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Diagnosis and Therapy for Ampullary Tumors: 63 Cases

B. Chareton, M.D., J. Coiffic, M.D., S. Landen, M.D., E. Bardaxoglou, M.D., J.P. Campion, M.D., B. Launois, M.D.

Department of Digestive Surgery and Transplant Unit, Hospital Pontchaillou, Rue Henri Le Guilloux, 35033 Rennes Cedex, France

Abstract. From 1970 to 1992 a total of 63 patients underwent operation for ampullary tumor: 40 pancreatoduodenectomies (PDs), 3 total PDs, 8 ampullectomies, and 12 bypass or exploratory laparotomies. The resectability rate was 68%. There were 9 benign tumors, 1 anaplastic tumor, and 53 adenocarcinomas. According to Martin's classification, there were 7 stage I, 11 stage II, 14 stage III, and 21 stage IV tumors. All patients with stage I, II, and III tumors underwent resection. Patients with stage IV tumors had either resection ($n = 11$) or bypass ($n = 10$). The mean duration of hospital stay was 20.6 days. Operative mortality was 12.7% for the whole series and 7.5% after PD (2.5% for the last 10 years). Overall survival was 40% at 5 years (85% for stage I, 65% for stage II, 44% for stage III, and 8% for stage IV). Survival was better for stages I, II, and III after PD than after ampullectomy. For stage IV patients survival was 70% after PD versus 20% after bypass at 1 year and 25% versus 0% after 2 years. In our opinion, PD should be proposed even for benign lesions because two of our patients had to undergo repeat operation (PD) 4 and 22 years later, respectively, for stage IV disease. PD is our choice for all tumors of the ampulla.

In 1720 Abrahamus Vater [1] presented a dissertation that described a new anatomic entity that today is called the ampulla of Vater. The ampulla of Vater is formed in most individuals by union of the terminal segments of the pancreatic and common bile ducts. In 25% of individuals, however, the ampulla is the termination of the common duct only, the pancreatic duct having its own entrance into the duodenum adjacent to the ampulla. In these individuals the ampulla may be difficult to define or is even nonexistent. The ampulla opens into the duodenum usually on the posteromedial wall through a small mucosal elevation, the papilla of Vater [2]. Tumors of the ampulla of Vater are called ampullomas or ampullary tumors. Ampullary tumors represent 2% of all digestive tract tumors and 20% of tumors of the extrahepatic bile ducts [3].

The objectives of this retrospective study were to analyze the methods used to diagnose these ampullary tumors and to evaluate the therapeutic modalities for them.

Patients and Methods

Patient records were retrospectively reviewed for clinical and paraclinical data, pathology, and operative reports of 63 patients undergoing operation for an ampullary tumor between January 1970 and December 1992 at the Clinique Chirurgicale of the University of Rennes, France. Patient status was determined according to the American Society of Anesthesiologists (ASA) classification [4]. As of March 1993, follow-up data were available for 62 of the 63 patients. The surviving patients were seen as outpatients by the surgeon, gastroenterologist, or family physician or were contacted by telephone or letter. The date and cause of death for deceased patients were obtained from the national civil registry or their families. Numerical values were expressed as means and standard deviations unless stated otherwise. Qualitative data were compared with the chi-square test, and means were compared with the Student t-test. p Values of 5% or less were considered significant.

Correspondence to: B. Chareton, M.D.

Results

The mean age (± SD) of the patients was 64.8 ± 9.8 years. There were 33 men (mean age 62.4 years) and 30 women (mean age 67.7 years) ($p < 0.03$). In regard to status, 14 were ASA I, 22 were ASA II, 23 were ASA III, and 4 were ASA IV. One patient had associated chronic pancreatitis, four had diabetes, and three had cirrhosis.

Jaundice, pain, and loss of more than 10% of body weight were the most common presenting symptoms (Table 1). The mean delay between the onset of symptoms and operation was 10.8 weeks (range 1–60 weeks). Hepatic function tests were normal in 12% of patients; 88% had cholestasis, which was associated with cytolysis in 50% of cases.

Diagnostic procedures changed during the 22-year period of this study. A duodenal barium swallow was performed in 14 cases and showed characteristic impingement of the internal margin of the duodenal loop in six and widening of the duodenal loop in one; it was considered normal in seven. Gastroduodenoscopy was performed in 52 cases and demonstrated tumor in 40 (77%) and an intraduodenal bulge in 4; the investigation was considered normal in 8.

Endoscopic retrograde cholangiography was performed in 23 cases. The tumor was seen in 22 (96%). Dilatation of the bile duct anatomy was demonstrated in all 14 patients who underwent this investigation. A cup-shaped stricture of the distal bile duct was seen in 12 cases. In nine cases for which there was strong suspicion of the diagnosis, no contrast medium was injected so as not to increase the risk of cholangitis. Papillotomy was performed in six cases to obtain biopsy specimens or to drain the bile ducts before

Table 1. Symptoms.

Symptoms	No. of cases	%
Jaundice	49	78
Pain	33	52
Loss of weight > 10%	32	50
Altered general status	17	27
Hemorrhage	11	18
Routine discovery	3	4

Table 2. Operations performed.

Operation	No. of cases	%
Pancreatoduodenectomy	40	63
Total pancreatoduodenectomy	3	5
Ampullectomy	8	13
Double bypass	7	11
Biliary bypass	2	3
Gastrointestinal bypass	1	2
Exploratory laparotomy	2	3

the operation. Endoscopic biopsy specimens were obtained in 46 cases; in 7 cases they were considered normal, and in 39 they contributed to the diagnosis of ampullary tumor. Percutaneous transhepatic cholangiography, performed in six cases early in this series, showed dilated bile ducts associated with a distal stenosis in all six.

Echoendoscopy was performed in two cases only and showed isolated dilation of the bile duct in one and homogeneous thickening of a nondilated bile duct wall that did not extend beyond the muscular layer in the other. Sonograms and computed tomography (CT) scans, obtained in 46 and 17 cases, respectively, showed dilatation of the bile ducts associated with dilatation of the gallbladder when the gallbladder had not been removed in 39 cases (85%) and 13 cases (76%), respectively; showed an abnormal image at the level of the ampulla in 6 (13%) and 4 (24%) cases, respectively; and were considered normal in 7 (15%) and 4 (24%) cases, respectively.

The 63 operations performed are listed in Table 2. Of the 40 patients undergoing pancreatoduodenectomy (PD), 19 were operated on by one of the senior authors (B.L., J.P.C.) and 21 by a junior staff surgeon. PD was associated with resection of the duodenojejunal flexure in 37 cases, whereas Winslow's pancreas and the duodenojejunal flexure were preserved in 3 cases. A pylorus-preserving operation was performed in 19 cases. The retroportal fibrous cellular sheath was divided with the TA mechanical device in 20 cases.

Reconstruction proceeded as follows: The pancreatojejunostomy was performed first, end-to-side; the hepaticojejunostomy was next, end-to-side; and the gastrojejunostomy or duodenojejunostomy was performed last, 70 cm distal to the hepaticojejunostomy. The jejunal loop was placed retromesenterically in two cases. The pancreaticojejunostomy was fashioned in one layer in 9 cases, in two layers in 12 cases, and in three layers in 17 cases. The anastomosis was intubated with a lost drain in 25 cases. In two cases the pancreatic remnant was left untouched because the anastomosis was deemed too difficult because of fragile tissues. Total PD was performed in three cases because of associated cardia carcinoma, antecedent total gastrectomy with distal splenopancreatectomy, and suspicion of associated carcinoma of the head of the pancreas at a time when we believed that total pancreatectomy was necessary for carcinoma of the head of the pancreas. Ampullectomy alone was performed for benign and malignant tumors in two and six cases, respectively.

Table 3. Martin's classification.

Stage	Criteria
I	Burgeoning tumor; intraampullary or duodenal, papillary, or villous structure; no infiltration of underlying structures
II	Infiltration of the walls of the Oddi sphincter, biliary tract, or duodenal submucosa without involvement of the duodenal muscular planes
III	More-or-less deep infiltration of the duodenal muscular plane, whatever the histologic structure or the volume
IV	Proximal or distal lymph node metastases or involvement of the periduodenal or nearby pancreatic space

Table 4. Type of operation according to Martin's classification.[a]

	No. of operations, by stage			
Operation	Stage I	Stage II	Stage III	Stage IV
PD + TPD	5	10	11	11
Ampullectomy	2	1	3	0
Bypass or laparotomy	0	0	0	10

PD: pancreatoduodenectomy; TPD: total pancreatoduodenectomy.
[a]Benign tumors were excluded.

In regard to pathology, there were 9 benign tumors, 1 anaplastic tumor, and 53 adenocarcinomas in this series. Among the latter, 7 were grade I, 11 were grade II, 14 were grade III, and 21 were grade IV according to the classification of Martin [5] (Table 3). The type of operation performed for each tumor is listed in Table 4. Two patients classified as grade IV (one having undergone PD, the other simple exploratory laparotomy) had undergone simple ampullectomy for benign disease 4 and 22 years before, respectively. PD was performed in the patient with anaplastic carcinoma. Benign tumors were treated by PD in five instances (two patients had severe dysplasia) and by ampullectomy and bypass in two cases each. In the latter category one ASA IV patient underwent a double bypass, whereas the other patient who underwent operation in the context of biliary peritonitis after hepatic aspiration biopsy had a biliary bypass only.

The postoperative course was simple in 42 patients (67%). As shown in Table 5, 21 complications developed in the others. Of the seven patients with pancreatitis of the pancreatic remnant, two were in patients who had nonanastomosed pancreatic remnants, and two other patients required repeat surgery 4 and 9 days after pancreatic resection for necrosectomy. Two patients experienced pancreaticojejunostomy breakdown. Both underwent revisional surgery 5 and 10 days after the initial PD. Both of these patients had had retromesenteric loop reconstruction. Two patients underwent repeat operation for peritonitis 13 and 21 days after PD with no cause found.

The duration of gastric aspiration was 10.5 ± 5.6 days after pyloric preservation versus 7.8 ± 5.2 days when the pylorus was not preserved (NS; $p > 0.05$). The number of units of blood transfused was significantly greater when the pylorus was not preserved (8.3 ± 5.0 blood units versus 4.5 ± 3.0 blood units ($p < 0.02$) (Table 6). The hospital stay was 20.6 ± 16.0 days overall and

Table 5. Postoperative complications.

Complications	No. of cases
Medical	
Blood-borne catheter infection	1
Myocardial infarction	1
Aspiration pneumonia	1
Surgical	
Pancreatoduodenectomy	
Remnant pancreatitis	7
Fistula	2
Peritonitis	2
Marginal ulceration	1
Gastrojejunal hemorrhage	1
Total pancreatoduodenectomy	
Infective toxic shock	1
Ampullectomy	
Hemorrhage	2
Bypass	
Peritonitis	1
Tumoral hemorrhage	1

Table 6. Blood units transfused.

Operation	No. of blood units transfused (mean)
PD without pylorus preservation	8.3
PD with pylorus preservation	4.5
PD without anastomosis of remnant	6.0
TPD	4.0
Ampullectomy	6.0

PD: pancreatoduodenectomy; TPD: total pancreatoduodenectomy.

Table 7. Postoperative mortality.

Cause	Postoperative days to death	Type of operation
Peritonitis	20	PD
Peritonitis	29	PD
Pancreatic necrosis	9	PD
Toxic shock	1	Total PD
Peritonitis	22	Biliary bypass
Aspiration pneumonia	8	Double bypass
Myocardial infarction	2	Exploratory laparotomy

PD: pancreatoduodenectomy.

24.8 ± 18.2 after PD. When patients with complicated courses were excluded, the hospital stay was similar regardless of whether the pylorus was preserved (16.2 versus 16.7 days). Postoperative mortality was 12.7% overall and 7.5% after PD (2.8% during the last 10 years). Details are given in Table 7. Of the 62 patients followed, 36 died during this 22-year period. There were eight postoperative deaths, nine deaths due to peritoneal carcinomatosis or local invasion, seven to hepatic metastases, one case of myocardial infarction, and two cerebral vascular accidents. In nine cases, the cause of death was unknown. Overall actuarial survival at 5 years was 40% (Fig. 1).

Survival after adenocarcinoma was 85% at 5 years for stage I disease, 65% for stage II disease, 44% for stage III disease, and 8% for stage IV (Fig. 2). Of the five patients undergoing ampullectomy for adenocarcinoma, the two stage I patients

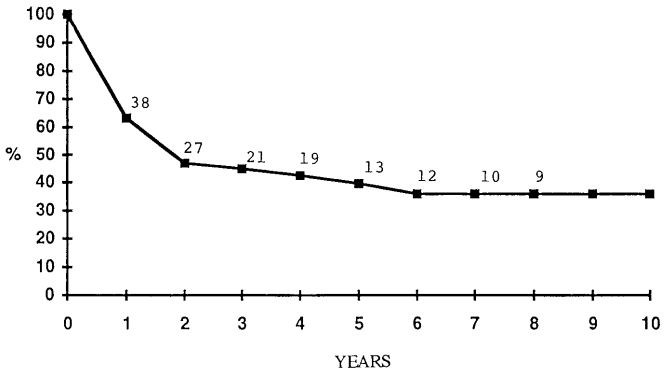

Fig. 1. Overall survival for 62 patients.

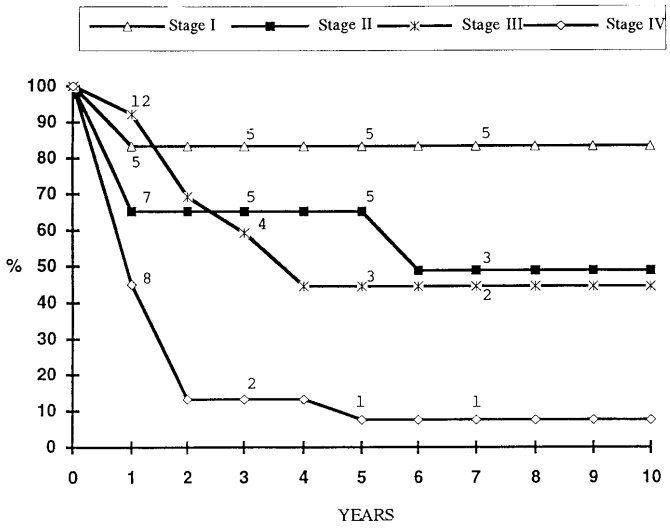

Fig. 2. Survival of patients with adenocarcinoma according to Martin's stage.

expired 4 months and 4 years after operation, respectively; the patient with stage II disease died 3 months after operation; and the two patients with stage III disease died 1 and 2 years later, respectively. The one patient lost to follow-up had undergone ampullectomy for stage III adenocarcinoma. The rate of survival among patients with stage IV disease undergoing PD was 70% at 1 year and 25% at 2 years, whereas those who had undergone bypass or exploration alone had a 1-year survival of 25% and 0% at 2 years (Fig. 3), respectively. The patients undergoing PD for anaplastic carcinoma died 5 months after operation. Of the nine patients operated on for benign tumors, four are alive at 4, 29, 72, and 120 months after PD, respectively. One patient died 9 days after PD owing to necrosis of the pancreatic remnant. There were two deaths 6 and 192 months after ampullectomy due to myocardial infarction and stroke, respectively. Two deaths occurred after bypass operations, one due to tumor hemorrhage and the other to peritonitis.

Discussion

There were nearly as many women as men in this series (30 versus 33), in contrast to other reports [6–11], which found more men

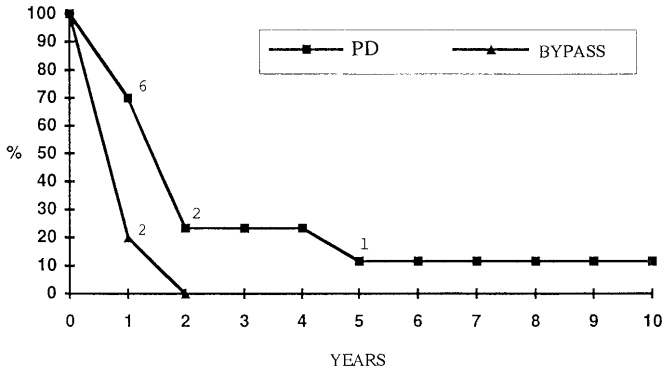

Fig. 3. Survival of stage IV patients according to the operation performed.

than women. The mean age of patients was within the sixth decade [6, 8–10, 12, 13]. As in the series of Seyrig et al. [14], the mean age of female patients was greater than that of male patients (67.7 years versus 62.4 years). Initial symptoms were present an average of 2.5 months before diagnosis in our series, which is comparable to other series in which the duration of symptoms ranged from 2 to 4 months [8, 10, 12, 14, 15]. In the study of Marchal and Hureau, the diagnosis was made 2.8 to 6.0 months before operation in 80% to 90% of cases [3]. These authors also reported that resectability was better when the duration of presentation was short, as 73% of the tumors were amenable to resection by PD when symptoms had been present 6 months or less. In other series, independent of the duration of symptoms, the PD rate ranged from 66% to 74% [8, 12, 13, 16, 17]. Jaundice was the most common initial symptom and has been found in 75% to 96% of cases [5–7, 10, 12, 13, 15]. Conversely, among Shutze et al.'s patients jaundice was the initial symptom in only 50% [10]. In fact, jaundice can be progressive but occasionally is recurrent or reversible. Yamaguchi and Enjoj [11] found the presence of jaundice variable in up to 11% of cases. Jaundice associated with abdominal pain and fever, as with cholangitis, occurs more rarely (5% of cases) [11]. In certain patients (up to as many as 18% of the cases of Jones et al. [7]), the initial clinical picture is one of pancreatitis. Similar confusion occurs with the patient in whom common bile duct stones are found, which may obscure the tumor of the ampulla. In this setting, the tumor is occasionally discovered by chance, as occurred in three cases in our series. Hayes et al. noted this association in 12 of their 37 patients, 9 of whom had undergone cholecystectomy during the 10 months preceding the diagnosis of ampullary tumor [6]. The association of intestinal tract hemorrhage with jaundice is suggestive of ampulloma, but it occurs infrequently. Hematemesis or jaundice was found in 12% of our cases and in 1% to 9% of other series in the literature [7, 9, 11, 14, 15]. Abdominal pain was noted in 30% to 72% of cases [7, 10, 14, 15, 16], and loss of weight has been seen in 28% 65% [7, 10, 14, 16].

Sonography or CT scanning can be performed rapidly and easily in the jaundiced patient, and each is capable of demonstrating the distal location of the obstruction and the dilatation of the common bile duct. Visualization of the ampullary tumor, however, is more difficult and operator-dependent. In our series, ampullary tumor was suggested in only 13% of patients undergoing sonography and in 23% of patients undergoing CT scanning. In the series of El Khoury et al., sonography led to a correct diagnosis in half of the cases [9]. In contrast, duodenoscopy revealed the ampullary tumor in 77% of cases and an intraduodenal bulge in 8%. Duodenoscopy with endoscopic retrograde cholangiopancreatography (ERCP), however, indisputably seems to be the best investigation for the diagnosis of tumor of the ampulla. ERCP contributed to the diagnosis in 96% of cases in our series and in 90% of the series of Seyrig et al. [14]. Associated endoscopic papillotomy allows us to see and obtain biopsy specimens of extraduodenal tumors and to achieve preoperative biliary drainage when indicated [14]. Echoendoscopy seems to hold promise for the evaluation of lymph node metastatic involvement or mesenteric portal vein encasement [18–20]. Dooley et al. favored preoperative angiography to evaluate the resectability of tumors with regard to the vessels in the portal system [21]. In any case, in the absence of contraindications to operation, the presence of obstruction of the distal biliary tract, and whether an ampullary tumor is obvious, exploratory laparotomy is indicated. In case of doubt, intraoperative cholangiograms and duodenotomy may be necessary to prove the presence of a tumor.

Whenever possible, tumors in the area of the ampulla must be removed; and in order to do so, PD may be necessary. Postoperative mortality associated with PD has decreased in our series from 7.5% for our first 40 cases to 2.8% during the last 10 years. In the literature, however, mortality has been evaluated differently and has ranged from 5% to 27% [6, 8, 9, 10, 13, 15, 17, 22–24]. Morbidity associated with PD is due essentially to fistulas, which were observed in two of our cases (5%) when the intestinal loop was behind the mesenteric vessels. We believe that the loop should be placed in front of these vessels in order to avoid obstruction. In accordance with the literature [25, 26], preservation of the pylorus did not alter the postoperative morbidity or the hospital stay in any significant way in our series. In one series [26], mortality was even slightly less (2% versus 5%) when the pylorus was not preserved. The duration of the operation, however, was shorter [26]. Moreover, in this same series [26], fewer blood units were transfused during the pylorus-preserving procedure (4.5 versus 8.3 units in our series). Only one patient in our series bled (from a gastrojejunal anastomosis). Preservation of the pylorus seems to improve postoperative digestive function and weight gain [25, 26]. Abandonment of the tail of the pancreas after suturing the divided pancreas or intracanalicular injection of glue has not eliminated the risk of fistula or pancreatitis of the pancreatic remnant [8], which were observed in the two cases in which the remnant was abandoned. Total PD does not seem to be indicated for treatment of tumors of the ampulla except when the tail of the pancreas must be or was previously resected for some other reason.

Survival is related to mural involvement. Five-year survivals in our series were 85%, 65%, 44%, and 8% for stages I through IV, respectively—similar to the report of El Khoury et al., who found the 5-year survivals to be 75%, 57%, 34%, and 8% for stages I through IV, respectively [9]. For Lerut et al., the 5-year survival was 76% for stages I, II, and III versus 0% for stage IV [15]. Neoptolemos et al. [27] found that survival was 75.5% for stage I disease compared to 16.5% for stages II, III, and IV. Yamagachi and Enjoj [11] reported survivals to be 85%, 11%, 25%, and 24%, for stages I, II, III, and IV, respectively. Patients with group IV tumors in our series can be divided into two groups: those who underwent PD and those who had a bypass. The prognosis was

better when resection was performed, probably due to the fact that this classification does not take into account distal lymph node involvement. Lymph node involvement, found in 26% to 45% of cases [6, 8, 10], is associated with a poor prognosis [6, 8–10, 12, 16].

The size of the tumor does not seem to influence outcome [15, 27], except for the patients reported by Delcore et al. [12]. On the other hand, cellular differentiation does seem to be important [27].

Limited resections, such as ampullectomy, are often inadequate [9]. Postoperative mortality is equivalent [8, 24] or even higher (19%) [3] than that after PD; long-term survival is not modified [9, 24]. Ampullectomy is often associated with postoperative hemorrhage [3, 8, 24], as was observed in two of our cases. In contrast with other authors [28, 29], we believe that limited resections should not be performed in patients who are aged or feeble or who have small tumors [28, 29]. Moreover, endoscopic surveillance is necessary every 6 months [28], and occasionally secondary PD is required [9]. The latter was reported by Tarazi et al. [24], who performed PD in 4 of 11 patients, and by El Khoury et al. [9], who performed three PDs in five patients. Ampullectomy has been proposed for benign tumors [28, 29]. Bergdahl and Anderson considered that benign tumors were precancerous [30]. As ampullectomy is a limited resection, the entire specimen cannot be studied pathologically, which does not allow us to affirm the benignity of the lesion [3]. As two of our patients underwent ampullectomy 4 and 22 years before undergoing PD and exploratory laparotomy, we believe that PD is the treatment of choice in this setting. When the tumor is unresectable, bypass operations have been proposed, even though their associated mortality and morbidity are high [8]. Moreover, these operations leave a potentially hemorrhagic tumor in place, as was the case in our series. For unresectable tumors, several authors have proposed laser destruction after papillotomy, sometimes associated with stent placement [31, 32]. Results have been deceiving, as mortality is close to 10%; and there have been no notable modifications in outcome, as the mean survival remains at approximatively 6 months. All stages included, the overall 5-year survival in our series was 40% at the middle of the classic 28.0 to 53.5 year range cited in the literature [6–9, 11–13, 15–17, 23, 24, 27].

In conclusion, jaundice is the most common symptom of onset in ampullary tumors. The best investigation is ERCP, which allows us to obtain specimens for biopsy. PD, which allows wide excision of lesions and is associated with low postoperative morbidity and mortality, is the operation of choice, even for benign tumors.

Résumé

En 1720 Abrahamus Vater présentait une dissertation anatomique dont le titre était «Novum Bilis diverticulum circa orificium ductus choledochi», sur l'entité anatomique appelée aujourd'hui «ampoule de Vater». L'ampoule de Vater est formée chez la plupart des individus par les segments terminaux des canaux pancréatique et cholédocien. Chez 25% des individus, cependant, l'ampoule est formée par la terminaison du cholédoque seul, le Wirsung se déversant directement dans le duodénum par un orifice séparé. Chez ces individus, l'ampoule peut être difficile à visualiser ou peut même être en défaut. L'ampoule s'ouvre habituellement dans la paroi postéro-médiane du duodénum à travers une surélévation muqueuse minime, appelée «papille de Vater». Les tumeurs de l'ampoule de Vater sont appelées encore ampullomes ou tumeur ampullaires et représentent 2% de toutes les tumeurs de l'intestin et 20% des tumeurs des voies biliaires extrahépatiques. Les buts de cette étude ont été d'analyser les méthodes diagnostiques et d'évaluer les différentes modalités thérapeutiques de ces tumeurs ampullaires;

Resumen

En 1720 Abrahamus Vater presentó una disertación anatómica titulada "Novum Bilis diverticulum circa orificium ductus choledochi"; esta nueva entidad anatómica es denominada actualmente ampolla de Vater. La ampolla de Vater está formada en la mayoría de los individuos por la unión de los segmentos terminales de los canales pancreático y colédoco. Sin embargo, en 25% de los individuos la ampolla es la terminación del colédoco solamente, con el canal pancreático desembocando en forma aislada al duodeno en la región vecina de la ampolla. En estos individuos, la ampolla puede ser muy difícil de visualizar, o puede estar ausente. La ampolla se abre al duodeno usualmente sobre la pared póstero-medial a través de una pequeña elevación mucosa, la papila de Vater. Los tumores de la ampolla de Vater son denominados ampulomas o tumores ampulares. Los tumores ampulares representan el 2% de todos los tumores del tracto digestivo y el 20% de los tumores de los canales biliares extrahepáticos. El objeto de este estudio retrospectivo fue analizar los métodos que se utilizan para diagnosticar y evaluar las diferentes modalidades terapéuticas en estos tumores ampulares.

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