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Peptide Receptor Radionuclide Therapy Is Effective for Clinical Control of Symptomatic Metastatic Insulinoma: A Long-Term Retrospective Analysis

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Metastatic insulinoma is a rare malignant neuroendocrine tumor characterized by inappropriate insulin secretion, resulting in life-threatening hypoglycemia, which is often difficult to treat. There is currently very limited information about the efficacy of peptide receptor radionuclide therapy (PRRT) for clinical control of hypoglycemia. The aim of this long-term retrospective study was to evaluate the therapeutic efficacy of PRRT for improving hypoglycemia, to evaluate the change of medication after PRRT, and to calculate progression-free survival (PFS) and overall survival (OS). **Methods:** Inclusion criteria were histologically proven somatostatin receptor–positive metastatic malignant insulinoma and at least 2 cycles of [^{90}Y]Y-DOTATOC or [^{177}Lu]Lu-DOTATOC therapy from early 2000 to early 2022. A semiquantitative scoring system was used to quantify the severity and frequency of hypoglycemic episodes under background antihypoglycemic therapy (somatostatin analog, diazoxide, everolimus, corticosteroids): score 0, no hypoglycemic episodes; score 1, hypoglycemic events requiring additional conservative treatment with optimization of nutrition; score 2, severe hypoglycemia necessitating hospitalization and combined medication or history of hypoglycemic coma. Hypoglycemic score before and after PRRT was analyzed. Time of benefit was defined as a time range of fewer hypoglycemic episodes in the observation period than at baseline. Information on antihypoglycemic medication before and after therapy, PFS, and OS was recorded. **Results:** Twenty-six of 32 patients with a total of 106 [^{90}Y]Y-DOTATOC/[^{177}Lu]Lu-DOTATOC cycles were included. The average observation period was 21.5 mo (range, 2.3–107.4 mo). Before therapy, 81% (n = 21) of the patients had a hypoglycemia score of 2 and 19% (n = 5) had a score of 1. After PRRT, 81% of patients (n = 21) had a decreased score, and the remaining 5 patients showed a stable situation. There was temporary worsening of hypoglycemia just after injection of [^{90}Y]Y-DOTATOC/[^{177}Lu]Lu-DOTATOC in 19% of patients. The average time of benefit in the observation period was 17.2 mo (range, 0–70.2 mo). Antihypoglycemic medication reduction was achieved in 58% (n = 15) of patients. The median OS and PFS after the start of PRRT were 19.7 mo (95% CI, 6.5–32.9 mo) and 11.7 mo (95% CI, 4.9–18.5 mo), respectively. **Conclusion:** To our knowledge, our study included the largest cohort of patients with malignant insulinoma to be evaluated. Long-lasting symptom control and reduction of antihypoglycemic medications were shown in most patients after late-line PRRT.

Key Words: malignant insulinoma; PRRT; [^{177}Lu]Lu-DOTATOC; [^{90}Y]Y-DOTATOC

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Insulinoma is a rare insulin-secreting pancreatic neuroendocrine tumor (NET) clinically characterized by the Whipple triad including documented hypoglycemia, neuroglycopenic symptoms, and prompt relief of symptoms after the administration of carbohydrates (*1*). The severity of symptoms can range from mild to life-threatening hypoglycemic events, leading to coma and death. Most insulinomas are benign, but approximately 6% of insulinomas develop metastases and are therefore considered malignant. The estimated incidence of metastatic insulinoma is about 0.3 cases per 1 million person-years (*2*). Because the primary tumor and metastases secrete insulin in an unregulated manner (autonomy), the clinical symptoms worsen over time in parallel with the progression of metastatic disease. Because of the rarity of the disease, the treatment strategies for malignant metastatic disease are ill defined; the 2 pivotal aims are symptom and antiproliferative tumor control (*3*). The general treatment approaches include surgery, medicaments (everolimus, somatostatin analogs, sunitinib, diazoxide, corticosteroids), and chemotherapy (e.g., streptozocin and 5-fluorouracil), as well as other approaches such as transcatheter arterial (chemo) embolization, radiofrequency ablation, and peptide receptor radionuclide therapy (PRRT) (*3,4*). There is currently very limited information on PRRT efficacy in metastatic malignant insulinoma. Importantly, benign insulinomas express a high quantity of glucagonlike peptide-1 receptors but show a lower expression of somatostatin receptor subtype 2. For the malignant counterpart, there is a significant switch, with reduced glucagonlike peptide-1 receptor expression and increased somatostatin receptor subtype 2 expression (*5*). Hence, metastatic insulinoma can be treated with PRRT, and previous case studies demonstrated promising results in symptom control with PRRT (*5–7*).

Our hospital is specialized in the diagnosis and treatment of secreting and nonsecreting NETs and started PRRT in the late

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TABLE 1
Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Histologically proven malignant insulinoma and inadequately increased insulin/C-peptide levels	Eastern Cooperative Oncology Group performance status > 3
Somatostatin receptor positivity in somatostatin receptor imaging prior therapy (Krenning score 3 or 4)	Pregnancy and breast feeding
Proven metastatic disease by imaging or biopsy	No observation period
Blood count	No available clinical data in observation period
Leukocytes ≥ 1,500/μL	
Hemoglobin ≥ 8 g/dL	
Platelets ≥ 70,000/μL	
Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2	
Received at least 2 treatment cycles of [^{90}Y]Y-DOTATOC or [^{177}Lu]Lu-DOTATOC therapy	
Episodes of hypoglycemia in anamnesis	

1990s (*8*), resulting in treating a large patient collective with rare NETs. The goal of our study was to identify and evaluate all patients since 2000 who had malignant insulinoma treated with PRRT and to determine whether [^{90}Y]Y-DOTATOC or [^{177}Lu]Lu-DOTATOC therapy improved symptoms and hypoglycemia control.

MATERIALS AND METHODS

This retrospective single-center study was approved by the regional ethics committee (Ethikkommission Nordwest und Zentralschweiz). The requirement for written informed consent was waived by the institutional board because of the rarity of the disease, inclusion of international patients, the retrospective nature of the analysis, and anonymization of the data. All patients with histologically proven metastatic malignant insulinoma who received [^{90}Y]Y-DOTATOC or [^{177}Lu]Lu-DOTATOC therapy at University Hospital Basel from January 1, 2000, to March 21, 2022, were included. Inclusion and exclusion criteria are demonstrated in Table 1. To analyze the effect on hypoglycemia, we defined the observation period as the time range from the first to the last PRRT cycle. The clinical data of patients (sex, age), tumor characteristics (clinical stage, site of metastases, proliferation rate, previous treatment), and therapy data (number of PRRT cycles, radiotracer type received, activity per therapy cycle), as well as laboratory parameters (hemoglobin, white blood cells, platelet count, lymphocyte count, liver parameters [alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, albumin, blood bilirubin] and kidney parameters [creatinine, estimated glomerular filtration rate, glucose, potassium levels]), were collected during the observation period by reviewing the paper-based patient record and the electronic patient file. The adverse events were classified according to the Common Terminology Criteria for Adverse Events version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

Manufacture of [^{90}Y]Y-DOTATOC and [^{177}Lu]Lu-DOTATOC and Posttherapeutic Imaging

[^{111}In]In-/[^{90}Y]Y-DOTATOC (referred to here as [^{90}Y]Y-DOTATOC) and [^{177}Lu]Lu-DOTATOC were synthesized as previously described (*9*). [^{90}Y]Y-DOTATOC was coinjected with approximately 111 MBq of [^{111}In]In-DOTATOC to increase the quality of posttherapeutic images. Posttherapeutic imaging was done 1 d later and included 1 whole-body scintigram and 1 coregistered SPECT/CT scan of the abdomen.

Treatment Efficiency

A semiquantitative scoring system was used to quantify the severity and frequency of hypoglycemic episodes under background antihypoglycemic therapy (somatostatin analogs, diazoxide, everolimus, or corticosteroids): score 0, no hypoglycemic episodes; score 1, some hypoglycemic events requiring additional conservative treatment with only optimization of nutritional intake; score 2, severe hypoglycemia requiring hospitalization and combined medication or history of hypoglycemic coma. The hypoglycemic scores before and after PRRT were compared. The duration of response (time of benefit) was defined as the time range of improvement in hypoglycemia score during the whole observation period from the first to the last PRRT cycle. The best response was defined as the lowest hypoglycemic score since the start of PRRT. We collected information on the hypoglycemic medications regularly taken before, during, and after therapy and determined whether—since the beginning of PRRT—additional medical therapy had been administered or medical therapy had been reduced.

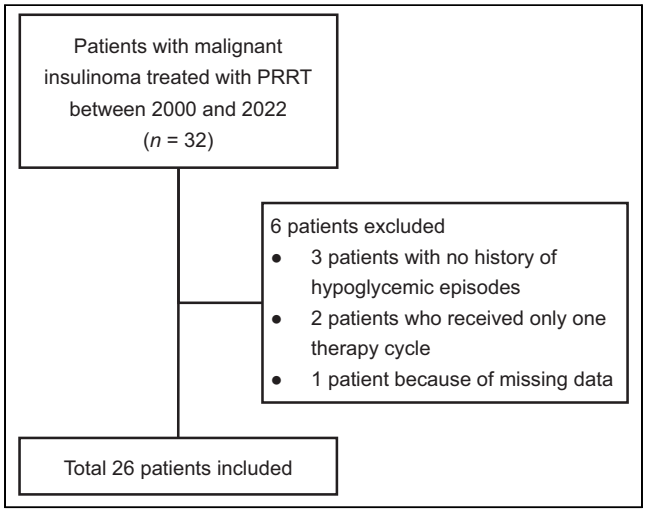

FIGURE 1. Flowchart of patient selection.

TABLE 2
Demographic Data of Study Population ($n = 26$)

Parameter	Data
Sex	
Female	12
Male	14
Mean age (±SD) at first treatment (y)	59.54 ± 14.64 (range, 25–78)
Site of metastasis	
Liver	100% ($n = 26$)
Bone	42% ($n = 11$)
Lymph node	35% ($n = 9$)
Lung	8% ($n = 2$)
Peritoneum	8% ($n = 2$)
Adrenal gland	4% ($n = 1$)
Previously received therapy	
Treatment-naïve	15% ($n = 4$)
Treated	85% ($n = 22$) (several therapeutic modalities per patient)
Surgery	15
Somatostatin analogs	7
Everolimus	7
TACE	7
Chemotherapy	4
Sunitinib	4
Diazoxide	4
Steroids	2
Glucagon	1
Other	3
Tumor grading (1–3) with Ki-67 values (maximal value)	
Grade 1, ≤ 2%	1
Grade 2, 3%–20%	10
Grade 3, >20%	5
Unknown	10

TACE = transarterial chemoembolization.

Progression-Free Survival (PFS) and Overall Survival (OS)

Information on patient survival and received therapy after the last PRRT was collected by reviewing paper-based and electronic patient records or by contacting the referring physician. PFS was defined as the time interval between the first PRRT cycle and either the start of disease progression (determined by imaging or worsening of hypoglycemia requiring another round of PRRT) or death. OS was defined as the time interval between the first PRRT cycle and death. The absolute

TABLE 3
PRRT Information of All 26 Included Patients

Parameter	Data
Mean ± SD number of therapy cycles delivered per patient	4.1 ± 2.2 (range, 2–10)
Received radiotracer	
Only [^{90}Y]Y-DOTATOC	7 patients
Only [^{177}Lu]Lu-DOTATOC	6 patients
Both	13 patients
Mean ± SD administered activity per therapy cycle (GBq)	[^{177}Lu]Lu 6.4 ± 1.1 (range, 3.7–7.4)
	[^{90}Y]Y 6.7 ± 0.7 (range, 4.8–8.1)

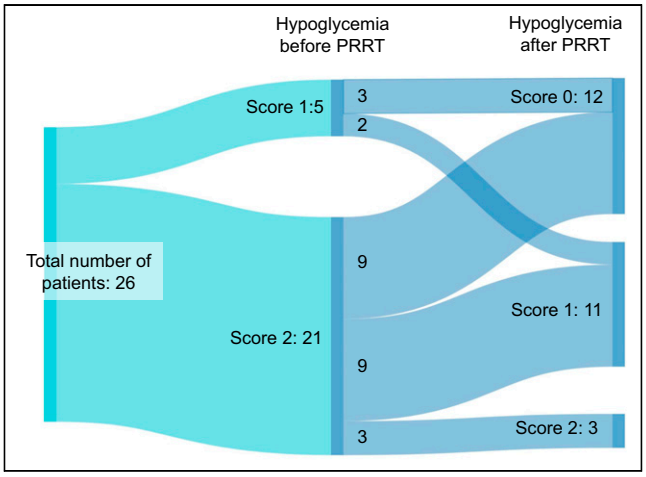

FIGURE 2. Sankey diagram of baseline hypoglycemic scores vs. best response.

survival rate was calculated as the percentage of patients who survived 5 y after the start of PRRT. The cutoff date of data collection was July 6, 2022.

Statistics

Data were collected in tabular form, and the IBM SPSS Statistics program (version 28.0) was used for statistical analysis. A Kaplan–Meier curve was used to demonstrate OS and PFS. In the survival analysis, censored patients were those who were alive (in the OS calculation) and those who did not experience disease progression (in the PFS calculation). A Sankey diagram for showing hypoglycemic episodes before and after therapy was created on the SankeyMATIC website (www.sankeymatic.com).

RESULTS

Study Population

There were 32 patients with malignant insulinoma treated with somatostatin receptor PRRT; 6 patients were excluded from the analysis (Fig. 1). Twenty-six patients with a total of 106 therapy cycles were finally included. All patients had stage IV disease with liver metastases. Of the patients, 85% were pretreated and 15% were treatment-naïve (Table 2; Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). The patients received an average of 4.1 ± 2.2 therapy cycles (range, 2–10 cycles per patient). Seven patients received 2 therapy cycles, 4 patients received 3 cycles, 8 patients received 4 cycles, 3 patients received 5 cycles, 1 patient received 6 cycles, 1 patient received 7 cycles, and 2 patients received 10 cycles. The mean administered radioactivity per cycle was 6.4 ± 0.9 GBq (range, 3.7–8.1 GBq) (Table 3; Supplemental Table 2).

Treatment Efficiency

Before the first cycle of therapy, 21 of 26 patients had a hypoglycemia score of 2 and 5 patients had a score of 1. In the long term, a total of 21 of 26 patients (81%) demonstrated improvement during the observation period (Fig. 2). The remaining 5 patients (3 patients with a score of 2 and 2 patients with a score of 1) were stable. Of the 26 patients, 5 (19%) experienced transient hypoglycemia after injection of [^{90}Y]Y-DOTATOC/[^{177}Lu]Lu-DOTATOC. In the long term, there were no cases of worsening symptoms compared with baseline during the observation period. A case presentation of 1 patient is shown in Figure 3.

After the first cycle of therapy, 17 patients showed an improved hypoglycemic score; 9 patients showed no improvement. Of these 9 patients who showed no improvement, 4 showed improvement after the second therapy cycle; 2 were stable since the start of PRRT, without improvement, and the remaining 3 received only 2 therapy cycles in total, with no follow-up available after the last PRRT.

The average observation period was 21.5 mo (range, 2.3–107.4 mo). The average time of benefit (improvement of hypoglycemia) was 17.2 mo (range, 0–70.2 mo), with no differences between tumor grade 1, 2, or 3: 12 of 26 patients had an improvement of hypoglycemic score during the whole (100%) observation period, 2 patients in 96%–97% of the observation period, 1 patient in 87% of the observation period, 3 patients in 62%–73% of the observation period, and 3 patients in 25%–42% of the observation period; 5 patients had no improvement (Fig. 4). In these 21 patients who showed improvement, the best response was observed at a median of 2.3 mo (interquartile range, 9.4 mo) after the start of PRRT.

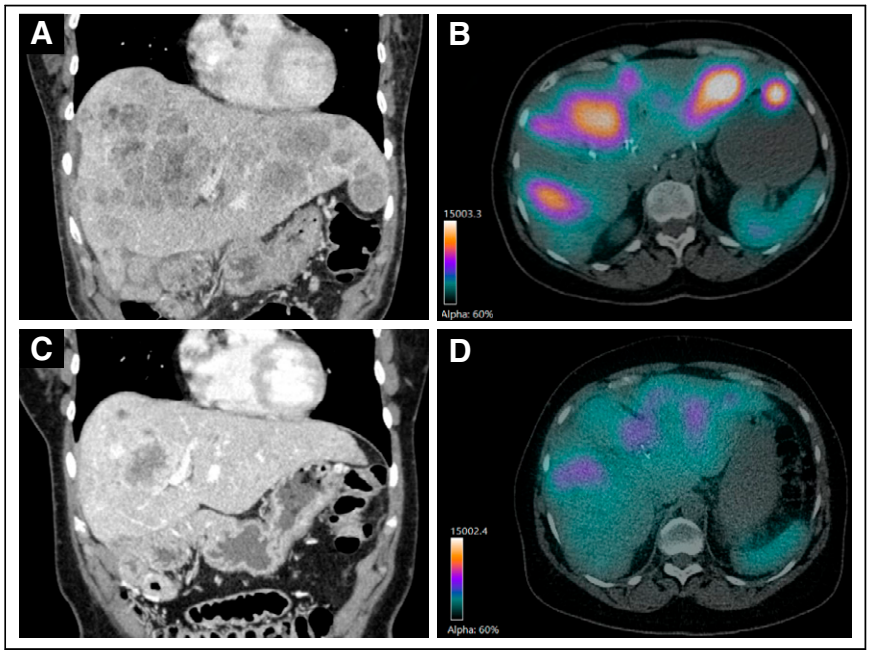

FIGURE 3. 62-y-old female patient who received 3 [^{90}Y]Y-DOTATOC and 1 [^{177}Lu]Lu-DOTATOC therapy cycles (total activity, 26.7 GBq) and benefited more than 15 of 18 mo of observation. Baseline CT scan (A) and intratherapeutic [^{90}Y]Y-DOTATOC SPECT/CT of second therapy cycle show multiple liver metastases (B). CT scan after second therapy cycle shows partial tumor response with significantly reduced tumor burden according to RECIST 1.1 (C). Intratherapeutic [^{90}Y]Y-DOTATOC SPECT/CT of fourth therapy cycle (D) shows reduced [^{90}Y]Y-DOTATOC uptake in liver metastases compared with [^{90}Y]Y-DOTATOC SPECT/CT of second therapy cycle (B), which also indicates treatment response.

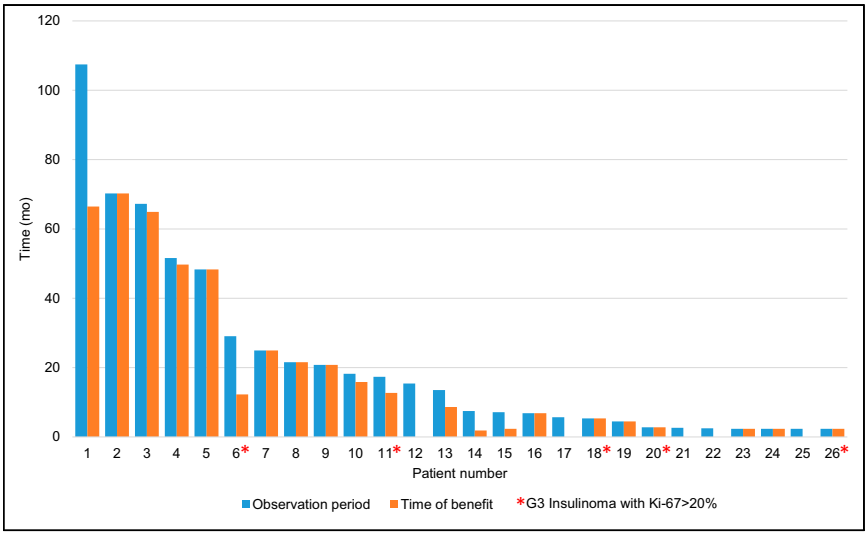

FIGURE 4. Observation period vs. time of benefit.

In total, 88% of patients (23/26) were using other medication to treat hypoglycemia during the observation period. In 58% of patients (15/26), a reduction of antihypoglycemic medication was achieved after PRRT during the observation period (Table 4). After the last PRRT cycle, 7 patients received no other therapy, 1 patient discontinued the previously received therapy, 13 patients received additional therapy, and 5 patients had no data available (Table 5).

OS and PFS

At the end of data collection, 20 patients had died, 4 patients were alive, and 2 patients had no information available. The median OS was 19.7 mo (95% CI, 6.5–32.9 mo) (Fig. 5). The survival rate since

TABLE 4
Detailed Information About Additional Hypoglycemic Medication Parallel to PRRT and Medication Reduction After PRRT

Parameter	Number of patients
Other medication to treat hypoglycemia (several therapeutic modalities per patient)	23
SSA	14
Diazoxide	12
Glucose	11
Everolimus	9
Steroids	8
Sunitinib	3
Cornstarch	2
Glucagon	1
Sirolimus	1
Reduction of antihypoglycemic medication after PRRT	15
Dose reduction of medication (diazoxide and steroids for ~2 mo)	1
Discontinuation of medication (several therapeutic modalities per patient)	11
Diazoxide	7
Glucose infusion	5
Everolimus	2
SSA	2
Steroids	1
Sunitinib	1
Cornstarch	1
Dose reduction + discontinuation of medication	3
Dose reduction of steroids and discontinuation of everolimus	1
Dose reduction of everolimus and discontinuation of diazoxide and glucagon	1
Dose reduction of steroids and discontinuation of diazoxide	1

SSA = somatostatin analog.

TABLE 5
Therapy Information After Last PRRT

Parameter	Data
No other therapy	7
Discontinuation of previously received therapy (steroids)	1
Additional therapy (several therapeutic modalities per patient)	13
Everolimus	4
Glucose	2
SSA	2
Radiotherapy of metastatic lesion	2
Chemotherapy	2
Surgery	2
SIRT	2
Denosumab (monoclonal antibodies)	1
Cytostatic	1
Glucagon	1
Steroids	1
Sunitinib	1
No data available	5

SSA = somatostatin analog; SIRT = selective internal radiation therapy.

the start of therapy was 71% (n = 17/24) at 1 y, 42% (n = 10) at 2 y, 33% (n = 8) at 3 y, 29% (n = 7) at 4 y, and 29% (n = 7) at 5 y.

When the data collection ended, 25 patients had already experienced the first progression after the start of PRRT; 1 patient experienced no disease progression. The median PFS was 11.7 mo (95% CI, 4.9–18.5 mo) (Fig. 6).

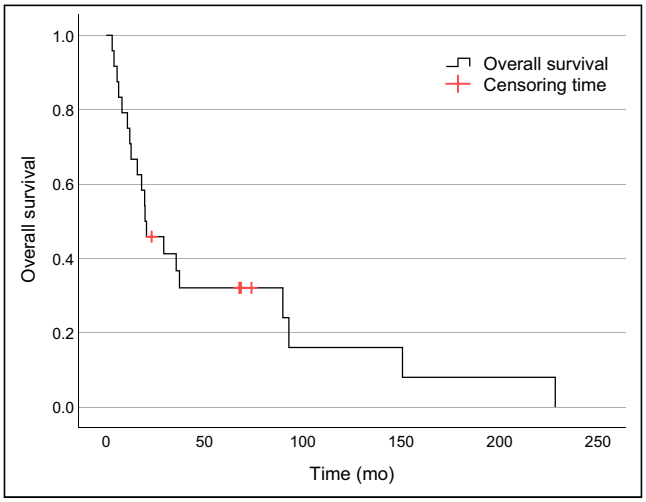

FIGURE 5. Kaplan–Meier survival analysis was performed for 24 patients with median OS of 19.7 mo (95% CI, 6.5–32.9 mo). Two patients were not included because of missing data, with 4 censored events (these patients are still alive).

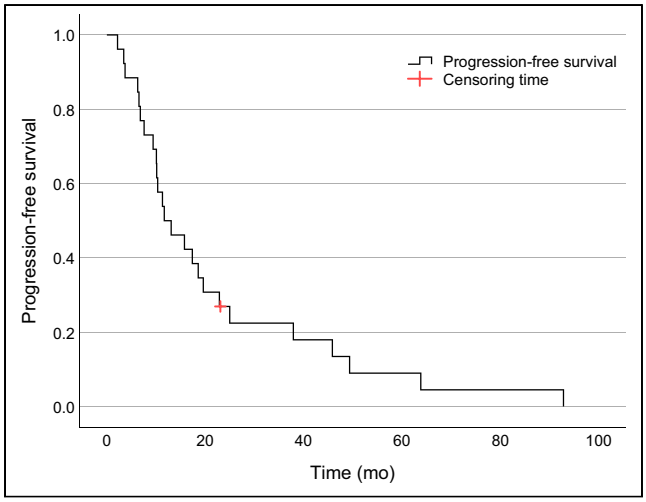

FIGURE 6. Kaplan–Meier survival analysis was performed for 26 patients with median PFS of 11.7 mo (95% CI, 4.9–18.5 mo), with 1 censored event due to patient who experienced no progression.

Side Effects

After at least 1 cycle of PRRT in patients without preexisting hematologic conditions, new grade 3 hematologic toxicity occurred in up to 15% of cases (12% anemia, 8% leukocytopenia, 15% lymphocytopenia, 0% thrombocytopenia), and new grade 4 hematotoxicity was observed in 4% of patients (1 patient with grade 4 lymphocytopenia, which improved to grade 3 at the time of the next PRRT) (Supplemental Table 3). Four patients with preexisting lymphocytopenia (grade 1 or 2) developed grade 3 lymphocytopenia after PRRT, and 1 patient progressed to grade 4. There was no new-onset grade 3 or 4 nephrotoxicity, although 1 patient with grade 1 renal disease at baseline progressed to grade 3 after 1 cycle of [^{90}Y]Y-DOTATOC and 2 cycles of [^{177}Lu]Lu-DOTATOC. Grade 3 hepatotoxicity developed in 19% of patients. No patients progressed to grade 4. Other symptoms reported included fatigue (3 patients), nausea (3 patients), fever (2 patients), and hair loss, insomnia, vomiting, dyspnea, and ankle edema (1 patient). One patient was diagnosed with acute myeloid leukemia 1 y after the last (fourth) PRRT cycle. During the hospital stay for PRRT, 19% of patients (5/26) experienced a temporary worsening of blood glucose, which was consistent with tumor lysis. Four patients with grade 1 or 2 hypoglycemia showed improvement within 1 day, 2 weeks, 1 month, and 1.5 months, respectively. One patient had grade 4 hypoglycemia (blood glucose level of 0.8 mmol/L); the episode was treated with 10% glucose infusion; corticosteroid therapy was started, and glucose levels returned to normal the next day. At the same time, there were no relevant changes in the potassium blood level (Supplemental Table 3).

DISCUSSION

To the best of our knowledge, this is the largest study to date of patients with metastatic malignant insulinoma treated with somatostatin-targeted PRRT. PRRT was effective in controlling hypoglycemia in 81% of the study population and enabled 58% of patients to reduce the use of other drugs to control hypoglycemic episodes, resulting in reduced potential drug side effects. OS and PFS were 19.7 and 11.7 mo, respectively.

The finding of controlled hypoglycemia in 81% of the patients after PRRT is similar to the finding of the second largest study,

which included 14 patients with malignant insulinoma treated with PRRT and achieved hypoglycemic control in 93% of patients (*6*). However, the duration of the therapeutic effect of this study was not documented. Zandee et al. reported the efficacy of PRRT on functioning pancreatic NETs in 34 patients, including 14 insulinoma patients (*10*). Six of 9 (67%) insulinoma patients with uncontrolled symptoms at baseline showed a reduction of hypoglycemic events. The median PFS was 18.1 mo, with no subgroup differences (14 insulinomas, 7 gastrinomas, 5 vasoactive intestinal peptide tumors, and 8 glucagonomas among the 34 patients). This PFS is slightly longer than our finding and may be explained by differences in study populations (slightly different metastatic spread) and pretreatment (24% of treatment-naïve patients in Zandee et al., in contrast to 15% in the current study). Other authors presented case reports or case series suggesting the efficacy of PRRT to control hypoglycemic episodes (*11–13*).

When the effectiveness of other commonly used drugs to control hypoglycemia is compared, the results of PRRT are promising. The effectiveness of somatostatin analogs and diazoxide to treat hypoglycemia is estimated to be approximately 50% and 50%–60%, respectively (*14,15*). Everolimus is also used to control hypoglycemia, although data on its efficacy are scarce. A retrospective study including 12 patients with metastatic insulinoma treated with everolimus achieved hypoglycemic control in 92% of patients, and the median time to first progression was 6.5 mo (*16*). Some case reports and case series also indicated a decrease in hypoglycemic events with everolimus (*17–19*). There are few data suggesting the effectiveness of sunitinib in controlling excess hormone levels in functional NETs (*20,21*).

The current study showed lower OS and PFS (19.7 and 11.7 mo, respectively) than in patients with ileal or gastroenteropancreatic NETs treated with PRRT (*22–24*) and similar PFS but lower OS than for targeted therapy (sunitinib and everolimus) in pancreatic NETs (*25–28*). The underlying mechanisms for a worse prognosis are ill defined but may be related to the insulin secretion with the associated additional medical therapy, the specific biology of the malignant insulinoma itself, or a Ki-67 value of greater than 20% in about 20% of patients. According to the European Society for Medical Oncology and European Neuroendocrine Tumor Society guidelines, PRRT is the last-line therapy for metastatic pancreatic NETs (*20,29*). The current findings demonstrate that PRRT is indicated at an earlier time point (e.g., first- or second-line therapy) in the management of somatostatin receptor subtype 2–positive metastatic insulin-secreting grade 1–3 pancreatic NETs.

The documented side effects, including hematologic, renal, and liver toxicity, in the current study are consistent with data from other studies using PRRT (*30–32*). Hormonal crisis as a consequence of PRRT has been reported to be in the range of 1%–9% (*10,33*). In the case of insulinoma, the result may be severe hypoglycemia and hypokalemia due to the insulin-mediated shift of extracellular potassium into the cells. In the present study, there was only 1 patient (4%) who developed severe grade IV hypoglycemia during the hospital stay for PRRT, and no significant hypokalemia could be documented during PRRT. In our setting, the therapy was usually well tolerated, whereas hypoglycemia remains the most worrisome complication, for which regular glucose measurements during and after the in-hospital treatment are warranted.

This study has some limitations. Because of the rarity of the disease, this is a retrospective study with a limited number of patients. Some came from abroad, which led to limitations in the available clinical, imaging, and laboratory data. To mitigate this bias, we measured the symptom and hypoglycemic control only between those therapy cycles for which the patient was followed on a regular basis. Because 50% of patients received additional therapy cycles after initial progression, the time of benefit may be a better factor than PFS in demonstrating efficacy of therapy. Furthermore, because we could not document hypoglycemic events after the last therapy, the time of benefit is likely to be underestimated, as the benefit may have lasted beyond the last therapy. Since there was no uniform scheme to assess tumor burden after therapy, these findings cannot be reported in a reliable way. As a proxy, we used inter- and posttherapeutic SPECT/CT to determine tracer uptake. With this examination, significant progress can be excluded. Finally, there is a potential bias in PRRT's effectiveness in controlling hypoglycemia, as 88% of patients concomitantly received other drugs to control hypoglycemia. In addition, a potential interaction and counteraction between PRRT and other drugs cannot be fully excluded. However, the reduction in the number of drugs administered to control hypoglycemia with the improvement in hypoglycemic episodes serves as robust evidence of treatment efficacy in this retrospective setting for an orphan disease.

CONCLUSION

To our knowledge, our study included the largest cohort of patients with malignant insulinoma treated with PRRT as a late-line therapy. Long-lasting symptom control and reduction of antihypoglycemic medication was shown in more than 80% and approximately 60% of patients, respectively. OS and PFS were lower than in other NET studies administering PRRT, a finding that is possibly related to the associated hypoglycemia, the particular biology of the tumor, or the high Ki-67 value of more than 20% in about 20% of patients.

DISCLOSURE

This work was supported by a grant from the Swiss National Foundation (no. 320030-175544). No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Does PRRT improve hypoglycemia and reduce antihypoglycemic medication in patients with hypoglycemic episodes due to an advanced metastatic insulinoma?

PERTINENT FINDINGS: This retrospective cohort study with symptomatic patients demonstrated long-lasting symptom control and reduction of antihypoglycemic medications in most patients after PRRT.

IMPLICATIONS FOR PATIENT CARE: This study demonstrated that PRRT is indicated at an earlier time point (e.g., first- or second-line therapy) for the treatment of patients with symptomatic somatostatin receptor subtype 2–positive metastatic insulin-secreting grade 1–3 pancreatic NETs.

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