

CASE REPORT

Neuroendocrine Tumor of the Ampulla of Vater: A Rare Neoplasm in an Atypical Site. Report of Three Cases and Review of the Literature

Jaques Waisberg¹, George Joppert-Netto¹, Raquel Yumi Yonamine¹, Daniel Reis Waisberg¹, Maria Isete Fares Franco²

Departments of ¹Surgery and ²Pathology, Hospital do Servidor Público Estadual, São Paulo, Brazil

ABSTRACT

Context The neuroendocrine tumor of the ampulla of Vater represents a rare disease and, although the majority of them are indolent, this neoplasm has a relatively poor prognosis. A quarter of cases of ampullary neuroendocrine tumors have been detected in patients with neurofibromatosis type I (von Recklinghausen's disease). The biological behavior of ampullary neuroendocrine tumor shows no association to the dimension of the tumor and they are more aggressive than non-ampullary duodenal neuroendocrine tumor. The most frequent symptoms are jaundice (60%) and abdominal pain (40%), followed by weight loss (10%). The determination of histopathology is of utmost importance and involves specific immunohistochemical staining. In most ampullary neuroendocrine tumors, the expression of neuroendocrine markers as chromogranin A, neuron specific enolase and synaptophysin, either isolated or in combination is positive. The carcinoid syndrome is uncommon, unless hepatic metastases are present. Most neuroendocrine tumor of the duodenal ampulla is diagnosed incidentally in the duodenoscopy. **Case report** The authors describe three cases involving neuroendocrine tumor of the ampulla of Vater that were operated upon a single institution and report the etiopathogenic, clinical, diagnostic, therapeutic and prognostic characteristics of this rare neoplasm. **Conclusions** Neuroendocrine tumors of the ampulla of Vater without invasion and a diameter of <2 cm seem to have a better prognosis. Radical resection should be the standard approach in most patients due to the poor accuracy of preoperative and intraoperative assessments of lymph node involvement and the high incidence of lymph node metastases, even in tumors that are smaller than 2 cm.

INTRODUCTION

Neuroendocrine tumors (NETs) are slow-growing neoplasms that are derived from the enterochromaffin cells situated in the crypts of Lieberkühn, which belongs to the neuroendocrine system [1]. Gastrointestinal NETs correspond to a group of well-differentiated neuroendocrine tumors originating from various neuroendocrine cells positioned in the gastrointestinal mucosa and submucosa [1]. Consequently, there is diversity in their clinical presentation, incidence at specific anatomic sites, biological behavior, hormone production, morphologic characteristics and immunophenotype [1].

A NET of the ampulla of Vater is a rare and little is known about its demographic, biologic behavior and

clinical performance [2, 3, 4, 5]. Further, the detailed prognostic factors of this tumor have not until now been established [6, 7].

These neoplasms correspond to 2% of the periampullary malignancies and less than 1% of gastrointestinal neuroendocrine tumors [1, 7, 8]. Less than 130 patients have been reported until 2013 in the majority as case reports [3, 9]. The most frequent age of patient involvement is between the 5th and 6th decades of life. Women are affected three times more often than men [4, 9].

The ultimate pre-operative diagnosis based on histology may be difficult since they present with a similar clinical picture to the adenocarcinomas of this region [9, 10, 11]. A quarter of cases of ampullary NETs have been detected in patients with neurofibromatosis type I (NF1) (von Recklinghausen's disease) [12].

The authors describe three cases of NET of the ampulla of Vater that were operated upon a single institution and report the etiopathogenic, clinical, diagnostic, therapeutic and prognostic characteristics of this unusual condition.

CASE REPORTS

Case #1

Male, white, fifty-eight-years-old; the patient complained of epigastric pain and weight loss. The duodenoscopy revealed a tumor in the major papilla, and a biopsy showed a malignant undifferentiated small

Received May 04th, 2016 - Accepted June 02nd, 2016
Keywords Ampulla of Vater; Carcinoid Tumor; Carcinoma, Neuroendocrine; Gastrointestinal Neoplasms; Neuroendocrine Tumors; Prognosis
Abbreviations NF1 neurofibromatosis type I; NSE neuron specific enolase
Correspondence Jaques Waisberg
Department of Surgery
Hospital do Servidor Público estadual
Avenida Ibirapuera 981, 2º andar - Vila Clementino
São Paulo - SP
04029-000
Phone +55 11 98256-0018
Fax +55 11 4436-8739
E-mail jaqueswaisberg@uol.com.br

cell tumor (**Figure 1**). The patient underwent a Whipple procedure. A pathological exam of the resected neoplasm showed a tumor situated in the major ampullary region, with a 2.5 cm diameter that was considered as a well differentiated (Low Grade, G1) NET with mitotic index of 1 mitose in 10 high-power fields (HPF). The lymph nodes were not infiltrated and there was no angiolymphatic or perineural invasion. The TNM classification [13] of the tumor was stage I (T2N0M0). The immunohistochemical stained of the neoplasia showed a positive expression of the neuroendocrine markers neuron specific enolase (NSE) and chromogranin A. The patient progressed uneventfully and, after seven years following the operation, he is asymptomatic with a normal serum chromogranin A level.

Case #2

Female, white, fifty-nine-years-old; the patient complained of weight loss of 10 kg without any apparent cause. The duodenoscopy revealed a submucosal tumor in the major papilla region and the endoscopic biopsies were inconclusive. The patient was submitted to a Whipple procedure. Pathological examination revealed a well differentiated (Low Grade, G1) carcinoma (**Figure 2**) in the region of the major duodenal ampulla, with a diameter of 3.5 cm and extensive areas of necrosis and hemorrhage, without lymph node metastases or angiolymphatic/perineural infiltration. The mitotic index was 2 mitoses in 10 HPF. The TNM classification of the neoplasm was stage I (T2N0M0). The immunohistochemical study of the neoplasia showed chromogranin A antibody expression. Nine years after the operation, the patient has no abnormalities and his serum chromogranin A level is normal.

Case #3

In a forty-seven-years-old white male with jaundice, the duodenoscopy revealed a tumor with a diameter of 2.8 cm situated in the major duodenal papilla. Biopsies of the lesion showed a moderately differentiated (Intermediate Grade, G2) neuroendocrine carcinoma with mitotic index of 3 mitoses in 10 HPF. It was also observed the presence of nuclear atypia. Immunohistochemical study showed the expression of chromogranin A (**Figure 3**), NSE, synaptophysin, and anti-cytokeratin AE1/AE3 antibodies. The computed tomography (CT) revealed disseminated metastases in both hepatic lobes. The patient underwent laparotomy and a large mass in the hepatic hilum was found. Despite this mass, a hepaticojejunal Roux-en-Y anastomosis was performed. The TNM classification of the neoplasm was stage IV (TxNxM1). The immunohistochemical stained of hepatic metastases showed the same expression of the tumor situated in the major duodenal papilla, but they were nonfunctional. The patient received systemic chemotherapy and died with active disease five years after the operation.

DISCUSSION

The World Health Organization (WHO) classification places neuroendocrine tumors into three main categories

which emphasize the tumor grade: well-differentiated neuroendocrine tumors, further subdivided into tumors with benign and those with uncertain behavior; well-differentiated (low grade) neuroendocrine carcinomas with low-grade malignant behavior and poorly differentiated (high grade) neuroendocrine carcinomas, which are the large cell neuroendocrine and small cell carcinomas [13, 14]. Historically, well-differentiated neuroendocrine neoplasms have been referred to as carcinoid tumors, a term which may cause confusion because clinically a carcinoid tumor is a serotonin producing tumor associated with functional manifestations of carcinoid syndrome [14].

NETs are also categorized as their mitotic activity and the presence of necrosis [4, 14]. The well differentiated (Low Grade, G1) NET show less than 2 mitotic figures per 10 HPF and a lack of necrotic areas. Differently, the moderately differentiated (Intermediate Grade, G2) neuroendocrine carcinoma reveals 2-20 mitotic figures per 10 HPF or the presence of necrotic *foci*. In turn, the poorly differentiated (High Grade, G3) neuroendocrine carcinomas disclose more than 20 mitotic figures per 10 HPF and the presence of necrotic *foci* [14].

The WHO categorizes neuroendocrine ampullary and duodenal neoplasms into an only one class, but studies [3, 4, 5] revealed that these neoplasms are actually different lesions. Unlike the non-ampullary duodenal NETs, the biological behavior of ampullary NETs shows no association to the dimension of the tumor and they are more aggressive than non-ampullary duodenal NETs. Moreover, ampullary NETs usually express somatostatin and are related with NF1, which is rare with duodenal NETs [4, 12, 14, 15].

NF1 patients are at increased risk of developing neoplasms in the gastrointestinal tract, including neuromas, gastrointestinal stromal tumors (GIST) and somatostatin-rich ampullary carcinoids [12]. Ampullary NETs are found in 30% of patients with NF1 and the presence of the NF1 is considered the only apparent risk factor for the development of the NET of the duodenal ampulla [12]. One

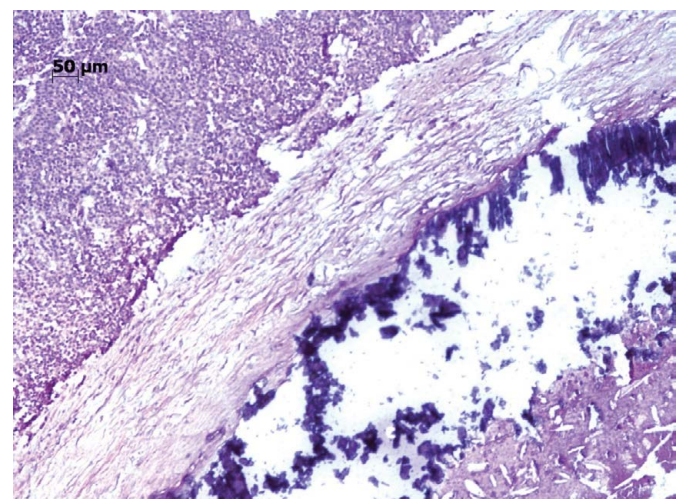


Figure 1. Photomicrograph of a neuroendocrine tumor of the ampulla of Vater. Pseudocapsules and the adjacent *foci* of the dystrophic calcification are represented by purplish areas. (HE, 100x).

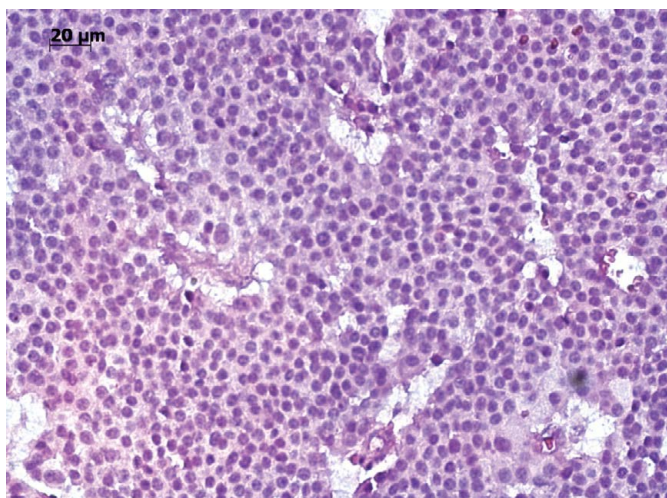


Figure 2. Photomicrograph of neuroendocrine tumor of the ampulla of Vater. The monotonous aspect of cell proliferation is due to the low polymorphism and the richly vascularized stroma. (HE, 400x).

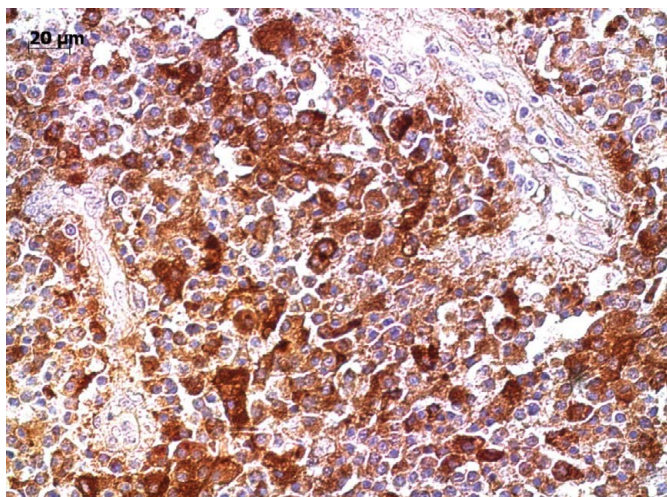


Figure 3. Photomicrograph of neuroendocrine tumor of the ampulla of Vater. A strong expression on the cytoplasmic membrane and in the cellular cytoplasm to the anti-chromogranin A antibody is represented by the brownish color, confirming the neuroendocrine nature of the neoplasm. (Immunohistochemistry, chromogranin A, 400x).

explanation for this risk is that, in patients with NF1, the tumors of a neural origin and NETs can occur as a result of the transformation of the endodermic-ectodermic complex near the papilla, due to the mutation of the NF1 tumor suppressor gene [12]. None of the cases in this report had alterations that were suggestive of NF-1.

In typical cases, NETs of the duodenal ampulla are composed of small islands of round cells and monomorphic nuclei that were surrounded by the cytoplasm with small edges. The pattern of trabecular or diffuse growth may be present. Mitoses are unusual and nuclear atypia may not be obvious [1, 4, 14], but both events were found in the third case of this series.

As a rule, NETs of the ampulla of Vater are not angioinvasive. They are <1 cm in diameter and show up to two mitoses per 10 HPF [14]. Conversely, the spread of the neoplasm to the muscularis propria, with a diameter of >2 cm and the high degree of mitotic activity (3 or more mitoses per 10 HPF) are considered risk factors for the onset of metastases [16, 17, 18], as occurred in case

#3 of this report. Furthermore, the duodenal papilla is a highly vascularized area, where even small tumors are likely to spread, which contributes to the dissemination of metastases, regardless of the size of the primary NET [17, 18] as observed in case #3. Over half of the patients with an ampullary NET of <2 cm showed positive lymph node disease; the metastases were identified in 66% of tumors that were <1 cm, in 50% of tumors between 1 and 2 cm and in 46% of tumors that were >2 cm [19, 20]. Metastases usually occur in the lymph nodes and liver, as occurred in the case #3 within this series.

The determination of histopathology is of utmost importance and involves specific immunohistochemical staining [4, 14, 16]. In most ampullary NETs, the expression of neuroendocrine markers as chromogranin A, NSE and synaptophysin, either isolated or in combination, is positive. The guidelines of The North American Neuroendocrine Tumor Society (NANETS) recommend the performing of chromogranin A and synaptophysin for the immunohistochemical study, and the obtaining of the mitotic rate or Ki67 expression as cell proliferation index [21]. The cases of this series were characterized as neuroendocrine origin by the immunohistochemical positivity of chromogranin and /or synaptophysin and the mitotic rates were obtained in all of them. In case #3, a neuroendocrine carcinoma, cytokeratin, which is considered a carcinoma marker [21], had its expression positive in the immunohistochemical study. The tumor cells can also express somatostatin (58%-67%), insulin (25%), serotonin (17%) and cholecystokinin (17%) [1, 4, 14]. Ampullary NETs usually do not express gastrin, unlike the non-ampullary duodenal carcinoids, in which positive gastrin immunoreactivity is positive in more than half of the patients [4]. The presence of the expression of cell proliferation markers PCNA and Ki-67 may reflect the more aggressive biological behavior and metastatic potential of an ampullary NETs [4, 11].

The most frequent symptoms of ampullary NETs are jaundice (60%) and abdominal pain (40%), followed by weight loss (10%), symptoms also observed in the cases of this series. Furthermore, upper gastrointestinal bleeding (3%) and acute pancreatitis (3 to 6%) may be observed [11, 22, 23]. The carcinoid syndrome is uncommon, unless hepatic metastases are present [11, 16, 22]. However, in case #3, despite the presence of hepatic metastases, the patient had no carcinoid syndrome probably because the primary tumor was nonfunctional. The NETs of the duodenal ampulla rarely cause functional syndrome associated with the overproduction of somatostatin, which can trigger diabetes mellitus, gallstones and steatorrhea; in this condition, the NET is named as somatostatinoma [11, 23, 24].

Most NETs of the duodenal ampulla is diagnosed incidentally in the duodenoscopy, as occurred with the case #2 of this report. The ampullary NETs often are covered by intact mucosa, which explains the high rate of false-negative or inconclusive biopsies [4, 11, 23]. Thus, the

histological diagnosis with samples obtained by preoperative endoscopic biopsies is performed in only 15% of patients [11, 22]. In this series, only the third case had a preoperative diagnosis that was made by endoscopic biopsy.

The abdominal CT, abdominal magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and duodenal endosonography (EUS) complete the assessment of a NET of the duodenal ampulla [11, 23, 25]. CT and MRI usually do not identify these small primary neoplasms in these cases because their sensitivity is only 33%. However, CT and MRI can reveal metastases in the liver or mesentery [25], as occurred in the third case in the present series. Magnetic resonance cholangiography associated with an angiography can simultaneously show the enhancement of a submucosal mass, as well the biliary and vascular structures [25]. The possible involvement of the bile duct can be clarified by the ERCP and/or EUS. To detect small tumors, the EUS can be extremely useful [11, 23].

A large variety of the ampullary NETs and their metastases can express a high density of somatostatin-specific receptors. Octreotide, a somatostatin analogue, has a high affinity and a sensitivity of 86% [23, 26] in the detection of NETs with somatostatin receptors. This sensitivity is markedly reduced when the size of the tumor or metastases are < 1.0 cm in diameter [4, 11, 23].

The differential diagnosis of an ampullary NET should mainly be performed with non-ampullary NETs, a Brunner's gland hamartoma, heterotopic pancreatic and gastric tissues, adenoma, adenocarcinoma, gangliocytic paraganglioma, gastrointestinal stromal tumor (GIST), lymphoid hyperplasia and mesenchymal tumors, such as neurofibromas and schwannomas [8, 10, 11, 23].

A radical excision represented by the pancreaticoduodenectomy with lymphadenectomy is recommended, regardless of the tumor size, because the published data indicates that these tumors metastasize in half of the cases, regardless of the primary tumor's size [8, 20, 26, 27]. The radical excision was adopted in two patients within this report, one with a well differentiated NET and other with a moderately differentiated neuroendocrine carcinoma. Both patients are alive seven and nine years after the operation, respectively.

Less radical treatment as a reasonable alternative to a duodenopancreatic resection to reduce surgical morbidity and preserve organ function has the risk of producing an incomplete removal of the tumor because the preoperative evaluation is often inaccurate, especially regarding the lymph node involvement [16, 28]. Furthermore, the local resection of ampullary NETs is technically difficult and presents significant morbidity [28, 29]. Thus, it is reasonable that patients should not be placed at risk of failing to detect and resect their metastatic lymph node disease, thus avoiding their cure by the appropriate oncologic operation. However, it should be considered that the long-term survival of patients with an ampullary

NETs was achieved with the local excision [19, 20, 23]. Consequently, the local excision may be considered for patients with highly differentiated, slow-growth tumors with a diameter <2 cm, but who are at high surgical risk and who are unable to tolerate a more extensive operation [22, 23].

An endoscopic ampullectomy may be a viable option in selected patients with mobile, superficial and well-differentiated tumors that are confined to the mucosal layer without vascular or lymphatic invasion [22, 26, 28]. A laparoscopic transduodenal resection is suggested as a feasible procedure in select patients with an ampullary NET [30].

In metastatic tumors, the resection of the primary neoplasm and the administration of somatostatin analogs may become stable the disease and improve the patient's quality of life [22, 25]. Likewise, in patients with hepatic metastases and carcinoid syndrome, the surgical resection and/or cytoreductive techniques, such as radiofrequency ablation and/or chemoembolization of the hepatic metastases, may improve symptoms that are mediated by hormones produced by the tumor. Somatostatin analogs, such as octreotide or lanreotide, may provoke symptomatic and biochemical responses and decrease the enlargement of metastases via a cytostatic effect [23, 24].

The serum chromogranin A levels reflect the tumor load of the NETs and is a useful tumor marker for the monitoring of disease response to the treatment, progression and, particularly, to detect relapse [27, 28, 31].

The presence of distant metastases is the most important prognostic factor in determining survival. Other tumor aspects, such as nodal involvement, size and resection margins, appear to be of lesser significance in the long-term survival [4, 24]. Even ampullary NETs in advanced stages have more insidious progress than ampullary carcinoma. Concerning case #3, the patient with neuroendocrine carcinoma and multiple liver metastases who underwent palliative operation and chemotherapy survived 5 years after the operation. The overall five-year survival of patients with a resected ampullary NETs reaches 90% for well-differentiated tumors, but markedly decreases with a lower differentiation of the tumor [4, 11, 24, 27]. The low-grade tumors show 5- and 10-year survival rates of 80% and 71%, respectively, whereas the high-grade NETs have 10-year survival rates of 15% [11, 27].

CONCLUSIONS

Although NET of the ampulla of Vater represents a rare disease and the majority of ampullary NETs is indolent, this neoplasm has been increasingly reported in recent years and is associated with a relatively poor prognosis. NETs without invasion and a diameter of <2 cm seem to have a better prognosis. Radical resection should be the standard approach in most patients with a NET of the ampulla of Vater, due to the poor accuracy of preoperative and intraoperative assessments of lymph node involvement and the high incidence of lymph node metastases, even in tumors that are smaller than 2 cm.

Conflict of Interest

The authors declare that they have no competing interests.

References'

1. Han SL, Cheng J, Zhou HZ, Guo SC, Jia ZR, Wang PF. Surgically treated primary malignant tumor of small bowel: a clinical analysis. *World J Gastroenterol* 2010; 16:1527-32. [PMID: 20333796]
2. Shafique MS, Fahim M, Shahbaz Bhatti ST, Khan JS, Khan MM. Ampullary carcinoid tumour presenting with extrahepatic biliary obstruction. *J Pak Med Assoc* 2015; 65:892-4. [PMID: 26228340]
3. Somani A, Jain AK, Dixit VK. Periampullary carcinoid: an uncommon tumor at an unusual site. *Indian J Cancer* 2011; 48:496-9. [PMID: 22293267]
4. Albores-Saavedra J, Hart A, Chablé-Montero F, Henson DE. Carcinoids and high-grade neuroendocrine carcinomas of the ampulla of Vater: a comparative analysis of 139 cases from the surveillance, epidemiology, and end results program—a population based study. *Arch Pathol Lab Med* 2010; 134:1692-6. [PMID: 21043824]
5. Terada T. Pathologic observations of the duodenum in 615 consecutive duodenal specimens in a single Japanese hospital: II. Malignant lesions. *Int J Clin Exp Pathol* 2012; 5:52-7. [PMID: 22295147]
6. Matsubayashi H, Matsunaga K, Sasaki K, Yamaguchi Y, Hasuie N, Ono H. Small carcinoid tumor of papilla of the Vater with lymph node metastases. *J Gastrointest Cancer* 2008; 39:61-5. [PMID: 19234807]
7. Rohan VS, Narendra H, Patel JJ, Tankshali RA. Carcinoid of ampulla of Vater. *Indian J Cancer* 2007; 44:90-2. [PMID: 17938486]
8. Waisberg J, Joppert-Netto G, Vasconcellos C, Sartini GH, Miranda LS, Franco MI. Carcinoid tumor of the duodenum: a rare tumor at an unusual site. Case series from a single institution. *Arq Gastroenterol* 2013; 50:3-9. [PMID: 23657299]
9. Randle RW, Ahmed S, Newman NA, Clark CJ. Clinical outcomes for neuroendocrine tumors of the duodenum and ampulla of Vater: a population-based study. *J Gastrointest Surg* 2014; 18:354-62. [PMID: 24114680]
10. Waisberg J, de Matos LL, Waisberg DR, dos Santos HV, Fernezljan SM, Capelozzi VL. Carcinoid of the minor duodenal papilla associated with pancreas divisum: case report and review of the literature. *Clinics* 2006; 61:365-8. [PMID: 16924332]
11. Jayant M, Punia R, Kaushik R, Sharma R, Sachdev A, Nadkarni NK, Attri A. Neuroendocrine tumors of the ampulla of Vater: presentation, pathology and prognosis. *JOP* 2012; 13:263-7. [PMID: 22572129]
12. Relles D, Baek J, Witkiewicz A, Yeo CJ. Periampullary and duodenal neoplasms in neurofibromatosis type 1: two cases and an updated 20-year review of the literature yielding 76 cases. *J Gastrointest Surg* 2010; 14:1052-61. [PMID: 20300877]
13. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Eriksson B et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; 449:395-401. [PMID: 16967267]
14. Washington MK, Tang LH, Berlin J, Branton PA, Burgart LJ, Carter DK, Compton CC et al. Protocol for the examination of specimens from patients with neuroendocrine tumors (carcinoid tumors) of the small intestine and ampulla. *Arch Pathol Lab Med* 2010; 134:181-6. [PMID: 20121604]
15. De Palma GD, Masone S, Siciliano S, Maione F, Falletti J, Mansueto G, De Rosa G et al. Endocrine carcinoma of the major papilla: report of two cases and review of the literature. *Surg Oncol* 2010; 19:235-42. [PMID: 19586767]
16. Poultsides GA, Frederick WA. Carcinoid of the ampulla of Vater: morphologic features and clinical implications. *World J Gastroenterol* 2006; 12:7058-60. [PMID: 17109507]
17. Watanabe Y, Yamada D, Ogawa Y, Fujino M, Kobayashi K, Ryu S, Tanaka M. Long-term survival of a patient with neuroendocrine carcinoma of the ampulla of Vater with lymph node micrometastasis. *Am Surg* 2013; 79:E199-201. [PMID: 23635569]
18. Beggs RE, Kelly ME, Eltayeb O, Crotty P, McDermott R, Ridgway PF. Large cell neuroendocrine carcinoma of the ampulla of Vater. *JOP* 2012; 13:470-5. [PMID: 22964952]
19. Krishna SG, Lamps LW, Rego RF. Ampullary carcinoid: diagnostic challenges and update on management. *Clin Gastroenterol Hepatol* 2010; 8:e5-6. [PMID: 19643204]
20. Hwang S, Lee SG, Lee YJ, Han DJ, Kim SC, Kwon SH, Ryu JH et al. Radical surgical resection for carcinoid tumors of the ampulla. *J Gastrointest Surg* 2008; 12:713-7. [PMID: 17992565]
21. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, et al. North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013; 42:557-77. [PMID: 23591432]
22. Karagiannis S, Eshagzai K, Duecker C, Feyerabend B, Mozdanzowski E, Faiss S. Endoscopic resection with the cap technique of a carcinoid tumor in the duodenal bulb. *Endoscopy* 2009; 41(Suppl 2):E288-9. [PMID: 19899043]
23. Carter JT, Grenert JP, Rubenstein L, Stewart L, Way LW. Neuroendocrine tumors of the ampulla of Vater: biological behavior and surgical management. *Arch Surg* 2009; 144:527-31. [PMID: 19528385]
24. Selvakumar E, Rajendran S, Balachandrar TG, Kannan DG, Jeswanth S, Ravichandran P, Surendran R. Neuroendocrine carcinoma of the ampulla of Vater: a clinicopathologic evaluation. *Hepatobiliary Pancreat Dis Int* 2008; 7:422-5. [PMID: 18693180]
25. Yano F, Hama Y, Abe K, Iwasaki Y, Hatsuse K, Kusano S. Carcinoid tumor of the ampulla of Vater. Magnetic resonance imaging findings. *Clin Imaging* 2005; 29:207-10. [PMID: 15855067]
26. Nikou GC, Toubanakis C, Moulakakis KG, Pavlatos S, Kosmidis C, Mallas E, Safioleas P et al. Carcinoid tumors of the duodenum and the ampulla of Vater: current diagnostic and therapeutic approach in a series of 8 patients. Case series. *Int J Surg* 2011; 9:248-53. [PMID: 21215338]
27. Dumitrascu T, Dima S, Herlea V, Tomulescu V, Ionescu M, Popescu I. Neuroendocrine tumours of the ampulla of Vater: clinico-pathological features, surgical approach and assessment of prognosis. *Langenbecks Arch Surg* 2012; 397:933-43. [PMID: 21215338]
28. Krishna SG, Lamps LW, Rego RF. Ampullary carcinoid: diagnostic challenges and update on management. *Clin Gastroenterol Hepatol* 2010; 8:e5-6. [PMID: 19643204]
29. Senda E, Fujimoto K, Ohnishi K, Higashida A, Ashida C, Okutani T, Sakano S et al. Minute ampullary carcinoid tumor with lymph node metastases: a case report and review of literature. *World J Surg Oncol* 2009; 7:9. [PMID: 19159493]
30. Zhang RC, Xu XW, Wu D, Zhou YC, Ajoodheha H, Chen K, Mou YP. Laparoscopic transduodenal local resection of periampullary neuroendocrine tumor: a case report. *World J Gastroenterol* 2013; 19:6693-8. [PMID: 24151401]
31. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; 26:3063-72. [PMID: 18565894]