SYSTEMATIC REVIEW

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Somatostatinoma of the Ampulla of Vater: A Systematic Review

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ABSTRACT

Background & Aims: Somatostatinoma of the ampulla of Vater (SAV) is a rare neuroendocrine tumor that usually appears with atypical clinical manifestations and is associated with Von Recklinghausen's disease. The aims of this study were to systematically review the literature regarding SAV and to highlight the clinicopathological characteristics and optimal therapeutic management of this rare entity.
Methods: A systematic search of the literature in PubMed/Medline and Scopus databases was performed by two independent investigators, including all case reports and case series concerning SAVs from 1980 until September 2021.
Results: In total, 37 articles were retrieved, including 43 patients, with a male to female ratio of 1.8:1 and a mean age of 46.8 ± 11.3 years (mean, SD). For 23 out of 43 patients (53.5%), Von Recklinghausen's disease was proved. The main clinical manifestations were abdominal pain (41.9%), jaundice (27.9%), weight loss (20.9%) and bowel disorders (20.9%). Typical histological findings included psammoma bodies, nests or clusters of epithelial cells with eosinophilic cytoplasm, while somatostatin staining was positive in 35 patients (81.4%), chromogranin-A in 21 patients (48.8%) and synaptophysin in 18 patients (41.9%). Surgery was the initial therapeutic approach in 34 patients (79.1%), whereas Whipple's procedure was the preferred surgical approach in 23 patients (53.4%). The longest survival among included patients was 13 years and only two postoperative deaths (4.7%) were reported.
Conclusions: Somatostatinomas of the ampulla of Vater are rare malignancies that require increased physicians' suspicion and accurate surgical approach in order to achieve optimal therapeutic results.

Key words: somatostatinoma - ampulla of Vater – duodenal somatostatinoma – ampullary somatostatinoma – endocrine neoplasms.

Abbreviations: CT: computed tomography; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance imaging; NF: neurofibromatosis; NSE: neuron-specific enolase; SAV: somatostatinoma of the ampulla of Vater.

INTRODUCTION

Somatostatinomas are rare neuroendocrine tumors that produce somatostatin and their incidence is 1 out of 40 million people [1]. Somatostatin is a cyclic tetra-decapeptide that derives from D cells of the pancreas, neuroendocrine cells of the duodenum, central nervous system and thyroid gland [2]. Somatostatinomas are mainly located at the head of the pancreas (70% of the reported cases), but they are also found in the small intestine, the duodenal papilla and the ampulla of Vater [3, 4]. Somatostatinomas are usually presented with manifestations of the "inhibitor syndrome", caused by the suppressive effects of somatostatin [5]. This hormone inhibits the release of insulin, glucagon, gastrin and cholecystokinin inducing the clinical triad of diabetes mellitus, cholelithiasis and steatorrhea [6, 7]. Somatostatin-producing tumors, especially those originating from the ampulla of Vater, have been associated with Von Recklinghausen's disease and sporadically with ganglioneuromas and paragangliomas [8, 9]. Von Recklinghausen's disease comprises an autosomal hereditary disease, which is clinically characterized by tan spots on the skin – café au lait spots- and cutaneous neurofibromas, whereas its incidence is 1 in 3,000 births [10].

Somatostatinoma of the ampulla of Vater (SAV) is an astonishingly rare entity with only few cases reported in the literature [3]. Patients with SAV could be asymptomatic or present with atypical clinical manifestations including obstructive jaundice, abdominal pain and symptoms of the inhibitory syndrome [11]. Although the pre-operative diagnosis of SAVs constitutes a real challenge for physicians, endoscopic procedures, such as endoscopic retrograde colangio-pancreatography (ERCP), or imaging studies, such as magnetic resonance imaging (MRI) and computed tomography (CT) scan, could help in identifying the primary location of these tumors [12]. The ultimate diagnosis of SAV relies on immunohistochemical staining for anti-somatostatin antibodies combined with specific histological features, showing psamommatous calcification [12, 13]. Their therapeutic approach mainly focuses on the surgical resection of the neuroendocrine tumor [14-16]. Finally, due to its rarity, the prognosis of SAV remains unclear, although it seems that large tumors mainly present with an aggressive and metastatic behavior [17].

The aims of this study were to systematically review the literature concerning SAVs and to demonstrate the clinicopathological findings and therapeutic management of this infrequent entity.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA guidelines) [18]. Two investigators (I.G., A.G.) searched independently PubMed/Medline and Scopus databases for eligible articles reporting on SAVs, from 1980 until September 2021. Initial agreement on literature search was excellent, as kappa-coefficient exceeded 0.8. Boolean operators (AND, OR) in combination with the following keywords were used for the search strategy: "somatostatinoma", "somatostatin tumors", "ampulla of Vater", "Vater's papilla" and "hepatopancreatic ampulla". Any controversy was solved by the interference of a senior investigator. Only articles written in the English language were included. Case reports and case series that referred to patients with SAVs were included in our systematic review, whereas reviews and meta-analyses were excluded. Moreover, letters to the editor and articles that could not be retrieved in full text via contact with international academic libraries, online purchase from journal's Web site or contact with the corresponding authors were excluded from the present systematic review. Studies reporting on somatostatinomas in locations other than the ampulla of Vater or other ampullary tumours, as well as articles with no clear diagnosis or insufficient data were excluded as irrelevant (Fig. 1).

Data Extraction

Two investigators (I.G., A.Z.) worked separately and extracted data from all included studies, using a predefined template. Information regarding gender, age, race, symptoms and medical history of the patients were compiled. In addition, the investigators collected data concerning imaging features, histological and immunohistochemical characteristics, metastatic lesions, treatment approach and survival.

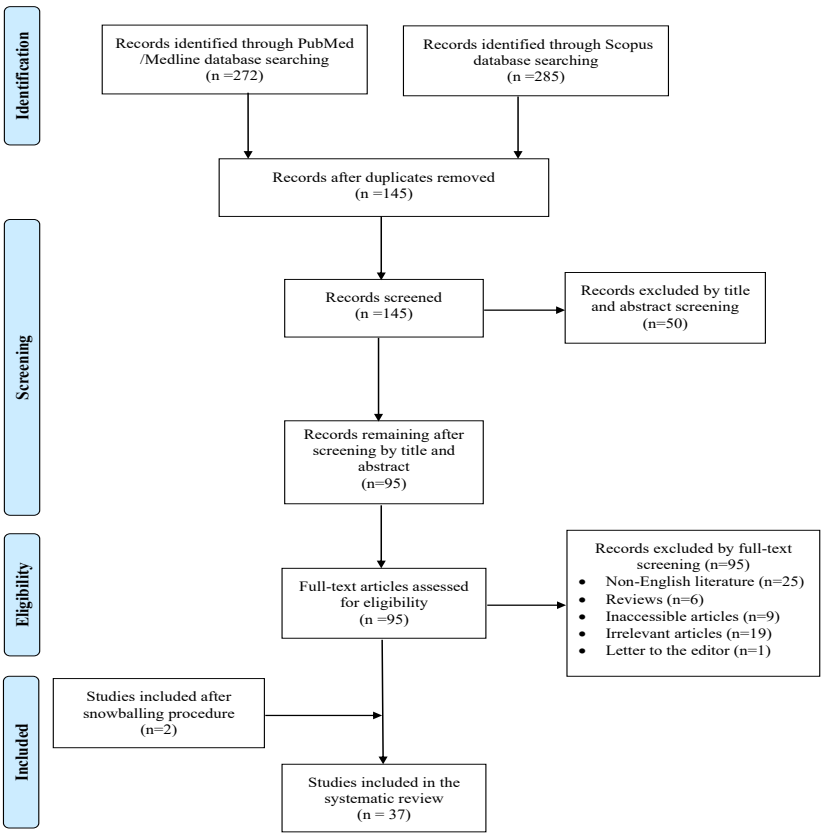

Fig. 1. Trial flow of this systematic review.

Statistical Analyses

Numerical variables were presented as mean ± standard deviation (SD) or as median (25%–75% quartiles), in case they were skewed. Categorical variables were presented using frequencies and percentages. Patients included in the case series were considered as unique cases, in order to estimate variables of interest. Several studies did not report on all outcomes of interest and therefore relative rates were estimated based on available data. No statistical relationship between included variants was tested. Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

RESULTS

The included articles enrolled 43 patients in total, 28 females (65.1%) and 15 males (34.9%), presenting with a 1.8:1 sex ratio. The mean age of patients with SAVs was 46.8 ± 11.3 years (mean, SD). Characteristics of included studies are summarized in Table I. Interestingly, 23 patients (53.5%) had a medical history of neurofibromatosis (NF) type 1, while 10 patients (23.3%) presented with a simultaneous history of another cancer.

The majority of included patients complained about abdominal pain (18 patients, 41.9%), while 8 patients (18.6%) were asymptomatic. Moreover, 12 patients (27.9%) presented with jaundice, 5 patients (11.6%) with nausea, 4 patients (9.3%) with vomiting and 9 patients (20.9%) reported significant weight loss. Other reported symptoms included blood loss and functional bowel problems. Detailed clinical manifestations of included patients are demonstrated in Table II.

Out of the 43 cases with SAVs, CT was utilized in 27 patients (62.8%) to detect the primary lesion, endoscopy in 17 patients (39.5%) and ultrasonography (US) in 19 patients (44.2%). Endoscopic retrograde cholangiopancreatography (21 patients, 48.8%), magnetic resonance cholangiopancreatography (MRCP) (5 patients, 11.6%) and MRI (3 patients, 7%) were also used in order to identify the primary location of the tumor. Somatostatin levels were calculated in 9 cases (21%) and were elevated in only 3 of them (33.3%). Additionally, open biopsy and fine needle aspiration or fine needle biopsy were performed in 21 patients (48.8%) and 3 patients (7%), respectively, while histopathologic findings were reported in 34 cases (79.1%). Presence of psammoma bodies and nests or clusters of epithelial cells with eosinophilic cytoplasm were the most common histologic findings. Furthermore, other documented histologic reports included atypical cells arranged in a trabecular manner, presence of amyloid sediments, perineural infiltration and vascular emboli (Table III). Concerning immunohistochemical staining of resected specimens, somatostatin was found positive in 35 patients (81.4%), chromogranin-A in 21 patients (48.8%), synaptophysin in 18 patients (41.9%) and neuron-specific enolase (NSE) in 7 patients (6.3%).

Surgical treatment was the initial therapeutic approach in the majority of patients (34 patients, 79.1%). Of note, surgery was the second therapeutic option for 10 patients following a non-surgical approach, such as endoscopic excision. Among surgical operations, Whipple's procedure was performed in 28 patients (68.3%) and ampullectomy in 13 patients (30.2%).

Table I. Characteristics of articles included in this systematic review

Author's Name	Type of study	Nr. of patients	Gender	Age (years)
Hendi et al., [19]	Case report	One	Female	53
Ambrose et al., [12]	Case report	One	Male	32
Borobia et al., [17]	Case report	One	Female	46
Bettini et al., [20]	Case report	One	Male	47
Kainuma et al., [10]	Case report	One	Female	44
Harris et al., [21]	Case report	One	Male	63
Frick et al., [22]	Case report	One	Female	43
Guercioni et al. [23]	Case report	One	Female	54
Guo et al., [24]	Case report	One	Female	41
French et al., [1]	Case report	One	Male	59
Chetty et al., [25]	Case report	One	Male	42
Deschamps et al., [26]	Case report	One	Female	49
Foad et al., [27]	Case report	One	Female	39
Kloska et al., [28]	Case report	One	Female	46
Sakorafas et al., [29]	Case report	One	Female	49
Oller et al., [30]	Case report	One	Male	26
South et al., [8]	Case report	One	Female	39
Stommer et al. (case 1), [31]	Case series	Two	Female	50
Stommer et al. (case 2), [31]	Case series	Two	Male	56
Tan et al., [11]	Case report	One	Female	21
Usui et al., [3]	Case report	One	Female	64
Rios et al., [32]	Case report	One	Male	21
Reynolds et al., [33]	Case report	One	Female	47
Mahajan et al., [34]	Case report	One	Female	49
Zakaria et al., [15]	Case report	One	Male	43
Sawady et al. (case 1), [35]	Case series	Two	Male	51
Sawady et al. (case 2), [35]	Case series	Two	Female	59
Marcial et al., [5]	Case report	One	Male	28
Fincher et al., [36]	Case report	One	Male	59
Trindade et al., [37]	Case report	One	Male	49
Budmiger et al., [38]	Case report	One	Female	55
Green at el., [39]	Case report	One	Female	48
Karatzas et al., [40]	Case report	One	Female	36
Tham et al., [41]	Case report	One	Female	49
Thavaraputta et al., [42]	Case report	One	Female	44
Varikatt et al. (case 1), [43]	Case series	Two	Female	37
Varikatt et al. (case 2), [43]	Case series	Two	Female	54
Williamson et al. (case 1), [44]	Case series	Five	Female	50
Williamson et al. (case 2), [44]	Case series	Five	Male	46
Witzigman et al. (case 3), [45]	Case series	Five	Male	46
Witzigman et al. (case 4), [45]	Case series	Five	Female	44
Witigman et al. (case 5), [45]	Case series	Five	Female	53
Yamamoto et al., [46]	Case report	One	Female	81

Table II. Clinical manifestations of SAV cases published in the literature

Symptoms	Patients (n=43)	Percentage
Abdominal Pain	18	41.9
Jaundice	12	27.9
Weight loss	9	20.9
Nausea	5	11.6
Vomiting	4	9.3
Blood loss	4	9.3
Upper GI bleeding	2	4.7
Anemia	1	2.3
Melena	1	2.3
Bowel problems	9	20.9
Diarrhea	4	9.3
Steatorrhea	3	7
Steatorrhea + Diarrhea	2	4.7
Asymptomatic	8	18.6

Patient's survival was reported only in 22 cases and the follow-up interval ranged from 6 months to 13 years among studies. The longest survival interval was 13 years, whereas only two deaths (4.7%) were reported. One patient died due to severe cardiac event four days after surgery and the other patient died due to aspiration pneumonia forty-nine days postoperatively. Metastatic tumors were reported in 19 patients, mainly in lymph nodes (16 patients) and liver (3 patients), while one patient presented with disseminated disease involving regional lymph nodes, liver and jejunum. Finally, recurrence of the primary lesion after initial treatment was reported only in 3 cases.

DISCUSSION

Somatostatinomas are rare neuroendocrine tumors originating from enterochromaffin cells and less than 200 clinical cases have been reported in the literature so far [47]. The embryologic origin of intestinal somatostatinomas remains unclear, but both an endodermal and neuroectodermal origin has been suggested [48]. These neuroendocrine malignancies are usually located in the pancreas or, less frequently, in the duodenal mucosa and small intestine [47]. Duodenal somatostatinomas are extremely rare, tend to appear in smaller size compared to pancreatic ones and mainly present with obstructive symptoms [33]. Concerning the ampulla of Vater, neurofibromas and carcinoids are the most frequently reported neuroendocrine tumors and the development of somatostatinomas remains uncommon, comprising only 6% of neuroendocrine tumors originating from the gastrointestinal tract [15]. Somatostatinomas of the ampulla of Vater are usually diagnosed in patients with mean age at 50 years, but they are rarely found in younger patients as well [32]. Additionally, these malignancies appear in 10% of patients diagnosed with von-Recklinghausen disease [15]. Although the association between NF type 1 and somatostatinomas is widely recognized, the exact incidence in SAVs remains undefined, due to under-recognition of clinical cases [11]. Our study demonstrated that the mean age of patients was 46.8 years, and 53.5% of included patients presented with a history of NF type 1. Additionally, 23.3% of patients presented with simultaneous occurrence or history of another malignancy. Consequently, patients with SAVs should be thoroughly examined and screened for NF type 1 or other malignancies [15].

As mentioned before, the release of somatostatin by somatostatinomas causes the inhibition of other hormones, such as gastrin, insulin, secretine and/or cholecystokinine, and leads to the appearance of several clinical conditions, such as lithiasis of the common biliary duct, steatorrhea,

Table III. Histologic findings of SAV cases published in the literature

Author's Name	Histologic findings
Marcial et al. [5]	polygonal or polyhedral cells separated by thin fibrovascular septa Presence of psammoma bodies
Stommer et al. [31]	Clusters and nests of large cells with eosinophilic cytoplasm Presence of psammoma bodies Atypical cells arranged in a trabecular manner
Harris et al. [21]	Nests of cells with eosinophilic cytoplasm and round nuclei
Sawady et al.	Polygonal to cuboidal cells with eosinophilic cytoplasm Presence of psammoma bodies
Mahajan et al. [34]	Cells arranged in nests with fibrous bands separating them
Kainuma et al. [10]	Small round cells with small and round nuclei Psammoma bodies
Tan et al. [11]	Islands and strands of cells with eosinophilic cytoplasm Presence of psammoma bodies
Fincher et al. [36]	Epithelioid tumor cells Presence of psammoma bodies
Chetty et al. [25]	Eosinophilic granular cells with solid nested foci Presence of psammoma bodies
Frick et al. [22]	Nests of epithelial tumor cells with nuclear pleomorphism and abundant pale cytoplasm
Borobia et al. [17]	Nests, clusters, cords of cells with granular cytoplasm
Rios et al. [32]	Large polygonal cells with trabecular or pseudoglandular differentiation Presence of psammoma bodies
Usui et al. [3]	Tumor cells in acinar form Presence of psammoma bodies
Hendi et al. [19]	Presence of psammoma bodies
Guercioni et al. [23]	Presence of psammoma bodies Presence of amyloid sediments
Sakorafas et al. [29]	Perineural infiltration and vascular emboli
South et al. [8]	Nests of neuroendocrine cells Presence of psammoma bodies
Deschamps et al. [26]	Cords or acini of endocrine cells with eosinophilic cytoplasm Presence of psammoma bodies
Oller et al.	Presence of psammoma bodies
Ambrose et al. [12]	Nests of cells with eosinophilic cytoplasm Presence of psammoma bodies
Reynolds et al. [33]	Infiltrative neuroendocrine nests and sheets Presence of psammoma bodies
Foad et al. [27]	Glandular structures and columnar cells with eosinophilic cytoplasm Presence of psammoma bodies

diabetes and gastric disorders (achlorydria, dyspepsia) [32]. These syndromes, and especially the clinical triad of diabetes mellitus, cholelithiasis and steatorrhea, are present in 85% of pancreatic somatostatinomas and in 15% of extra-pancreatic primary tumors [34]. Extra-pancreatic somatostatinomas, such as SAVs, are mainly asymptomatic or present with atypical clinical manifestations [49]. Due to their location in the ampulla of Vater, they cause local symptoms that depend on the size of the primary tumor, while the aforementioned clinical triad has not been reported in tumors smaller than 1 cm [34]. In our systematic review, abdominal pain, jaundice and loss of weight were the most commonly reported symptoms, while almost one fifth (18.6%) of patients were asymptomatic. Due to non-specific symptoms of these tumors, their diagnosis mainly depends on the clinical suspicion of physicians. However, in the majority of cases, their clinical presentation is usually underestimated and they are usually discovered accidentally during various surgical procedures, such as cholecystectomy or during screening for other reasons [15].

Increased plasma levels of somatostatin combined with imaging techniques contribute to the identification of SAVs [32]. Somatostatin levels more than 30 pg/ml in the plasma are considered diagnostic for somatostatinomas [15]. However, the majority of patients could present normal somatostatin levels, the diagnosis of these tumors being a real challenge [34]. In our systematic review, somatostatin levels were found increased in only one third of cases. Computed tomography, abdominal ultrasound and esophagogastroduodenoscopy constitute the diagnostic armamentarium for the identification of this rare entity [32]. Magnetic resonance imaging and MRCP are useful in order to estimate the extent of tumor invasion to adjacent organs, and especially pancreatic infiltration [32]. Endoscopic ultrasound presents higher sensitivity compared to MRI or CT for the assessment of pancreatic invasion and lymph node involvement [23]. Octreoscan detects extra-abdominal metastases [15]. Furthermore, positron emission tomography/ computed tomography (PET/CT) contributes to higher imaging resolutions providing increased sensitivity for the detection of smaller lesions [15]. In our study, abdominal CT (62.8%), ERCP (48.8%) and esophagogastroduodenoscopy (44.2%) comprised the most frequently used imaging modalities for the detection of the primary lesion. Despite the advancement of diagnostic modalities, the identification of SAVs remains challenging and they should be differentiated from other clinical entities that could be developed in the ampulla of Vater (Table IV).

Table IV. Differential diagnosis of tumors developed in the ampulla of Vater

Entity	Incidence	Age (years)	Sex ratio (male:female)	CT	US	MRI
Adenoma [55-57]	0.04–0.12% (of all cancers)	30-90 (usually 60-80)	1:1	Dilation of common bile and pancreatic ducts Soft tissue attenuation mass or bulging and enhancing papilla	Lesion with absence of muscular invasion	Smoothly marginated, mass or bulging and enhancing papilla Enhanced ampullary mass with gadolinium-based contrast agent Dilation of bile ducts
Adenocarcinoma [55]	0.5-0.7 per 100.000	30-90 (usually in 60-80)	1.5:1	Hypoattenuating soft mass (40 HU) Enhancement on arterial and portal venous phase Dilation of common bile and pancreatic ducts	Dilation of common bile and pancreatic ducts	NR
GIST [58,59]	3%-5% (of all GISTs)	50-60	0.8:1	Hypervascular uniformly or peripherally enhanced masses Common bile duct and/or pancreatic duct dilatation	Dilation of common bile and pancreatic ducts Hypoechoic mass	NR
Lipoma [55]	NR	70-80	Male predominance	Smooth well-marginated masses with fat attenuation(≤20 HU)	Smooth well-marginated mass	Smooth well-marginated mass with fat signal intensity
Adenomyomatosis [60]	Few cases	18–81	1:1	Bulging papilla Dilation of common bile and pancreatic ducts Tumor-like mass in the papilla region	Hypoechogenic mass Lesion with wall muscular-layer involvement	Bulging papilla Dilation of common bile and pancreatic ducts Tumor-like mass in the papilla region

NR: non-recorded; CT: computed tomography; US: ultrasonography; MRI: magnetic resonance imaging.

The final diagnosis of these tumors relies on histopathological findings and immunohistochemical staining of resected specimens. Interestingly, SAVs present with distinct histologic features consisting of abundant psammoma bodies that differ histologically from other carcinoid tumors [15, 50]. In our systematic review, psammomatous calcification was found in 82.4% of cases. Furthermore, the identification of large secretory granules in histopathologic analysis is indicative of endocrine D-cells and their presence is confirmed by staining for anti-somatostatin antibodies [15]. In our study, somatostatin, chromogranin-A and synaptophysin markers were found positive in 81.4%, 48.8% and 41.9% of included cases, respectively, indicating the diagnosis of somatostatinoma. However, an atypical histological feature along with atypical immunohistochemical staining could make the diagnosis of this rare entity extremely challenging.

Surgery remains the mainstay of treatment for SAVs, either with local resection of the tumor or with more radical surgical procedures [23]. The extent of surgical resection depends on the size of the tumor, because larger tumors are associated with greater incidence of pancreatic invasion and lymph node involvement. Therefore, the majority of published studies suggest local resection of the lesion only in tumors less than 2 cm and more radical surgical approaches, such as Whipple's procedure in larger tumors [23]. In our study Whipple's procedure was performed in 65.1% of included cases and ampullectomy in 12.2%. The diameter of 2 cm is considered as the cut-off point for treatment options, since tumors greater than 2 cm are associated with increased incidence of metastatic spread [51]. However, according to our findings, out of the 12 cases that were initially treated with local excision, a second radical surgical procedure was necessary in 83.3% of them, suggesting possible upfront implementation of radical operations even for smaller tumors in the future.

Medical treatment for the management of gastrointestinal somatostatinomas is considered of high significance, aiming to control clinical manifestations associated with excess somatostatin production and restrict tumor growth [53, 54]. However, there are no current guidelines concerning the administration of chemotherapeutic regimens for duodenal somatostatinomas, and especially SAVs, due to lack of randomized controlled trials for this subgroup of patients. Concerning systematic therapy of SAVs, treatment with targeted agents, such as everolimus, should be the first option for systemic disease, while the administration of temozolomide, capecitabine and streptozotocin alone or in combination with 5-FU should comprise alternative options [54]. Finally, peptide receptor radionuclide therapy should be applied only in ampullary tumors with increased expression of somatostatin receptors [54].

To the best of our knowledge, this is the first systematic review of the literature concerning epidemiology, clinical appearance, diagnostic approach and therapeutic management of SAVs. Due to the scarcity of these malignancies, extended eligibility criteria were used to include all case reports of SAVs published in the literature. However, our systematic analysis is subject to certain limitations. Our study included only case reports and case series with sufficient data whose credibility mainly depends on accurate record keeping. In addition, the heterogeneity among institutions concerning surgical approaches, chemotherapy and record keeping definitely affects outcomes and time-to-event analysis. Finally, the majority of included studies (72%) were published before 2010, showing that further studies, recently published, are needed to elucidate the optimal management of this rare entity.

CONCLUSION

Somatostatinomas of ampulla of Vater are extremely rare malignant tumors that are present mainly in middle-aged patients and are strongly associated with a medical history of NF type 1 or other malignancies. They are asymptomatic or could appear with atypical clinical presentation, representing a diagnostic challenge for physicians. Increased somatostatin levels along with imaging modalities are combined to identify the primary lesion. Final diagnosis is confirmed by immunohistochemical staining along with specific histological evidence. Surgical resection of the malignancy, either with local excision or more radical procedures, constitutes the mainstay of treatment. Increased clinical suspicion is necessary for accurate diagnosis, while therapeutic management and follow-up strategies should follow consensus guidelines in order to optimize outcomes for this rare entity.

Conflicts of interest: None to declare.

Authors' contribution: I.G., D.S. conceived and designed the study, collected and analyzed the data and drafted the manuscript; I.G., D.S., A.G, A.Z.: collected data. I.G., D.S., M.F., N.K., K.V., K.T.: interpreted the results, analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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