Multidisciplinary management of refractory insulinomas

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Summary
Insulinomas are predominantly benign (~90%), pancreatic neuroendocrine tumours characterized by hyperinsulinaemic hypoglycaemia. They usually present as a small (<2 cm), well-demarcated, solitary nodule that can arise in any part of the organ. Treatment for sporadic insulinomas is generally aimed at curative surgical resection with special consideration in genetic syndromes. Patients with significant hypoglycaemia can pose a difficult management challenge. In isolated cases where the patient is not medically fit for surgery or with metastatic spread, other treatment options are employed. Medical therapy with diazoxide or somatostatin analogues is commonly used first line for symptom control, albeit with variable efficacy. Other medical options are emerging, including newer targeted biological therapies, including everolimus (an mTOR inhibitor), sunitinib (a tyrosine kinase inhibitor) and pasireotide, a multisomatostatin receptor ligand. Pasireotide and everolimus both cause hyperglycaemia by physiological mechanisms synergistic with its antitumour/antiproliferative effects. Minimally invasive treatment modalities such as ethanol ablation are available in selected cases (particularly in patients unfit for surgery), peptide receptor radionuclide therapy (PRRT) can effectively control tumour growth or provide symptomatic benefit in metastatic disease, while cytotoxic chemotherapy can be used in patients with higher-grade tumours. This review considers the developments in the medical and other nonsurgical management options for cases refractory to standard medical management. Early referral to a dedicated neuroendocrine multidisciplinary team is critical considering the array of medical, oncological, interventional radiological and nuclear medical options. We discuss the evolving armamentarium for insulinomas when standard medical therapy fails.

KEYWORDS
ablation, everolimus, insulinoma, neuroendocrine tumours, pasireotide, peptide receptor radionuclide therapy, sunitinib

1 INTRODUCTION
Insulinomas are rare, functioning pancreatic neuroendocrine tumours (pNETs), with an estimated incidence of 4 cases per million per year.1 Insulinomas usually occur sporadically but in a small number of cases occur as part of an inherited syndrome, most commonly as a feature of multiple endocrine neoplasia type 1 (MEN-1; <5%) and more rarely von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF-1) and tuberous sclerosis complex (TSC).2
1.1 | Diagnosis of insulinomas

The presence of Whipple's triad: symptoms and signs of hypoglycaemia with low plasma glucose levels, which are reversed by the administration of carbohydrate, are the characteristic diagnostic features. The evaluation and management of hypoglycaemia in patients with evidence of Whipple's triad has been clearly described.3 Hyperinsulinenaemic hypoglycaemia should be suspected in an otherwise fit and well individual after exclusion of medication use (oral hypoglycaemic agents, insulin administration), factitious hypoglycaemia, noninsulinoma pancreatogenous hypoglycaemia and rarely nonislet cell tumours.4 The most common cause of hyperinsulinaemic hypoglycaemia in adults is an insulinoma. Hypoglycaemia occurs primarily in the fasting state, although occasionally only in the postprandial period, and can pose a significant management challenge and cause of morbidity.5

1.2 | Localization of disease

Having confirmed the biochemical diagnosis, localization of disease can be challenging. Conventional imaging (ie, CT/MRI) and, if available, endoscopic ultrasound form the basis of localization and diagnosis of suspected insulinomas. 68Ga-DOTATATE PET-CT has a clear place in localizing insulinomas because of the high affinity of the 68Ga-DOTA peptides for somatostatin receptors (a 10-fold higher affinity than 111In-octreotide).6 Glucagon-like peptide-1 receptors (GLP1-R) are also highly expressed in almost all benign insulinomas, and so recently, we have seen the application of 68Ga-DOTA-exendin 4 PET-CT to facilitate the localization of occult insulinomas.7 In contrast, malignant insulinoma often lacks these GLP1-R.8 Once localized, surgical resection of sporadic insulinomas is standard treatment as most tumours are small (<2 cm), benign and can be surgically cured; however, there is an associated high risk of complications and only limited patients may be eligible.9

1.3 | Classification of pNETs

The management and prognosis of pNETs is governed by the size, histological grade and disease staging.10,11 For staging and grading of insulinomas, World Health Organization (WHO),12 American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC)13 and European Neuroendocrine Tumour Society (ENETS)14 guidelines for pNETs may be applied based on histological findings from tissue biopsy, size of tumour and extent of spread. The 2010 WHO classification subdivides pNETs into three grades (G1, G2 and G3) on the basis of Ki-67 nuclear antigen expression (<2%, 2%-20% and >20%) and mitotic rate (<2, 2-20 and >20): G1 and G2 are referred to as NETs and G3 as neuroendocrine carcinomas (NECs).12 Well and moderately differentiated NETs (G1/G2) have a significantly better survival compared to poorly differentiated neuroendocrine carcinomas (G3). According to the TNM classification, the tumour is classified as T1a (<1 cm), T1b (1-2 cm) and T2 (larger than 2 cm); T3 and T4 are locally advanced tumours.13

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**FIGURE 1** Treatment options for insulinomas

- **Suspected insulinoma**
  - Consider surgery
  - Curative
  - Non-Curative
  - Symptomatic: Diazoxide +/- Somatostatin analogues (SSAs)
  - Residual tumour: Surveillance
  - Well differentiated
  - Metastatic disease: SSAs
  - Liver metastases: Surgery
    - Locoregional therapies: e.g. embolisation
    - Chemotherapy
    - Novel drug trial
  - Somatostatin receptor positive disease: Peptide receptor radionuclide therapy (PRRT)
  - Poorly differentiated
    - Not fit for surgery + localized disease: eg, EUS ethanol ablation
    - Metastatic disease: SSAs
    - Liver metastases: Surgery
      - Locoregional therapies: e.g. embolisation
      - Chemotherapy
    - Chemotherapy
2 | THERAPEUTIC OPTIONS AVAILABLE FOR INSULINOMAS

Recent consensus guidance has been published on the management of functional and nonfunctional pNETs.14-16 Based on the suspected aggressiveness of the disease, patients may be offered different treatment regimens (Figure 1). In insulinomas of genetic aetiology, the clinical features may differ (eg, earlier age of onset, multifocal nature of disease, natural history) compared to sporadic insulinomas, and this should be considered when considering treatment options.

2.1 | Surgery

Surgery is the treatment of choice whenever possible. It provides both symptomatic control and long-term cure. In the presence of primary and well-differentiated metastatic functional pNETs, surgery with curative intent must always be considered, even if there is liver or lymph node involvement. For unresectable metastatic disease, the resection of the functional primary NET, like insulinomas, is controversial due to the marginal improvement in symptomatic control in this palliative setting, and the potential morbidities associated with the surgery. Despite this, studies have suggested that there could possibly be improvement of long-term overall and progression-free survival after primary tumour resection in this advanced stage.

2.2 | Conventional advice and medical therapy

Surgery remains the preferred treatment whenever possible, but prior to surgery or if surgery cannot be performed, medical treatment is needed. Simple dietary modifications are explained to all patients involving frequent small carbohydrate-rich meals throughout the day and evening to avoid hypoglycaemia. There is currently no specific Driver and Vehicle Licensing Agency (DVLA) advice for drivers with an insulinoma, only for patients with type 1 or type 2 diabetes mellitus prone to recurrent hypoglycaemic episodes. The patient should be advised to inform the DVLA of their diagnosis.

2.3 | Diazoxide

Medical treatment is available to those who are unable or unwilling to undergo surgical treatment and as an adjunct to other treatment modalities. Diazoxide, an antihypertensive benzothiadiazine which acts as a potassium channel activator, has formed the mainstay of medical management in symptomatic control of insulinomas for over 30 years.19 Diazoxide is generally regarded as first-line treatment for control of hypoglycaemia in patients with insulinomas, frequently used preoperatively when dietary and lifestyle advice fails to prevent hypoglycaemia. Potential glycaemic mechanisms include inhibition of insulin release by direct action on β-cells through the stimulation of α-adrenergic receptors or increasing hepatic gluconeogenesis and reduced skeletal muscle glucose uptake.20 Initiation doses of 50-300 mg daily titrated to a maximum daily dose of 600 mg (higher doses may be used in refractory hypoglycaemia) are used. Unfortunately, side effects are common (eg, fluid retention, hirsutism, headache, gastrointestinal upset, rash) but usually not problematic, and it offers symptom control in about 50%-60% of patients.22 Long-term treatment appears to be safe.

2.4 | Somatostatin analogues

Somatostatin, produced in the pancreatic β-cells, acts as a paracrine regulator of insulin and glucagon secretion and regulates cell proliferation, via interaction with five different (G-protein-coupled) somatostatin receptors (SSTR1-5). These SSTR subtypes have distinct molecular structures, tissue distribution, intracellular signalling and pharmacological characteristics inhibiting different hormones. SSTR2 is the dominant receptor in both α-cells (glucagon) and β-cells (insulin).

2.4.1 | Octreotide and lanreotide

Inhibitory effect on hormone production by the tumour

Synthetic somatostatin analogues (SSAs) have a unique binding affinity profile for each SSTR. These SSAs will suppress insulin and glucagon release from normal pancreatic cells via SSTR2. NETs in general often express SSTRs at high levels, with SSTR2 being the most prevalent subtype, while in contrast insulinomas have much lower SSTR2 expression. Octreotide and lanreotide have a preferential affinity for mainly SSTR2 and much less to SSTR5. This differential SSTR subtype distribution explains the variable glycaemic response to SSAs treatment in insulinomas: SSAs can increase or reduce blood glucose concentrations, in insulinoma patients, depending on the SSTR pattern of expression on the insulinoma cells. Higher expression of SSTR2 in the insulinoma cells was associated with an improvement of hypoglycaemia in response to SSAs/octreotide; in contrast, low/absent expression of the receptor subtype, SSTR2 in the insulinoma cells, is associated with paradoxical severe hypoglycaemia with SSA therapy, through suppression of glucagon, and a short initial clinical trial of SSA is recommended.

Antiproliferative effects

The antiproliferative effect of SSAs in the treatment for NETs was demonstrated in two major randomized, placebo-controlled studies: PROMID (octreotide LAR) and CLARINET (lanreotide; Table S1).25,26 In PROMID, 85 patients with well-differentiated midgut NETs were randomly assigned to receive octreotide LAR 30 mg vs. placebo. Octreotide significantly prolonged time to progression (TTP) when compared with placebo (14.3 vs. 6 months; hazard ratio [HR], 0.34; 95% CI, 0.20 to 0.59; P < .001); there was no difference in overall survival (OS). In CLARINET (n = 204), patients with advanced gastroenteropancreatic NETs (GEP-NETs) treated with lanreotide autogel had improvement in progression-free survival (PFS) when compared with placebo (PFS, not reached vs. 18 months and HR, 0.47; 95% CI 0.30-0.73; P < .001). Because of this antiproliferative effect, SSAs may be considered first-line treatment in inoperable malignant insulinomas, capable of stabilizing tumour growth in patients with metastatic insulinomas, although more information is needed on the duration and predictors of response.
3 | OPTIONS FOR REFRACTORY CASES

In patients with refractory insulinomas, whose symptoms have not responded to diazoxide or SSAs, there are several treatment options available. The optimal sequence for these treatments is unknown.

3.1 | Novel somatostatin analogues (pasireotide)

Mechanism of action
Pasireotide is a novel multireceptor somatostatin analogue that binds with high affinity to four somatostatin receptor subtypes (SSTR1, 2, 3, 5; dubbed a “pan-receptor” SSA). Its receptor binding affinity is 30-40 times higher for SSTR2 and SSTR5 than for octreotide.27 The low expression of SSTR2 in many insulinomas, with malignant insulinomas in particular overexpressing SSTR5,28 may explain why conventional SSAs are ineffective and pasireotide becomes necessary. Already approved for the treatment of pituitary tumours associated with Cushing’s disease or acromegaly,27 pasireotide is not yet approved for the treatment of pNETs.

Evidence to support pasireotide use in pNETs
Several case reports have demonstrated the efficacy of pasireotide in the treatment for refractory hypoglycaemia in malignant insulinoma.29,30 Future clinical trials are being designed to assess the antiproliferative effects of pasireotide in NETs.

Mechanism for the hyperglycaemic effects of pasireotide
Use of pasireotide in Cushing’s disease, acromegaly and in phase 2 studies in NETs (including pNETs) has highlighted significant hyperglycaemia (79%) and development of type 2 diabetes (Figure 2).31 This adverse effect on glucose metabolism is welcomed in patients with insulinomas. Henry et al32 conducted an elegant study to determine the mechanism by which pasireotide causes hyperglycaemia, involving consecutive oral glucose tolerance tests (to measure serum glucose excursions), hyperglycaemic clamps (to determine pancreatic insulin secretion) and hyperinsulinaemic, euglycaemic clamps (to measure hepatic and peripheral insulin sensitivity) in healthy volunteers, given pasireotide 600, 900 and 1200 mcg b.d. for 7 days. It was clearly demonstrated that hyperglycaemia is mediated by reduced pancreatic insulin secretion, a reduced incretin (both GLP1 and GIP) response but with unchanged peripheral (hepatic and peripheral insulin sensitivity). The greater hyperglycaemic effect of pasireotide, relative to octreotide or lanreotide, is explained by the different binding affinities of pasireotide to the different SSTR subtypes. The associated hyperglycaemia can be best managed with use of the antidiabetic agents, vildagliptin and liraglutide.33

3.2 | Molecularly targeted agents

3.2.1 | Everolimus (an mTOR receptor inhibitor)

Mechanism of antiproliferative effect
mTOR inhibitors have an antiproliferative effect by inhibiting signalling in the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is involved in the signal transduction response to insulin, growth factor and other nutrients via the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.24 In patients with pNETs, dysregulation of the Akt/mTOR pathway occurs, resulting in unrestrained cell growth, proliferation and reduced apoptosis.35

Mechanism for the hyperglycaemic action of everolimus
The Akt/mTOR pathway is also involved in the control of glucose homeostasis and dysregulated mTOR signalling is implicated in peripheral insulin...
Inhibition of mTOR by everolimus causes hyperglycaemia by several mechanisms synergistically: (i) inducing peripheral (skeletal muscle and hepatic) insulin resistance through reduced Akt phosphorylation in skeletal muscle and liver, respectively, (ii) reducing beta-cell insulin secretion, (iii) reducing tumour cell proliferation by Akt-mediated inhibition of protein synthesis (adapted from Asayama et al, 2017)37

Resistance through several distinct mechanisms: (i) impaired skeletal muscle and adipose tissue glucose uptake via GLUT4 translocation, (ii) impaired insulin-mediated suppression of hepatic gluconeogenesis and (iii) impaired pancreatic beta-cell insulin secretion (Figures 3 and 4).36 mTOR inhibition pharmacologically has a similar effect, resembling a state of peripheral insulin resistance.37 Everolimus has also been shown to directly inhibit proinsulin secretion by insulinoma cells, and this effect has been suggested from clinical experience.37 Thus, everolimus as an mTOR inhibitor has an effect on tumour progression but will have secondary effects correcting hyperglycaemia.

Evidence to support everolimus use in pNETs
Kulke was the first to report symptomatic relief of hypoglycaemia with everolimus30 associated with a reduction in insulin levels with numerous subsequent case reports supporting this.37,39

Efficacy and safety
The efficacy and safety of everolimus in the treatment for NETs of different origins has been explored in the RADIANT trials (Table S2A).40-42 In the phase 3 RADIANT-3 trial (RAD001 in advanced neuroendocrine tumours), patients with advanced pancreatic NETs were randomized to receive everolimus, 10 mg oral daily or placebo.42 Everolimus prolonged progression-free survival (PFS) with PFS of 11 months with everolimus vs. 4.6 months in placebo patients (hazard ratio, 0.35; 95% confidence interval, 0.27-0.45; P < .001). The response rate (RR) was 5% in the everolimus arm compared to 2% in the placebo arm, although significant side effects were noted. Bernard et al39 retrospectively analysed the 12 insulinoma cases from the RADIANT-3 trial and noted the added benefit of improved glycaemic control in 11 of the 12 patients treated with everolimus. It must be highlighted that 3 patients discontinued everolimus because of cardiopulmonary adverse events. 2 patients were reported to have grade 4 pulmonary toxicity, leading to death in both cases, despite drug withdrawal.

Side effects
mTOR inhibitors demonstrate similar class-specific adverse effects, including rash, stomatitis, fatigue, hyperglycaemia and gastrointestinal upset. Generally, these symptoms are manageable. Opportunistic infections and interstitial lung disease are adverse events of importance with potential significant morbidity and mortality. Guidelines for close lung surveillance have been published with baseline pretreatment imaging recommended.44

Positioning in the clinical pathway
Whereas tumour remissions are rare with everolimus, disease stabilization is observed in a high proportion of patients (60%-80%). Lack of head-to-head trials means that everolimus has mostly been used in advanced metastatic disease after the failure of SSAs and/or systemic chemotherapies and is generally reserved for progressive disease due to potential toxicities.

3.2.2  |  Sunitinib (a tyrosine kinase inhibitor)

Mechanism of action
Sunitinib is an oral multитargeted receptor tyrosine kinase inhibitor. Sunitinib displays antiangiogenic and antitumour activity by inhibiting a number of molecular pathways involved in angiogenesis.45

Evidence to support everolimus use in pNETs
Previously approved for other malignancies (eg, renal cell carcinomas and gastrointestinal stromal tumours), it has recently being approved for the treatment of advanced pNETs.46,47 In a double-blind phase 3 trial, in 171 patients with progressive, low-grade or intermediate-grade pNETs, sunitinib 37.5 mg demonstrated impressive PFS benefits compared to placebo (Table S2B).48 The trial was discontinued prematurely as sunitinib clearly offered improvements
3.3 | Cytotoxic chemotherapy

For patients with highly proliferating, rapidly progressive and/or symptomatic pancreatic NETs, cytotoxic chemotherapy may yield greater tumour shrinkage than SSAs or molecularly targeted agents. 5-Fluorouracil (5-FU), doxorubicin and streptozocin have commonly been implicated in the treatment for inoperable malignant insulinomas. Other agents (dacarbazine, cisplatin, etoposide, capectabine and temozolomide) have also been evaluated. These combination treatments may help symptom control and have resulted in an objective response of 6%-70% of patients with pNETs; however, these studies included small numbers of insulinomas and a significant proportion of patients responded poorly with significant toxicity.

3.4 | Locoablative and locoregional techniques

3.4.1 | Ablative therapy

Use of ablative therapy, either endoscopically directed or percutaneously, with radiological direction has also been reported to be successful. In recent years, EUS ethanol ablation has become a valuable alternative to surgical resection of primary disease. Under ultrasound guidance, introduction of ethanol directly into the tumour causes cell membrane lysis and necrosis. The consequent destruction of the hypersecreting cells results in euglycaemia and amelioration of symptoms, the main aim of the procedure. The procedure is usually reserved for patients who are elderly, have refused surgery, have high anaesthetic risk or in those with recurrent disease where reoperation is infeasible, for example, postsurgical fibrosis. It is best suited for single, small (1-2 cm) pNET lesions that are not close to major blood vessels.

Limited case series and reports describe the use of ethanol ablation and describe a relatively strong safety profile with promising results in small, localized disease (Table 1). Levy et al. reported the largest case series (8 patients) for ethanol ablation of insulinomas. Five of those patients underwent EUS-guided ethanol injection and the remaining three underwent intraoperative ultrasound (IOUS)-guided ethanol injection. It was observed that the hypoglycaemic symptoms were relieved almost immediately post-procedure in all patients who underwent ethanol ablation and that this symptomatic relief was maintained throughout the follow-up (range, 5-38 months). Currently, there is no consensus as to the most appropriate volume and concentration of ethanol injection with potential intraoperator variability. With the risk of severe adverse events, there is need to perform the technique in centres with good experience.

Commonly reported complications from case reports include upper abdominal pain, localized bleeding and transient rises in lipase and amylase. Severe adverse events such as pancreatitis have been reported in limited cases. However, the advantage is that it is a minimally invasive procedure, is associated with a shorter hospital stay and is associated with a lower risk of complications.
TABLE 1 Ultrasound-guided ethanol ablation of sporadic insulinomas: case reports

| Authors            | n | Guidance | Maximum diameter (mm) | Total ethanol (mL) | Ethanol (%) | Complications                  |
|--------------------|---|----------|-----------------------|-------------------|-------------|-------------------------------|
| Levy et al62       | 5 | EUS      | 8.20                  | 0.1-3.0           | 95-99       | None                          |
| Qin et al64        | 4 | EUS      | 5.4-11.8              | 0.25-0.5          | 95          | None                          |
| Paik et al61       | 3 | EUS      | 9.14                  | 1.2-3.0           | 99          | Abdominal pain                |
| Trikudanathan et al65 | 1 | EUS      | 14                    | 1.0               | -           | None                          |
| Vleggar et al66    | 1 | EUS      | 10                    | 0.3               | 96          | None                          |
| Deprez et al63     | 1 | EUS      | -                     | 3.5               | 98          | Mild elevation pancreatic enzymes, haematoma |
| Jurgensen et al60  | 1 | EUS      | 13                    | 8.0               | -           | Abdominal pain, mild elevation pancreatic lipase |
| Burghardt et al59  | 1 | EUS      | 11                    | 1.0               | 96          | None                          |

EUS, endoscopic ultrasound; IOUS, intraoperative ultrasound; –, data not available.

Further studies evaluating dosing and long-term follow-up in insulinomas are required. The major limitations of ethanol ablation are the possibility of late recurrence that would require retreatment, incomplete ablation and the risk of progression during the follow-up. Further literature is awaited to fully assess the long-term efficacy of ablation in a large RCT with longer follow-up of patients with localized disease. Its use in metastatic disease for symptom control only is also a possibility.67

3.4.2 Embolization

In patients with a large hepatic burden of disease, hepatic resection and hepatic embolization (bland embolization, chemoembolization and radio-embolization) may also be considered with the intention of ameliorating clinical symptoms. Selective embolization of peripheral arteries induces temporary, but complete ischemia.68 Due to the small number of metastatic insulinomas, there are no RCTs comparing locoregional therapies, palliative liver surgery or medical management with limited case reports. Locoregional procedures are most frequently used in combination with SSAs when surgery is not feasible. Systemic medical therapies or PRRT is often used preferentially, particularly in functioning pNETs (eg, insulinomas) or when extrahepatic tumour load is greater than hepatic tumour burden.

3.5 Nuclear medicine

3.5.1 Peptide receptor radionuclide therapy

Mechanism of action

The use of peptide receptor radionuclide therapy (PRRT) depends on the binding of radiolabelled peptide hormones to the SSTRs on the tumour cell surface, with subsequent internalization to deliver localized radiotherapy to the tumour cell with little effect on surrounding tissue. The most frequently used radiopeptides for targeted therapy include yttrium (90Y) or lutetium (177Lu) linked to a somatostatin analogue.69 Prior to therapy, it is imperative to demonstrate expression of SSTRs on the tumour cells; hence, a pretreatment 111In-octreotide or a gallium68 DOTANOC PET-CT scan is performed.

Evidence to support use of PRRT in pNETs

Data from nonrandomized trials of 177lutetium-DOTATATE and 99yttrium-DOTATOC have consistently yielded impressive therapeutic benefits in patients with GEP-NETs, including pNETs.70,71 NETTER-1 was the first large RCT of PRRT, comparing treatment with 177Lu-DOTATOC-Tyr3-octreotate plus best supportive care including octreotide LAR vs. high-dose octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor-positive midgut neuroendocrine tumours (Table S3).72 Treatment with 177Lu-DOTATATE resulted in markedly longer PFS and a significantly higher response rate than the treatment with high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumours. In this study, median PFS was 8 months on the high-dose octreotide arm and was not yet reached on the 177 Lu-DOTATATE arm, translating to a 79% improvement in PFS (P < .00001). Outcomes may be determined by patient characteristics including the amount of SSTR uptake at diagnosis71 and tumour/liver burden.

There have been two small case series of patients with metastatic insulinoma that have demonstrated that PRRT can control hyperinsulinaemic hypoglycaemia: euglycaemia persisted even in the face of tumour progression, suggesting that favourable symptomatic responses can be observed even with no objective evidence of tumour response.79,73

Side effects

Peptide receptor radionuclide therapy is generally well tolerated. Acute side effects are usually mild and include nausea and gastrointestinal upset. Importantly rare but serious side effects may occur, including severe bone marrow disease (pancytopenia, acute myelogenous leukaemia, myelodysplastic syndrome) and renal toxicity.70,74 Another study of 265 patients undergoing PRRT found significant quality-of-life (QoL) improvements, regardless of treatment outcome.75
Positioning in the clinical pathway

In general, use of PRRT follows failed first-line medical therapy (Figure 5). Somatostatin receptor-positive disease is a prerequisite for starting treatment. PRRT offers a valuable treatment option for inoperable or metastatic pNETs, with promising responses and QoL improvements. In selected cases, PRRT may be beneficial as a neoadjuvant therapy to render a patient accessible to surgery. There is need for RCTs in pNETs comparing PRRT to current best available treatment, including chemotherapy, everolimus and sunitinib. Moreover, data assessing dosing and the effectiveness of PRRT specifically in insulinoma patients are warranted.

4 | CONCLUSIONS

In sporadic insulinomas, surgical resection remains the primary treatment option. In the absence of surgical cure, early referral to an experienced specialist neuroendocrine MDT is vital, so alternative treatments can be considered early to limit tumour growth and/or treat symptoms. A comprehensive review of the patient’s medical history, pathology, imaging and staging impacts upon therapy allocation.

The publication of landmark studies (namely PROMID, CLARINET, RADIANT and NETTER-1) has been a significant development when considering therapeutic options for NETs, although the studies have been performed in only small numbers with insulinomas. SSAs are typically used first line in patients with unresectable disease for control of symptoms and tumour growth. With disease progression, other medical therapies (eg, pasireotide, everolimus, sunitinib) appear to be effective treatments for patients with metastatic disease and refractory hypoglycaemia although tolerance should be monitored carefully. In the case of pasireotide and everolimus, these provide favourable effects on glucose concentrations in insulinoma patients, independent of a measurable tumour response. EUS-guided ethanol ablation is technically feasible, allows targeted intervention and is relatively safe with good treatment responses in limited case reports of small localized disease, ideal for patients who refuse or are not eligible for surgery. Emerging therapeutic options undoubtedly offer the potential to improve patient outcomes and provide symptom control but sequence of therapy and efficacy and safety of therapy combinations remains an area for future research.
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SUPPORTING INFORMATION
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