A clinical analysis on functioning pancreatic neuroendocrine tumors (focusing on VIPomas): a single-center experience

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Abstract. VIPomas are generally rare functioning pancreatic neuroendocrine tumors (PanNETs) that cause watery diarrhea, hypokalemia, and achlorhydria. Due to their extreme rarity, the clinicopathological features and outcomes of VIPomas have not been well reported. This study aimed to determine the diagnostic and therapeutic characteristics and prognosis of VIPomas and to compare them with other PanNETs at a Japanese reference hospital. Medical records of 293 patients with PanNETs were collected. Patient and tumor characteristics and outcomes were retrospectively reviewed. This cohort had only 1.4% (four patients) of patients with VIPomas, and three of these patients changed from non-functioning (NF-) PanNETs during their disease course. Recurrences of hormonal symptoms were observed in all patients despite the initial controls, and all of them died from their disease, more specifically mainly from hormonal symptoms. Compared to the other PanNETs, VIPomas were all located at the pancreatic tail, were larger, and had a higher Ki-67 index and more metastasis. The median survival time was significantly shorter for patients with VIPoma than for those with NF-PanNET (5.9 vs. 26.7 years, \( p < 0.0001 \)), insulinoma (21.8 years, \( p < 0.0001 \)), and gastrinoma (12.3 years, \( p = 0.0325 \)). This study presents the possibility of shifting from non-symptomatic to symptomatic VIPomas as they grow or of transforming from NF-PanNETs to VIPomas. VIPomas should be considered in patients with relatively large NF-PanNETs, especially those located in the pancreatic tail, when diarrhea is continuously observed. As hormonal symptoms are an important cause of death in VIPomas, long-term symptomatic control, which is relatively difficult, is of great significance.

Key words: Neuroendocrine tumor, VIPoma, Vasoactive intestinal peptide tumor, Verner–Morrison syndrome, Watery diarrhea-hypokalemia-achlorhydria syndrome (WDHA)

NEUROENDOCRINE NEOPLASMS (NENs) are malignant neoplasms that originate in the neural crest. NENs can occur anywhere in the body, but the pancreas and gastrointestinal tract are the most frequent sites [1]. Moreover, the incidence rate of pancreatic NENs (PanNENs) has been increasing worldwide because of the dissemination of the disease concept and advancement in diagnostic modalities [2, 3].

PanNENs are divided into pancreatic neuroendocrine tumors (PanNETs) and pancreatic neuroendocrine carcinomas (PanNECs) based on their molecular differences, and the former are further classified as functioning (F-) or non-functioning (NF-) tumors based on the absence or presence of their specific hormonal hyperexpression symptoms. Functional status has been reported to be favorable in patients undergoing surgical resection [4]. In contrast, functionality was not a significant prognostic factor associated with unresectable PanNENs [5]. There is still room for discussion about the prognosis between F- and NF-PanNETs because they included various types of F-PanNETs, such as insulinomas, which were hypothesized to be originally benign tumors and were affected by heterogeneities of F-PanNETs.
VIPomas are significantly rare F-NETs that frequently occur in the pancreas and were first reported by Verner and Morrison in 1958 [6]. VIPomas are characterized by the excessive secretion of vasoactive intestinal peptide (VIP), which may cause various symptoms, with watery diarrhea, hypokalemia, and achlorhydria being the main symptoms (WDHA syndrome) [7]. A Japanese nationwide epidemiological study revealed that the most frequent F-PanNETs are insulinomas, in 20.9% of PanNETs, and, conversely, VIPomas, in only 0.6% [2]. Because of their extreme rarity, their clinicopathological features and outcomes and comparisons with other PanNETs have not been well reported.

Therefore, this study aimed to determine the diagnostic and therapeutic characteristics and prognosis of VIPomas and to compare them with other PanNETs at a Japanese reference hospital.

Materials and Methods

Patients and data collection

The medical records of 326 patients with PanNENs treated at Kyushu University Hospital between 1987 and September 2021 were collected, and 33 patients were excluded because of insufficient medical records or PanNECs. A total of 293 patients were retrospectively reviewed. The clinicopathological factors analyzed in all patients were as follows: age, sex, presence of inherited diseases (multiple endocrine neoplasia type 1 or von Hippel–Lindau disease), functionality, tumor location, tumor size, Ki-67 index, tumor grade according to the World Health Organization 2019 classification, Union for International Cancer Control staging (8th edition), serum VIP levels, treatment methods, treatment outcomes, and prognosis.

In case of multiple tumors in the pancreas, the most clinically important tumors including hormone-secreting tumors or the largest tumors in NF-PanNETs were evaluated. F-PanNETs were defined as whether or not the presence of the elevated serum hormone levels (at least higher than the upper normal limit) and/or positive target antigens on immunohistochemical staining in addition to characteristic hormonal symptoms (Figs. 1 and 2). Serum VIP levels, which could not be measured in clinical practice in Japan, were used if previously measured. However, in the recent case (Case 4), they were measured using an enzyme-linked immunosorbent assay kit (USCN Life Science, Houston, TX, USA) according to the manufacturer’s protocol.

Statistical analyses were performed using JMP version 12 (SAS Institute, Inc.). Kaplan–Meier plots with log-rank testing were used to analyze overall survival.

This study was approved by the Institutional Review Board of Kyushu University Hospital (2021-161 and 2021-369). Because this was a retrospective observational study without any invasion and targeted patients who had visited our hospital in the past, we published the materials on the homepage to disseminate the information of this study and provided the participants an opportunity to refuse participation (opt-out form).

Results

Patient and tumor characteristics of four VIPomas

Fig. 3 shows the breakdown of the PanNENs in this study. In total, 27.3% of patients had F-PanNENs. The most frequent F-PanNETs were insulinomas (15.3%), and conversely, the proportion of VIPomas was only 1.4%.

Table 1 shows the characteristics of the four patients with VIPomas. The four presented cases followed an interesting course. Patients in Cases 1, 2, and 3, who were initially diagnosed with NF-PanNETs because of the absence of hormone-excess symptoms, were diagnosed with VIPomas during their disease course. The serum VIP level itself was significantly higher than the upper normal limit in Case 1 at the initial diagnosis (initial serum VIP levels were not available in Cases 2 and 3). There were multiple exacerbations of the hormone-

![Fig. 1](image_url) Contrast-enhanced computed tomography (CT) at initial diagnosis in Case 4

Contrast-enhanced CT revealed a hypodense tumor of the pancreatic tail (a) and multiple liver lesions (b) (arrows).
excess state in each patient; however, radiological images were not relevant to the relapse of hormonal symptoms. Furthermore, the activation of hormonal symptoms (WDHA syndrome) was prior to the imaging findings of recurrence in Case 3, who had previously undergone curative resection for NF-PanNET. In contrast, a positive correlation was observed between serum VIP levels and remission or exacerbation of hormonal symptoms in patients with continuous measurements of serum VIP levels.

All of the patients could initially achieve good control of hormonal symptoms with somatostatin analogs (SSAs), but in all patients, relapses of symptoms were observed. Multiple treatments were used, but SSA \( n = 2 \) (including re-introduction, double dose, or continuous intravenous injection), debulking surgery \( n = 1 \), and
chemotherapy (streptozocin and 5-fluorouracil) \((n = 1)\), in addition to antidiarrheals, showed an effect on cumulative relapses of diarrhea. However, the symptoms were eventually uncontrolled in three cases (Cases 2, 3, and 4). All of them died from their disease, and more specifically, three died from hormonal symptoms, two with fatal bowel infection and the other with acute renal failure secondary to uncontrolled diarrhea.

**Patient and tumor characteristics of each pancreatic neuroendocrine tumor**

Table 2 shows the clinicopathological characteristics of NF-PanNETs, gastrinomas, insulinomas, VIPomas, and other F-PanNETs. All the VIPomas were located in the pancreatic tail. VIPomas were larger and had a higher Ki-67 index, more metastases, and a higher recurrence rate than the other F-PanNETs. The surgical resection rate was low in VIPomas and, conversely, high in other PanNETs, including gastrinomas, in which there were relatively many cases with metastasis. Patients with VIPoma and NF-PanNET mostly died of tumors.

**Prognosis of VIPoma**

Fig. 4 shows the results of the Kaplan–Meier survival analysis. The comparison of overall survival showed no significant difference between the patients with and without functionality. In contrast, the median survival time (MST) was significantly shorter for patients with VIPoma than for those with NF-PanNET \((5.9 \text{ vs. } 26.7 \text{ years, } p < 0.0001)\), insulinoma \((21.8 \text{ years, } p < 0.0001)\), and gastrinoma \((12.3 \text{ years, } p = 0.0325)\).

**Discussion**

According to Japanese clinical practice guidelines for gastroenteropancreatic NENs, the diagnosis of VIPoma is based on a combination of symptoms (such as profuse watery diarrhea, muscle weakness, cramps, and shortness of breath), laboratory findings (such as hypokalemia, hypochloremia, metabolic acidosis, hyperglycemia, and hypercalcemia), imaging findings, and pathological findings [8]. Measurement of stool osmotic gap and serum VIP levels are also useful, but the latter currently cannot be measured in Japan [8]. Establishing the diagnosis of VIPoma is sometimes difficult because the severity of diarrhea varies depending on the individuals, and VIPomas may be hiding in 1% of chronic diarrhea [7, 9]. VIPomas are a significantly rare disease but should be considered one of the causes of chronic diarrhea.

In the acute phase of VIPoma, the most important thing is to improve the general medical condition by correcting dehydration and electrolyte abnormalities. Apart from that, their essential treatment is not only antitumor but also antihormonal therapies. Curative surgery is also a principle for hormonal control, but it is often difficult because metastases are present at the time of diagnosis in 80% of patients with VIPomas [2]. In metastatic cases, the mainstay of treatment is SSA, which has been
reported to achieve symptomatic improvement and tumor shrinkage in 83% and 20% of patients with VIPoma, respectively [10]. In addition, the efficacy of other treatments, including sunitinib, trans-arterial chemoembolization, and peptide receptor radionuclide therapy, which might control hormone-excess state by directly suppressing hormone expression or antitumoral effects, was reported in a case report or case series with a small number of patients [11-13]. A recent multicenter study reported that curative-intent surgery, chemotherapy, and sunitinib showed the best combined antitumor and anti-

### Table 1  Patient characteristics of VIPomas

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>42</td>
<td>52</td>
<td>82</td>
<td>75</td>
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<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td><strong>Presence of MEN-1 or VHL</strong></td>
<td>Absence</td>
<td>Absence</td>
<td>Absence</td>
<td>Absence</td>
</tr>
<tr>
<td><strong>Tumor size, mm</strong></td>
<td>60</td>
<td>70</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td><strong>Tumor location</strong></td>
<td>Tail</td>
<td>Tail</td>
<td>Tail</td>
<td>Tail</td>
</tr>
<tr>
<td><strong>Ki-67 index, % (grade)</strong></td>
<td>1.0 (NET G1)</td>
<td>8.0 (NET G2)</td>
<td>17.0 (NET G2)</td>
<td>25.0 (NET G3)</td>
</tr>
<tr>
<td><strong>Stage</strong>*</td>
<td>IV</td>
<td>IV</td>
<td>II</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Type of PanNETs at initial diagnosis</strong></td>
<td>Non-functioning</td>
<td>Non-functioning</td>
<td>Non-functioning</td>
<td>VIPoma</td>
</tr>
<tr>
<td><strong>Serum VIP level at initial diagnosis, pg/mL</strong></td>
<td>144.8</td>
<td>Not available</td>
<td>Not available</td>
<td>118</td>
</tr>
<tr>
<td><strong>Serum VIP level at first symptoms, pg/mL</strong></td>
<td>418.6</td>
<td>2,150</td>
<td>500</td>
<td>118</td>
</tr>
<tr>
<td><strong>Serum VIP level at remission of first symptoms, pg/mL</strong></td>
<td>21.4</td>
<td>401</td>
<td>Not available</td>
<td>66.9*</td>
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<td><strong>Treatment method (cumulative)</strong></td>
<td>Surgical resection/curative resection</td>
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<td>1/0</td>
<td>1/1</td>
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<td><strong>Chemotherapy</strong></td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Targeted therapy</strong></td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
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<td><strong>Somatostatin analog</strong></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Local hepatic therapy</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Peptide receptor radionuclide therapy</strong></td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td><strong>Recurrence of symptoms during the disease</strong></td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
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<tr>
<td><strong>Treatments of successful control of hormonal symptoms</strong></td>
<td>①Somatostatin analog</td>
<td>①Somatostatin analog</td>
<td>②Debulking surgery</td>
<td>①Somatostatin analog</td>
</tr>
<tr>
<td><strong>Overall survival, years</strong></td>
<td>9.4</td>
<td>7.8</td>
<td>4.1</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td>Tumor</td>
<td>Infection***</td>
<td>Acute renal failure***</td>
<td>Infection***</td>
</tr>
</tbody>
</table>

Abbreviations: PanNETs, pancreatic neuroendocrine tumors; STZ/5-FU, streptozocin and 5-fluorouracil.

* The 8th edition of the Union for International Cancer Control tumor-node-metastasis classification ** Include double dose or continuous intravenous injection *** Triggered by hormone-excess symptoms (diarrhea)
Table 2  Patient characteristics of each PanNET

<table>
<thead>
<tr>
<th>Variables</th>
<th>NF-PanNET (n = 213)</th>
<th>Gastrinoma (n = 27)</th>
<th>Insulinoma (n = 45)</th>
<th>VIPoma (n = 4)</th>
<th>Other F-PanNETs (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median [range])</td>
<td>57 (21–82)</td>
<td>51 (19–72)</td>
<td>59 (20–86)</td>
<td>63.5 (42–82)</td>
<td>57 (26–70)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>107/106</td>
<td>11/16</td>
<td>16/29</td>
<td>3/1</td>
<td>3/1</td>
</tr>
<tr>
<td>Presence of MEN-1 or VHL, number (%)</td>
<td>24 (10.3)</td>
<td>8 (30.0)</td>
<td>7 (15.6)</td>
<td>0 (0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Tumor size, mm (median [range])</td>
<td>18 (4–130)</td>
<td>25 (4–144)</td>
<td>12 (6–60)</td>
<td>47.5 (13–70)</td>
<td>9.5 (5–45)</td>
</tr>
<tr>
<td>Tumor location, Ph/Pb/Pt/other*</td>
<td>69/56/71/17</td>
<td>8/7/5/7</td>
<td>16/7/18/4</td>
<td>0/0/4/0</td>
<td>2/1/0/1</td>
</tr>
<tr>
<td>Ki-67 index, % (median [range])</td>
<td>2.0 (0–68)</td>
<td>1.5 (0.1–17)</td>
<td>1 (0–15)</td>
<td>12.5 (1–25)</td>
<td>0.55 (0.1–1)</td>
</tr>
<tr>
<td>Stage**, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>109 (51.1)</td>
<td>7 (25.9)</td>
<td>32 (71.1)</td>
<td>0 (0)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>II</td>
<td>34 (16.0)</td>
<td>2 (7.4)</td>
<td>4 (8.9)</td>
<td>1 (25.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>III</td>
<td>20 (9.4)</td>
<td>6 (22.2)</td>
<td>4 (8.9)</td>
<td>0 (0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>IV</td>
<td>50 (23.5)</td>
<td>12 (44.4)</td>
<td>5 (11.1)</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Surgical resection, number (%)</td>
<td>142 (66.7)</td>
<td>19 (70.3)</td>
<td>40 (88.9)</td>
<td>2 (50.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Curative resection</td>
<td>132 (62.0)</td>
<td>12 (44.4)</td>
<td>39 (86.7)</td>
<td>1 (25.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>43 (20.2)</td>
<td>9 (33.3)</td>
<td>1 (2.2)</td>
<td>2 (50.0)</td>
<td>1 (25.0)</td>
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<tr>
<td>Targeted therapy</td>
<td>65 (30.5)</td>
<td>13 (48.1)</td>
<td>3 (6.7)</td>
<td>3 (75.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Somatostatin analog</td>
<td>48 (22.5)</td>
<td>12 (44.4)</td>
<td>3 (6.7)</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Local hepatic therapy</td>
<td>22 (10.3)</td>
<td>10 (37.0)</td>
<td>3 (6.7)</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Recurrence after curative resection, number (%)</td>
<td>39 (29.5)</td>
<td>6 (50.0)</td>
<td>2 (5.1)</td>
<td>1 (100)</td>
<td>1 (33.3)</td>
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<tr>
<td>Tumor death/All death (Tumor death rate, %)</td>
<td>33/42 (78.6)</td>
<td>13/22 (59.1)</td>
<td>1/9 (11.1)</td>
<td>4/4 (100)</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

Abbreviations: PanNET, pancreatic neuroendocrine tumor; NF-, non-functioning; F-, functioning; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail.

* Replaced whole pancreas or multiple lesions ** The 8th edition of the Union for International Cancer Control tumor-node-metastasis classification

Fig. 4  Kaplan–Meier survival curves of this study
(a) Overall survival of F-PanNET and NF-PanNET. (b) Overall survival of NF-PanNET and each F-PanNET. The MST was significantly shorter for patients with VIPoma than for those with NF-PanNET (5.9 vs. 26.7 years, p < 0.0001), insulinoma (21.8 years, p < 0.0001), and gastrinoma (12.3 years, p = 0.0325).

F-PanNET, functioning pancreatic neuroendocrine tumor; NF-PanNET, non-functioning neuroendocrine tumor; MST, median survival time.
could temporarily relieve hormonal symptoms, but the effect diminished or disappeared in all our patients. In addition, relapse of hormonal symptoms is sometimes observed during tumor growth. Because hormonal symptoms are an important cause of death in VIPomas, long-term symptomatic control, which is relatively difficult, is of great significance.

In contrast, relapses of hormonal symptoms are sometimes unrelated to tumor growth on imaging. In fact, in most cases, there was no gross change in tumor size when hormonal symptoms relapsed. Furthermore, we experienced a case of hormonal symptoms prior to imaging findings of recurrence in a patient with curatively resected NF-PanNET (Case 3). Although serum VIP cannot be measured in Japan, it has been reported to be useful for diagnosis, therapy evaluation, detection of recurrence, and prediction of prognosis in VIPomas [14, 15]. Furthermore, it may also be useful for the diagnosis of the localization of the lesion responsible for symptoms with selective venous sampling or selective arterial secretin injection (SACI) test [16, 17].

VIPomas had a larger tumor size, higher Ki-67 labeling index, and more metastasis than other F-PanNETs or NF-PanNETs. Three patients developed VIP during their disease course. In one patient, the initial serum VIP level was high despite the absence of hormone-excess symptoms (in the other two patients, the initial serum VIP level was not available). This study shows the possibility that a certain tumor volume may be required to shift from non-symptomatic to symptomatic VIPomas or to transform from NF-PanNENs to VIPomas [18]. In any case, VIPomas should be considered in patients with relatively large NF-PanNETs, especially those located in the pancreatic tail, when diarrhea is continuously observed.

Although the observation periods were different, patients with VIPomas died more of the tumor than those with other PanNETs did. Furthermore, exacerbation of hormonal symptoms seems to be more related to the cause of death in patients with VIPomas than in those with other F-PanNETs. One possible reason is that effective drug therapies to control the hormone-excess state, such as diazoxide for insulinomas or proton pump inhibitors for gastrinomas, do not exist for VIPomas [19, 20]. The second possible explanation is that many patients with other F-PanNETs mostly achieved control of hormonal symptoms by surgery because the lesion was single or the lesion responsible for symptoms could be localized using the SACI test, even in gastrinomas that had relatively many metastases, such as VIPomas in this study. In our case (Case 4), there was divergence in the immunohistochemical staining of VIP between the primary and metastatic sites (Fig. 2). There is no way to detect the lesion responsible for hormonal symptoms in patients with metastatic VIPomas at this time (the SACI test might also be useful for VIPomas, as mentioned above). If we can identify the lesion responsible for hormonal symptoms in patients with metastatic VIPomas, debulking surgery or local hepatic treatment could be selected more correctly in such cases.

Table 3 shows previous VIPoma series and case reports, which were reported in the last decade (using “VIPoma,” “WDHA syndrome,” and “Verner–Morrison syndrome” as keywords in PubMed [21-25]), in addition to our four cases. Similar to our study, tumor size was relatively large, many of them were located at the pancreatic tail, tumor grade was relatively high, and metastases were often observed at initial diagnosis. Similar to our Case 3, NF-PanNEN was changed to VIPoma at recurrence in one case [21]. In contrast, the prognosis varied because the follow-up time was relatively different (especially in case reports).

Our study has some limitations. First, this was a retrospective, single-center study, and the clinical characteristics were heterogeneous owing to the nature of the disease. Second, patients with F-PanNENs, especially VIPomas, were significantly few; therefore, it was difficult to compare each PanNEN in detail. Despite these limitations, our study, which reflects real-world data, has important clinical value. Nevertheless, a multicenter study with a large sample size would overcome the challenges of this study.

Conclusion

VIPomas should be considered one of the causes of chronic diarrhea and also during the course of NF-PanNENs. Controlling hormonal symptoms of VIPoma is not difficult at the initial diagnosis, but it frequently recurs during the clinical course. As hormonal symptoms are an important cause of death in VIPomas, long-term symptomatic control, which is relatively difficult, is of great significance.

Funding Information

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Disclosure

None of the authors have any potential conflicts of interest associated with this study.
Table 3 Patient characteristics of VIPoma reported in the last decade

<table>
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<tbody>
<tr>
<td>Patients, number</td>
<td>15</td>
<td>22</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Age (median [range])</td>
<td>69 (58–76)</td>
<td>51.5 (47.3–66.8)</td>
<td>59 (47–72)</td>
<td>63.5 (42–82)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/8</td>
<td>11/11</td>
<td>2/3</td>
<td>3/1</td>
</tr>
<tr>
<td>Presence of MEN-1, number (%)</td>
<td>Not available</td>
<td>3 (13.6)</td>
<td>1 (20.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serum VIP level, pg/mL (mean ± SD)</td>
<td>212 ± 190</td>
<td>654</td>
<td>512.3 ± 184.2</td>
<td>676.7 ± 796.7</td>
</tr>
<tr>
<td>Tumor size, mm (median [range])</td>
<td>44 (25–65)</td>
<td>57.5 (36.3–77.5)</td>
<td>32 (25–65)</td>
<td>47.5 (13–70)</td>
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<tr>
<td>Tumor location, Ph/Pb/Pt</td>
<td>3/3/8</td>
<td>4/1/13</td>
<td>1/0/4</td>
<td>0/0/4</td>
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<tr>
<td>Ki-67 index, % (median [range])</td>
<td>Not available</td>
<td>6 (5–9.3)</td>
<td>5.0 (3.0–10.4)</td>
<td>12.5 (1–25)</td>
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<td>Grade, number, number (%)</td>
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</tr>
<tr>
<td>1</td>
<td>4 (26.7)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>1 (25.0)</td>
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<tr>
<td>2</td>
<td>10 (66.7)</td>
<td>15 (68.2)</td>
<td>4 (80.0)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (6.7)</td>
<td>2 (9.1)</td>
<td>0</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Metastasis at initial diagnosis, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>9 (60.0)</td>
<td>17 (77.3)</td>
<td>3 (60.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1 (20.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Treatment method, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical resection</td>
<td>12 (80.0)</td>
<td>Not available</td>
<td>4 (80.0)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>Curative resection</td>
<td>6 (40.0)</td>
<td>12 (54.5)</td>
<td>3 (60.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5 (33.3)</td>
<td>13 (59.1)</td>
<td>0 (0)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>6 (40.0)</td>
<td>15 (68.2)</td>
<td>1 (20.0)</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Somatostatin analog</td>
<td>13 (86.7)</td>
<td>11 (50.0)</td>
<td>2 (40.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Local hepatic therapy</td>
<td>4 (26.7)</td>
<td>11 (50.0)</td>
<td>2 (40.0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Peptide receptor radionuclide therapy</td>
<td>6 (40.0)</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Recurrence after curative resection, number (%)</td>
<td>4 (66.7)</td>
<td>4 (80.0)**</td>
<td>1 (33.3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Mortality number (rate, %)</td>
<td>3 (20)</td>
<td>8 (36.4)</td>
<td>0 (0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Median survival time, years</td>
<td>Not reached</td>
<td>Not reached</td>
<td>Not reached</td>
<td>5.9</td>
</tr>
<tr>
<td>5-year surviving rate, %</td>
<td>93.3</td>
<td>63.6</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: MEN-1, multiple endocrine neoplasia; type1; SD, standard deviation; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail.

* Summarized five case reports reported from Japan in the last decade [21–25] ** Parameter was 5; only nonmetastatic patients

References

6. Verner JV, Morrison AB (1958) Islet cell tumor and a syn-