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Glucagonoma of the pancreas: diagnostic approach and therapeutic algorithm for a rare nosological entity

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Abstract

Glucagonoma remains a very rare neuroendocrine tumor of the pancreas, accounting for 2% of all islet-cell carcinomas. The aim of this review is to highlight important aspects of pancreatic glucagonoma, including epidemiology, clinical presentation and diagnostic evaluation, and to elucidate the current therapeutic management of this nosologic entity. A combined automated and manual systematic search of the literature was performed using electronic search engines (Medline/PubMed, Scopus, Ovid and Cochrane Library), until April 2025. Glucagonoma originates from the a-cells of the pancreatic Langerhans islets. Its reported incidence is 1 in 20,000,000 per year. Typical clinical manifestations include necrolytic migratory erythema, diabetes mellitus (DM), weight loss and anemia, along with elevated serum glucagon levels. Other symptoms, such as venous thrombosis, neuropsychiatric findings known as 4D (dermatitis, DM, deep-vein thrombosis, depression), or diarrhea can also be present. Unfortunately, metastases are encountered in the majority of patients. Prompt diagnosis is usually accomplished by computed tomography and magnetic resonance imaging. The only treatment option is the surgical resection of the tumor. Conservative management, based on the administration of chemotherapy, somatostatin analogs, molecular targeted therapy and peptide receptor radionuclide therapy is also an alternative.

Keywords Glucagonoma, pancreas, therapeutic management, prognostic parameters

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Introduction

Glucagonoma remains a very rare neuroendocrine tumor of the pancreas (pNET) accounting for 2% of all islet-cell carcinomas [1]. It originates from the a-cells of the pancreatic Langerhans islets [2]. In 1942, Becker *et al* first reported the coexistence of cutaneous lesions with a pancreatic tumor and diabetes mellitus (DM). However, the first official diagnosis of glucagonoma was made by McGavran and his colleagues in 1966, reporting on a patient with skin erosions, elevated serum glucagon levels, DM and a secreting pancreatic tumor, features that comprise a clinical syndrome later named "glucagonoma syndrome" (GS) [1,3,4]. The reported incidence of GS is 1 in 20,000,000 per year, and it usually affects the body and tail of the pancreas [5,6]. Typical clinical manifestations include a distinct rash called necrolytic migratory erythema (NME), DM, weight loss and anemia, along with elevated serum glucagon levels. Other symptoms, such as venous thrombosis, neuropsychiatric findings known as 4D (dermatitis, DM, deep-vein thrombosis, depression), or diarrhea can also be present, though less frequently.

Unfortunately, metastases are encountered in the majority of patients at presentation, partly because of delayed detection

or misdiagnosis [7-11]. Prompt diagnosis can be challenging, owing to the rarity of this entity and the extensive differential diagnosis; however, it is usually accomplished by imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI) [5]. The only treatment option offering a possible cure is the surgical resection of the tumor; the type of procedure differs for each case, depending on the tumor's location and size, and the potential invasion of nearby organs. On the other hand, conservative management, based on the administration of chemotherapy or somatostatin analogs (SSAs), is also an alternative, especially when surgery cannot be performed [4,6,12]. The aim of this review is to highlight important aspects of pancreatic glucagonoma, including epidemiology, clinical presentation, diagnostic modalities and histopathological evaluation, and to elucidate the current therapeutic management of this rare nosologic entity. A combined automated and manual systematic search of the relevant medical literature was performed using electronic search engines (Medline, PubMed, Scopus, Ovid and Cochrane Library). Publications of interest included randomized and non-randomized studies, systematic reviews, meta-analyses, case series, case reports, letters to the editor and conference abstracts.

Epidemiology and classification

NETs are a type of tumors with various clinical characteristics that emerge in different parts of the body. Amongst the most frequent NETs are pNETs, which are derived from the endocrine pancreas and are considered foregut-NETs [13,14]. They represent 1-2% of all pancreatic malignancies and their estimated incidence is 1-5 per 100,000 people per year. However, autopsy studies indicate that fewer than 1 per 1000 pNETs actually cause symptoms, and 0.5-1.5% of the general population may actually be affected. The most common pNETs are insulinomas, gastrinomas, VIPomas, glucagonomas and somatostatinomas, secreting insulin, gastrin, vasoactive intestinal peptide, glucagon and somatostatin, respectively [15-17].

Glucagonomas appear as 1% of all NETs, 2-7% of all pNETs and 1.2% of all neoplasms of the pancreas [17-19]. Their annual prevalence is 1 per 20,000,000, and they affect males and females equally, despite the initial marginal report of more female cases [8]. A glucagonoma typically occurs in the fourth to sixth decade of life, with a peak at the age of 53.5 years; reported ages range from 15-90 years, with only few incidents occurring in pediatric patients [20-23]. Glucagonomas are more frequently located in the distal pancreas, and in about 85% of cases involve the body or tail. The lack of specificity of the clinical manifestations and the slow progression of the tumor mean that the final diagnosis is usually achieved approximately 3 years after the establishment of the first symptoms; therefore, the disease is already advanced and malignant in most cases [6,12,24]. At diagnosis, the average tumor size is between 0.4 and 25 cm; however, in most instances it is larger than 5 cm [6,25]. With regard to the outcome, non-metastatic cases present an almost 100% 10-year survival, while in patients with metastatic lesions this reduces to 51.6%. The 5-year survival rate is 76% and the mean survival time is estimated to be 3-7 years, more specifically around 4.9 years [1,24,26].

Glucagonomas are almost always solitary pancreatic lesions (99%), and the vast majority occur sporadically (80%), unless they are part of an inherited familial disorder [27,28]. Such syndromes are multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau syndrome (vHL) and Mahvash disease [14]. MEN1 is an autosomal dominant disorder related to the tumor suppressor gene MEN1. Typically, diagnosis of the syndrome is suspected when cancerous abnormalities are detected in at least 2 of the 3 typically affected organs (parathyroid glands, endocrine pancreas and anterior pituitary gland) [29,30]. This entity accounts for 80% of MEN1-related pNETs, whereas glucagonoma is rather rare, accounting for only 3% of pNETs, despite presenting the most malignant characteristics [31]. vHL syndrome is an autosomal dominant disorder associated with the development of various neoplasms and cysts. Usually, it appears as hemangioblastoma in the central nervous system and retina, renal cell carcinoma as well as benign renal cysts, pheochromocytoma along with pNET. In addition, pancreatic involvement in the syndrome is most frequently encountered as cystadenomas, while NETs are present in approximately 17% of affected cases [14,32]. Finally, Mahvash disease is a disorder caused by an homozygous inactivating mutation in the glucagon receptor gene, resulting in α-cell hyperplasia, glucagonoma and high glucagon serum levels [14]. Although glucagonomas typically originate from the α-cells of the pancreatic Langerhans islets, a case of a primary hepatic glucagonoma has been described [33].

Clinical features

The clinical manifestations of glucagonoma vary, though it remains asymptomatic in 50% of cases [34,35]. NME, new-onset DM and weight loss are 3 characteristic symptoms of the functional syndrome associated with glucagonoma [36-39]. NME is a dermatological disorder that presents as a migratory, painful and pruritic cutaneous rash, consisting of irregular erythematous plaques and patches with superficial necrosis, bullae and erosions, alongside central healing. These lesions are typically encountered in the perineum and perineal region, lower abdomen, thighs, distal extremities and perioral region, though they can be widespread. Among patients with GS, NME appears in 70-80%, DM in 76-94%, and weight loss in 66-96% of the affected cases [3,11,26].

Other common symptoms include diarrhea (30%), normocytic normochromic anemia (49.6%), deep vein thrombosis (DVT) (50%), cachexia, glossitis, angular cheilitis, abdominal pain (7.5-33%), and neuropsychiatric disorders including depression, dementia, psychosis, agitation, paranoid delusions, ataxia, hyperreflexia, nervousness, left-sided migraine, headache, and numbness (20%) [32,36,37]. Symptoms such as anorexia, steatorrhea, back pain, pitting edema of legs,

fatigue, impaired vision, hair loss, vulvovaginitis, vomiting/gastrointestinal dysfunction, fingernail deformity and fragility, candidiasis, hydroelectric disorders and renal dysfunction have also been described [34,36]. Glucagonoma-related reversible dilated cardiomyopathy, as well as congestive heart failure, have also been reported in the literature. Laboratory findings include markedly elevated serum glucagon levels, fasting hyperglycemia, hyperinsulinemic hyperglycemia, hypoaminoacidemia, as well as a deficiency in vitamin B, fatty acids, zinc and other minerals [16,26,34,36,40,41].

About half of the patients present with metastatic disease at diagnosis, and thus suffer from symptoms related to continuous hormone secretion from the metastatic foci. The most common metastatic sites are the liver (79-90%) and regional lymph nodes (30-37.8%). Widespread metastatic disease in the liver leads to disrupted organ function, including reduced glucagon metabolism and further elevation of glucagon serum levels, worsening the symptoms [16,26]. Life expectancy is reduced by half in the case of coexisting liver metastases. There have been reports of bone metastases, more particularly in the vertebrae (able to cause spinal cord compression), the ribs and sacrum [16]. Other foci include the adrenal glands, kidneys and lungs [16]. A single case of metastasis to the right ovary has also been described [20].

Histopathology and immunochemistry

Glucagonoma derives from the pancreatic α-cells, located in the Langerhans islets. Normally, a pathological analysis can reveal an unencapsulated mass with recognizable and clear outlines, made up of uniform cuboidal, round or polygonal cells that usually create nest-like, rosette or trabecular formations [18,20,42-44]. These cells consist of an oval or round, pale, centrally located nucleus with stippled chromatin and minimal atypia inside an eosinophilic, granular cytoplasm [8,18,22,32,45]. The parenchyma surrounding the lesion typically develops a scant stromal reaction, while depositions of amyloid substance may also be detected. Additionally, calcifications may be observed, along with the dilated tumor vessels, yet necrosis is rather uncommonly encountered [32,46].

Immunochemically, the most characteristic positive markers of all NETs are chromogranin A (CgA) and synaptophysin (Syn) [47,48]. Apart from these, there are a few more that may occasionally be detected as positive: these include neuron-specific enolase (NSE), CD56, S100, CDX2, PAX2, TTF-1, SSR2, SSR5, serotonin, Vimentin, E-cadherin, CK5/6, AE1 and AE3 [49]. The immunohistochemical expression of somatostatin receptors (SSTR) 2 and 5 is substantial, since it has a prognostic but also a therapeutic role. Furthermore, there have been reports of glucagonomas positive for prolactin receptors (PR), CD34, CD31, CA-19,9, CEA, aFP, CK20, PCK, EMA, pancreatin, cholecystokinin (CCK), PP, CK19, and C-met [43]. It has also been observed that strong positivity for CgA and negative or weakly positive immunostaining of PGP 9.5 (a ubiquitin-carboxyl hydrolase that is expressed in nerve tissues) are associated with worse prognosis and poorer outcome. Finally, the death domain associated proteins ATRX/DAXX, might be inactivated; thus, tumor staining for these is likely to be nearly absent, while alternative lengthening of telomeres is usually positive [44,45].

Diagnostic modalities

The diagnosis of glucagonoma is based on the combination of characteristic clinical findings, the detection of elevated serum glucagon levels (>500 pg/mL), as well as the localization and imaging of a pancreatic tumor. Stacpoole, in his 1981 paper, stated that glucagon immunostaining on a tumor biopsy is also implemented, though biopsies are not always performed during evaluation [18,50]. Laboratory findings also include abnormal glucose tolerance, anemia, zinc and vitamins B3 and B7 deficiency. Other markers include elevated NSE and CgA, the former being an indicator of advanced disease. The patient also needs to be questioned about their personal or family history regarding MEN-1 syndrome.

Various imaging techniques carry significance in the diagnosis of pancreatic glucagonoma. CT scan with the use of intravenous contrast is often used to locate the tumor, which appears as a homogenous, isodense mass without contrast, and as a homogenous hyperdense or isodense tumor during the arterial phase of the enhancement. A CT scan can also demonstrate the existence of calcifications within the tumor [11,22,51]. MRI can also be employed, though its role in the diagnosis of glucagonoma remains unclear. The tumor appears as a low-signal mass in T1-weighted images, and as a high-signal mass in T2-weighted images, with fat suppression images offering higher sensitivity [50-52]. On the other hand endoscopic ultrasound is a highly sensitive diagnostic alternative [50].

For smaller lesions, functional imaging is employed. Somatostatin receptor scintigraphy, combined with SPECT/CT scan using the ^{111}In radioisotope with somatostatin analogs, is the ideal modality for staging the malignancy and localizing metastases. However, the drug has low uptake in poorly-differentiated tumors, as well as augmented uptake in non-specific inflammation [22,51]. A newer diagnostic tool, namely positron emission tomography (PET)/CT scan with the use of ^{68}Ga-DOTA-peptides (DOTATATE, DOTATOC, DOTANOC) offers higher sensitivity in the detection and staging of the tumor than its predecessor, and can be used for the selection of patients for targeted treatment, as it presents high uptake in well differentiated/low-grade tumors [51,52]. PET/CT scan with the use of the ^{18}F-FDG glucose analog offers lower specificity, though it is well attenuated by poorly differentiated/high grade tumors [51,52], while ^{18}F-DOPA offers the highest sensitivity of all functional imaging modalities, but its availability is limited. Nevertheless, in recent years, several new tracers were designed to exploit potential targets of the neuroendocrine cells, and were employed in clinical trials for both imaging and therapy. Currently, the real-life clinical impact of these tracers remains controversial; however, the favorable biodistribution

(e.g., [68Ga]Ga-FAPI, SSTR antagonists) and the possibility of applying new theranostic pairs may provide novel diagnostic as well as therapeutic alternatives (e.g., [68Ga]Ga-PSMA, [64Cu]Cu-SARTATE, [68Ga]Ga-CXCR4) for NET patients [53]. Visceral arteriography is considered the gold standard for the diagnosis of glucagonoma, though it is not always warranted given its invasive nature [50]. A biopsy of the tumor confirms the diagnosis and differentiates glucagonoma from pancreatic adenocarcinoma, although as aforementioned, it is not always performed [14,49,50].

The differential diagnosis can be vast. Pseudoglucagonoma syndrome can be caused by malnutrition due to abdominal surgery, alcoholism, anorexia nervosa, cystic fibrosis, celiac disease, pulmonary or renal glucagonoma, acute or chronic pancreatitis, liver disease, cirrhosis, infection, Crohn's disease or glucagon-secreting bronchial cancer [11]. In addition, NME can stem from other pNETs, liver cirrhosis, malnutrition, Crohn's disease, autoimmune progesterone dermatitis, lipase hypersecretion syndrome, acrodermatitis enteropathica, zinc deficiency, psoriasis, eczema, seborrheic dermatitis, chronic mucocutaneous candidiasis, pemphigus, and as a side effect of chemotherapy [38]. Elevated serum glucagon levels can also be derived from liver cirrhosis, chronic renal failure, pancreatitis, DM, familial hyperglucagonemia, sepsis, Cushing's syndrome, diabetic ketoacidosis and acute trauma [54]. Finally, adenocarcinoma of the pancreas needs to be ruled out, especially when the lesion is located in the head of the pancreas [55].

Therapeutic approach

Therapeutic modalities include surgery, chemotherapy, SSAs, molecular targeted therapy (MTT) and peptide receptor radionuclide therapy (PRRT) (Fig. 1). Surgical resection is the recommended approach, and is the only curative method for localized lesions [4,32]. Distal pancreatectomy, typically with splenectomy, is performed for lesions on the body and tail of the pancreas; however, depending on the location of the tumor, pancreaticoduodenectomy and total pancreatectomy may be performed. Spleen-preserving distal pancreatectomy has been reported with favorable results. Tumor enucleation can also be performed in low-grade tumors. Regardless of the chosen path, lymphadenectomy must always be included in the operation. Moreover, the decision between an open or a laparoscopic procedure remains at the discretion of the surgeon [4]. In the presence of liver metastases, resection of the primary tumor remains controversial. As far as liver metastases are concerned, management includes synchronous surgical resection, provided there are no other sites of metastases and liver function is adequate [32]. Liver transplantation may also be considered in selected cases. For non-resectable tumors, surgical palliative methods include microwave and radiofrequency ablation, cryoablation, hepatic artery embolization and chemoembolization, as well as injection of radioactive materials [32,56].

If surgery is not an option, because of contraindications, advanced disease or patient's preference, several palliative drug therapies have been discovered that aim to slow down the progression of the tumor. Most commonly used are the SSAs, which include mainly first generation SSAs octreotide and lanreotide, and more recently the second generation SSA pasireotide. The mechanism of action entails an endogenous inhibition of the release of glucagon, thus resulting in smaller concentrations, decreased activity and related symptom relief [4]. In addition, the CLARINET and PROMID trials revealed better survival rates and potential slight tumor shrinkage, but only the former study included pNETs [4,46]. SSAs are generally well-tolerated and safe; nonetheless, adverse effects have been documented, including diarrhea, abdominal pain, cholelithiasis, tachyphylaxis phenomena and rebound hypersecretion upon treatment pause [39]. According to the recent guidelines SSAs, together with nutritional support, are considered first-line palliative treatment, whereas short-acting SSAs can also be given preoperatively to control symptoms [36,57]. Besides nutritional support with supplementation of amino acids, zinc and fatty acids, topical dermatological therapy—and perhaps insulin or blood glucose lowering agents for a more rapid hyperglycemia resolution—may be added on occasion. Finally, the treatment plan needs to encompass the preoperative administration of low-dose heparin for DVT prevention [58].

PRRT is also an important component of glucagonoma management. This method uses radiolabeled SSAs to achieve localized radiotherapy in high somatostatin receptor (SSR)-expressing tumors, resulting in radical treatment and improved prognosis [32]. It can be employed when other medical treatment fails or there are recurrent tumors. PRRT has already been administered in case reports or small case series, and has also been given in a neoadjuvant setting [55,59,60]. Regarding adverse effects, renal and liver toxicity have been reported, as well as thrombocytopenia and leukocytopenia. The combined use of radionuclide conjugates has shown better clinical efficacy over the use of individual compounds, and concomitant administration of fluorouracil or cisplatin has demonstrated better delivery and efficacy of the drug. Agents administered include ^{177}Lutetium-DOTATATE, ^{90}Ytrium-DOTATOC/DOTATATE/DOTALAN and ^{111}Indium-DTPAOC [51,54]. Other considerations include management of hyperglycemia or ketoacidosis with the use of insulin.

In the context of MTTs, despite the fact that non-encouraging outcomes have been published specifically for patients with glucagonomas, sunitinib, along with cabozantinib as a tyrosine kinase inhibitor (TKI) and everolimus as an inhibitor of mechanistic target of rapamycin (mTORi), have received approval for unresectable pNETs. Specifically, in the trial approving sunitinib for advanced pNETs, 3 patients in the drug arm and 2 in the placebo arm suffered from glucagonoma; however, the investigators did not report their specific efficacy [61]. Moreover, the role of everolimus in altering glucose homeostasis, by reducing insulin secretion together with glucagon hypersecretion, dictates a cautious approach. Other biological treatments include bevacizumab and TKIs such as sulfatinib, and temsirolimus as mTORi but

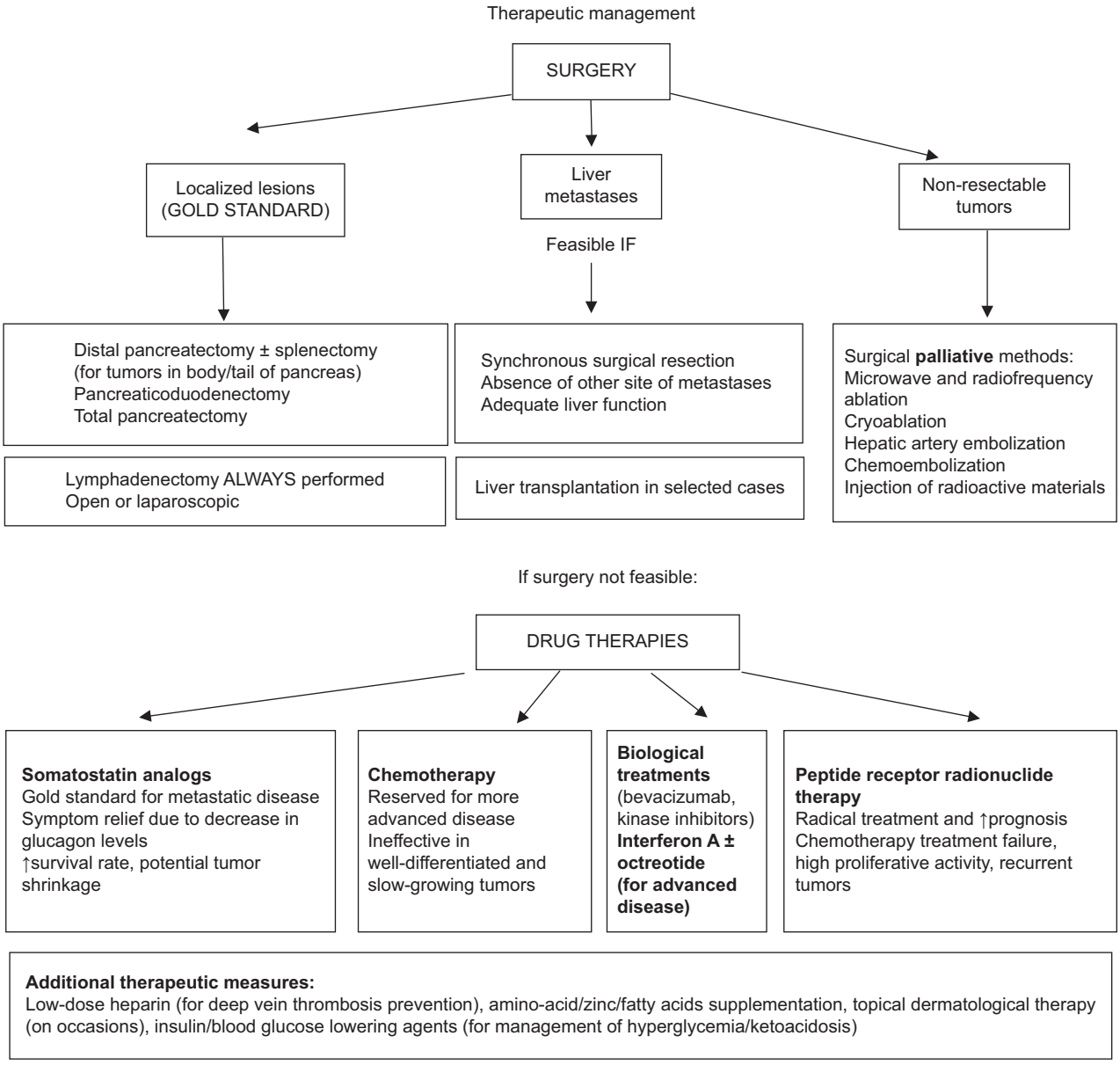

Figure 1 Diagnostic and therapeutic algorithm for pancreatic glucagonoma

again no specific referral in patient with glucagonoma has been accomplished. Nevertheless, case reports assessing that MTTs were administered as a component of a combination treatment have been recently published [21,56,57]. Interferon-A, alone or in combination with octreotide, can also be used in advanced disease [16].

Another option for patients who are unable to undergo surgery can be chemotherapy, particularly with streptozotocin, which aims to damage the pancreatic islets more selectively. Systemic chemotherapy is usually reserved for more advanced disease [2,22]. In case of well-differentiated tumors with slow progression, streptozotocin and doxorubicin, or capecitabine and temozolomide have been used, whereas gemcitabine, 5-fluoro uracil, irinotecan, etoposide, platinum compounds and taxanes are reserved for more aggressive cases [16,22]. Nevertheless, glucagonomas may exhibit aggressive behaviors or resistance to treatment, challenging clinicians to employ sequential multimodal therapeutic regimens that combine systemic strategies with local therapeutic options [62]. Finally, an ongoing clinical trial aiming to evaluate progression-free survival associated with temozolomide alone or temozolomide and capecitabine in patients with advanced pancreatic glucagonomas remains under thoughtful consideration.

All things considered, the prompt diagnosis of glucagonoma can be challenging, owing to the rarity of the tumor and the extensive differential diagnosis; however, it is usually based on laboratory evidence, CT, MRI and functional imaging. The only treatment option offering adequate cure is the surgical resection of the tumor, with the type of intervention depending on the location, size and the potential invasion of nearby

organs. If surgery is not an option, because of contraindications, advanced disease or patient's preference, several drug therapies based on the administration of chemotherapy or SSAs might be administered at the discretion of the attending physician. PRRT is also an important alternative therapeutic modality for glucagonoma management.

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