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RESEARCH

Diagnostic characteristics, treatment outcomes, and prognostic factors in glucagonomas

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Abstract

Objective: Glucagonomas are rare islet cell tumours, accounting for 2% of such tumours, with an annual incidence of 0.01–0.1 per million. This study aimed to describe diagnostic characteristics and treatment outcomes in patients with glucagonoma from a major referral centre.

Design: A retrospective case series included patients diagnosed with glucagonoma at the ENETS Centre of Excellence, Royal Free Hospital, London, UK.

Methods: Electronic patient records were reviewed to document baseline disease characteristics and treatment outcomes. Disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) were calculated using the Kaplan–Meier method.

Results: Twenty patients (75% male, age 56.6 ± 11.6 years, mean Ki-67 index 7.3 ± 7, mean ± SD) were included; 50% had liver metastases at diagnosis. The median OS was 34 months (95% CI: 30.3–37.7). Median OS was 34, 9, and 71 months for patients with liver, lung, and skeletal metastases, respectively. At diagnosis, migratory necrolytic erythema was linked to poorer OS (22 months, 95% CI: 14.3–29.7). Median DFS following surgery was 25 months (95% CI: 3.5–46.5). For inoperable disease, Lutetium-177 (^{177}Lu)-DOTATATE peptide receptor radionuclide therapy (PRRT) demonstrated efficacy in disease control. Other treatments included somatostatin analogues, chemotherapy, and molecular-targeted agents.

Conclusion: Tumour grade, metastases, and NME at diagnosis influence OS in glucagonoma. Surgery is associated with the best PFS as first-line therapy, while ^{177}Lu-DOTATATE PRRT effectively controls disease progression. Further studies are needed to optimise treatment sequencing for advanced glucagonoma.

Keywords: glucagonoma; treatment lines; progression-free survival; overall survival

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Introduction

Pancreatic neuroendocrine tumours (Pan-NETs) represent a heterogeneous group of tumours, comprising 2–3% of all pancreatic neoplasms and 30% of gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) (Hallet *et al.* 2015, Pavel *et al.* 2020). The majority of Pan-NETs are non-functional, but 10–40% can produce hormones with associated symptoms, and are known as functional Pan-NETs (Metz & Jensen 2008). Glucagonomas, which account for 2% islet cell tumours, originate from the alpha cells of the pancreatic islets and are located mainly in the tail of the pancreas (Lo *et al.* 2014). The annual incidence of glucagonomas is reported as 0.01–0.1 per million (Ma *et al.* 2020).

Excessive glucagon secretion by pancreatic islet alpha cells contributes to the development of the related paraneoplastic syndrome, known as the glucagonoma syndrome (Eldor *et al.* 2011). The physiological actions of glucagon consist of an increase in hepatic glucose output and an attenuation of protein synthesis (Lefèbvre 1995, Charlton *et al.* 1996). However, the major symptoms associated with excessive glucagon production include migratory necrolytic erythema (MNE) and diabetes mellitus (DM), along with other effects such as weight loss, glucose intolerance, normochromic normocytic anaemia, and hypoaminoacidaemia. Less common features include diarrhoea, thromboembolism, glossitis, and cheilitis, as well as psychiatric symptoms (Metz & Jensen 2008).

Glucagonomas have been reported to show aggressive metastatic behaviour in 60% cases (Van Beek *et al.* 2004, Metz & Jensen 2008), and therefore surgical resection of the primary tumour, and if possible metastasectomy, is the recommended first-line treatment (Pavel *et al.* 2020). The use of somatostatin receptor analogues (SSAs) is an additional standard first-line therapy in patients diagnosed with functioning NETs (Pavel *et al.* 2020). It has been demonstrated that SSA therapy is beneficial in managing the severity of NME in patients with glucagonoma (Sandru *et al.* 2020).

However, given the low prevalence of this tumour type, published experience on the management of glucagonomas is limited, and often reflects extrapolation from other GEP-NETs (John & Schwartz 2016), with only individual case reports detailing patients diagnosed with glucagonomas (Wermers *et al.* 1996, Kindmark *et al.* 2007, Lo *et al.* 2014, Al-Faouri *et al.* 2016, Mavi & Tuncel 2021, Yacine *et al.* 2022). Two case series of comparable sample size (Wermers *et al.* 1996, Kindmark *et al.* 2007) were published approximately 20 years ago and presented data according to the imaging modalities and treatment options available at that time. To expand knowledge on this rare tumour, we now present the clinical and biochemical features of patients with localised and advanced glucagonomas, symptom and tumour control rates across various treatment lines, as well as factors influencing overall patient survival, based on data from a large centre specialising in NETs.

Methods

For the purpose of this study, we selected all patients with a documented diagnosis of Pan-NETs producing glucagon, based on glucagon levels exceeding twice the upper normal limit, regardless of whether they exhibited the classical symptomatology, from the database of the Neuroendocrine Tumour Department in the ENETS Centre of Excellence, Royal Free Hospital, London, UK. A total of 22 patients were retrieved, of whom 20 were considered eligible for inclusion in this study as they had a complete data file, while the information was incomplete for the remaining two patients.

According to the standard protocol of our centre, patients with radiological evidence of a pancreatic neuroendocrine tumour and clinical features suggestive of glucagonoma – such as necrolytic migratory erythema, weight loss, new-onset diabetes, and anaemia – underwent fasting gut hormone testing, including serum glucagon levels, to biochemically confirm the diagnosis and assess tumour functionality. The extent of disease at the time of diagnosis was estimated using cross-sectional and molecular imaging to estimate the radiological characteristics of the primary and/or any metastatic disease. Radiological assessment was conducted based on RECIST criteria, classifying treatment outcomes as complete response, partial response, stable disease, or progressive disease (Eisenhauer *et al.* 2009). All patients were evaluated through a thorough consultation, during which detailed personal and family history was obtained, and a comprehensive clinical assessment was performed to identify features suggestive of genetic syndromes associated with glucagonoma. Patients with findings raising suspicion for a hereditary syndrome were referred for genetic testing in accordance with the guidelines of the North American Neuroendocrine Tumor Society (NANETS) (Halfdanarson *et al.* 2020). Although this was a retrospective study, referrals were made at the time of clinical suspicion, reflecting both historical practice at our institution and guideline-concordant care.

The disease was regularly monitored, with follow-up appointments at least twice a year in the outpatient clinic. Each follow-up visit included a symptom review (using a 'symptom score' to assess clinical response to treatment, categorising symptom reduction as >50%, <50%, or no change), biochemical evaluation, and radiological assessment using computed tomography (CT) and/or magnetic resonance imaging. All critical results were discussed in the setting of a multi-disciplinary meeting for the optimisation of treatment plans.

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All information was retrieved after retrospectively reviewing electronic patient files. We documented the descriptive characteristics and the treatment options offered to our patients. As this study was a retrospective clinical audit using anonymised data, ethical approval was not required, and patient consent was implied in accordance with the UK Policy Framework for Health and Social Care Research.

Statistical analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS version 23.0). Continuous parameters were presented using mean value and range (minimum to maximum) or median values. Dichotomous parameters were presented as frequencies (%). Differences between continuous parameters were assessed using analysis of variance (ANOVA). Survival analysis using the Kaplan–Meier method was used to estimate the median disease-free survival (DFS) and/or median progression-free survival (PFS) overall, calculated from the date of treatment initiation to the date of radiological progression, and for each administered treatment. The median overall survival (OS), the time from treatment initiation to death from any cause, was estimated and associated with tumour features at diagnosis. Secondarily, the median OS was evaluated according to the location of metastatic disease and baseline symptoms related to the glucagonoma, including diabetes, MNE, abdominal pain, and weight loss. Time points of interest included the time to progression after initiation of treatment, specifically up to the fifth progression point. All numbers shown include standard deviations (SDs) unless otherwise described. Statistical significance was set at the level of P value <0.05.

Results

Descriptive analysis

Follow-up was complete in a total of 20 patients of the 22 retrieved (90.9%). The median follow-up was 49.5 months (IQR 22.8–84.5). The main results of the demographic characteristics and the main biochemical, radiological, and histological features of the primary tumour are presented in Table 1. The mean age (± SD) of patients at the time of diagnosis was 56.6 ± 11.6 years, with 35% of them being currently alive at the time of data collection. In one such case, genetic testing was performed and returned negative for Von Hippel–Lindau syndrome. Presenting symptoms included NME in nine patients (45%), DM in ten patients (50%), weight loss in seven patients (35%), and abdominal pain in four patients (20%). In two patients, the diagnosis was based only on elevated glucagon levels. The primary tumour was located in the pancreatic tail (40%), head (25%), or body (15%), or remained undefined (20%); in 60% patients, the size of the primary lesion was >3 cm. Overall, in the course of the disease, ten patients (50%) had evidence of liver metastases, and seven of these patients (35%) had tumour volumes <25% liver. Abdominal lymph node metastases were evident in 20% patients (four patients), while skeletal involvement was evident in five (25%). Histologically, 20% tumours were classified as WHO (Rindi *et al.* 2022) grade 1 (G1),

Table 1 Baseline descriptive characteristics for the patients of this study (n = 20).

	Frequency (%) or mean ± SD
Demographic characteristics	
Alive with disease	35% (7/20)
Age at diagnosis (years)	56.6 ± 11.6
Gender (male)	75% (15/20)
Presenting symptoms	
MNE	45% (9/20)
DM	50% (10/20)
Weight loss	35% (7/20)
Abdominal pain	20% (4/20)
Primary tumour characteristics	
Pancreas location	
Body	15% (3/20)
Head	25% (5/20)
Tail	40% (8/20)
Undefined	20% (4/20)
Size of primary tumour	
>3 cm	60% (12/20)
<3 cm	10% (2/20)
Unknown	30% (6/20)
Histology	
G1	20% (4/20)
G2	65% (13/20)
G3	5% (1/20)
Unknown	10% (2/20)
Ki-67 index	7.27 ± 6.98
Metastatic spread	
Liver	50% (10/20)
<25%	35% (7/20)
25–50%	5% (1/20)
>50%	10% (2/20)
Abdominal lymph nodes	20% (4/20)
Bones	25% (5/20)
Metastatic at diagnosis	
No metastases	35% (7/20)
Liver metastases	50% (10/20)
Bone metastases	10% (2/10)
Unknown	15% (3/20)
Presenting biochemistry	
Glucagon levels	
>3 × ULN	85% (17/20)
<3 × ULN	5% (1/20)
Other	10% (2/20)
	- One had positive histology staining for glucagon - One had qualitative not quantitative results

MNE, migratory necrolytic erythema; DM, diabetes mellitus; ULN, upper limit of normal.

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65% as G2, and 5% as G3, while the grade was unknown in 10% patients. According to biochemical data available on presentation, approximately 60% patients (n = 12) had documented evidence of markedly elevated plasma glucagon levels (defined as more than three times the upper limit of normal). One additional patient (5%) had glucagon levels below this threshold. However, glucagon measurement was not uniformly performed at initial evaluation, particularly in earlier years of the study period when assay availability and clinical awareness were limited. In such cases, diagnosis was based on a combination of characteristic clinical features (e.g. necrolytic migratory erythema, DM, weight loss), histopathological confirmation of a pancreatic neuroendocrine tumour, and the subsequent clinical course. This approach reflects real-world diagnostic practices in rare neuroendocrine tumours before the routine use of sensitive glucagon assays. In addition, one patient demonstrated positive immunohistochemical staining for glucagon, supporting the diagnosis. Another patient referred to our centre after a complete external work-up had a qualitative description of elevated glucagon levels but lacked quantitative data. Regarding anticoagulation treatment, data from 12 patients revealed that five received prophylactic anticoagulation (aspirin three patients, low molecular weight heparin two patients).

Clinical, biochemical, and progression-free survival after several lines of treatment

Table 2 presents the main treatment options offered in the first-line setting and includes the patients' symptom and biochemical response rates. Accordingly, 45% patients underwent initial surgery for the resection of the primary tumour. Unfortunately, given the timing of presentation and the distribution of metastases, metastasectomy was not technically feasible. In addition, 45% patients were originally administered treatment with long-acting somatostatin analogues (SSA), while 10% received chemotherapy in the first-line setting (a combination of 5-fluorouracil, platinum, and streptozocin). Regarding the clinical response, seven patients (35%) exhibited reduction of the symptom score by more than 50%, three patients (15%) exhibited clinical improvement at rates of less than 50%, while six patients did not report any change in their symptom score (30%). Regarding biochemical responses, three patients (15%) showed a reduction in glucagon levels by >50%, three patients (15%) showed a reduction in glucagon levels by <50%, while the effect of treatment on glucagon levels remained unknown in 14 patients due to missing glucagon values at the follow-up appointments. With regards to the progress of NME, treatment with SSA monotherapy or a combination of surgery and SSA resulted in complete resolution of NME rash in one patient and partial resolution in two others. One patient experienced spontaneous improvement, while follow-up data were unavailable for one patient. One further patient described deterioration of the MNE rash post Lutetium-177 (^{177}Lu)-DOTATATE peptide receptor radionuclide therapy (PRRT).

Table 3 presents the main systemic treatment options received in the second-, third- and fourth-line settings. In our cohort, second-line treatment was offered to 12 patients: 17% were treated with SSA (two out of 12 patients), 33% received PRRT (four out of 12 patients), 25% received molecular targeted agents with everolimus or sunitinib (three out of 12 patients), and 25% received chemotherapy (three out of 12 patients). Third-line treatment was offered to nine patients: 45% received ^{177}Lu-DOTATATE PRRT (four out of nine patients), 22% received molecular targeted agents (two out of nine patients), while 33% received chemotherapy (three out of nine patients). Fourth-line treatment was offered to six patients: 50% received ^{177}Lu-DOTATATE PRRT (three out of six patients), 33% received everolimus (two out of six patients), and 17% received chemotherapy (one out of six patients). Fifth-line treatment was offered to three patients: 67% were treated with chemotherapy (two out of three patients) and 33% were treated with sunitinib (one out of three patients).

Table 4 presents the treatment efficacy following the individual lines of treatment.

Table 2 Clinical and biochemical response rates stratified per the type of first-line treatment.

		Surgery (n = 9)	SSA (n = 9)	Chemotherapy (n = 2)	Total (n = 20)	P-value
Symptom score	>50% improvement	5% (1/20)	20% (4/20)	5% (1/20)	30% (6/20)	0.225
	<50% improvement	0	15% (3/20)	0	15% (3/20)	
	No change	20% (4/20)	5% (1/20)	5% (1/20)	30% (6/20)	
	Unknown	15% (3/20)	5% (1/20)	0	20% (4/20)	
Biochemical response	Reduction of glucagon levels >50%	0	10% (2/20)	5% (1/20)	15% (3/20)	0.103
	Reduction of glucagon levels <50%	0	15% (3/20)	0	15% (3/20)	
	Unknown	40% (8/20)	25% (5/20)	5% (1/20)	70% (14/20)	

SSA, somatostatin analogues.
Statistical significance was set at $P < 0.05$.

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Table 3 Treatment options that were administered in the second-, third-, and fourth-line settings.

Lines of treatment	Frequency (%) and number of patients
Second-line treatment	*n* = 12
SSA	16.7% (2/12)
^{177}Lu-DOTATATE PRRT	33.3% (4/12)
Molecular targets	25.0% (3/12)
Chemotherapy	25.0% (3/12)
Capecitabine (*n* = 1)	
5-Fluorouracil, cisplatin, streptozocin (*n* = 2)	
Third-line treatment	*n* = 9
^{177}Lu-DOTATATE PRRT	44.5% (4/9)
Molecular agents	22.2% (2/9)
Chemotherapy	33.3% (3/9)
Streptozocin (*n* = 1)	
5-Fluorouracil, carboplatin, streptozocin (*n* = 1)	
5-Fluorouracil, irinotecan, leucovorin (*n* = 1)	
Fourth-line treatment	*n* = 6
^{177}Lu-DOTATATE PRRT	50% (3/6)
Everolimus	33.4% (2/6)
Chemotherapy	16.6% (1/6)
Fluorouracil, carboplatin, streptozocin (*n* = 1)	
Fifth-line treatment	*n* = 3
Chemotherapy	66.7% (2/3)
5-Fluorouracil, carboplatin, streptozocin (*n* = 1)	
Streptozocin, capecitabine (*n* = 1)	
Sunitinib	33.3% (1/3)

SSA, somatostatin receptor analogues; ^{177}Lu, Lutetium-177; PRRT, peptide receptor radionuclide therapy.

Table 4 Progression-free survival post-treatment lines.

Progression-free survival	Median value (months)	95% CI	Log-rank *P*-value
Post first-line treatment			
Overall	13.0	0–30.1	0.633
Surgery	25.0	3.5–46.5	
SSA	13.0	10.1–15.9	
Chemotherapy	10.0	n.e.	
Post second-line treatment			
Overall	14.0	9.4–18.6	0.574
SSA	19.0	n.e.	
^{177}Lu-DOTATATE PRRT	14.0	9.1–18.9	
Molecular targets	13.0	3.4–22.6	
Chemotherapy	8.0	n.e.	
Post third-line treatment			
Overall	6.0	1.8–10.2	0.045
^{177}Lu-DOTATATE PRRT	8.0	0–25.6	
Molecular agents	5.0	n.e.	
Chemotherapy	4.0	n.e.	
Post fourth-line treatment			
Overall	16.0	0–33.2	0.059
^{177}Lu-DOTATATE PRRT	17.0	15.4–18.6	
Everolimus	4.0	n.e.	
Chemotherapy	8.0	n.e.	
Post fifth-line treatment			
Overall	4.0	1.0–8.8	0.157
Chemotherapy	4.0	n.e.	
Sunitinib	1.0	n.e.	

Statistical significance was set at the level of *P*-value <0.05.
SSA, somatostatin receptor analogues; ^{177}Lu, Lutetium-177; PRRT, peptide receptor radionuclide therapy; n.e., not estimable (due to low event count).

After first-line treatment

After administration of the first-line treatment, the median DFS following surgery was estimated as 25 months (95% CI: 3.5–46.5). The median PFS following commencement of SSA treatment was 13 months (95% CI: 10.1–15.9), and following chemotherapy 10 months (95% CI: not estimable). Overall, the median PFS/DFS following first-line treatment was estimated as 13 months (95% CI: 0–30.1), with no significant difference between treatment arms (log-rank *P* value 0.633).

After second-line treatment

After administration of the second-line treatment, the overall median PFS was 14 months (95% CI: 9.4–18.6). Median PFS corresponding to SSA treatment was 19 months (one patient); PRRT 14 months (95% CI: 9.1–18.9); molecular targeted therapy 13 months (95% CI: 3.4–22.6); chemotherapy 8 months (95% CI: not estimable). There was no statistically significant difference between treatment arms (log-rank *P* value 0.574).

After third-line treatment

After administration of the third-line treatment, the overall median PFS was 6 months (95% CI: 1.8–10.2), with evidence of a statistically significant difference between treatment arms (log-rank *P* value 0.045). The regimen-specific median PFS was as follows: after PRRT 8 months (95% CI: 0–25.6), molecular targeted agents 5 months (95% CI: not estimable), chemotherapy 4 months (95% CI: not estimable). We compared the effect of treatment, comparing PRRT versus other types (molecular targeted agents or chemotherapy), and found a difference in median PFS, although this did not reach statistical significance (PRRT versus molecular targeted agents/chemotherapy: median 8 months, 95% CI: 0–25.6 vs 5 months, 95% CI: 4.2–5.9; log-rank *P* value 0.093, Fig. 1).

After fourth-line treatment

After administration of fourth-line treatment, the overall median PFS was 16 months (95% CI: 0–33.2), with a borderline difference between treatment arms (log-rank *P* value 0.059). Regimen-specific median PFS was as follows: PRRT 17 months (95% CI: 15.4–18.6), everolimus 4 months (one patient), chemotherapy 8 months (one patient). We compared the effect of treatment, comparing PRRT versus other types (molecular targeted agents and chemotherapy), and found a statistically significant difference (PRRT versus molecular agents/chemotherapy: median value 17 months, 95% CI: 15.4–18.6 versus 6 months, 95% CI: not estimable; log-rank *P* value 0.039, Fig. 2).

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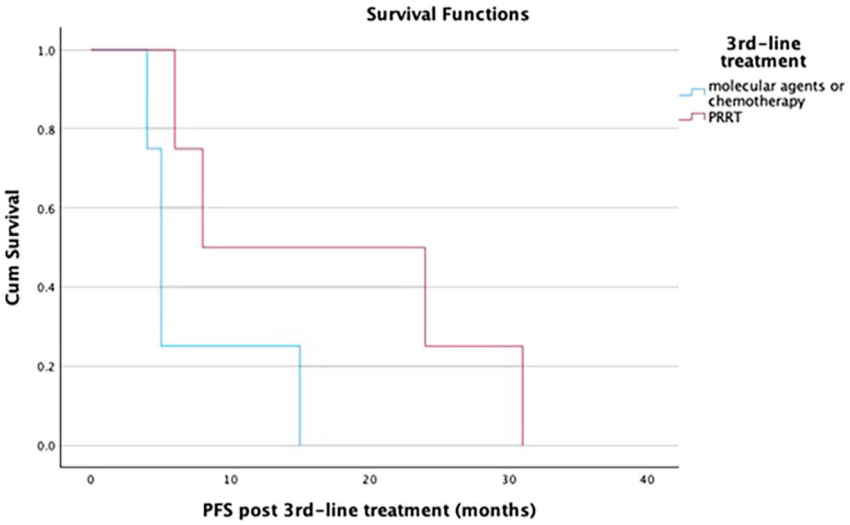

Number at risk

Time (months)	0	6	12	18	24	30	40
PRRT	4	3	2	2	1	1	0
Molecular agents/ Chemotherapy	4	1	0	0	0	0	0

Figure 1

Third-line treatment: median values of PFS comparing PRRT vs other agents (molecular agents or chemotherapy).

After fifth-line treatment

After administration of fifth-line treatment, the overall median PFS was 4 months (95% CI: 0–8.8), and did not differ significantly between treatment options (log-rank *P* value 0.157). Considering the individual regimen, chemotherapy median PFS was 4 months (95% CI: not estimable) and the sunitinib median PFS was 1 month (one patient).

Survival analysis

The median OS for the total cohort of patients (Fig. 3), using Kaplan–Meier analysis, was found to be 34 months (95% CI: 30.3–37.7). Moreover, we evaluated the possible association between median OS and the presence of glucagonoma-specific features at baseline. Accordingly, we observed that patients with evidence of MNE at presentation (Fig. 4) had significantly lower median OS compared to those without (erythema present versus absent, median OS 22 months, 95% CI: 14.3–29.7 versus 71 months, 95% CI: 11.9–130; log-rank *P* value 0.048). In addition, we evaluated median OS between patients with DM at the time of diagnosis (Fig. 5). The presence of DM was associated with a marginally longer median OS compared to patients without DM at the time of the glucagonoma diagnosis, but this did not attain statistical significance (DM present versus absent, median OS 35 months, 95% CI: 0–91.8 versus 22 months, 95% CI: 5.2–38.8, log-rank *P* value 0.069). The median OS did not differ between patients presenting with or without weight loss or abdominal pain at the time of the glucagonoma diagnosis (median OS, weight loss symptoms yes vs no, 48 months, 95% CI: 10.8–85.2 versus 23 months, 95% CI: 4.4–41.6, log-rank *P* value 0.268; abdominal pain yes versus no, 48 months, 95% CI: 24–72 vs 34 months, 95% CI: 19.9–48, log-rank *P* value 0.645).

In addition, we estimated median OS values according to the presence or absence of metastatic disease (Table 5). Although the presence of metastatic disease at the time of diagnosis did not seem to have an impact on OS in our small series, we also assessed the development of new metastases in the course of the disease. Specifically, lung metastases were associated with the shortest median OS of 9 months (95% CI: not estimable), followed by hepatic metastases (median OS 34 months, 95% CI: 17.4–50.6), abdominal lymph node metastases (median OS 48 months, 95% CI: 1.6–94.4), and bone metastases (median OS 71 months, 95% CI: 0–150.4).

Discussion

The results of this retrospective study highlight the main clinical features of this rare group of NETs, as well as their

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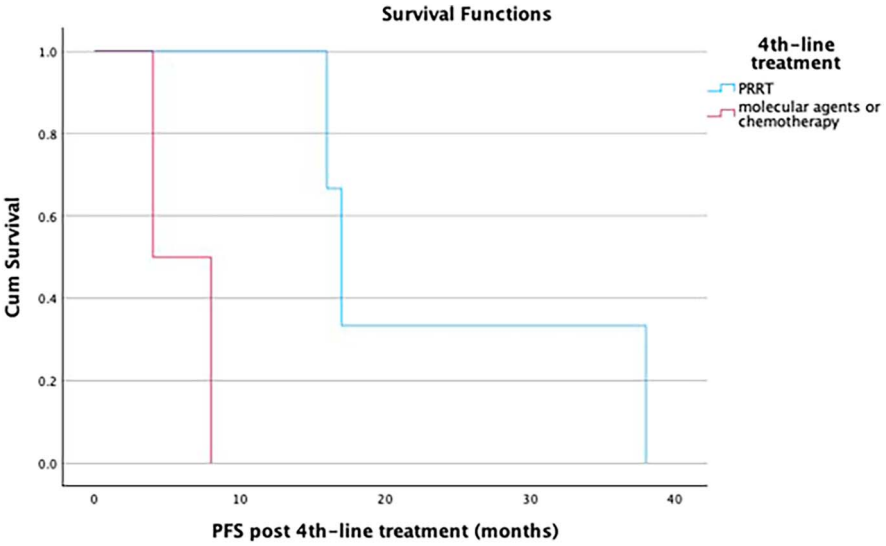


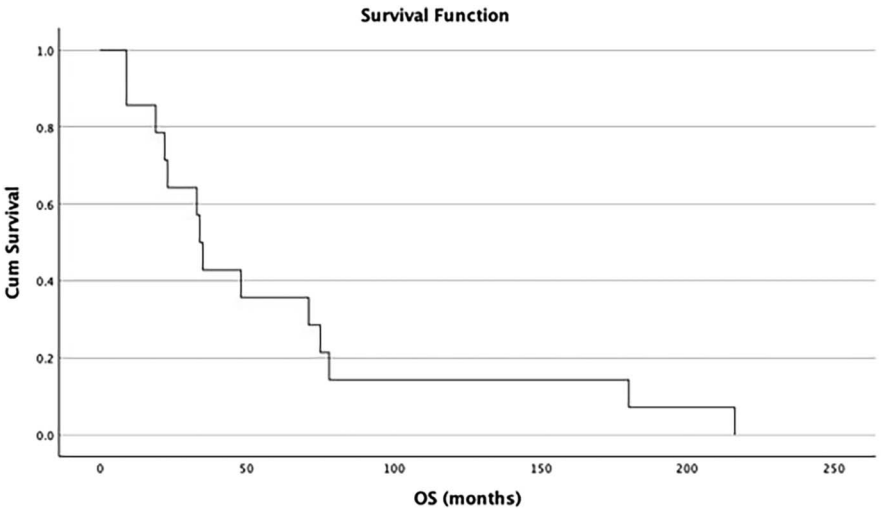
Number at risk

Time (months)	0	6	12	18	24	30	36
PRRT	3	2	2	1	1	1	0
Molecular agents/ Chemotherapy	2	1	0	0	0	0	0

Figure 2

Fourth-line treatment: median values of PFS comparing PRRT vs other agents (molecular agents or chemotherapy).

biological behaviour. According to our findings, surgery with the intention of primary tumour resection, when feasible, was associated with a median DFS of 25 months. With regards to further treatment options, SSA represents an effective first-line systemic treatment, while PRRT seems to be associated with the most prolonged PFS in the treatment lines assessed. We also describe the factors affecting OS: tumour grade, the extent of hepatic involvement, and the presence of paraneoplastic features such as NME.



Number at risk

Time (months)	0	24	48	72	96	120	144	168	192	216
All patients	14	9	5	4	3	2	2	1	1	0

Figure 3

Mean OS for the total cohort of patients.

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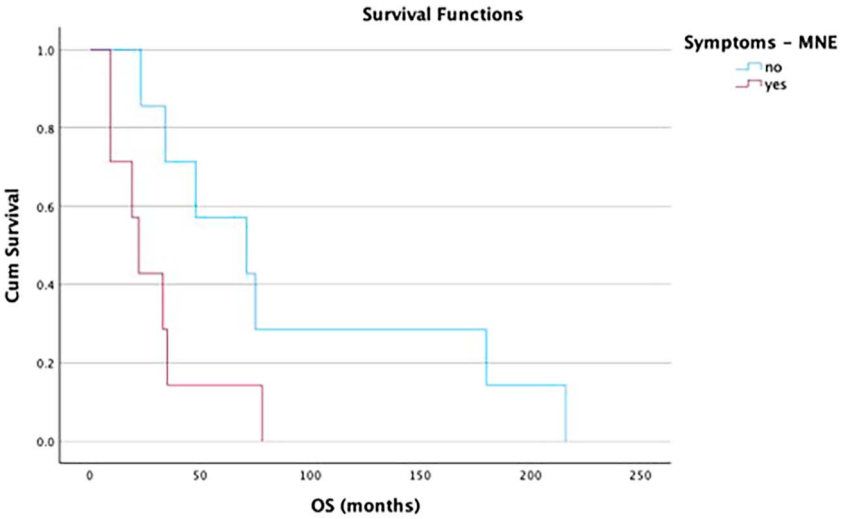
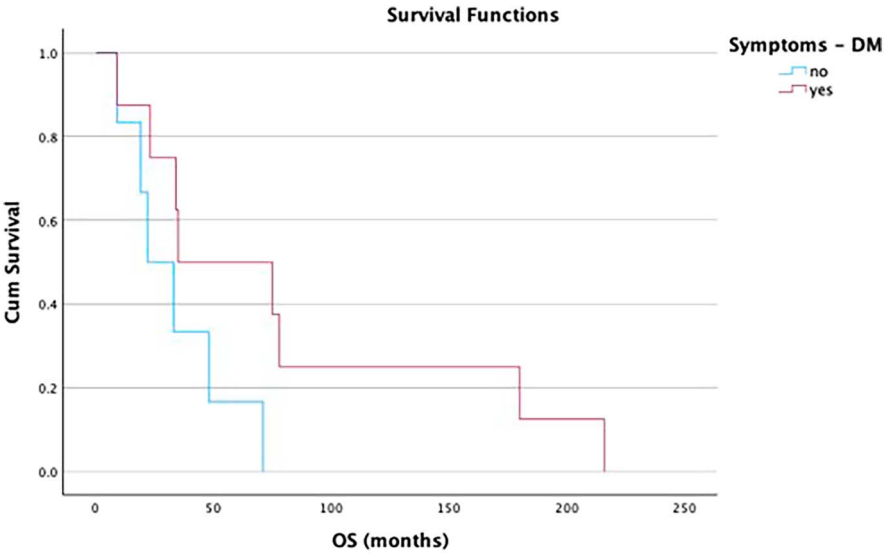


Number at risk	OS (months)										
Time (months)	**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**250**
MNE absent	7	6	4	3	2	2	1	1	1	0	0
MNE present	7	5	4	3	2	2	1	0	0	0	0

Figure 4

Median OS according to the presence of MNE at presentation.

Regarding the presenting characteristics, we observed that DM, NME and weight loss were the most frequent symptoms at the time of diagnosis, affecting 50, 45, and 35% patients, respectively. These rates are comparable with those reported in papers from the late 1990s (Wermers *et al.* 1996) and early 2000s (Kindmark *et al.* 2007). In our cohort, many patients had evidence of metastatic disease at presentation (60% overall – 50%



Number at risk										
Time (months)	**0**	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**
DM absent	6	4	1	1	1	0	0	0	0	0
DM present	8	6	5	4	3	2	2	1	1	0

Figure 5

Median OS according to the presence of DM at presentation.

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Table 5 Median overall survival stratified according to the location of metastatic disease.

	Median value OS (months)	95% CI
Abdominal lymph node metastases	48.0	1.6–94.4
Lung metastases	9.0	n.e.
Bone metastases	71.0	0–150.4
Hepatic metastases	34.0	17.4–50.6
<25%	23.0	20.9–25.1
25–50%	71.0	n.e.
>50%	34.0	n.e.

n.e., not estimable (due to low event count).

with liver metastases and 10% with bone metastasis). The glucagonoma case series of 21 patients published in the late 1990s described liver metastases in 95% patients, while 43% presented with lymph node involvement, whereas bone metastases were identified only in 19% patients (Wermers *et al.* 1996). In a later series of 23 patients (Kindmark *et al.* 2007), there was evidence of liver metastases in all patients, while bone metastases were identified in 35% patients. In our cohort, the median OS was 34 months regardless of treatment administered. This was comparable to the study by Wermers *et al.* and shorter than the study by Kindmark *et al.* (OS of 58.92 months (Wermers *et al.* 1996) and 80 months (Kindmark *et al.* 2007), respectively).

The characteristics of patients diagnosed with a glucagonoma appear to differ between the decades; patients in our cohort presented with a lower metastatic burden and lower rates of paraneoplastic manifestations in comparison with the studies published in previous years (Wermers *et al.* 1996, Kindmark *et al.* 2007). This difference is likely related to earlier diagnosis, which is not surprising considering the widespread use of biochemical investigation, specifically the glucagon assay.

According to the available data, glucagonomas tend to show metastatic behaviour in up to 60% cases, while more than 50% have already metastasised at the time of diagnosis (Anderson & Bennett 2016). From the 20 cases assessed in the present sample, a total of 12 were found to have distant metastases at initial presentation. Presentation with features of the glucagonoma syndrome was found to be associated with poorer OS. More specifically, the presence of NME was found to be linked with a lower OS compared to patients with no skin signs, likely due to the fact that these patients had more advanced bulky metastatic disease. In addition, the diagnosis of secondary DM associated with glucagonoma was found to be linked with higher OS compared to patients with normal glucose levels, but this finding was not statistically significant in our small series. It seems probable that secondary DM is diagnosed earlier in comparison with the skin manifestations attributed to glucagonoma, hence these patients benefit from earlier initiation of treatment (Resmini *et al.* 2009).

With regards to treatment options, the administration of SSAs appears to have a recognised efficacy even in the control of a rare pan-NET such as glucagonomas, in agreement with the European Neuroendocrine Tumor Society (ENETs) 2023 guidelines on functioning pancreatic neuroendocrine tumour (PanNET) syndromes (Hofland *et al.* 2023). In our cohort, the use of SSAs was associated with a median PFS of 13 months when offered as first-line treatment. Earlier evidence showed that treatment with SSAs was associated with symptomatic improvement, where five out of the six treated patients showed improvement in the extent of the skin rash and the severity of weight loss, as well as a biochemical response with reduction of plasma glucagon levels by >50%, but no radiological responses (Eldor *et al.* 2011). Earlier published studies highlighted that SSA monotherapy was associated with a PFS of 12 months in one patient and not effective in two further patients (Kindmark *et al.* 2007). Others have demonstrated the efficacy of SSAs in controlling the clinical symptoms of patients diagnosed with glucagonoma, namely NME and diarrhoea (Wermers *et al.* 1996, Kindmark *et al.* 2007, Grozinsky-Glasberg *et al.* 2022).

The role of ^{177}Lu-DOTATATE PRRT in the management of glucagonomas has not been extensively evaluated to date. In our cohort of patients, four patients received PRRT as second-line treatment (median PFS 14 months), four received PRRT as third-line treatment (median PFS 8 months), and three received PRRT as fourth-line treatment (median PFS 17 months). In a sample of eight patients with glucagonomas who were followed up for 39.3 months, those treated with ^{177}Lu-DOTATATE PRRT achieved a symptomatic response with a decrease in their skin rash or an increase in weight (71.4% patients), a statistically significant reduction in mean glucagon levels by 87% (P-value = 0.004), and stable disease in 50% the evaluated cases (n = 4 out of eight patients) (Zandee *et al.* 2019). The median PFS was estimated as 18 months after the first cycle of ^{177}Lu-DOTATATE PRRT (Zandee *et al.* 2019). An earlier study described local experience after offering treatment with ^{90}Y-DOTATOC PRRT to three glucagonoma patients: one experienced a radiological partial response, the second showed minimal response, and the third achieved stability of disease (Eldor *et al.* 2011). In a case report of a 56-year-old man, originally treated with two prior surgical resections, administration of ^{177}Lu-DOTATATE PRRT (four induction and two maintenance cycles) resulted in both radiological stabilisation of disease and biochemical control of glucagon levels, with an estimated PFS of 23 months (Makis *et al.* 2015).

The results of our study offer additional experience with regards to the efficacy of mTOR antagonists in the treatment of glucagonomas. Indeed, mTOR antagonists were used only in a small number of patients in our

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series, but overall, this treatment choice was less effective as the disease was progressing, and the number of patients treated with mTOR antagonists was too small to draw firm conclusions. The efficacy of everolimus in the control of glucagon levels in patients with progressive Pan-NET was evaluated in a re-analysis of the RADIANT-1 trial (single-arm phase II, n = 27 patients with raised glucagon levels, prior treatment with one line of chemotherapy), where everolimus induced a sustained decrease in glucagon levels to approximately 70% baseline (concomitant SSA treatment, 5%). The RADIANT-3 trial (placebo-controlled phase III, n = 69 patients with raised glucagon levels, no previous medical treatment) showed that everolimus treatment effectively reduced glucagon levels by approximately 40% in comparison with placebo (concomitant SSA treatment, 35%) (Pavel *et al.* 2020). Regarding the precise effect of mTOR inhibitors, earlier evidence from mice highlighted that loss of mTOR complex-1 signalling can impair glucagon secretion and alter the mass of pancreatic alpha cells (Bozadjieva *et al.* 2017). This effect has to be weighed against the glycaemic effect of rapamycin analogues, which have been reported to affect both peripheral insulin sensitivity and beta-cell function (Fraenkel *et al.* 2008, Yang *et al.* 2012) and thus possibly cause deterioration in the severity of hyperglycaemia.

Chemotherapy, while not the first line of treatment for glucagonomas, plays a crucial role in managing advanced or metastatic disease (Hofland *et al.* 2023). Its primary aim is to control tumour growth and alleviate hormone-related symptoms when other measures such as surgery or somatostatin analogues prove insufficient. Although the presence of functioning syndromes does not specifically stratify the evidence supporting chemotherapy, the choice to utilise it should carefully consider the potential side effects, particularly in patients already experiencing significant hormonal complications (Hofland *et al.* 2023). A commonly used regimen combines capecitabine and temozolomide, demonstrating a 40% response rate in well-differentiated grade 1–3 PanNETs (Hofland *et al.* 2023). Alternatively, streptozotocin-based chemotherapy remains viable, having been used for decades in functioning PanNETs. Combining these treatments with SSA can further improve overall symptom control (Hofland *et al.* 2023).

The results of our study also contribute to the pool of clinical experience on the management of patients with a diagnosis of Pan-NET compatible with glucagonomas. Similar to gastroenteric pancreatic NETs (Zandee *et al.* 2021), administration of PRRT with ^{177}Lu-DOTATATE in our cohort appears to improve disease and symptom control in patients with somatostatin receptor-positive glucagonomas (Hofland *et al.* 2022).

This study has certain limitations that should be acknowledged. First, the sample size is relatively small and could not provide sufficient power for further statistical analyses or robust comparisons of treatments. Second, we present data on patients' clinical symptoms only at the time of first presentation. Third, glucagon values were not routinely assessed after the time of first disease progression. Hence, the effect of treatment lines on glucagon levels could not be estimated appropriately due to missing values. Fourth, this study was conducted in a single tertiary referral centre, representing only local experience. The results only indicate the local clinical practices, as treatment protocols and patient characteristics may not be comparable to those in smaller centres. Moreover, the use of a pragmatic, non-validated symptom score to categorise clinical response (>50% improvement, <50% improvement, or no change), based on retrospective review of clinician notes and patient-reported outcomes, represents a potential limitation due to inherent subjectivity and lack of standardisation. Finally, the retrospective design of the study should also be highlighted. On the other hand, to our knowledge, this is the largest series available describing the management and disease progression in patients with a glucagonoma diagnosis.

In conclusion, this study depicts the main characteristics of patients with a diagnosis of glucagonoma. We observed that patients with paraneoplastic features at baseline tend to have a worse outcome. Compared to previous studies, we were able to report on factors affecting patients' OS. A poorer OS appears to be related to the grade of the tumour, the extent of lung and hepatic involvement, and the presence of distant metastatic disease in the course of the disease, while it is also significantly associated with the presence of NME at the time of presentation. With regards to the efficacy of therapeutic regimens, surgery is associated with the best outcome in terms of PFS as a first-line treatment. Considering the effect of subsequent lines of treatment, PRRT showed promising results irrespective of whether the patients had received prior lines of therapy. These results are encouraging for the use of PRRT in an attempt to control disease progression in patients with glucagonoma. Further prospective/multicentre studies are required to confirm our results and assess the optimal sequence of systemic treatments in patients with advanced glucagonomas, and international collaboration is imperative given the rarity of this patient cohort.

Declaration of interest

The authors have no conflict of interest that could be perceived as prejudicing the impartiality of this work.

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Author contribution statement

EA was responsible for manuscript drafting and statistical analysis. AB helped in data collection and manuscript drafting. JP helped in data collection and manuscript drafting. DM was responsible for data collection. ARH helped in data

collection, literature review, and manuscript editing. AM was responsible for manuscript drafting and statistical analysis. SN, GG, and AMQ helped in data collection. ABG and MC were responsible for data collection, senior review of the manuscript and analysis. CT conceived the study, contributed to data collection, and was responsible for senior review of the manuscript and analysis.

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