the EA group and SA group was that all SA patients had intracanal extension. This treatment bias is explained by the fact that it is not possible to resect intracanal lesions endoscopically. This makes it difficult to compare the two populations. Nevertheless, one should remember that the majority of the series in the literature compared EA with CPD, *i.e.*, two even more disparate populations. In our series EA and SA were certainly not comparable, mainly because of the intracanal criterion. At present, given the morbidity and mortality results of EA and SA, it seems unethical to set up a study comparing EA and SA on the same populations, and the use of older data would introduce methodological bias.

For ampulloma, three intimately entangled problems make its management complex.

Firstly, there is a histological problem, because of the multitude of lesions of different histological nature that may involve the papilla, which occur moreover on a complex mucosa. The AV is a particularly complex region with many anatomical variations [1] and the site of confluence of several different types of mucosa (Figure 1). This complicates the diagnosis and management of tumors of the AV. The histologies of these tumors are diverse. They can be: benign or malignant epithelial tumors, benign or malignant mesenchymal tumors, ampullary metastases, endocrine tumors, or a direct extension to the papilla from a neighboring tumor [21]. In the context of ampullomas, it is the adenoma that interests us. The confluence of different types of mucosa and the risk of false-positive biopsies after sphincterotomy explain the existence of non-adenomatous lesions that wind up being managed by EA.

Secondly, it is difficult to assess tumor extent prior to ampullectomy, and the decision of local or radical excision (*i.e.*, ampullectomy vs. CPD) is conditioned by the involvement of the *muscularis mucosae* (Figure 1-2). Indeed, if the tumor has breached this barrier, a radical excision must be proposed to the patient because of the risk of lymph node spread. The problem is that pre-treatment diagnosis of *muscularis mucosae* infraction is only feasible by use of the 20MHz endoscopic ultrasound (EUS) [22], which allows classification of the lesions according to the Japanese classification as  $_{us}T1D0$  or  $_{us}T1D1$  [23]. The risk of lymph node involvement increases from 0% for a D0 lesion to 30% for a D1 lesion [18]. This type of EUS equipment is not widely available in France. Apart from a few particular situations (*i.e.*, an extensive, ulcerated lesion) where invasion of the *muscularis mucosae* is very probable, it is technically not possible

to determine with certainty whether the *muscular mucosae* is invaded or not before excision. This finding explains why some advanced lesions were found in the SA group (26% invasive adenocarcinoma).

Thirdly, the possibility of several initial approaches complicates the indication of the gesture (two initial approaches, three possible treatments). Ampullectomy is an endoscopic or surgical mucosectomy, intended only for lesions that do not cross the *muscularis mucosae* (During SA, one must not resect pancreatic parenchyma, which increases morbidity [24]).

In sum, the risk of lymph node involvement for tumors that breach the *muscularis mucosae* is 30%. This requires a radical gesture for a complete excision and satisfactory lymph node dissection. CPD is the preferred therapeutic option.

For lesions confined to the mucosa, a local, less invasive and less morbid procedure will be favored: EA or SA. In the case of a large lesion with intracanal extension, a complete *en bloc* resection is favored, *i.e.*, SA. If a prior sphincterotomy has been performed, the choice of endoscopic versus surgical route for ampullectomy is difficult: sphincterotomy, although preferably avoided, does not technically prevent performance of EA, but the resection in this case is not monobloc, which increases the risk of incomplete resection; the procedure is technically delicate, and imposes the need for long-term regular surveillance endoscopy follow-up in view of the risk of an R1 resection. A previous sphincterotomy is an argument in favor of SA over EA, but does not impose it.

The treatment of ampullomas has evolved in recent years, especially with the development of EA, which offers the advantages of a low-morbidity technique and a short LOS. This increasing role of endoscopy has transformed the management of adenomatous lesions of the AV, favoring EA for T0 and T1D0 lesions, while more advanced lesions should undergo CPD. However, when EA is technically impossible, the technical possibility of SA is often forgotten [25-26]. For the T1D0 lesion, either SA or EA may be indicated. Intracanal extension contraindicates EA, but this is not the case for SA. The low morbidity and mortality of endoscopy tend to make one forget the possibility of a local surgical resection, which still has its indications. Indeed, there is a population of patients with localized lesions that are endoscopically unresectable and who are not candidates for CPD in view of their history and overall condition. These patients can nevertheless benefit from complete local resection by SA [26]. Moreover, in our series, SA offered superior histological results compared to EA, resulting in a higher rate of complete resection. The 30% rate of R1 resection by EA in our series was due, mainly to the impossibility of analyzing the lateral or deep margins of piecemeal resections in five patients. Our results are comparable to data from the literature, which found an average of 33% of R1 resections (18-53%). Regarding the rate of local recurrence after EA, the literature reports vary from 10% to 25%, and this rate falls below 10% in case of monobloc resection. These results are superimposable on those of our series [27-31]. Depending on the series, the local recurrence rate after EA may be more than twice the local recurrence rate after SA [27]. In our series, the local recurrence rate in EA was the same as that reported in the literature [28-31], and all patients with recurrence were able to undergo a second endoscopic resection that resulted in

an R0 resection. The higher rate of R0 resection after SA was obtained at the cost of higher morbidity and a longer duration of stay. Moreover, recurrence after EA does not burn any bridges to further endoscopic management (mucosectomy for recurrence), whereas repeat SA after recurrence after an initial SA is rarely proposed. Finally, one must keep in mind that EA and SA are complex gestures requiring a significant learning curve for the operator performing the mucosectomy, which may explain higher rates of R1 at the beginning of the operator's experience with the procedure. For comparison, 90 procedures is the threshold for competency in endoscopic polyp resection [32]. The fact that the lesions in the SA group were more advanced seems to correspond with the fact that all the lesions were intracanalicular. In our experience, it seems preferable to manage all lesions with demonstrated or suspected intracanalicular extension by SA from the outset. When an EA for a non-intracanalicular lesion results in an R1, a second endoscopic procedure is generally feasible with good histological results. Over the course of our experience, we have observed a fall in the frequency of SA conversion to CPD after initial exploratory duodenotomy. All five such patients in our series were operated at the beginning of our experience when we did not systematically repeat the pre-operative assessment in our center. Lesions were therefore under-evaluated and patients selected for SA had to be converted to CPD because of the intra-operative findings. Since we began to systematically repeat the pre-operative assessment in our center, this event has no longer recurred. Nevertheless, some lesions are still under-evaluated by initial endoscopic biopsies. In patients where final pathology following resection finally showed their submucosal character, secondary CPD was required (this was the case for seven patients in our experience) theoretically at one week after the initial intervention. However, we now usually perform secondary CPD somewhat later at one to two months following the initial intervention, because we encountered complications following the first early re-interventions in our center. Of these first cases, all patients had Clavien-Dindo Class IVb morbidity with grade C pancreatic fistulas. Since we began to defer CPD for 1-2 months, the morbidities of all patients were Clavien-Dindo Class II, with 50% of them presenting with Grade A fistulas. We recognize that this is a small sample size from which to draw conclusions, but we chose to maintain this attitude.

Our experience has led us to develop a management protocol aiming to optimize the management of patients eligible for local resection of tumors of the AV. This consists in repeating the morphological assessment at our own institution to avoid under-evaluation of lesions that would result in conversions from local to radical surgery. This assessment includes: Upper GI Series, duodenoscopy, EUS and a new systematic series of biopsies. Once this assessment is completed, each patient is presented at the CAPENDOS meeting, a multidisciplinary meeting bringing together endoscopists, surgeons and radiologists to determine the patient's eligibility for radical or local treatment. If the patient is eligible for local treatment, the modality for ampullectomy, either EA or SA, is decided based on criteria of morbidity, technical feasibility and the possibility of complete resection. This course of action has its limitations, relying essentially on a monocentric and retrospective experience with a small staff, and

as such it cannot be formally recommended. Nevertheless, this attitude has allowed us to reduce our need to convert from local to radical resection, to reduce morbidity and to strengthen relationships among surgical, endoscopic and radiologic colleagues.

## Conclusion

Currently there is no formal recommendation regarding the technical performance of ampullectomy. Patients eligible for this therapeutic modality are very heterogeneous, and indications for EA or SA vary from center to center. Our experience has shown that patients/lesions treated by endoscopic or surgical ampullectomy are not the same. The short-term and long-term results are different. The lesions treated by EA are less severe, with simpler sequelae. The lesions treated by SA are more severe, with more morbid consequences, but with a better rate of complete resection and better long-term results for surgery. It should be kept in mind that an ampullectomy is a macrobiopsy that both confirms the diagnosis with certainty and achieves, at the same time, the treatment of the lesion [26].

## Declaration of interest

The authors declare that they have no conflicts of interest.

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**Table 1: Results**

		EA n= 36	SA n= 30	
<b>Echoendoscopy (EUS)</b>				
	<sup>us</sup> T1	25	20	
	<sup>us</sup> T2	0	1	
	<sup>us</sup> Tx (*)	6	3	
	<sup>us</sup> N0	31	22	
	<sup>us</sup> Nx (*)	0	2	
	Intracanalicular invasion	5	24	
	Missing data	5	6	
<b>Lesion size</b>				
	0-10 mm	4	5	
	10-20 mm	19	9	
	20-30 mm	10	11	
	30-40 mm	3	5	
<b>Appearance of the papilla</b>				
	Hypertrophied	9	5	
	Budding	6	5	
	Protruding	5	6	
	Adenomatous	4	3	
	Exophytic	10	5	
	Ulcerated	0	2	
	Villous plaque	2	4	
<b>Pre-treatment biopsy</b>				
	Non-adenoma	0	0	
	Low-grade dysplasia	21	18	
	High-grade dysplasia	10	12	
	Adenocarcinoma	0	0	
	Not done	5	0	
<b>Sphincterotomy</b>				
	Yes	11	14	
	No	25	16	
<b>Final pathology</b>				
	Non-adenoma	9 (25%)	0	p= 0.007
	Low-grade dysplasia	10 (28%)	1 (4%)	p= 0.02
	High-grade dysplasia	11 (30%)	13 (54%)	p= 0.06
	Adenocarcinoma-	6 (17%)	3 (13%)	ns

	in-situ			
	Invasive adenocarcinoma	0	7 (29%)	p<0.001
		AE	AC	
Validated indication for ampullectomy		27	24	
R1		8 (30%)	0	p=0.004
R2		0	0	ns
Recurrence		6 (22%)	0	p=0.02
Complete resection		13/27 (48%)	17/24 (71%)	p=0.1
Mean length of stay		3.3 days	10 days	ns
Median follow-up		20 months (1-118)	21 months (1-118)	
Biliary stricture at >1 year		2%	8%	ns
ns : non-significative (*) The TNM classification was not precisely established for some echoendoscopies				



## Captions for figures

Figure 1: Diagram of a typical Ampulla of Vater showing the different types of mucosa and transitional areas as well as the *muscularis mucosae* and duodenal mucosa. 1: mucous membrane of the papilla or ampullary mucosa; 2: Duodenal or ampullary muscularis; 3: Sphincter of Oddi.; 4: Common bile duct (CBD) epithelium; 5: Pancreatic duct epithelium.; 6: Duodenal mucosa; 7: *Muscularis mucosae*; 8: Ampullary region; 9: Ampulla of Vater:  $\alpha$ : Duodenal lumen.  $\beta$ : CBD.  $\omega$ : Pancreatic duct.

Figure 2: Risk of lymph node involvement relative to depth of invasion.

A: Reminder of the epithelial constituents of the ampullary region: the localization of the *muscularis mucosae* and the duodenal *muscularis* has been specified. Positions of T1 (D0, D1) and T2 lesions in the epithelium [18-19].

B: Correlation between level of epithelial involvement (with the different definitions according to the revised Vienna classification) and T status of the TNM classification with the observed risk of lymph node involvement [20].

Figure 3: Surgical ampullectomy, step-by-step.

A: Duodenotomy centered over the lesion, with the biliary cannula visible, and injection of epinephrine solution into the mucosa.

B: The pancreatic duct is marked with a stylette.

C: Progressive dissection of the lesion starting with the pancreatic duct.

D: End of procedure, with the lesion resected, and bile and pancreatic ducts re-attached.

Figure 4: Endoscopic ampullectomy.

A: Ampullary lesion.

B: Scar immediately after resection.

C: Scar at one month.

D: Scar at three months.

Figure 5: Flow chart of the study

Figure 1.

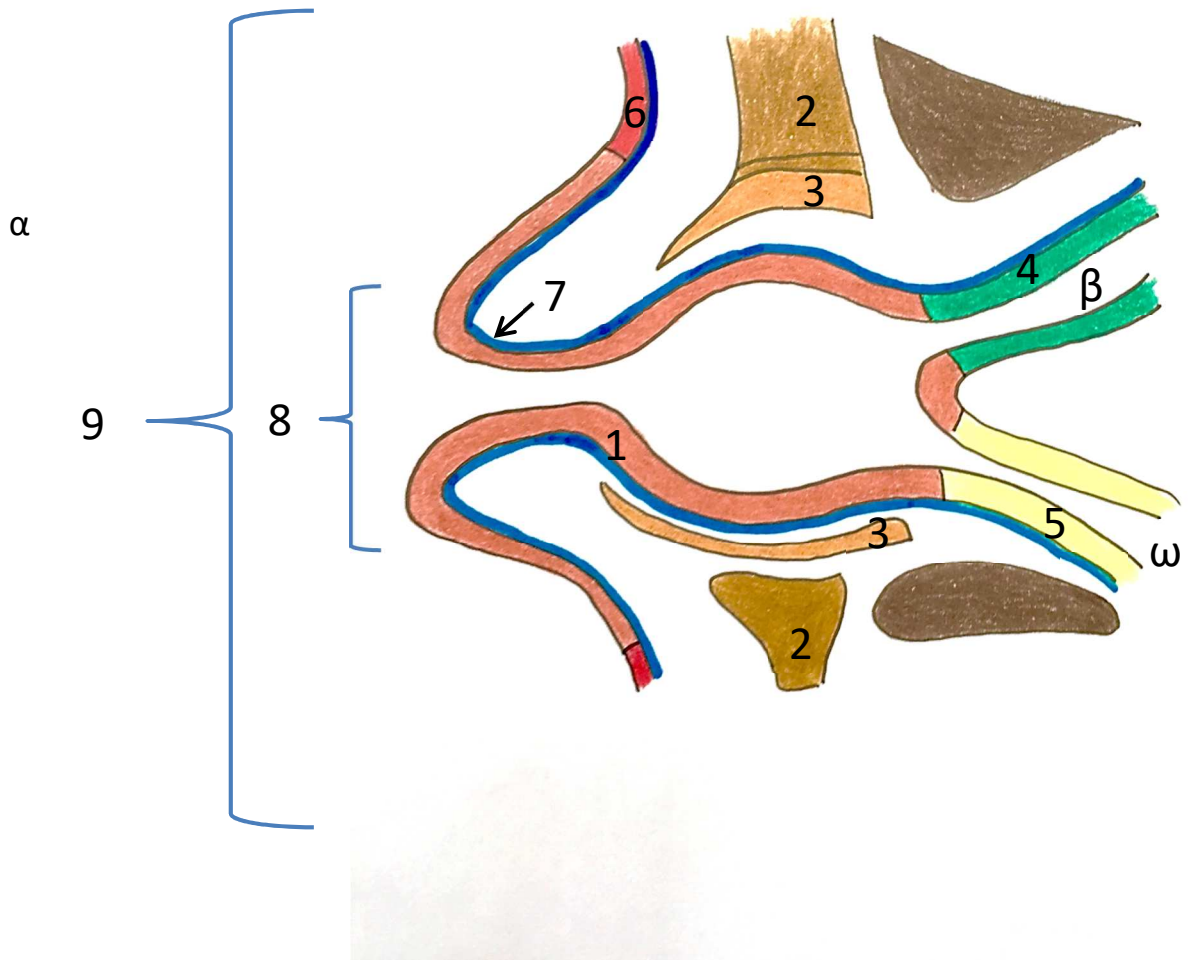


Figure 3.

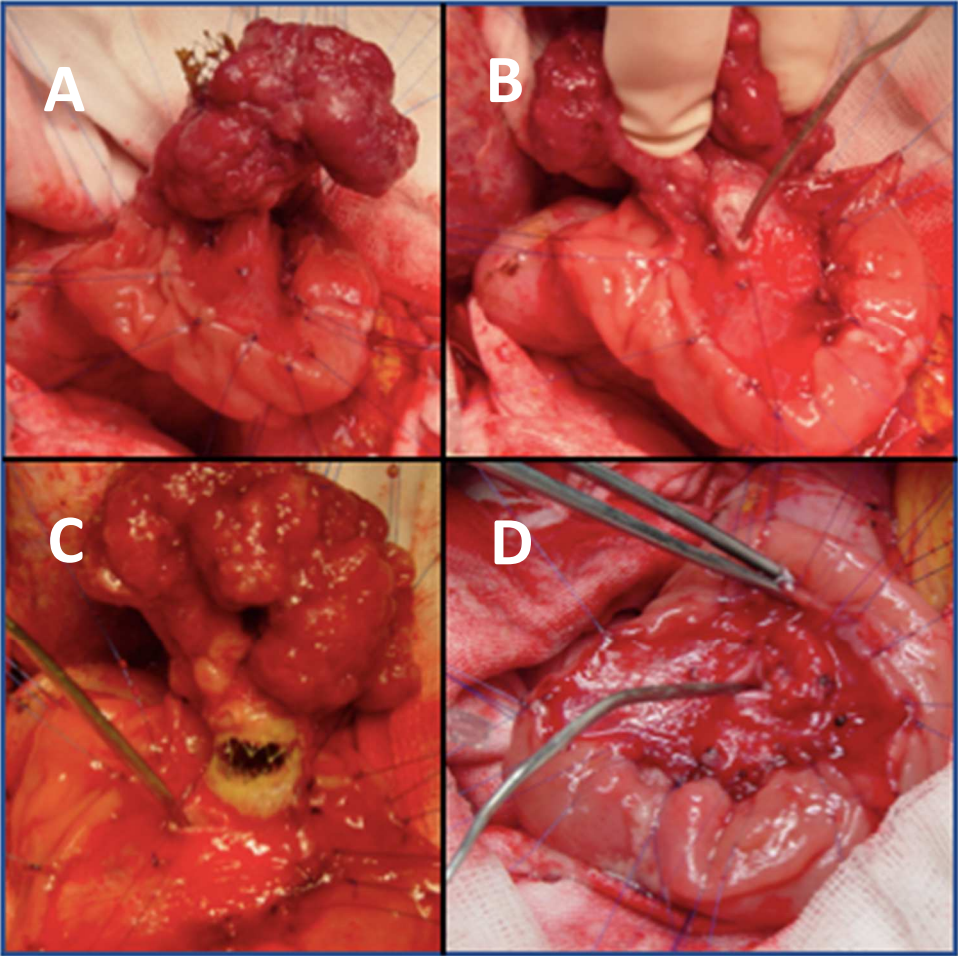


Figure 4.

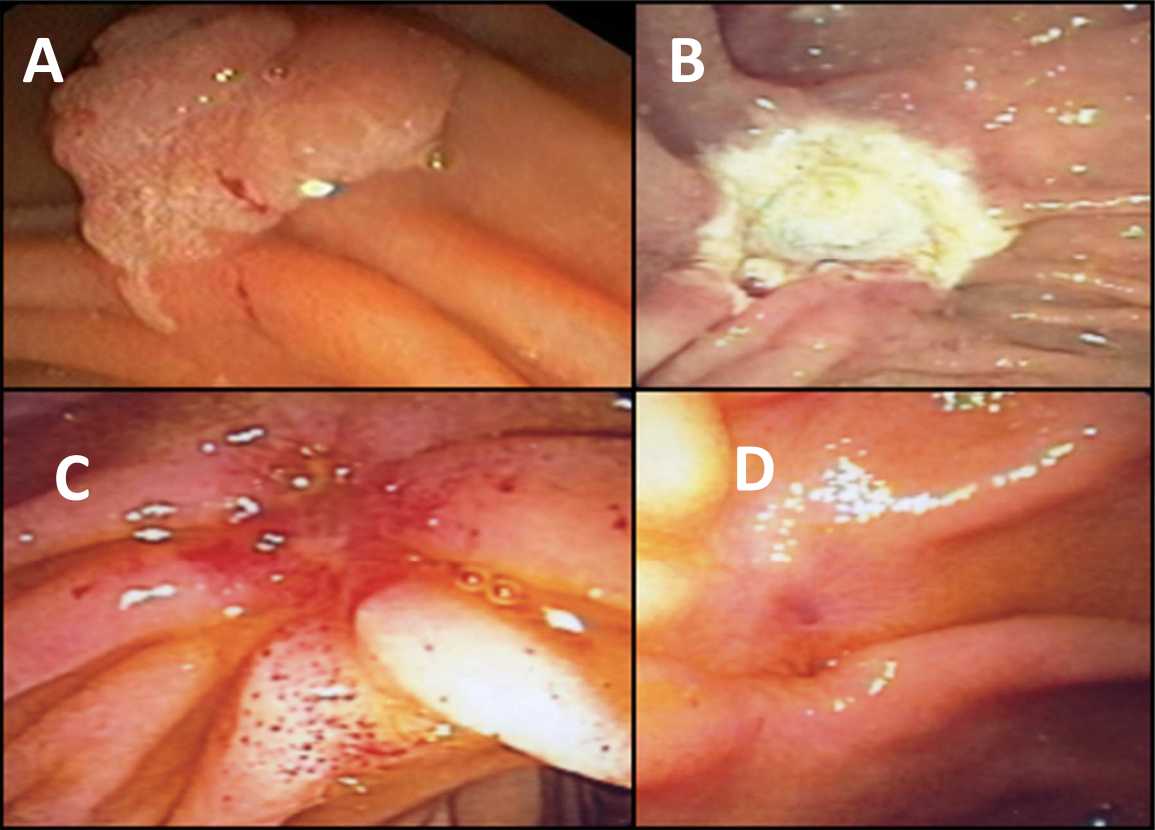
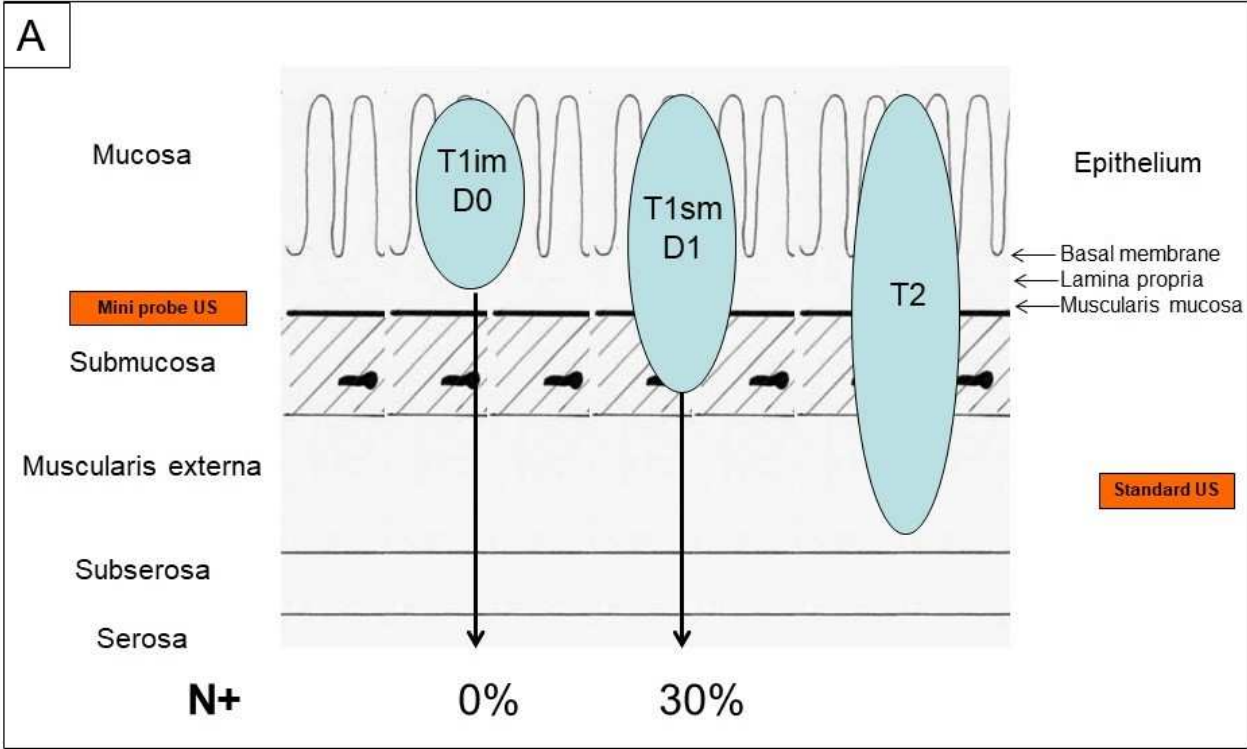


Figure 2 V anglais



**B**

Vienna Classification

Category 1 Negative for neoplasia/dysplasia

Category 2 Indefinite for neoplasia/dysplasia

Category 3 Non invasive low grade neoplasia (low grade adenoma/dysplasia)

Category 4 Non invasive high grade dysplasia

4.1 High grade neoplasia/dysplasia

4.2 Non invasive carcinoma (carcinoma in situ)

4.3 suspicion of invasive carcinoma

Category 5 Invasive neoplasia

5.1 Intramucosal carcinoma

5.2 Submucosal carcinoma

**T1**

**Lymp node involvement**

4 =T1 D0

0%

5 =T1 D1

30%



Figure 5.

