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Article type : 5 Unsolicited Review

Multi-disciplinary management of refractory insulinomas

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Summary

Insulinomas are predominantly benign (~90%), pancreatic neuroendocrine tumours characterised by hyperinsulinaemic hypoglycaemia. They usually present as a small (<2cm), well demarcated, solitary nodule that can arise in any part of the organ. Treatment of 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 are 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 multi-somatostatin receptor ligand. Pasireotide and everolimus both cause hyperglycaemia by physiological mechanisms synergistic with its anti-tumour/anti-proliferative 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 non-surgical 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: Insulinoma, neuroendocrine tumours, pasireotide, everolimus, sunitinib, ablation, peptide receptor radionuclide therapy.

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 hypoglycemia with low plasma glucose levels, that 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]** Hyperinsulinaemic hypoglycaemia should be suspected in an otherwise fit and well individual after exclusion of medication use (oral hypoglycaemic agents, insulin administration), factitious hypoglycaemia, non-insulinoma pancreatogenous hypoglycaemia and rarely non-islet 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 post-prandial period, and can pose a significant management challenge and cause of morbidity.**[5]**

1.2 Localisation of disease

Having confirmed the biochemical diagnosis, localisation of disease can be challenging. Conventional imaging (i.e. CT/MRI) and, if available, endoscopic ultrasound form the basis of localisation and diagnosis of suspected insulinomas. ^{68}Ga-DOTATATE PET-CT has a clear place in localising insulinomas because of the high affinity of the ^{68}Ga-DOTA peptides for somatostatin receptors (a 10-

fold higher affinity than ^{111}In-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 ^{68}Ga-DOTA-exendin 4 PET-CT to facilitate the localisation of occult insulinomas.**[7]** In contrast, malignant insulinoma often lack these GLP1-R.**[8]** Once localised, surgical resection of sporadic insulinomas is standard treatment since most tumours are small (<2cm), 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 both 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 sub-divides pNETs in 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]**

2. THERAPEUTIC OPTIONS AVAILABLE FOR INSULINOMAS

Recent consensus guidance has been published on the management of functional and non-functional 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 (e.g. earlier age of onset, multi-focal 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 as well as 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.**[17,18]**

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 anti-hypertensive 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 pre-operatively when dietary and lifestyle advice fails to prevent hypoglycaemia. Potential glycaemic mechanisms include inhibition of insulin release by direct action on β-cells through stimulation of α-adrenergic receptors**[20]** or increasing hepatic gluconeogenesis and reduced skeletal muscle glucose uptake.**[21]** Initiation doses of 50-300mg daily titrated to a maximum daily dose of 600mg (higher doses may be used in refractory hypoglycaemia) are used. Unfortunately side-effects are common (e.g. 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 (SSAs)

Somatostatin, produced in the pancreatic δ-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 ($SSTR_{1-5}$). These SSTR subtypes have distinct molecular structures, tissue distribution, intracellular signalling and pharmacological characteristics inhibiting different hormones. $SSTR_2$ is the dominant receptor in both α cells (glucagon) and β cells (insulin).**[23]**

2.4.1 Octreotide and Lanreotide

Inhibitory effect on hormone production by the tumour Synthetic SSAs have a unique binding affinity profile for each SSTR. These SSAs will suppress insulin and glucagon release from normal pancreatic cells via $SSTR_2$. NETs in general often express SSTRs at high levels, with $SSTR_2$ being the most prevalent subtype, while in contrast insulinomas have much lower $SSTR_2$ expression. Octreotide and lanreotide have a preferential affinity for mainly $SSTR_2$ and much less to $SSTR_5$. This differential SSTR sub-type 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 $SSTR_2$ in the insulinoma cells was associated with an improvement of hypoglycaemia in response to SSAs/octreotide; in contrast, low/absent expression of the receptor sub-type, $SSTR_2$ 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.**[24]**

Anti-proliferative effects The anti-proliferative effect of SSAs in the treatment of NETs was demonstrated in two major randomised, placebo-controlled studies: PROMID (octreotide LAR) and CLARINET (lanreotide) (Table 1, OSM).**[25,26]** In PROMID, 85 patients with well differentiated midgut NETs were randomly assigned to receive octreotide LAR 30mg *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; $P<0.001$); 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; $P<0.001$). Because of this anti-proliferative effect, SSAs may be considered first-line treatment in inoperable malignant insulinomas, capable of stabilising 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 multi-receptor somatostatin analogue that binds with high affinity to four somatostatin receptor subtypes ($SSTR_{1, 2, 3, 5}$) (dubbed a *'pan-receptor'* SSA). Its receptor binding affinity is 30-40 times higher for $SSTR_1$ and $SSTR_5$ than for octreotide.**[27]** The low expression of $SSTR_2$ in many insulinomas, with malignant insulinomas in particular over-expressing $SSTR_5$**[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 of refractory hypoglycaemia in malignant insulinoma.**[29,30]** Future clinical trials are being designed to assess the anti-proliferative effects of pasireotide in NETs.

Mechanism for the hyperglycaemic effects of pasireotide (Figure 2) Use of pasireotide in Cushing's disease, acromegaly and in phase 2 studies in NETs (including pNETs) have highlighted significant hyperglycaemia (79%) and development of type 2 diabetes.**[31]** This adverse effect on glucose metabolism is welcomed in patients with insulinomas. Henry *et al* 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.**[32]** 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 anti-diabetic agents, vildagliptin and liraglutide.**[33]**

3.2 Molecular targeted agents

3.2.1 Everolimus (an mTOR receptor inhibitor)

Mechanism of anti-proliferative effect mTOR inhibitors have an anti-proliferative 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.**[34]** 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 **(**Figure 3 and 4) The Akt/mTOR pathway is also involved in the control of glucose homeostasis and dysregulated mTOR signalling is implicated in peripheral insulin 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.**[36]** mTOR inhibition pharmacologically has a similar effect, resembling a state of peripheral insulin resistance.**[37]** Everolimus has also been shown to directly inhibit (pro)insulin 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 hypoglycaemia.

Evidence to support everolimus use in pNETs Kulke was the first to report symptomatic relief of hypoglycaemia with everolimus**[38]** 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 of NETs of different origins has been explored in the RADIANT trials (Table 2A, OSM).**[40-42]** In the phase 3 RADIANT-3 trial (RAD001 in Advanced Neuroendocrine Tumours) patients with advanced pancreatic NETs were randomised to receive everolimus, 10mg 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 <0.001). 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 al.* retrospectively analysed the 12 insulinoma cases from the RADIANT-3 trial and noted the added benefit of improved glycaemic control in 11 out of the 12 patients treated with everolimus.**[43]** 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 pre-treatment imaging recommended.**[44]**

Positioning in the clinical pathway Whereas tumour remissions are rare with everolimus, disease stabilisation 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 multi-targeted receptor tyrosine kinase inhibitor. Sunitinib displays anti-angiogenic and anti-tumour activity by inhibiting a number of molecular pathways involved in angiogenesis.**[45]**

Evidence to support everolimus use in pNETs Previously approved for other malignancies (e.g. 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 37.5mg demonstrated impressive PFS benefits compared to placebo (Table 2B, OSM).**[48]** The trial was discontinued prematurely as sunitinib clearly offered improvements in PFS compared to placebo. Median PFS was 11.4 months in the sunitinib arm compared with 5.5 months in the placebo arm (hazard ratio, 0.42; 95% confidence interval, 0.26-0.66; $P < 0.001$). RRs in the sunitinib and placebo arms were 9.3% and 0% respectively. Unfortunately, only 2 patients receiving sunitinib had an insulinoma and the outcome of these particular patients was not described. Unlike everolimus this drug does not appear to have a direct action on glycaemic control.

Side effects Cutaneous adverse events include mucositis, rash and hand–foot syndrome (HFS), characterised by palmar-plantar lesions. The most frequent side-effects reported include diarrhoea, nausea, vomiting, asthenia and fatigue. Hypertension and neutropenia are

the most frequent serious side-effects reported. Evidence suggests that sunitinib can worsen hypoglycaemia.**[49]**

Positioning in the clinical pathway Despite the reported benefits of PFS in pNETs reported with sunitinib, the consequences of worsened hypoglycaemia may outweigh such benefits specifically in malignant insulinomas.

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-Fluourouracil (5-FU), doxorubicin and streptozocin have commonly been implicated in the treatment of inoperable malignant insulinomas.**[50]** Other agents (dacarbazine, cisplatin, etoposide, capecitabine and temozolamide) 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.**[51-57]**

3.4 Loco-ablative and loco-regional 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.**[58]** 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 e.g. post-surgical fibrosis. It is best suited for single, small (1-2cm) 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, localised disease (Table 1).**[59-66]** Levy *et al.* reported the largest case series (8 patients) for ethanol ablation of insulinomas.**[62]** Five of those patients underwent EUS-guided ethanol injection and the remaining three underwent intra-operative 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 follow-up (range, 5–38 months). Currently there is no consensus as to the most appropriate volume and concentration of ethanol injection with potential intra-operator 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, localised bleeding and transient rises in lipase and amylase.**[59-66]** Severe adverse events such as pancreatitis have been reported in limited cases.**[61]** However the advantage is that it is a minimally invasive procedure, associated with a shorter hospital stay and is associated with a lower risk of complications.

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 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 localised disease. Its use in metastatic disease for symptom control only is also a possibility.**[67]**

3.4.2 Embolisation

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

3.5 Nuclear medicine

3.5.1 Peptide receptor radionuclide therapy (PRRT)

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 internalisation to deliver localised radiotherapy to the tumour cell with little effect on surrounding tissue. The most frequently used radio-peptides for targeted therapy include Yttrium (^{90}Y) or Lutetium (^{177}Lu) linked to a somatostatin analogue.**[69]** Prior to therapy, it is imperative to demonstrate expression of SSTRs on the tumour cells, hence a pre-treatment ^{111}In-Octreotide or a Gallium^{68} DOTANOC PET-CT scan is performed.

Evidence to support use of PRRT in pNETs Data from non-randomised trials of ^{177}Lutetium-DOTATATE and ^{90}Yttrium-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 ^{177}Lu-DOTA0-Tyr3-Octreotate plus best supportive care including octreotide LAR *versus* high-

dose octreotide LAR (60mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor positive midgut neuroendocrine tumours (Table 3, OSM).**[72]** Treatment with ^{177}Lu-Dotatate resulted in markedly longer PFS and a significantly higher response rate than 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 <0.00001). Outcomes may be determined by patient characteristics including the amount of SSTR uptake at diagnosis**[71]** 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 favourable symptomatic responses can be observed even with no objective evidence of tumour response.**[39,73]**

Side effects PRRT 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 leukemia, 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). Positive 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 is 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 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 (e.g. 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 localised 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.

Table 1 Ultrasound guided ethanol ablation of sporadic insulinomas: case reports

Authors *et al.*	n	Guidance	Maximum diameter (mm)	Total ethanol (mL)	Ethanol (%)	Complications
Levy[62]	5	EUS	8-20	0.1-3.0	95-99	None
	3	IOUS	11-12	0.7-1.5	95-98	Pancreatitis, pseudocyst
Qin[64]	4	EUS	5.4-11.8	0.25-0.5	95	None
Paik[61]	3	EUS	9-14	1.2-3.0	99	Abdominal pain
Trikudanathan[65]	1	EUS	14	1.0	-	None
Vleggar[66]	1	EUS	10	0.3	96	None
Deprez [63]	1	EUS	-	3.5	98	Mild elevation pancreatic enzymes, haematoma
Jurgensen[60]	1	EUS	13	8.0	95	Abdominal pain, mild elevation pancreatic lipase
Burghardt[59]	1	EUS	11	1.0	96	None

EUS, endoscopic ultrasound; IOUS, intraoperative ultrasound; -, data not available

Figure 1 Treatment options for insulinomas

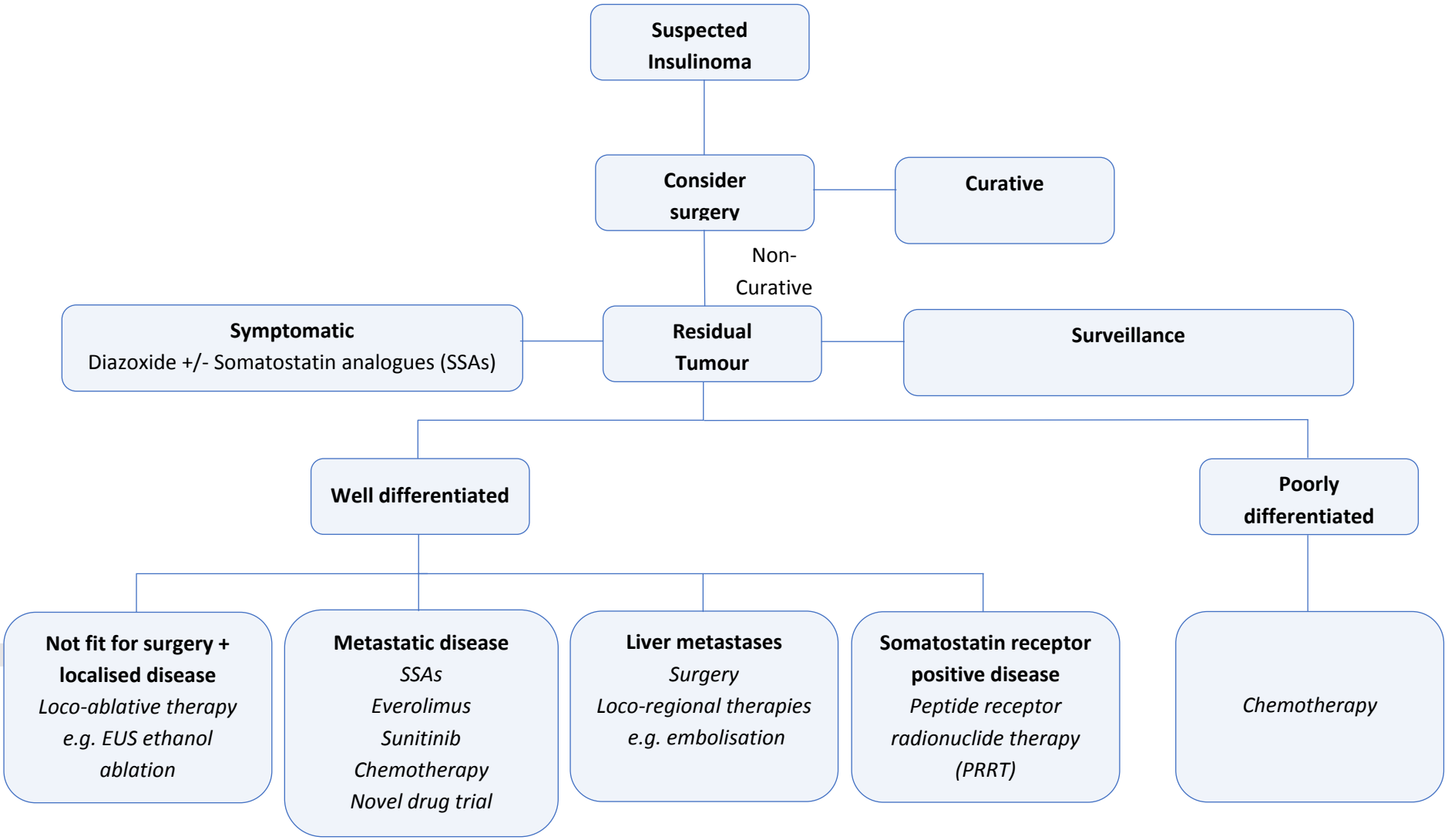


Figure 2 Pasireotide, a novel multi-receptor somatostatin analogue, acts predominantly via somatostatin receptor subtypes 2 and 5 and causes hyperglycaemia, through both DIRECT and INDIRECT effects.

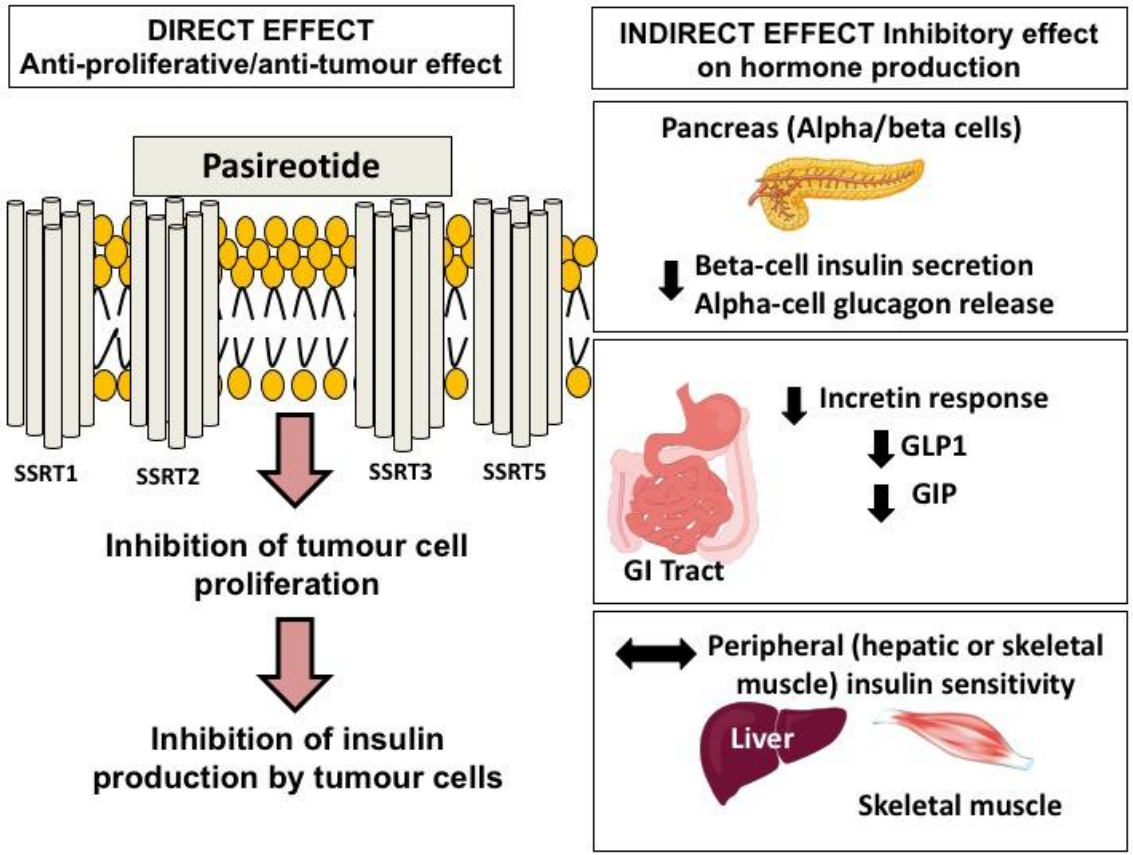


Figure 3 Inhibition of mTOR by everolimus causes hyperglycaemia by several mechanisms synergistically: i) inducing peripheral (skeletal muscle and hepatic) insulin resistance through reduced Akt phosphorylation in skeletal muscle and liver respectively, ii) reducing beta cell insulin secretion, iii) reducing tumour cell proliferation by Akt-mediated inhibition of protein synthesis (Adapted from **[76]**).

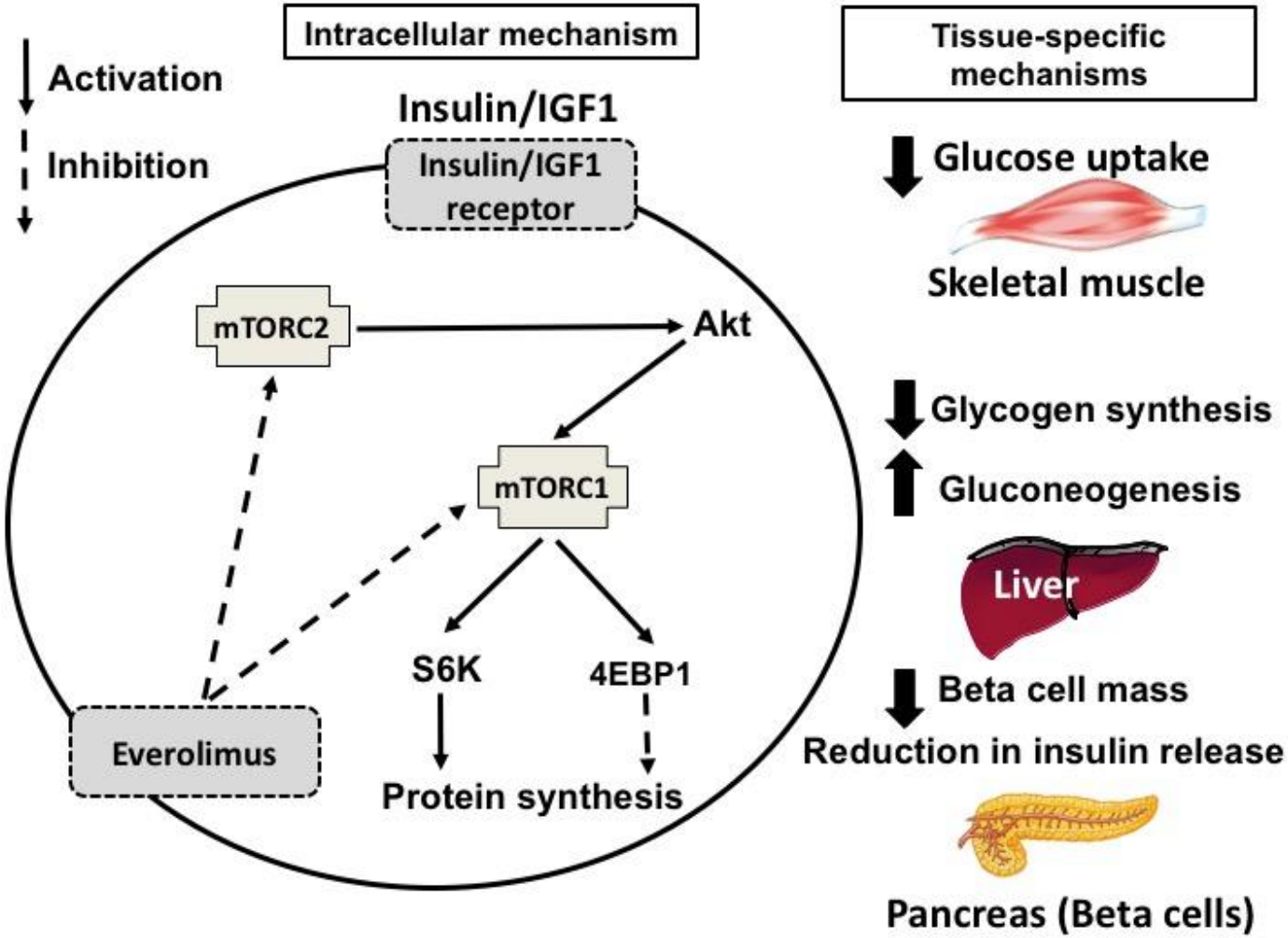
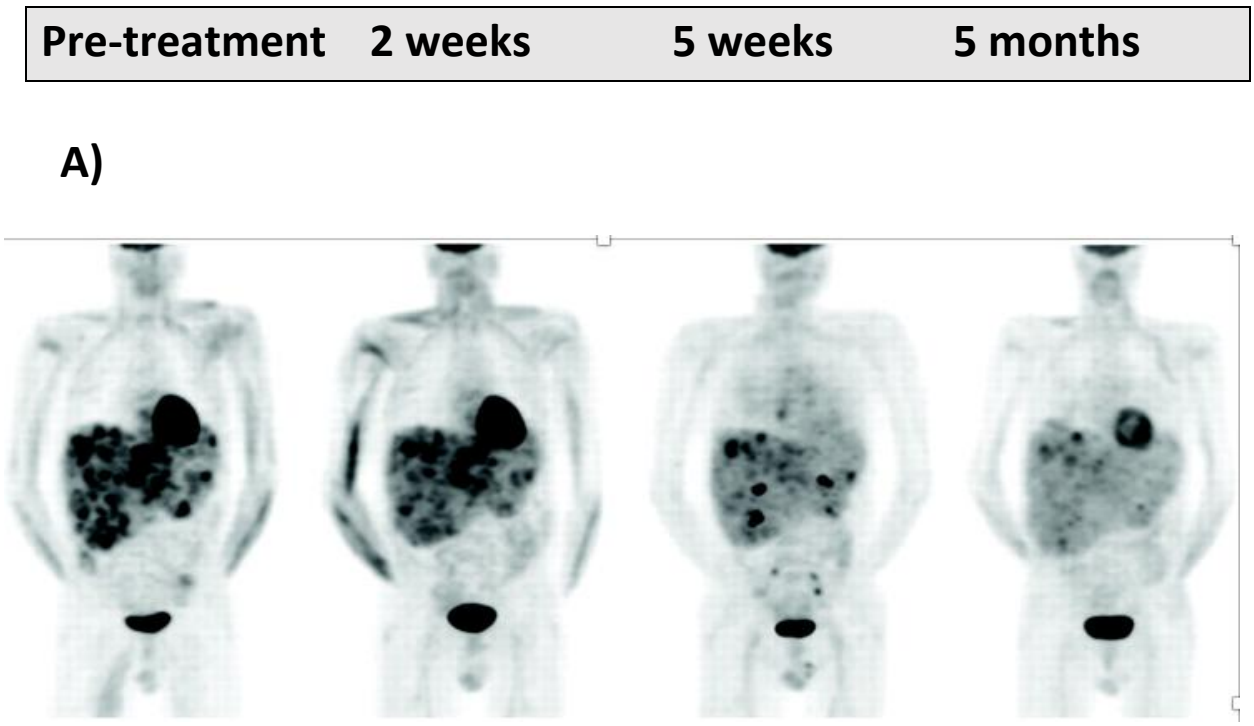


Figure 4 Direct and indirect mechanism of action of everolimus in insulinoma
^{18}F-FDG-PET scanning demonstrate the **A)** reduced *pathological* tumour glucose uptake in liver and reduced *physiological* uptake in the muscles and myocardium during treatment with everolimus. **B)** Maximum standardised uptake values showing reduction in uptake in myocardium (solid, dark circles), forearm (open diamonds) and uptake in the hottest three tumour lesions averaged per patient (taken from **[37]**).



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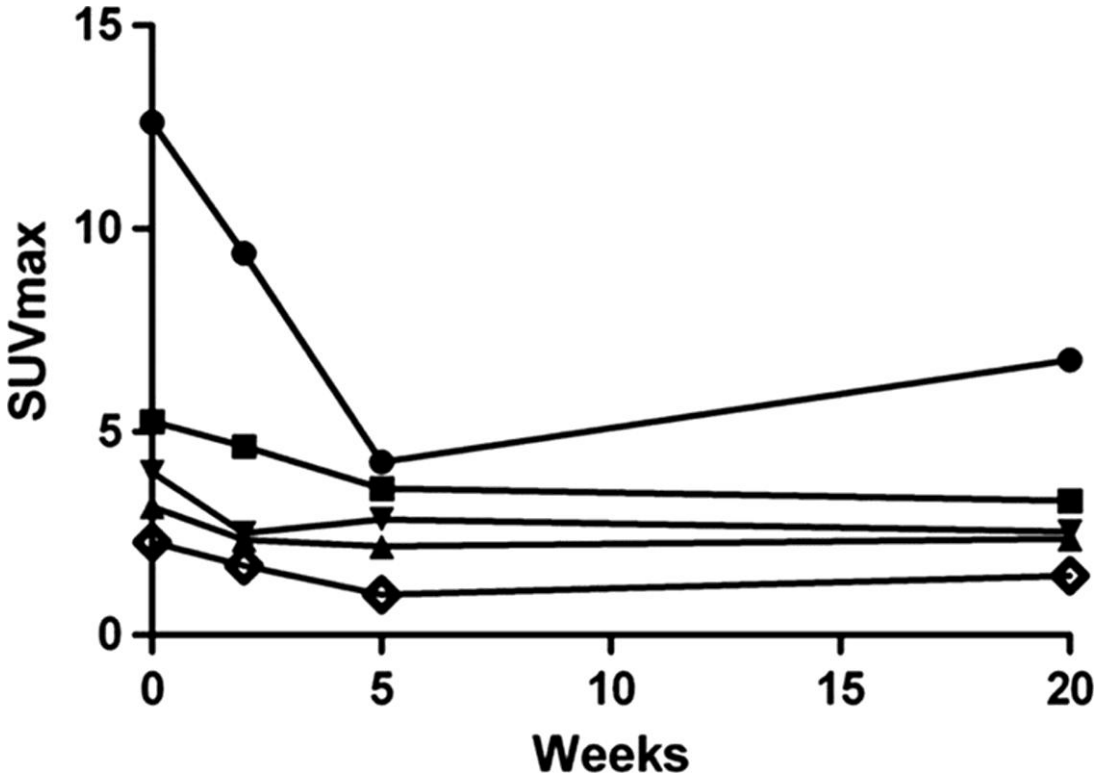
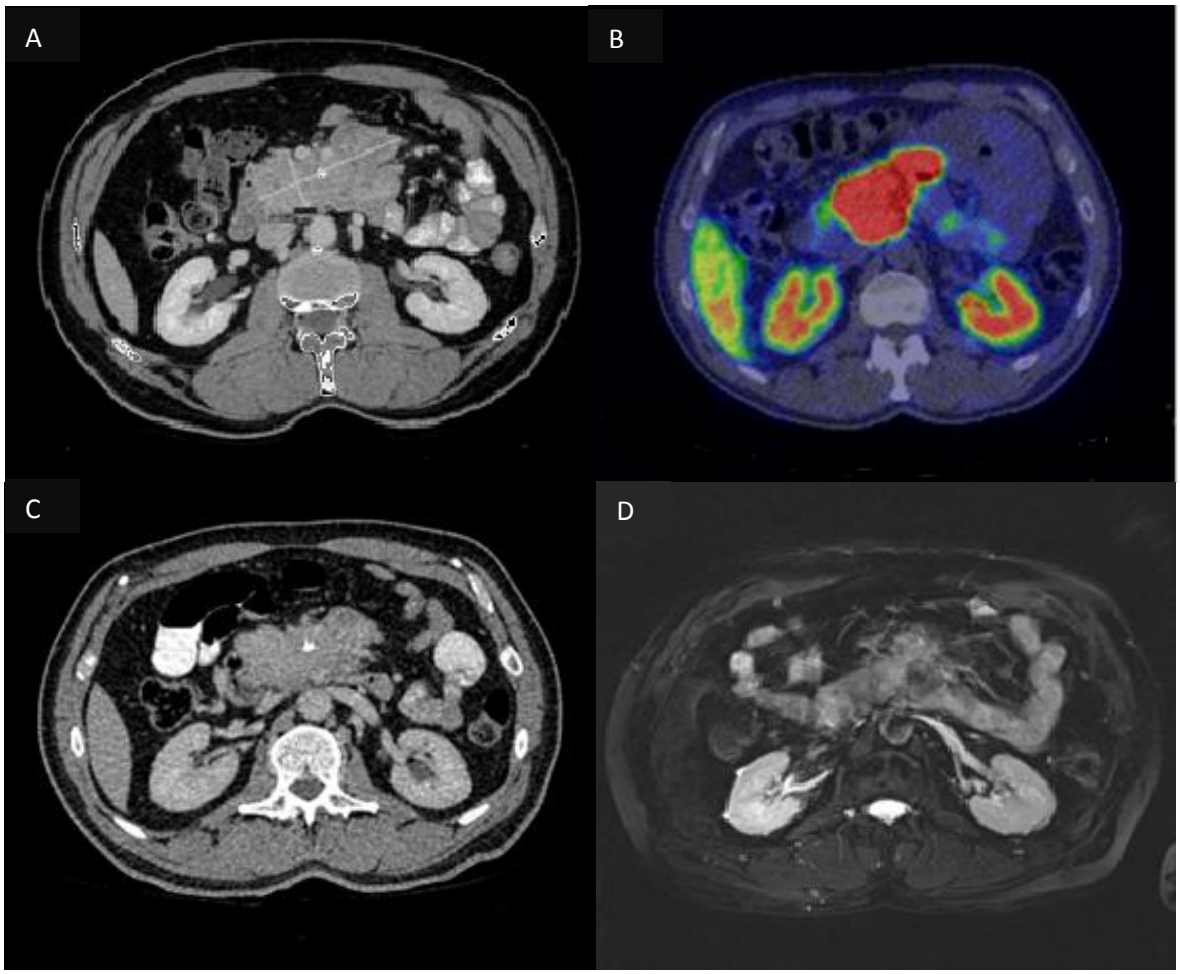


Figure 5 A case of refractory insulinoma: a 58 year old taxi driver



(A) CT abdomen pre-treatment. Large peripancreatic mass (9.6 x 3.7cm) with lymph node involvement, deemed inoperable. Histology from this tumour demonstrated a grade 2 pancreatic neuroendocrine tumour (Ki-67 10%). Biochemical investigations confirmed endogenous hyperinsulinaemic hypoglycaemia (glucose 2.9 mmol/L, insulin 226 pmol/L and C-peptide 1853pmol/L).

(B) Gallium^{68} DOTANOC PET-CT. The large retroperitoneal irregular mass lesion demonstrates intense tracer uptake. The patient remained symptomatic with hypoglycaemia despite treatment with diazoxide and somatostatin analogues (sandostatin LAR 30mg).

(C) CT abdomen 3 months post-treatment with everolimus. The mass lesion in the retroperitoneum had reduced in size (7.4 x 3.2 cm) associated with a good clinical response. Unfortunately, the patient developed a severe pneumonia requiring admission to intensive care. Everolimus was discontinued.

(D) MRI pancreas after 3 cycles of peptide receptor radionuclide therapy. The known peripancreatic retroperitoneal lobulated lesion has regressed in size (8 x 6.2 cm (11.3 x 6.4 cm immediately prior to PRRT)). There is still surrounding upper abdominal lymphadenopathy centred around the coeliac axis and head of the pancreas but the patient was asymptomatic.