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Original Article

Metastatic insulinoma—outcomes in the current era

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Abstract

Background: Multimodal interventions in neuroendocrine tumors appear to have a beneficial impact on survival. Metastatic insulinoma is associated with hypoglycemia and, historically, a shortened life expectancy.

Methods: The authors retrospectively analyzed the clinical outcomes of patients with metastatic insulinomas treated at a tertiary care center between 2006 and 2023.

Results: Clinical data on 14 patients with metastatic insulinoma (metastases to the liver, skeleton, and lung) were reviewed in this descriptive study. The patients underwent various treatments including surgery; liver directed therapies (embolization, selective internal radiotherapy), somatostatin analogs; targeted agents (everolimus); systemic chemotherapy (capecitabine/temozolomide; carboplatin/etoposide); external beam radiation; and peptide receptor radiotherapy. Seven subjects died during follow-up. The time of the 7 deaths ranged from 2.5 to 10.4 years (median time to death was 8.2 years). This compares to previous reports of median survival of about 2 years. Seven subjects are alive 1.2-12.3 years after diagnosis. Hypoglycemia was well-controlled and did not cause the deaths.

Conclusions: Multimodal interventions in metastatic insulinoma can be effective in managing hypoglycemia. The patients on multimodal treatments also lived a long time when considering previous published reports of median survival of just 2 years. Our findings challenge previous assumptions regarding clinical outcomes in this patient population.

Key words: insulinoma; metastatic.

Implications for practice

Historically, patients with metastatic insulinoma had median survival in the range of 2 years and hypoglycemia was often difficult to manage. We report that with multimodal intervention, the survival of these patients is much improved and hypoglycemia can be controlled.

Introduction

The incidence of gastroenteropancreatic neuroendocrine tumors appears to be increasing.[1] An analysis of the Surveillance, Epidemiology and End Results (SEER) database from 1975 to 2012 noted that in individuals aged 40-75 years, the absolute rise in pancreatic neuroendocrine tumors was 0.33 cases per 100 000.[2]A nationwide survey performed in Japan reported that the incidence of pancreatic neuroendocrine tumors is about 12.7 per million population. Of these, 32% (4.1 per million population) were functional tumors. The commonest of these functional tumors were insulinomas—about 1/5 of all the functional tumors (0.8 per million population).[3]

The vast majority of insulinomas are benign single tumors localized in the pancreas (~90%). The remainder are malignant tumors. The malignant tumors can be categorized into those with locoregional extension outside the pancreas; or metastatic lesions elsewhere in the body, principally the liver.[4,5] Surgical resection of the benign single tumors in the pancreas results in a cure with a very low risk for recurrence. Among the malignant insulinomas, those with locoregional extension, the disease is slowly progressive, and long-term survival is the norm.[4,6] It is the metastatic insulinomas, with tumor metastases predominantly to the liver and bone, where the life expectancy is shortened with previously reported median survival of approximately 2 years.[7-9]

There are now multiple modalities to treat malignant pancreatic neuroendocrine tumors.[5,8,10-12] The optimal sequence of therapies remains unknown, and treatment strategies typically are individualized based on patient co-morbidities and preferences, as well as variables such as functional status, tumor location, extent, and rate of growth. When feasible, surgical resection of primary tumors as well as metastases is considered. Other cytoreductive therapies include liver-directed treatment with transarterial embolization (TAE); transarterial chemoembolization (TACE) and radiofrequency ablation with Yttrium-90 microspheres as well as systemic interventions like peptide receptor radiotherapy (PRRT) with 177-Lutetium labeled somatostatin analogs; and chemotherapy, for example, capecitabine plus temozolomide or carboplatin and etoposide.[10,13-15] Additionally, cytostatic agents that are commonly employed include the mTOr inhibitor everolimus or the tyrosine kinase inhibitor, sunitinib.[16]

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mTOr—mammalian target of rapamycin is a serine-threonine protein kinase that functions downstream of phosphatidylinositol 3-kinase and Akt and is abnormally activated in a number of cancers. Sunitinib acts on a number of molecular pathways involved in angiogenesis. The somatostatin analogs (octreotide, lanreotide, and pasireotide) inhibit proliferation through both cytostatic and cytotoxic pathways. Many of these treatments not only control tumor growth but also limit insulin secretion and prevent hypoglycemia.

With the availability of multiple interventions, we retrospectively reviewed cases of metastatic insulinomas treated at our institution to assess the impact of treatment on survival and prevention of hypoglycemia. We hypothesized that survival would be prolonged compared to previously published reports and that hypoglycemia was manageable.

Methods

All cases of malignant insulinoma managed at our tertiary care institution between 2006 and 2023 were reviewed. The cases were identified by (1) querying our institutional neuroendocrine tumor (NET) database; (2) searching the electronic medical record (ICD codes); and (3) screening patients scheduled for follow-up at the UCSF Center for Neuroendocrine Tumors or Endocrinology Clinic. Individual patient charts were then reviewed to see if they met the case definition of insulinoma with metastases to the liver or other sites. They were reviewed with respect to treatment, management of hypoglycemia, the results of germline testing (if performed in the context of clinical care), and survival.

This analysis is descriptive. Clinical, treatment, and outcomes data are reported in detail and using summary statistics. Survival from the initial diagnosis of a neuroendocrine tumor is estimated using Kaplan-Meier technique. Ethical conduct of research: IRB approval for the retrospective case analysis was obtained from the UCSF Committee for Human Research (UCSF Neuroendocrine Tumor Outcomes Database IRB # 10-00854).

Results

We identified 16 patients who carried a diagnosis of malignant insulin-producing pancreatic neuroendocrine tumor (malignant insulinoma) between 2006 and 2023. We reviewed all the medical records until the end of July 2023. We excluded 2 patients from the analysis. One of these patients was diagnosed with nonfunctional metastatic neuroendocrine tumor. He survived for 7 years and symptomatic hypoglycemia was only present for 3 weeks prior to his death. The other patient is alive 12 years after diagnosis of insulin-producing pancreatic neuroendocrine tumor and had 2 identified loci of disease in the pancreas—a lesion in the tail which was resected and a lesion near the pancreatic head that was not resected because it encases the common bile duct, superior mesenteric vein, and common hepatic artery. This patient does not have metastatic disease in the liver or elsewhere, that is, only has unresectable locoregional disease. The data analyses in this report are therefore limited to 14 patients—7 men and 7 women—with distant metastatic disease (Table 1). The mean age at diagnosis of insulinoma was 55.9 ± 15.1 years (SD; range 20-73 years).

Nine of the 14 subjects presented with hypoglycemic symptoms. Five subjects developed hypoglycemic symptoms after the diagnosis of the pancreatic neuroendocrine tumor. The mean time to development of hypoglycemia in these 5 subjects after the initial diagnosis of the pancreatic neuroendocrine tumor was 30 months ± 21 {SD; range 8-60 months]. The average laboratory glucose level for the patients at time of evaluation for hypoglycemia was 45 ± 2 mg/dL (SD, range 36-59 mg/dL); The mean insulin level was 50.4 mU/L ± 53.7 (SD, range 18.1-181 mU/L) and the mean proinsulin level was 358.9 ± 233.9 (SD; range 93-700 pmol/L).

Ten of the 14 had synchronous metastases in the liver at the time of diagnosis of pancreatic neuroendocrine tumor. The 4 subjects who did not have visible liver metastases at diagnosis went into clinical remission after the initial surgery for a duration of 2.5-9 years before presenting again with hypoglycemia and liver metastases (metachronous liver metastases). With disease progression, there was not only an increase in the number and size of the liver lesions but also many patients developed osseous (n = 7) and lung metastases (n = 4). All the patients underwent imaging with radiolabeled somatostatin analogs (68 Ga-DOTATATE, 68 Ga-DOTATOC, Indium labeled octreotide).

The cytological and histological evaluation noted that 9 individuals (64%) had WHO grade 2 disease (Ki 67 proliferation index ranging from 3.5% to 20%). Three individuals (21%) had WHO grade 1 disease (Ki 67 index <1% to 1.3%) and 1 individual had WHO grade 3 disease (Ki 67 index, 80%){Rindi, 2022 #14830;, #14897}. All the tumors were well-differentiated neuroendocrine tumors including the WHO grade 3 tumor. Samples were sent for germline testing to Invitae; Ambry Genetics; Aliso Viejo, Athena Diagnostics, Worcester, MA; and genetics lab at University of California (UC500—coding regions of 529 cancer genes and select introns of 47 genes). None of the subjects reported in this case series had phenotype features of MEN1 syndrome. Germline testing was available in 10 of the 14 cases. None of these cases had mutations in the MEN1 gene.

Table 1 summarizes the treatments used to control the disease in these patients. Treatments included surgery; other liver-directed therapies; somatostatin analogs; targeted agents; systemic chemotherapy, external radiation (stereotactic body radiation therapy), and peptide receptor radionuclide therapy. Liver-directed therapies (LDT) include transarterial embolization (TAE); transarterial chemotherapy (TACE), microwave ablation, and selective internal radiotherapy (SIRT). The main oral targeted agent employed was the mTOR inhibitor, everolimus. Two patients were treated with the tyrosine kinase inhibitor, sunitinib. Immunotherapies are not typically considered effective in neuroendocrine tumors but were used in 4 patients in the setting of clinical trials. Another patient (number 14) was given pembrolizumab outside a clinical trial because he had a high tumor mutation burden (> 10).

Nine of 14 subjects underwent surgeries at some point during the course of the disease. Surgeries included partial pancreatectomy to remove the primary tumor; partial hepatectomy; and enucleation of hepatic lesions. Thirteen of 14 subjects received long-term somatostatin analog therapy. The one subject not given somatostatin analog therapy had a negative DOTATATE PET MR scan. Liver-directed therapy (TAE, TACE, SIRT) was performed on 11 of 14 subjects. Five of the subjects had more than one such treatment to control the disease. When octreotide, surgery, and liver-directed interventions were not sufficient to control growth or symptoms, the next treatment most often introduced was everolimus (5

Table 1. Clinical characteristics of 14 patients with metastatic insulinoma.

Subject	Gender	Age of diagnosis	WHO grading/Ki67 index	Primary tumor and metastases at diagnosis. Subsequent progression to other sites	Synchronous or metachronous liver metastases	Germline testing	Hypoglycemia at presentation? yes or no. If no, when did hypoglycemia occur? Glucose mg/dL/ insulin mU/L/ proinsulin pmol/L levels at diagnosis.	Treatments provided during follow-up	Order and timing of treatment in relation to original diagnosis of insulinoma. Treatments that led to control of hypoglycemia.	Follow up duration
1	M	54	2; Ki67 11.6%	CT abdomen 3.1 × 1.9 × 2.1 cm lesion in pancreas. > 20 liver metastases. No skeletal metastases	Synchronous	Invitae cancer genetics panel (130 genes tested, 2018). Pathogenic variant in NBN: c.657_661del-ACAAA (p.Ly-s219Asnfs*16).	Yes, at diagnosis. 45/51.2/700.	Surgeries X 2 TACE x 3 Everolimus	Distal pancreatectomy; enucleation large liver lesion at 2 months. TACE at 3 months, 7 months; 12 months. Everolimus at 8 months for a total of 7 months. Hepatectomy at 34 months. Hypoglycemia resolved after 4 months following surgery and TACE x 2.	4.9; alive
2	M	65	2; Ki67 15%;	CT abdomen: 2 cm lesion in pancreas. Liver metas-tases noted 9 years later. No skeletal metastases	Metachronous	NA	Yes, at diagnosis. 47/34.2/93	Surgery TAE Lanreotide	Surgery at diagnosis. TAE 9 years later. Hypoglycemia controlled by lanreotide.	10.9; alive
3	F	55	2; Ki67 5%	MR abdomen up to 10 cm in pancreas, liver metastases. Octreoscan noted lesions in liver, pancreas, porta hepatis and spleen near hilum; lung nodules; L2 vertebral body. Subsequently devel-opment of more meta-static disease in skeleton & lungs	Synchronous	(Athena diagnostics MEN 1 mutation analysis, 2013). Negative MEN1 screen	Yes, at diagnosis. 40/35/297 .	Octreotide Everolimus PRRT x3 Lanreotide Capecitabine/ temozolomide cabozantinib Nivolumab/ ipilimumab SIRT SBRT	No surgery. Octreotide at diagnosis. Everolimus at 2 months after diagnosis. PRRT 7 months,10 months 12 months after diagnosis. Switched to lanreotide at 1.6 years. SIRT and SBRT (liver) at 2 yrs. Capecitabine/temozolomide at 2.6 years. Cabozantinib at 3.8 years. Briefly participated in a nivolumab/ ipilimumab clinical trial before death (at 4.5 years after diagnosis). Hypoglycemia resolved after PRRT treatment.	4.7; died
4	F	65	2; Ki-67 7.3%	CT abdomen: pancre-atic mass 3.6 cm; 4 liver metastases. 8 years later developed periportal and retroperitoneal nodes; cervical spine body lesion	Synchronous	Invitae cancer genetics panel 71 genes tested, 2016. VUS FLCN gene(c.748C > A, p.Leu250Met)	Yes, at diagnosis. 47/181/657	octreotide TAE x 4 Surgery TACE x 1 microwave ablation SBRT FOLFOX	First treated with octreotide. TAE x 2 at 5 yrs. Distal pancreatectomy and left hepa-tectomy at 5 yrs. TAE 5 yrs. TACE 5.5 yrs. TAE, 5.6 yrs., Microwave ablation 5.7 yrs. Briefly given sunitinib but stopped because of intratumoral bleed. SBRT to hepatic mets at 6.9 yrs. FOLFOX at 7 yrs. Octreotide controlled hypoglycemia. TAE temporarily reduced need for octreotide to control hypoglycemia.	8.2; died

Table 1. Continued

Subject	Gender	Age of diagnosis	WHO grading/Ki67 index	Primary tumor and metastases at diagnosis. Subsequent progression to other sites	Synchronous or metachronous liver metastases	Germline testing	Hypoglycemia at presentation? yes or no. If no, when did hypoglycemia occur? Glucose mg/dL/ insulin mU/L/ proinsulin pmol/L levels at diagnosis.	Treatments provided during follow-up	Order and timing of treatment in relation to original diagnosis of insulinoma. Treatments that led to control of hypoglycemia.	Follow up duration
5	M	48	NA	CT abdomen and PET/CT scan: pancreatic and sub-centimeter liver lesions. 4.2 years later, mass right iliac bone multiple foci retroperitoneal nodes and widespread metastases in skeleton	Synchronous	NA	Yes, at diagnosis. 36/37/160	Diazoxide Octreotide TACE Capecitabine/ temozolomide Everolimus Sunitinib SBRT	Initially treated with diazoxide but had persistent hypoglycemia. Unclear if patient took drug consistently. Octreotide 6 months after diagnosis. TACE at 3 yrs. - octreotide held for one year before restarting. Capecitabine/temozolomide at 4.5 yrs. for progression. SBRT to right iliac bone at 4.6 yrs. Everolimus at 4.9 yrs. Hypoglycemia better after TACE. Then had mild hypoglycemia which resolved with octreotide therapy.	5.4; died
6	F	58	1; Ki 67 < 2% (1.3%)	DOTATE PET CT scan—pancreatic tail lesion and liver metastases.. One year later widespread skeletal metastases..	Synchronous	(Ambry genetics 49 panel 2015). Negative MEN1 screen	Yes, at diagnosis. 38/79.6/700	Surgery TACE x 2 Octreotide Everolimus Carboplatin/ etoposide PRRT x 4 SBRT x3	Diazoxide and octreotide at diagnosis. TACE at 2 weeks and 2 months. Hypoglycemia resolved and diazoxide discontinued. Distal pancreatectomy, hepatectomy at 1.9 yrs. External radiation spine for metastatic disease at 2.3 yrs. Everolimus initiated. External radiation left hip and femur 3. 8 years. Everolimus discontinued. PRRT 4 cycles at 4 years. External radiation the sacrum, spine, rib. Restart everolimus 4.5 years. Recurrent hypoglycemia and started on carboplatin/etoposide at 4.8 years. Died 5 yrs. after diagnosis. Hypoglycemia controlled after TACE, octreotide and surgery. Recurrent hypoglycemia with progression and controlled with carboplatin/etoposide.	5.1; died

Table 1. Continued

Subject	Gender	Age of diagnosis	WHO grading/Ki67 index	Primary tumor and metastases at diagnosis. Subsequent progression to other sites	Synchronous or metachronous liver metastases	Germline testing	Hypoglycemia at presentation? yes or no. If no, when did hypoglycemia occur? Glucose mg/dL/ insulin mU/L/ proinsulin pmol/L levels at diagnosis.	Treatments provided during follow-up	Order and timing of treatment in relation to original diagnosis of insulinoma. Treatments that led to control of hypoglycemia.	Follow up duration
7	F	67	2; Ki 67 16%;	CT abdomen 2.8 cm pancreatic body lesion & hepatic masses. 10 years later lung nodules measuring up to 2.6 cm.	synchronous	NA	No, hypoglycemia occurred 8 months after diagnosis. 42/104/260	Octreotide TACE x 1 PRRT x 5 carboplatin/ etoposide capecitabine/ temozolomide SBRT	Hypoglycemia 8 months after diagnosis. PRRT two cycles eight months later. Also, TACE. Hypoglycemia controlled on octreotide. PRRT two cycles at 3.5 yrs. Carboplatin etoposide at 4 years. Switched to capecitabine/temozolomide for 1.8 yrs. and discontinued for progression. Remained on octreotide. External radiation to liver mets at 8.6 yrs. One more dose PRRT at 9.5 yrs. Died 10.4 yrs. after diagnosis. Hypoglycemia controlled after PRRT and octreotide.	10.4; died
8	M,	73	1; Ki67 1.3%	CT abdomen showed 6.4 cm pancreatic lesion and lymph node involvement. 2.5 years, later liver metastases. Subsequently developed retroperitoneal nodes; osseous metastatic disease; small degree of lung disease	Metachronous	Cancer susceptibility multigene panel, 2015. Ambry Cancer Next Panel 2017. Negative for MEN1 mutations. VUS MRE11A gene	Yes, at diagnosis. 39/NA/NA	Surgery x 3 TAE x4 Octreotide Diazoxide Everolimus Capecitabine/ temozolomide PRRT x 4	Distal pancreatectomy at diagnosis with resolution of hypoglycemia. Liver metastases 2.5 years after diagnosis. Started Octreotide at 2.6 years. TAE 2.6 years; 3.3 years. Diazoxide at 3.5 years with mild improvement hypoglycemia. Resection liver metastasis with LN dissection at 4 yrs. - significant improvement in hypoglycemia. Everolimus at 4.8 yrs. with immediate resolution of hypoglycemia. TAE at 5.3 yrs.; 5.5 yrs. Partial hepatectomy & LN dissection 5.8 yrs. Everolimus & octreotide discontinued. Interval progression of metastatic disease. Restarted octreotide at 6.3 yrs. PRRT 6.4, 6.5. 6.8. 7 yrs. Capecitabine/temozolomide at 11 yrs. for progression of disease. Also, on octreotide. Hypoglycemia controlled with surgeries and everolimus.	12.3; alive
9	F	62	2; Ki 67 3.5 %	Initially only pancreas. Portocaval nodes; liver nodules noted 3.75 yrs. Later	Metachronous	Invitae Genetics 79 gene panel 2016. Negative MEN1 screen	Yes, at diagnosis. 56/105.8/294	Surgery Octreotide SBRT	Pancreatectomy at diagnosis. Recurrent hypoglycemia 3 years later. Liver metastases noted at 3.75 yrs. Octreotide therapy at 4 yrs. SBRT at 5 yrs. Died from cirrhosis related to NASH. Hypoglycemia controlled once patient went on octreotide.	5.8;died

Table 1. Continued

Subject	Gender	Age of diagnosis	WHO grading/Ki67 index	Primary tumor and metastases at diagnosis. Subsequent progression to other sites	Synchronous or metachronous liver metastases	Germline testing	Hypoglycemia at presentation? yes or no. If no, when did hypoglycemia occur? Glucose mg/dL/ insulin mU/L/ proinsulin pmol/L levels at diagnosis.	Treatments provided during follow-up	Order and timing of treatment in relation to original diagnosis of insulinoma. Treatments that led to control of hypoglycemia.	Follow up duration
10	F	20	2, Ki 67 20%	CT 3.9 cm lesion splenic hilum; hepatic lesions; breast, L1 lesion; osseous mets. Rt internal mammary node	Synchronous	UC500 germline panel negative	No, hypoglycemia documented 1.5 years after diagnosis, 48/45.1/195.	Capecitabine/ temozolomide Pembrolizumab PRRT Lanreotide	capecitabine/Temozolomide at diagnosis for 1 year. TACE at 1.4 years; than pembrolizumab + PRRT clinical trial (2 cycles) at 1.6 years. Also started lanreotide at 1.6 years Hypoglycemia controlled with combination of pembrolizumab, PRRT and lanreotide	1.9 alive
11	M	71	3, Ki 67 80% (high-grade neuroendocrine neoplasm)	CT abdomen 4.9 cm mass pancreatic head; liver metastases; skeleton	Synchronous	Invitae 62 gene germline panel negative	Yes, at diagnosis, 60/49/664.2	Surgery Octreotide, Lanreotide, pembrolizumab PRRT	Octreotide soon after diagnosis; Whipple procedure + RFA 2 months later. carboplatin + etoposide 6 cycles started 4 months later. pembrolizumab + PRRT clinical trial (2 cycles) 10 months later. Lanreotide 10 months later Hypoglycemia controlled after PRRT and lanreotide	1.2 alive
12	M	50	2, Ki67 8%	MR abdomen 4 × 2.5 cm mass distal body/tail of pancreas; multiple metastases in liver	Synchronous	----	No, hypoglycemia 5 years after diagnosis 53/34/96.5	Microwave ablation liver metastases. Surgery octreotide PRRT	Microwave ablation liver metastases 2 months after diagnosis.; Y90 SIRT at 5 months; Resection pancreatic tumor and lymph node dissection at 9 months. Octreotide at 1.4 years. PRRT x 2 cycles at 7 years. Hypoglycemia controlled after PRRT and octreotide	7.3 alive
13	F	64	2, Ki67 17.3%	CT abdomen 4.5 × 3.5 × 3.3 cm mass pancreatic tail and multiple metastases in liver	Synchronous	UC500 germline panel negative.	No, hypoglycemia 1.7 years after diagnosis. 36/18.1/320	Octreotide Capecitabine/ temozolomide PRRT SBRT Pembrolizumab FOLFOX Carboplatin/ etoposide	Octreotide at 2 months after diagnosis. Capecitabine/Temozolomide at 6 months. PRRT x 4 cycles at 1 year. SBRT to acetabulum and L4 met at 1.4 years. Pembrolizumab one dose + Y90 radioembolization at 1.6 years clinical trial.; FOLFOX at 1.8 years; carboplatin/etoposide 3 cycles at 2 years. Hypoglycemia controlled after treatment with FOLFOX	2.5 died

Table 1. Continued

Subject	Gender	Age of diagnosis	WHO grading/Ki67 index	Primary tumor and metastases at diagnosis. Subsequent progression to other sites	Synchronous or metachronous liver metastases	Germline testing	Hypoglycemia at presentation? yes or no. If no, when did hypoglycemia occur? Glucose mg/dL/ insulin mU/L/ proinsulin pmol/L levels at diagnosis.	Treatments provided during follow-up	Order and timing of treatment in relation to original diagnosis of insulinoma. Treatments that led to control of hypoglycemia.	Follow up duration
14	M	30	1, Ki67 < 1%	5 cm tumor pancreatic head. Liver metastases first noted 3.4 years later	Metachronous	Germline testing UC500 germline panel MSH2 pL556S (c. 1667T > C, pLeu556Ser)—missense variant in the MSG2 DNA mismatch (MMR) protein—likely pathogenic for hereditary colorectal cancer	No, hypoglycemia 3.5 years after diagnosis. 41/20/229.7	Surgeries x 2 Lanreotide Sunitinib Pembrolizumab Diazoxide Capecitabine/ temozolomide	Whipple procedure at diagnosis; Lanreotide at 1.8 years; sunitinib at 6 years Liver resection and microwave ablation at 7.4 years. Pembrolizumab at 8. 3 years (for high tumor mutation burden). Diazoxide at 9 years. Capecitabine/temozolomide 9.1 years Hypoglycemia controlled with food and diazoxide	9.1 alive

Abbreviations: PRRT, peptide receptor radionucleotide therapy with 177-Lutetium labelled somatostatin analogs; SBRT, stereotactic body radiation therapy; SIR, selective internal radiation therapy; TACE, transarterial chemoembolization; TAE, transarterial embolization.

of 14 patients). Sunitinib was given to 2 patients but discontinued because of side effects (bleeding and neutropenia). PRRT was performed in 8 subjects. Four of the subjects who underwent PRRT died at a median interval of 4.9 years and 4 individuals are still alive after 1.2, 1.9, 7.3, and 12.3 years. The median survival in 3 individuals who died and did not receive PRRT was 6.3 years. Stereotactic body radiation therapy was performed on 5 subjects. Capecitabine and temozolomide are one of the suggested treatment regimens for progressive well-differentiated neuroendocrine tumors[17] Seven of the subjects were treated with these agents—5 were given these agents when other treatments failed. Four patients were treated with carboplatin and etoposide. One patient was treated with cabozantinib without benefit.

Hypoglycemia was easily managed in most patients with treatment. Surgery and TACE and/or somatostatin analogs (SSA, octreotide, or lanreotide) therapy were effective in 6 of the subjects in eliminating or managing hypoglycemia. Figure 1 illustrates the impact of lanreotide therapy on glucose levels in subject 2 (Table 1). In 1 subject, hypoglycemia resolved after PRRT therapy. In 2 subjects, PRRT followed by somatostatin analog therapy controlled the hypoglycemia. In our cohort, we only had limited use of diazoxide [4 subjects]. Two subjects stated that diazoxide was ineffective but it is unclear if they took the drug consistently. In 1 subject, diazoxide was insufficient to control hypoglycemia and the problem was resolved only after octreotide was added. This subject then underwent TACE with a resolution of hypoglycemia and discontinued the diazoxide treatment. The fourth subject had a resolution of hypoglycemia with diazoxide use.

In summary, 97 treatments were utilized across 14 patients. The most popular types of treatments were liver-directed therapy used 17 times in 11 patients (79%), SSA used 17 times in 13 patients (93%), surgery used 13 times in 9 (69%) patients, and systemic chemotherapy used 13 times in 10 patients (71%). The sequences of the 9 treatment types utilized by each patient are presented in Figure 2. Every patient had a sequence of at least 3 treatments, and 2 patients had a sequence of 11 treatments.

Seven subjects died during follow up—the median life expectancy was 8.2 years (time of death ranged from 2.5 to 10.4 years). Table 1; Figure 3. There is a wide confidence interval because of the small sample size. The 95% lower bound confidence interval is 4.7 years. The upper bound is not calculable because of insufficient data but would be >12 years (Figure 3). Seven subjects are alive— 1 individual has survived for 12.2 years after diagnosis. Six of the 7 subjects died because of the progression of their malignancy. One patient died from cirrhosis of the liver due to nonalcoholic fatty liver disease and not from progressive pancreatic neuroendocrine disease. Two of the individuals who are alive have WHO grade 1 disease and 4 have WHO grade 2 disease. The individual with WHO grade 3 disease is alive 1.1 years after diagnosis. The individual who is alive 10 years (subject 2, Table 1) after the initial diagnosis of insulinoma had WHO grade 2 disease and presented with recurrent hypoglycemia and liver metastases 9 years after the original surgery for insulinoma.

Discussion

There are limited case series on the treatment and outcomes of patients with metastatic insulinoma.[6,7,18-20] Some of the series had only limited duration follow-up.[18] Another case series combined all cases of malignant insulinoma–metastatic as well as those with locoregional extension.[20-22] The individuals with locoregional disease alone, however, have prolonged survival and do not behave like the insulinoma cases that are metastatic to the liver and elsewhere. We specifically evaluated patients with metastatic insulinoma and reviewed outcomes with multimodal treatment.

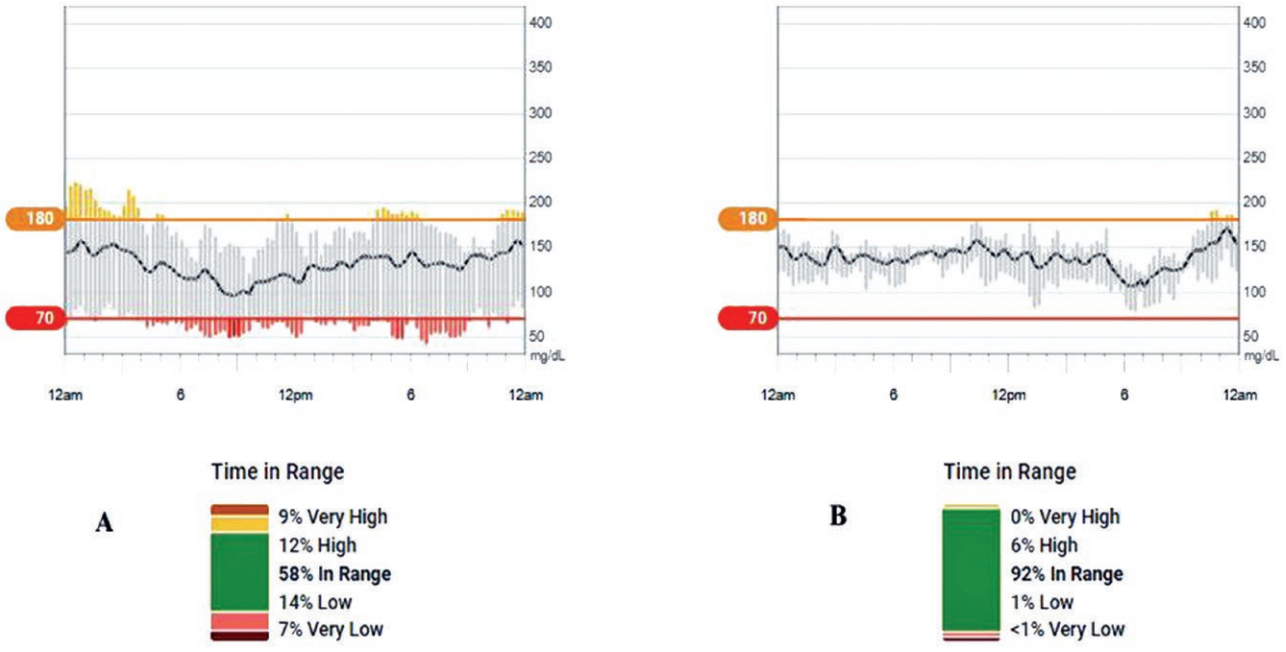

Figure 1. Continuous glucose monitoring (DexCom G6) for 2 weeks before (panel A) and after (panel B) lanreotide therapy in subject 2. The average glucose for the 2 weeks before lanreotide therapy was 7.2 + 4.7 mmol/L(SD); 7 % of the glucose levels were <3 mmol/L and 14 % of the glucose levels were in the 3-3.8 mmol/L range. In the 2 weeks following injection of lanreotide, the average glucose was 7.7 + 1.5 mmol/L (SD); and there were no glucose levels below 3 mmol/L mg/dL and only 1 % were in the 3-3.8 mmol/L range.

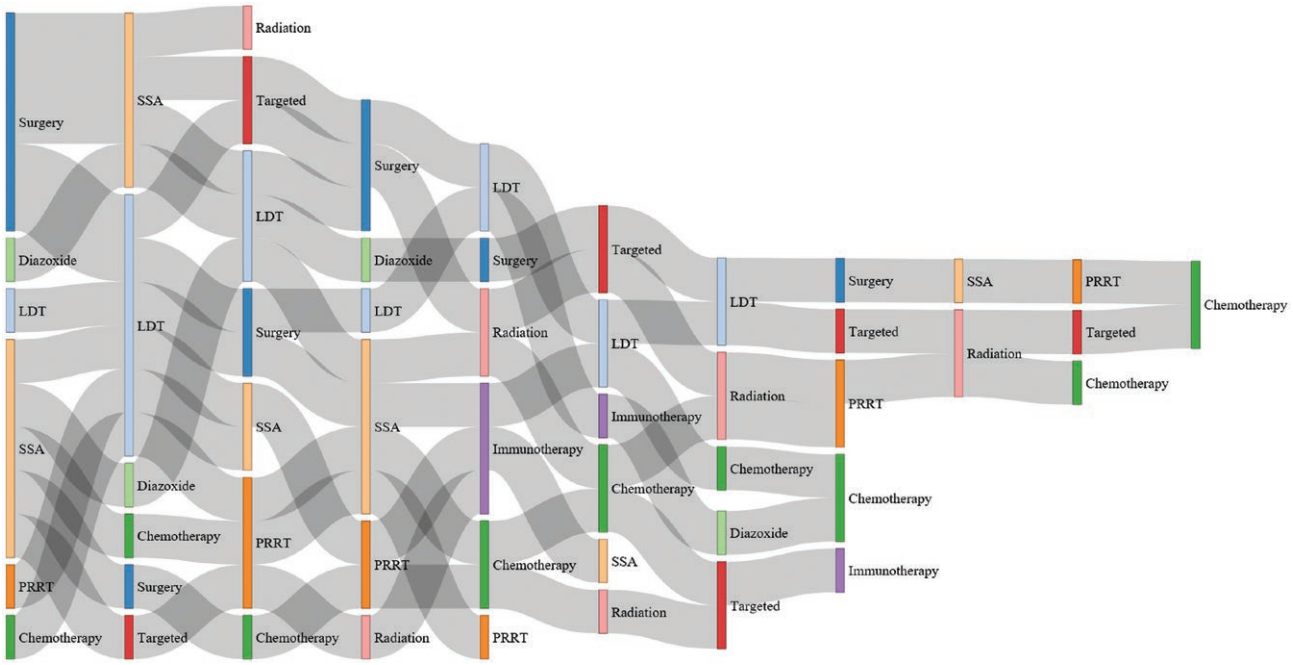

Figure 2. Sankey diagrams illustrating treatment sequence from first line to ninth line therapies.

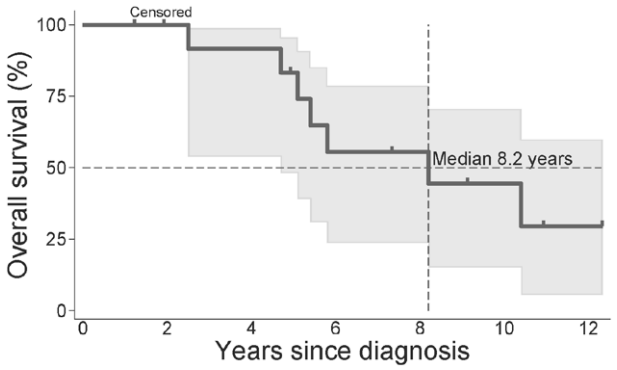

Figure 3. Survival time for all 14 individuals diagnosed with metastatic insulinoma since 2006.

We observe that in this series, synchronous metastases were more common than metachronous metastases. Ten of 14 had metastases at the time of diagnosis of pancreatic neuroendocrine tumor. The 4 subjects who did not have known metastases at the time of diagnosis, were observed to have liver metastases 2.5-9 years after the initial presentation. This is similar to what has been reported previously that metachronous metastases can appear a number of years after the original insulinoma diagnosis.[4,18] Our data reporting that the liver is usually the first site for metastatic insulinoma is also consistent with the literature reports of relative liver tropism for all pancreatic neuroendocrine tumors.[23] With progression, osseous metastases occurred and some patients also developed lung metastases.

We had histopathological evaluation on 13 individuals. Nine of them had WHO grade 2 disease (Ki-67 3.5%-17.3%] and 3 of them had WHO grade 1 disease [Ki-67 1.3%]. This finding is consistent with the literature that higher-grade tumors are associated with metastatic disease. We, however, note in our clinical case series, that grade 1 disease can still present with metastases and it should not be assumed that if a patient has grade 1 disease the course will be benign. Patients with grade 1 disease, therefore, should be monitored for many years. As reported in this series as well as in previously published series,[4,24] MEN1 syndrome does not appear to be a common genetic reason for metastases to the liver. None of the subjects reported in this case series had phenotype features of MEN1 syndrome. Germline testing was available in 10 subjects and they did not have mutations in the MEN 1 gene. In a study of 55 patients with MEN1 patients with insulinoma, only 1 had liver metastasis at the time of diagnosis, and 4 developed liver metastases at followup[24,25]

We report that with multimodal intervention, the median survival of these patients was 8.2 years. Previous case series reported median survival of metastatic insulinoma patients to be in the region of 2 years.[26] In an analysis of the SEER US national database (1973-2013), the observed survival of all pancreatic neuroendocrine tumors was 4.1 years, and functional tumors (not necessarily metastatic) were 7.3 years.[27] The likely reason for better outcomes for functional tumors in the SEER analyses was that the subjects were diagnosed earlier and underwent surgery before the disease metastasized. In the SEER cohort, metastatic high-grade tumors not amenable to surgery had a life expectancy of only 2-4 years if diagnosed at age 50 and 1-2 years if diagnosed at age 70.[27]

Seven of our patients underwent PRRT therapy. Since the subjects also had other treatments, it is not possible to determine if this form of therapy was specifically beneficial. Of the 7 patients who died, 3 received PRRT and 3 did not. The median survival was 4.9 years and 6.3 years, respectively. We note that the NETTER-1 trial—the largest study utilizing PRRT for midgut neuroendocrine tumors reported longer progression-free survival with PRRT.[28] The study, however, did not include pancreatic neuroendocrine tumors. On a follow-up report from the NETTER 1 study, PRRT did increase median overall survival by approximately 1 year compared to high-dose octreotide therapy[29] but the difference was not statistically significant. The primary analysis of the

NETTER-2 trial regarding the impact of PRRT on grade 2 and grade 3 gastropancreatic neuroendocrine tumors (54% were pancreatic) has reported prolongation of progression-free survival by about 14 months.[30] In a retrospective analysis of 133 Dutch patients with pancreatic neuroendocrine tumors (functional and nonfunctional), PRRT resulted in progressive free survival of 30 months and overall survival of 71 months.[31] Hepatectomy and orthotopic liver transplantation can be considered for patients with hepatic metastases without systemic dissemination and can be curative.[21,32] None of the patients in our series were candidates for this form of treatment.

It has been reported that chromosomal instability is the best predictor of aggressive behavior of insulinomas. Mutations in the genes ATRX and DAXX; and immunohistochemical expression of Arx1, alpha 1 antitrypsin, and loss of expression of insulin, PDX1, and GLP!-receptor agonists also predict aggressive behavior.[24,33] We do not have molecular or immunochemistry testing for this retrospective cohort and cannot therefore report if outcomes would have varied based on molecular profiling.

Hypoglycemia is a defining characteristic of insulinoma but the problem was manageable in the patients in our clinical series. Surgical resection of the primary tumor and debulking of the liver metastases mostly ameliorated the problem. If hypoglycemia was still present after these interventions, then the addition of a somatostatin analog (octreotide or lanreotide) was usually effective. In one of our patients, PRRT resolved the hypoglycemia. There are now a number of reports in the literature that PRRT can effectively control hypoglycemia.[19,34-36] An additional option is the use of everolimus, an mTOR inhibitor, that is not only cytostatic but also inhibits insulin secretion[37,38] and can be effective in controlling hypoglycemia.[39,40] In our experience, diazoxide seems to be of limited benefit in these patients with metastatic disease although it was not systematically evaluated.

A major limitation of this study is that the treatment decisions were individualized so it is not possible to assess the efficacy of specific treatments. It is also not possible to determine the optimal sequence of specific treatments for the greatest benefit.

In summary, modern multimodal treatment of metastatic insulinoma ameliorates the symptoms of hypoglycemia and is associated with encouraging overall survival compared to earlier reports in the literature.

Author contributions

Umesh Masharani: Conceptualization, Data curation, Formal Analysis, Writing—original draft, Writing—review & editing; Sheila Lindsay: Data curation, Writing—review & editing; Farhana Moon: Data curation, Writing—review & editing; Alan Paciorek: Formal Analysis, Methodology, Visualization, Writing—review & editing; Emily Bergsland: Data curation, Formal Analysis, Writing—review & editing.

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Conflicts of interest

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Data availability

The data underlying this article are available in the article.

References

1. Leoncini E, Boffetta P, Shafir M, et al. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine*. 2017;58:368-379. https://doi.org/10.1007/s12020-017-1273-x
2. Lee MR, Harris C, Baeg KJ, et al. Incidence trends of gastroenteropancreatic neuroendocrine tumors in the United States. *Clin Gastroenterol Hepatol*. 2019;17:2212-2217.e1. https://doi.org/10.1016/j.cgh.2018.12.017
3. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol*. 2015;50:58-64. https://doi.org/10.1007/s00535-014-0934-2
4. Hirshberg B, Cochran C, Skarulis MC, et al. Malignant insulinoma: spectrum of unusual clinical features. *Cancer*. 2005;104:264-272. https://doi.org/10.1002/cncr.21179
5. Baudin E, Caron P, Lombard-Bohas C, et al; Société française d'endocrinologie. Malignant insulinoma: recommendations for characterisation and treatment. *Ann Endocrinol (Paris)*. 2013;74:523-533. https://doi.org/10.1016/j.ando.2013.07.001
6. Sada A, Glasgow AE, Vella A, et al. Malignant insulinoma: a rare form of neuroendocrine tumor. *World J Surg*. 2020;44:2288-2294. https://doi.org/10.1007/s00268-020-05445-x
7. Starke A, Saddig C, Mansfeld L, et al. Malignant metastatic insulinoma-postoperative treatment and follow-up. *World J Surg*. 2005;29:789-793. https://doi.org/10.1007/s00268-005-7743-y
8. Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. *J Neuroendocrinol*. 2023;35:e13318. https://doi.org/10.1111/jne.13318
9. Danforth DN Jr, Gorden P, Brennan MF. Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. *Surgery*. 1984;96:1027-1037.
10. Oberg K. Management of functional neuroendocrine tumors of the pancreas. *Gland Surg*. 2018;7:20-27. https://doi.org/10.21037/gs.2017.10.08
11. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S. Emerging therapies for advanced insulinomas and glucagonomas. *Endocr Relat Cancer*. 2023;30:e230020. https://doi.org/10.1530/ERC-23-0020
12. Brown E, Watkin D, Evans J, Yip V, Cuthbertson DJ. Multidisciplinary management of refractory insulinomas. *Clin Endocrinol (Oxf)*. 2018;88:615-624. https://doi.org/10.1111/cen.13528
13. Jensen RT, Cadiot G, Brandi ML, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology*. 2012;95:98-119. https://doi.org/10.1159/000335591
14. Howe JR, Merchant NB, Conrad C, et al. The North American neuroendocrine tumor society consensus paper on the surgical management of pancreatic neuroendocrine tumors. *Pancreas*. 2020;49:1-33. https://doi.org/10.1097/MPA.0000000000001454
15. Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine tumor society consensus guidelines for surveillance and medical management of pancreatic neuroendocrine tumors. *Pancreas*. 2020;49:863-881. https://doi.org/10.1097/MPA.0000000000001597
16. Yao J, Pham AT. Optimising therapeutic options for patients with advanced pancreatic neuroendocrine tumours. *Eur. J. Haematol*. 2012;8:7.
17. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic

pancreatic endocrine carcinomas. *Cancer*. 2011;117:268-275. https://doi.org/10.1002/cncr.25425
18. Yu J, Ping F, Zhang H, et al. Clinical Management of Malignant Insulinoma: a single Institution's experience over three decades. *BMC Endocr Disord*. 2018;18:92. https://doi.org/10.1186/s12902-018-0321-8
19. van Schaik E, van Vliet EI, Feelders RA, et al. Improved control of severe hypoglycemia in patients with malignant insulinomas by peptide receptor radionuclide therapy. *J Clin Endocrinol Metab*. 2011;96:3381-3389. https://doi.org/10.1210/jc.2011-1563
20. Veltroni A, Cosaro E, Spada F, et al. Clinico-pathological features, treatments and survival of malignant insulinomas: a multicenter study. *Eur J Endocrinol*. 2020;182:439-446. https://doi.org/10.1530/EJE-19-0989
21. Begu-Le Corroller A, Valero R, Moutardier V, et al. Aggressive multimodal therapy of sporadic malignant insulinoma can improve survival: a retrospective 35-year study of 12 patients. *Diabetes Metab*. 2008;34:343-348. https://doi.org/10.1016/j.diabet.2008.01.013
22. Sada A, Yamashita TS, Glasgow AE, et al. Comparison of benign and malignant insulinoma. *Am J Surg*. 2021;221:437-447. https://doi.org/10.1016/j.amjsurg.2020.08.003
23. Riihimaki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in Neuroendocrine tumors. *Int J Cancer*. 2016;139:2679-2686. https://doi.org/10.1002/ijc.30400
24. Hackeng WM, Brosens LAA, Dreijerink KMA. Aggressive versus indolent insulinomas: new clinicopathological insights. *Endocr Relat Cancer*. 2023;30:e220321. https://doi.org/10.1530/ERC-22-0321
25. Zhao Y, Yu J, Liu Y, et al. Analysis of 55 patients with multiple endocrine neoplasia type 1-associated insulinoma from a single center in China. *Orphanet J Rare Dis*. 2022;17:219. https://doi.org/10.1186/s13023-022-02370-1
26. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*. 1991;66:711-719. https://doi.org/10.1016/s0025-6196(12)62083-7
27. Brooks JC, Shavelle RM, Vavra-Musser KN. Life expectancy in pancreatic neuroendocrine cancer. *Clin Res Hepatol Gastroenterol*. 2019;43:88-97. https://doi.org/10.1016/j.clinre.2018.08.005
28. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376:125-135. https://doi.org/10.1056/NEJMoa1607427
29. Strosberg JR, Caplin ME, Kunz PL, et al; NETTER-1 investigators. (177)Lu-Dotatate plus long-acting octreotide versus highdose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22:1752-1763. https://doi.org/10.1016/S1470-2045(21)00572-6
30. Singh S, Halperin D, Myrehaug S, et al. [177Lu]Lu-DOTA-TATE in newly diagnosed patients with advanced grade 2 and grade 3, well differentiated Gastroenteropancreatic Neuroendocrine tumors: primary analysis of the phase 3 Randomized NETTER-2 study. *J Clin Oncol*. 2024;42:LBA588. https://doi.org/10.1200/JCO.2024.42.3_suppl.LBA588
31. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. *Clin Cancer Res*. 2017;23:4617-4624. https://doi.org/10.1158/1078-0432.CCR-16-2743
32. Sutcliffe R, Maguire D, Ramage J, Rela M, Heaton N. Management of neuroendocrine liver metastases. *Am J Surg*. 2004;187:39-46. https://doi.org/10.1016/j.amjsurg.2003.04.007
33. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol*. 2022;33:115-154. https://doi.org/10.1007/s12022-022-09708-2
34. Kumar S, Melek M, Rohl P. Case report: hypoglycemia due to metastatic insulinoma in insulin-dependent type 2 diabetes successfully treated with 177 Lu-DOTATATE. *Front Endocrinol (Lausanne)*. 2022;13:906012. https://doi.org/10.3389/fendo.2022.906012
35. Zandee WT, Brabander T, Blazevic A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2019;104:1336-1344. https://doi.org/10.1210/jc.2018-01991
36. Friebe L, Freitag MT, Braun M, et al. Peptide receptor radionuclide therapy is effective for clinical control of symptomatic metastatic insulinoma: a long-term retrospective analysis. *J Nucl Med*. 2024;65:228-235. https://doi.org/10.2967/jnumed.123.265894
37. Tanimura J, Nakagawa H, Tanaka T, et al. The clinical course and potential underlying mechanisms of everolimus-induced hyperglycemia. *Endocr J*. 2019;66:615-620. https://doi.org/10.1507/endocrj.EJ18-0542
38. Suzuki L, Miyatsuka T, Himuro M, et al. Everolimus directly suppresses insulin secretion independently of cell growth inhibition. *J Endocr Soc*. 2018;2:589-596. https://doi.org/10.1210/js.2017-00475
39. Bernard V, Lombard-Bohas C, Taquet MC, et al; French Group of Endocrine Tumors. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *Eur J Endocrinol*. 2013;168:665-674. https://doi.org/10.1530/EJE-12-1101
40. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. *N Engl J Med*. 2009;360:195-197. https://doi.org/10.1056/NEJMc0806740