

# Spleen-preserving distal pancreatectomy and lymphadenectomy for glucagonoma syndrome

## A case report

Xuefeng Cao, MS<sup>a</sup>, Xixiu Wang, MS<sup>b</sup>, Yanmin Lu, MS<sup>c</sup>, Baolei Zhao, MD<sup>a</sup>, Jian Shi, MS<sup>a</sup>, Qinghai Guan, MS<sup>a</sup>, Xingyuan Zhang, MS<sup>a,\*</sup>

### Abstract

**Rationale:** Glucagonoma is a rare type of functional pancreatic neuroendocrine tumor that is characterized by distinctive clinical manifestations; among these, necrolytic migratory erythema represents the hallmark clinical sign of glucagonoma syndrome and is usually presented as the initial complaint of patients.

**Patient concerns:** A 30-year-old male patient was admitted to our hospital with a complaint of diffuse erythematous ulcerating skin rash for more than 10 months. He also complained of hyperglycemia and a weight loss of 15 kg in those months.

**Diagnosis:** This patient underwent a contrast-enhanced computed tomography scan which showed a pancreatic body mass measuring approximately 6 cm with low density accompanied by partial calcification in plain scanning images and uneven enhancement in strengthening periods. In addition, laboratory tests indicated elevated fasting blood glucagon (1109 pg/mL, normal range: 50–150 pg/mL) levels. Glucagonoma syndrome was ultimately diagnosed in clinical.

**Intervention:** Spleen-preserving distal pancreatectomy was conducted and postoperative pathology revealed the presence of glucagonoma.

**Outcomes:** The patient recovered uneventfully with the glucagonoma syndrome disappeared soon after surgery, and the postoperative plasma glucagon decreased to a normal level. Follow-up showed no recurrence for 5 years since the surgery.

**Lessons:** The treatment of glucagonoma should be directed according to the stage at which the disease is diagnosed. Surgery is currently the only method available to cure the tumor, although medications are given to patients who present with advanced glucagonoma and who are not candidates for operation. Multidisciplinary therapy and multimodality treatment are advised, although these have been systematically evaluated to a lesser degree.

**Abbreviations:** CA-199 = carbohydrate antigen-199, CEA = carcinoembryonic antigen, CgA = chromogranin A, CRP = C-reactive protein, CT = computed tomography, DM = diabetes mellitus, ESR = erythrocyte sedimentation rate, FDA = Food and Drug Administration, NME = necrolytic migratory erythema, NSE = neuron specific enolase, pNET = pancreatic neuroendocrine tumor, PPRT = peptide receptor radiotherapy, RBC = red blood cell count, SSAs = somatostatin analogues, Syn = synaptophysin, WBC = white blood cell count.

**Keywords:** case report, glucagonoma syndrome, pancreas, treatment

## 1. Introduction

Glucagonoma is a pancreatic neuroendocrine tumor (pNET) derived from the alpha cells of the islets of Langerhans.<sup>[1]</sup> It is usually discovered through the identification of a glucagonoma

syndrome, which is a rare paraneoplastic phenomenon with an estimated incidence of one in 20 million that is caused by the autonomous production of glucagon by the tumor and is characterized by distinctive clinical manifestations, including

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Case reports are exempt from formal ethical approval in our hospital. Informed written consent was obtained from the patient for publication of this case report and any accompanying images.

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<sup>a</sup> Department of Hepatobiliary Surgery, <sup>b</sup> Department of Medicine-Cardiovascular, <sup>c</sup> Department of Nutrition, Hospital of Binzhou Medical University, Shandong Province, China.

\* Correspondence: Xingyuan Zhang, Department of Hepatobiliary Surgery, Hospital of Binzhou Medical University, No. 661 Huanghe 2nd Road, Binzhou, Shandong 256603, China (e-mail: byfzyx@163.com).

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necrolytic migratory erythema (NME), diabetes mellitus (DM), weight loss, deep-vein thrombosis, neuropsychiatric disorders and diarrhea, among which NME represents the hallmark clinical sign of glucagonoma syndrome and is usually presented as the initial complaint of patients.<sup>[2]</sup> Once a glucagonoma is diagnosed, complete surgical resection of the neoplasm provides the only chance of a cure. Herein, we report the case of a 30-year-old male suffering glucagonoma with a typical skin disorder of NME who underwent surgical treatment and was cured.

## 2. Case presentation

In December 2013, a 30-year-old male patient was admitted to hospital with a complaint of diffuse erythematous ulcerating skin rash for more than 10 months. The rash initially appeared in the perineal area and the lower extremities of the body, but slowly progressed throughout the body. In addition, rashes tended to occur in crops that later blistered and sloughed while new lesions occur in another area. The patient also complained of hyperglycemia and a weight loss of 15 kg in the previous 10 months. His clinical history revealed that he had undergone a dermatological biopsy and was diagnosed as having eczema and erythema polyformis. Therapeutic drugs corresponding to this disease including oral drugs and externally used drugs were given to the patient, but unfortunately there was no obvious improvement of the skin disorder. Sexually transmitted diseases were also considered during diagnosis, but unsafe sex was denied

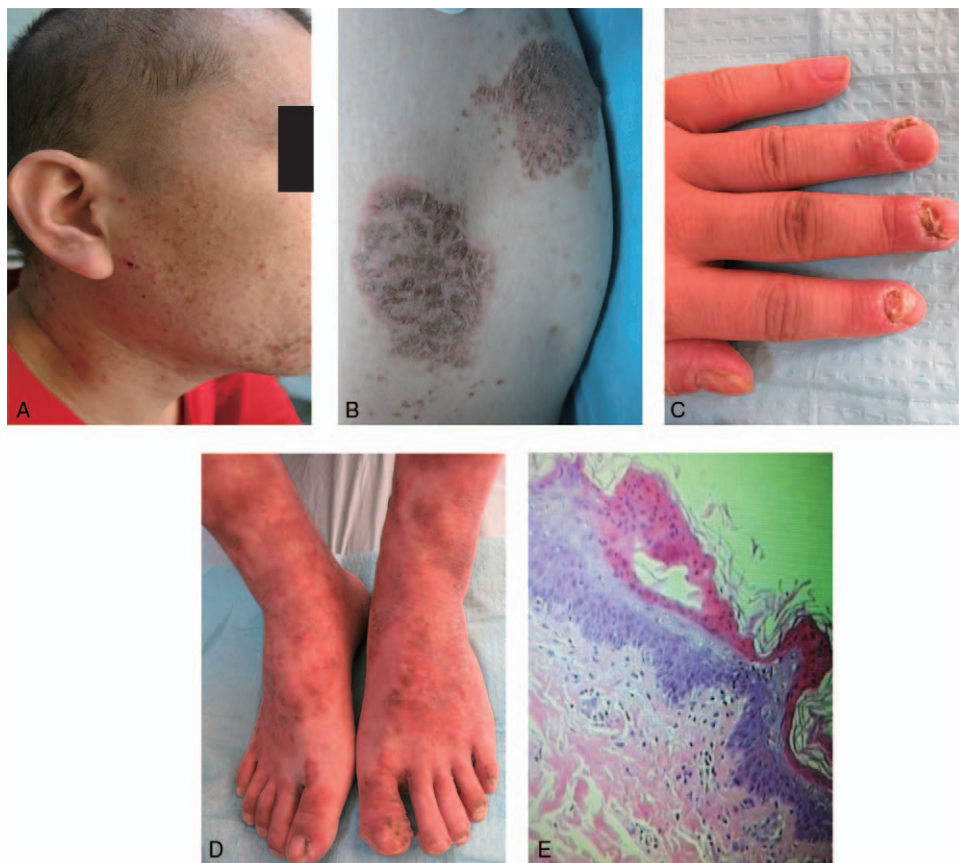
by the patient, and relevant laboratory testing showed no abnormality. The family history was negative for multiple endocrine neoplasia and for DM.

Physical examination revealed a diffuse erythematous scaly rash with areas of hyperpigmentation that were especially serious on the face and lower limbs. Hypotrichosis and onychia periungualis were also present (Fig. 1A–E). Vital signs and abdominal examination were found normal during the examination.

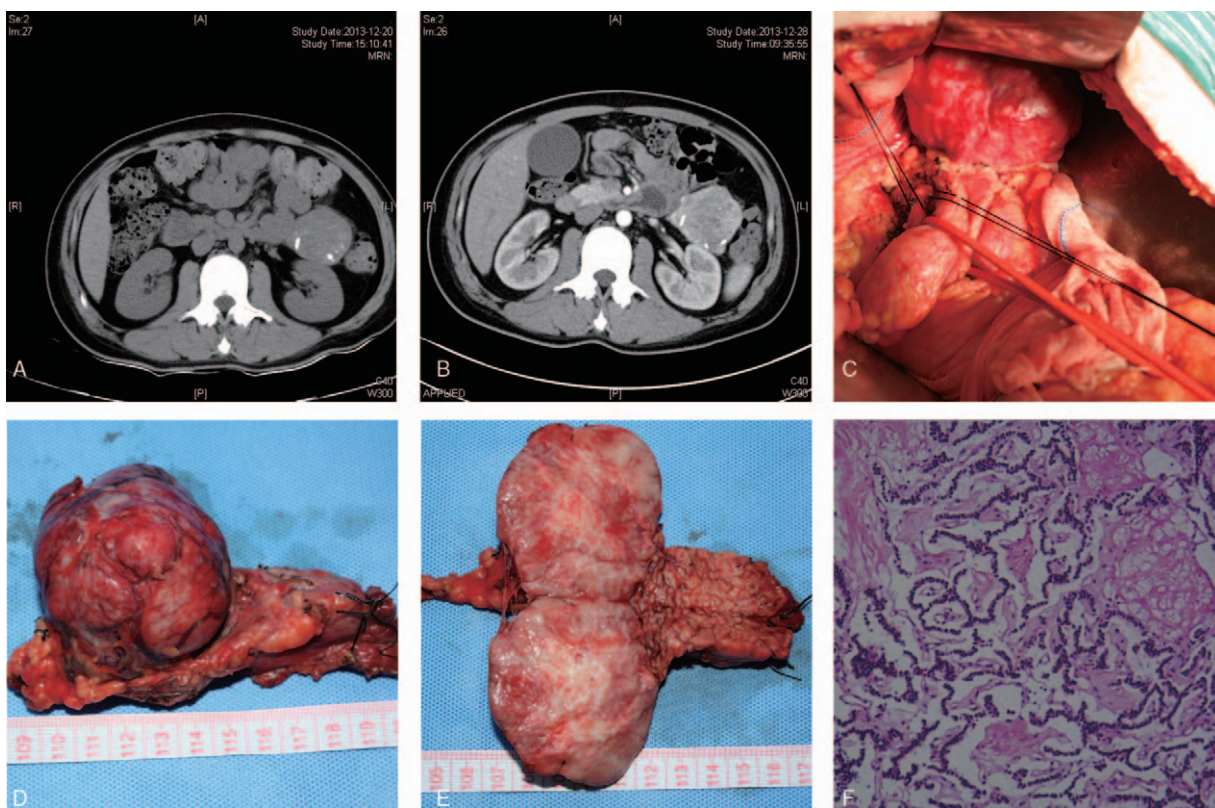
Laboratory tests indicated elevated fasting blood glucose (maximum 8.29 mmol/L, normal range: 3.90–6.10 mmol/L) and fasting blood glucagon (1109 pg/mL, normal range: 50–150 pg/mL) levels. Routine and immunological laboratory findings including white blood cell count (WBC), red blood cell count (RBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum complement C3/C4, carbohydrate antigen-199 (CA-199) and carcinoembryonic antigen (CEA) were unremarkable.

Following admission, the patient underwent abdominal computed tomography (CT) scanning, which disclosed a pancreatic body mass measuring approximately 6 cm with low density accompanied by partial calcification in plain scanning images and uneven enhancement in strengthening periods. Liver metastasis and enlarged lymph nodes were absent in the CT scan (Fig. 2A and B).

Given his history of the skin rash, DM, elevated fasting blood glucagon and the pancreatic mass, a diagnosis of glucagonoma



**Figure 1.** (A) Facial skin with NME; (B) Body trunk pigmentation of skin; (C) Hand with onychia periungualis; (D) Foot skin with NME and onychia periungualis; (E) Pathology of dermatological biopsy. NME = necrolytic migratory erythema.



**Figure 2.** (A, B) Preoperative computed tomography (CT) examination of the tumor; (C–E) Intraoperative images of the tumor; (F) Postoperative pathology.

was made, and the surgical procedure of spleen-preserving distal pancreatectomy combined with lymphadenectomy was subsequently performed (Fig. 2C–E). One week after the surgery, the skin lesions disappeared gradually, and postoperative plasma glucagon levels decreased to 70 pg/mL (Fig. 3A, B and D). Postoperative pathological examination confirmed the diagnosis of glucagonoma, and immunohistochemical staining revealed positive staining for neuron specific enolase (NSE), chromogranin A (CgA) and synaptophysin (Syn) (Fig. 2F). The patient has shown no recurrence for 5 years since the surgery and remains asymptomatic (Fig. 3C and E).

### 3. Discussion

The understanding of glucagonoma as a rare type of functional pNET has had a gradual historical course. In 1942, Becker et al were the first to document an erosive cutaneous eruption in a patient with DM and a pancreatic islet cell tumor.<sup>[3]</sup> McGavran et al identified elevated glucagon levels in the blood and tumor tissue of a patient with DM, NME and a pancreatic tumor in 1966.<sup>[4]</sup> In 1973, Wilkinson first coined the term ‘necrolytic migratory erythema’ to describe the distinctive rash.<sup>[5]</sup> In 1974, Mallinson et al delineated the ‘glucagonoma syndrome’ in 9 patients with NME, weight loss and glucagon hypersecretion by alpha cell tumors of the pancreas for the first time.<sup>[6]</sup> Since then, numerous sporadic cases and several small case series have been reported in succession.<sup>[7–9]</sup>

With the increased understanding of this rare disease and the rapid development of imaging technology and laboratory testing, especially the test for fasting blood glucagon levels, it is not

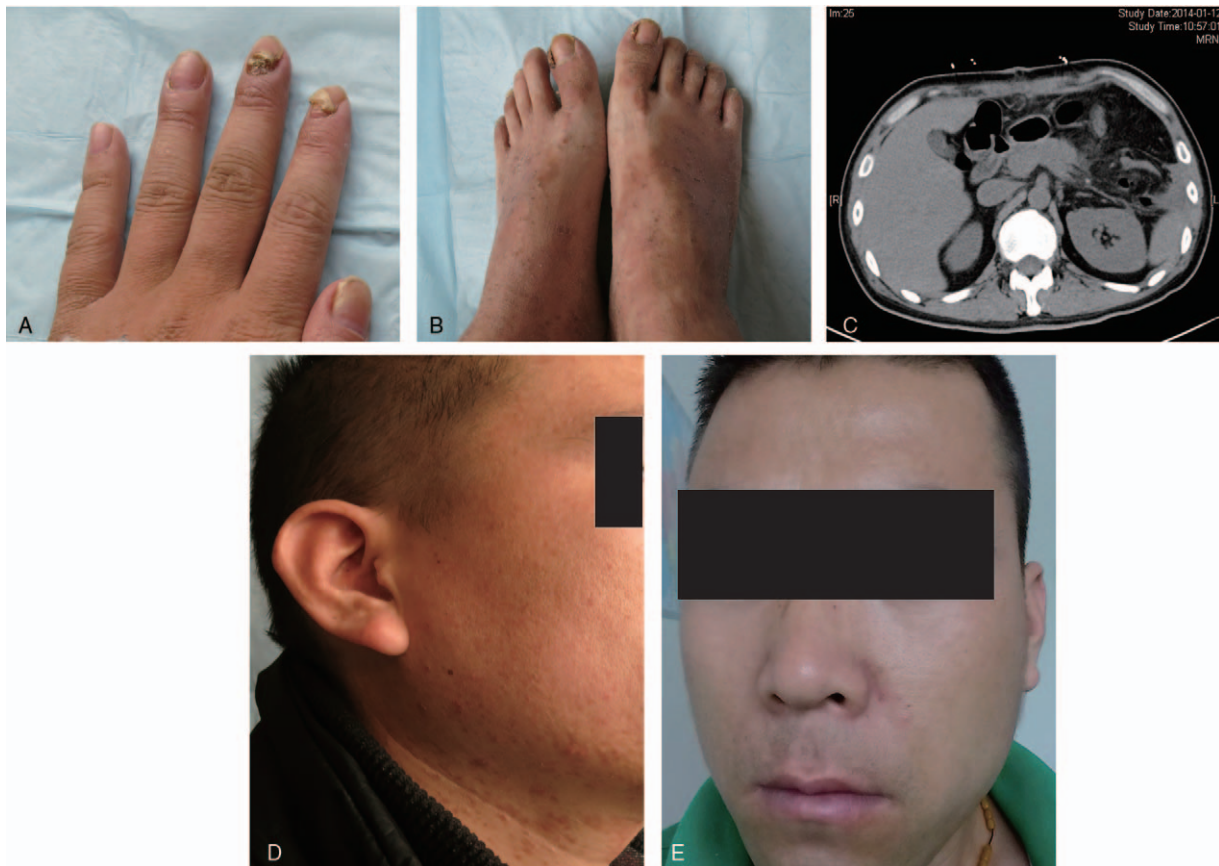
difficult to make a diagnosis. However, because the tumor is a rare type of pNET, it has been difficult to accumulate sufficient cases to determine pertinent clinical guidelines until recently.

Appropriate therapy is determined based on an accurate staging of the glucagonoma, which is based on the TNM classification. Surgical resection, when possible, is the only potentially curative therapy. Most patients, however, present with a metastatic disease, most commonly liver metastasis. In this case, the purpose of treating the advanced tumor is to palliate the symptoms of glucagon excess and lengthen survival time as much as possible. This requires a multidisciplinary approach or multimodal treatment, including cytoreductive surgery when appropriate, directed therapy for the treatment of liver metastases when possible, and systemic medical therapy.<sup>[10]</sup>

As mentioned previously, surgical resection is the only potentially curative therapy for glucagonoma. Optional operations include simple enucleation, distal pancreatectomy with splenectomy, spleen-preserving distal pancreatectomy, central pancreatectomy, pancreaticoduodenectomy, and total pancreatectomy. Given that the tumor is a malignancy or a low-grade malignancy, the use of enucleation has been called into question, although the surgical procedure has advantages in terms of the duration of surgery, estimated blood loss, and improved preservation of postoperative endocrine/exocrine pancreatic function.<sup>[11]</sup>

Patients suffering small glucagonomas that lie in the neck or body of pancreas, close to the pancreatic duct, may be candidates for central pancreatectomy, which has the advantage of retaining gastrointestinal continuity, preventing injury of the pancreatic





**Figure 3.** (A, B, D) Skin of hands, feet the face at 1 week after surgery; (C) Abdominal computed tomography (CT) examination at 1 week after surgery; (E) Skin of the face at 4.5 years after surgery.

duct and postoperative fistula caused by simple enucleation, and preserving the function of the spleen. However, this surgical procedure shares shortcomings with simple enucleation, including inadequate lymph node dissection. Thus, this procedure is only appropriate for selected patients who might have been enucleated were it not for the location of the neoplasm being deep in the pancreatic parenchyma.<sup>[12,13]</sup>

Complete oncologic resection for glucagonoma includes distal pancreatectomy with or without splenectomy, pancreaticoduodenectomy and total pancreatectomy. Distal pancreatectomy is indicated for tumors in the body or tail of the pancreas, pancreaticoduodenectomy is indicated for lesions in the head of the pancreas, and total pancreatectomy is indicated for glucagonoma throughout the pancreas. Due to the malignant or low-grade malignant property of the tumor, it remains controversial whether the spleen should be preserved in distal pancreatectomy, which may not ensure adequate lymph node harvest.<sup>[14]</sup> However, because of the low-grade malignant property of glucagonoma, spleen-preserving distal pancreatectomy can be used when the tumor is evaluated at an early stage and when no enlarged regional lymph nodes are present. For the patient we reported in this study, it was better to preserve the function of spleen because of his younger age and early tumor stage. The postoperative follow-up for 5 years showing no recurrence and metastasis also confirms the practicability of the surgical procedure, although it is just 1 case. Pancreaticoduodenectomy and total pancreatectomy,<sup>[15,16]</sup> while not at issue,

could achieve the purpose of complete oncologic resection, although associated morbidity may set in; however, advances in perioperative management have made this procedure a feasible option. In addition to the abovementioned, regardless of the type of surgery procedure chosen, lymphadenectomy should be combined with the procedure rather than ignored.

Traditionally, pancreatic surgery has been performed as an open procedure; however, with the development of laparoscopy, laparoscopic approaches to each of the aforementioned operational procedures, including laparoscopic distal pancreatectomy with or without splenectomy, laparoscopic central pancreatectomy and laparoscopic pancreaticoduodenectomy, have been reported and are widely adopted, especially at major pancreatic centers. Comparison with the open procedure showed that the laparoscopic approach in pancreatic resections has improvements in terms of less estimated blood loss, a decreased use of blood transfusions, and shorter hospital/ICU stays; no difference was demonstrated in morbidity, including postoperative fistula and delayed gastric emptying.<sup>[17]</sup>

Since approximately 50% to 90% of well-differentiated glucagonomas present local or distant metastasis at time of diagnosis, most commonly liver metastasis, surgical resection is not always feasible in those cases. However, a more recent study continues to recommend surgical removal, even in patients with vascular invasion and local or distant metastases. Patients with liver metastases can be treated with partial hepatectomy combined with pancreatic resection if at least 30% of the liver

tissue can be retained and if there is no sufficient evidence of non-resectable extrahepatic metastases.<sup>[18]</sup> In certain cases, liver transplantation may be suggested.<sup>[19]</sup> Local ablative techniques, including microwave ablation and radiofrequency ablation, are suitable for patients with a small number of lesions that are less than 5 cm in size.<sup>[20]</sup> While in some non-resectable cases, hepatic artery embolization can be used to diminish hepatic arterial circulation aiming at tumor inactivation. Other options, such as ultrasound or CT-guided radioactive seed implantation, transcatheter arterial chemoembolization or the transhepatic arterial injection of radioactive materials to inhibit angiogenesis and destroy existing blood vessels, are also feasible in clinical practice.<sup>[21,22]</sup>

While the main therapy for glucagonoma is surgical removal, many patients who present with advanced tumors are not candidates for resection. Likewise, patients with contraindications to surgery are also unsuitable for operation. Medications, including chemotherapeutics, somatostatin analogues (SSAs), peptide receptor radionuclide and molecular targeted drugs, in this case, have advanced to the stage where they are used to control the excessive secretion of glucagon. Among these drugs, SSAs target somatostatin receptors that are overexpressed on glucagonomas and can achieve tumor shrinkage and reduce glucagon release into the blood, particularly in glucagonomas that express somatostatin receptors, thus, relieving glucagonoma symptoms such as NME and hyperglycemia.<sup>[23]</sup> This is a bridge therapy at present, and its representative drug is octreotide, a synthetic octapeptide derivative of natural somatostatin. Peptide receptor radiotherapy (PPRT) is performed by coupling peptide receptor radionuclide to SSAs, thus enabling the selective delivery of radiotherapy to glucagonoma cells; this is a novel treatment, and research on its efficacy is in progress.<sup>[24,25]</sup> Targeted molecular therapy,<sup>[26]</sup> another novel therapy, for which everolimus and sunitinib (an oral rapamycin target protein inhibitor and a tyrosine kinase inhibitor respectively) are representative drugs, was recently approved by the Food and Drug Administration (FDA) as a first-line therapy for advanced glucagonoma based on the treatment effect found in some controlled clinical trials.<sup>[25,27]</sup> Chemotherapy is used as a last-resort therapeutic method for glucagonoma, and its use is limited due to its side-effects, which include flu-like symptoms, depression, fatigue, nausea and vomiting, hepatotoxicity, nephrotoxicity, and myelosuppression.<sup>[28]</sup>

More recently, novel perspectives advocate treating tumors with multidisciplinary therapy and multimodal treatments,<sup>[29,30]</sup> such as surgery combined with oncological treatments or surgical resection combined with targeted drug therapy or radiotherapy, and glucagonoma is no exception. Unfortunately, however, fewer studies have been conducted in recent years due to the rarity of the tumor, making it impossible to systematically evaluate glucagonoma treatments. However, we believe that multidisciplinary therapy and multimodal treatments for glucagonoma will provide promising results in the near future due to advances in diagnostic techniques and therapeutic methods.

In conclusion, glucagonoma is a rare type of functional pNET. Its treatment should be directed according to the stage at which the disease is diagnosed. Surgery is currently the only method of curing the tumor. Surgical resection with curative intent or debulking procedures may lead to long-term palliation. Medications, including chemotherapeutics, SSAs, peptide receptor radionuclide and molecular targeted drugs are other therapeutic methods that can be used with patients who present with

advanced glucagonoma and are not candidates for resection. Multidisciplinary therapy and multimodal treatments are advocated, although less systematic evaluation of these has been conducted.

## Author contributions

**Conceptualization:** Xuefeng Cao, Qinghai Guan.

**Data curation:** Xixiu Wang, Yanmin Lu, Qinghai Guan.

**Formal analysis:** Qinghai Guan.

**Funding acquisition:** Baolei Zhao.

**Investigation:** Jian Shi, Qinghai Guan.

**Methodology:** Jian Shi, Qinghai Guan.

**Project administration:** Xuefeng Cao, Qinghai Guan.

**Resources:** Xuefeng Cao, Qinghai Guan.

**Software:** Yanmin Lu.

**Supervision:** Xuefeng Cao.

**Validation:** Xuefeng Cao.

**Writing – original draft:** Xuefeng Cao, Xixiu Wang.

**Writing – review & editing:** Xuefeng Cao, Xingyuan Zhang.

## References

- Hellman P, Andersson M, Rastad J, et al. Surgical strategy for large or malignant endocrine pancreatic tumors. *World J Surg* 2000;24:1353–60.
- Chastain MA. The glucagonoma syndrome: a review of its features and discussion of new perspectives. *Am J Med Sci* 2001;321:306–20.
- Becker SW, Kahn D, Rothman S. Cutaneous manifestations of internal malignant tumors. *Arch Dermatol Syphilol* 1942;45:1069–80.
- McGavran MH, Unger RH, Recant L, et al. A glucagon-secreting alpha-cell carcinoma of the pancreas. *N Engl J Med* 1966;274:1408–13.
- Wilkinson DS. Necrolytic migratory erythema with pancreatic carcinoma. *Proc R Soc Med* 1971;64:1197–8.
- Mallinson CN, Bloom SR, Warin AP, et al. A glucagonoma syndrome. *Lancet* 1974;2:1–5.
- Huo J, Liu P, Chen X, et al. Delayed diagnosis of glucagonoma syndrome: a case report. *Int J Dermatol* 2016;55:1272–4.
- Wei J, Lin S, Wang C, et al. Glucagonoma syndrome: a case report. *Oncol Lett* 2015;10:1113–6.
- Fang S, Li S, Cai T. Glucagonoma syndrome: a case report with focus on skin disorders. *Onco Targets Ther* 2014;14:1449–53.
- McKenna LR, Edil BH. Update on pancreatic neuroendocrine tumors. *Gland Surg* 2014;3:258–75.
- Zhang M, Xu X, Shen Y, et al. Clinical experience in diagnosis and treatment of glucagonoma syndrome. *Hepatobiliary Pancreat Dis Int* 2004;3:473–5.
- Ferrarese A, Borello A, Gentile V, et al. Meso-pancreatectomy for pancreatic neuroendocrine tumor. *Int J Surg* 2014;12(Suppl 1):S123–5.
- Du ZY, Chen S, Han BS, et al. Middle segmental pancreatectomy: a safe and organ-preserving option for benign and low-grade malignant lesions. *World J Gastroenterol* 2013;19:1458–65.
- Kimura W, Tezuka K, Hirai I. Surgical management of pancreatic neuroendocrine tumors. *Surg Today* 2011;41:1332–43.
- Gao C, Fu X, Pan Y, et al. Surgical treatment of pancreatic neuroendocrine tumors: report of 112 cases. *Dig Surg* 2010;27:197–204.
- Matthews BD, Smith TI, Kercher KW, et al. Surgical experience with functioning pancreatic neuroendocrine tumors. *Am Surg* 2002;68:660–5.
- Pierce RA, Spittler JA, Hawkins WG, et al. Outcomes analysis of laparoscopic resection of pancreatic neoplasms. *Surg Endosc* 2007;21:579–86.
- Gaujoux S, Gonen M, Tang L, et al. Synchronous resection of primary and liver metastases for neuroendocrine tumors. *Ann Surg Oncol* 2012;19:4270–7.
- Gedaly R, Daily MF, Davenport D, et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Arch Surg* 2011;146:953–8.
- Poggi G, Villani L, Bernardo G. Multimodality treatment of unresectable hepatic metastases from pancreatic glucagonoma. *Rare Tumors* 2009;22:e61.

- [21] King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. *Cancer* 2008;113:921–9.
- [22] Frilling A, Modlin IM, Kidd M, et al. Working Group on Neuroendocrine Liver Metastases Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 2014;15:e8–21.
- [23] Eldor R, Glaser B, Fraenkel M, et al. Glucagonoma and the glucagonoma syndrome-cumulative experience with an elusive endocrine tumour. *Clin Endocrinol (Oxf)* 2011;74:593–8.
- [24] Makis W, McCann K, Riauka TA, et al. Glucagonoma pancreatic neuroendocrine tumor treated with <sup>177</sup>Lu DOTATATE induction and maintenance peptide receptor radionuclide therapy. *Clin Nucl Med* 2015;40:877–9.
- [25] Öberg K. Management of functional neuroendocrine tumors of the pancreas. *Gland Surg* 2018;7:20–7.
- [26] Halperin DM, Kulke MH, Yao JC. A tale of two tumors: treating pancreatic and extrapancreatic neuroendocrine tumors. *Annu Rev Med* 2015;66:1–6.
- [27] Berruti A, Pia A, Terzolo M. Advances in pancreatic neuroendocrine tumor treatment. *N Engl J Med* 2011;364:1871–2.
- [28] John AM, Schwartz RA. Glucagonoma syndrome: a review and update on treatment. *J Eur Acad Dermatol Venereol* 2016;30:2016–22.
- [29] Ro C, Chai W, Yu VE, et al. Pancreatic neuroendocrine tumors: biology, diagnosis, and treatment. *Chin J Cancer* 2013;32:312–24.
- [30] Müssig K, Dudziak K, Horger M, et al. Diagnostics and treatment in functional pancreatic neuroendocrine tumours. *Dtsch Med Wochenschr* 2011;136:1319–30.