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ORIGINAL ARTICLE

Outcomes of Peptide Receptor Radionuclide Therapy in Metastatic Neuroendocrine Tumours

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ABSTRACT

Introduction: *Peptide receptor radionuclide therapy (PRRT) using lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y) are established treatments for metastatic neuroendocrine tumours (NETs). However, data on Chinese population remain limited. This study aimed to examine the efficacy and safety of PRRT in Chinese patients with metastatic NETs.*

Methods: *We retrospectively analysed 21 Chinese patients with metastatic NETs treated with either ^{177}Lu or a combination of ^{177}Lu and ^{90}Y PRRT at Queen Elizabeth Hospital, Hong Kong, between 2018 and 2022. Tumour response was evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. Kaplan–Meier analysis was used to estimate progression-free survival (PFS) and overall survival (OS). Cox regression was used to identify prognostic factors. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.03.*

Results: *The most common primary tumour site was the pancreas (71.4%), followed by the rectum (23.8%) and stomach (4.8%). ^{177}Lu PRRT was used in 90.5% of cases, and a combination of ^{177}Lu and ^{90}Y in 9.5%. Treatment results showed partial response in 47.6%, stable disease in 23.8%, and disease progression in 28.6%. Median PFS was 22.3 months and median OS was 45.2 months. Multivariate analysis showed that bone metastasis significantly worsened PFS ($p = 0.02$) and OS ($p = 0.038$), while a high liver metastatic burden (≥50% liver involvement) was significantly associated with worse OS ($p = 0.042$).*

Conclusion: *PRRT is an effective and well-tolerated treatment for metastatic NETs in the Chinese population. Bone metastases were associated with worse PFS and OS, while a high liver metastatic burden was associated with shorter OS. These results can help clinicians in Hong Kong optimise patient selection and management strategies, though larger prospective studies are needed to validate these findings.*

Key Words: *Gastrointestinal tract; Lutetium; Neuroendocrine tumors; Progression-free survival; Yttrium*

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中文摘要

轉移性神經內分泌腫瘤患者接受肽受體放射性核素治療的治療結果

黃偉軒、林河清、歐陽定勤

引言：肽受體放射性核素治療（PRRT）使用^{177}鎦或^{90}釔已被確立為治療轉移性神經內分泌腫瘤（NETs）的標準療法。然而，有關華人群體的數據仍然有限。本研究旨在評估PRRT在華籍轉移性NET患者中的療效與安全性。

方法：本研究回顧分析了2018年至2022年間，於香港伊利沙伯醫院接受^{177}鎦或^{177}鎦與^{90}釔聯合PRRT治療的21位華籍轉移性NET患者。腫瘤反應根據實體腫瘤反應評估準則（RECIST）第1.1版進行評估。我們採用Kaplan–Meier方法估算無惡化存活期及總存活期，並使用Cox迴歸分析找出預後因素。副作用根據美國國家癌症研究所通用不良事件術語標準（CTCAE）第4.03版進行分級。

結果：最常見的原發腫瘤部位為胰臟（71.4%），其次為直腸（23.8%）及胃部（4.8%）。90.5%患者接受^{177}鎦治療，9.5%接受^{177}鎦與^{90}釔聯合治療。治療結果顯示47.6%達到部分緩解，23.8%為疾病穩定，28.6%為疾病惡化。中位無惡化存活期為22.3個月，中位總存活期為45.2個月。多變量分析顯示骨轉移與較差無惡化存活期（$p = 0.02$）及總存活期（$p = 0.038$）顯著相關；肝轉移負荷高（肝臟受累≥50%）亦與較短總存活期有顯著關聯（$p = 0.042$）。

結論：PRRT對華籍轉移性NET患者而言是一種有效且耐受性良好的治療方法。骨轉移與無惡化存活期及總存活期下降顯著相關，而高肝轉移負荷則與較短的總存活期有關。這些結果有助香港臨床醫生優化病人篩選及治療策略。不過，仍需進一步的大型前瞻性研究以驗證本研究的發現。

INTRODUCTION

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells located in various anatomical sites, predominantly the gastrointestinal (GI) tract, pancreas, and lungs.[1] Approximately 20% of cases present with metastatic disease at the time of diagnosis.[2,3] For cases not amenable to local treatment, systemic treatments commonly include somatostatin analogues, targeted agents such as sunitinib or everolimus, chemotherapy, and peptide receptor radionuclide therapy (PRRT).[4-6]

PRRT exploits the high expression of somatostatin receptors on NET cells,[7] enabling the targeted delivery of radionuclides conjugated to somatostatin analogues.[8] The two primary radionuclides used are yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu). While ^{90}Y emits high-energy beta particles to induce cytotoxic effects, ^{177}Lu emits lower-energy beta particles with a shorter path length of 1 to 2 mm, allowing more precise radiation delivery to smaller metastases and reducing the overall toxicity.

The NETTER-1 phase 3 randomised trial demonstrated that patients with well-differentiated, metastatic midgut NETs treated with ^{177}Lu in combination with a somatostatin analogue had a progression-free survival (PFS) rate of 65.2% at 20 months, compared to 10.8% in those receiving octreotide long-acting repeatable alone.[9] The treatment was well tolerated, with significant myelosuppression occurring in fewer than 10% of patients and no observed renal toxicity during the study period.[9] Subsequently, the US Food and Drug Administration approved ^{177}Lu-dotatate in 2018 for the treatment of somatostatin receptor–positive NETs, and it has since become a standard of care in clinical practice.[10]

Despite the extensive data on PRRT from Europe and the US,[11-15] there is a lack of local data for the Chinese population. This retrospective study aimed to address this gap by reporting treatment responses, survival outcomes, and toxicity associated with PRRT in Chinese patients treated at a hospital in Hong Kong.

METHODS

A retrospective cohort study was conducted on patients with NETs treated with either ^{177}Lu alone or in combination with ^{90}Y at the Department of Nuclear Medicine, Queen Elizabeth Hospital, Hong Kong, between August 2018

and August 2022. The intended PRRT regimen consisted of four to six cycles administered, with 8 to 12 weeks between each cycle. An amino acid infusion was given for renal protection, reducing kidney radiation by limiting reabsorption and enhancing clearance of the radiotracer. A post-therapy scan was performed on day 4 following each treatment cycle.

Eligible patients were Chinese individuals aged 18 years or above with histologically confirmed metastatic NETs. All patients underwent either a baseline octreotide scan or a ^{68}Gallium-Dotatate positron emission tomography scan to confirm somatostatin receptor expression, defined as tumour uptake equal to or greater than that of normal liver tissue. Patients receiving PRRT for paraganglioma were excluded, as these tumours exhibit different biological behaviour compared to epithelial NETs.

Electronic medical records were reviewed to extract patient demographics, including sex, date of birth, date of death (if applicable), date of NET diagnosis, primary tumour location, World Health Organization grade, Ki-67 index, sites of metastases, hepatic metastatic burden, and date of last follow-up. Data on previous treatments was also collected, including surgical resection, locoregional therapies such as transarterial chemoembolisation and radiofrequency ablation, somatostatin analogues (octreotide or lanreotide), targeted therapies (everolimus or sunitinib), and chemotherapy (e.g., temozolomide or capecitabine plus oxaliplatin). Laboratory parameters were recorded before and after each course of PRRT, including haemoglobin, neutrophil and lymphocyte counts, creatinine levels, bilirubin, and alanine transaminase levels. Symptoms after each course of PRRT were extracted from the medical records.

Treatment response was assessed by comparing pre- and post-PRRT imaging using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. Survival outcomes were analysed using Kaplan–Meier curves. PFS was defined as the date from the first PRRT to disease progression or death from any cause, and overall survival (OS) was defined as the time from the first PRRT to death. Toxicities were evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) version 4.03, with follow-up blood tests recorded at each visit. Patients alive at the time of final analysis or lost to follow-up were censored at the date they were last known to be alive.

Two patients who demonstrated an initial response following their course of PRRT subsequently developed disease progression and underwent retreatment with PRRT. Retreatment PFS for these two patients was presented separately and was not pooled with the cohort PFS and OS analyses.

Normally distributed data are shown as means (standard deviations), whereas non-normally distributed data are shown as medians (ranges). Univariable Cox proportional hazards regression was performed to assess the association of baseline factors with PFS and OS. Variables showing at least a trend towards significance ($p < 0.1$) in the univariate analysis were subsequently included in the multivariate analysis using the Cox proportional hazards model. All tests were two-sided, with a significance threshold of $p < 0.05$. Analyses were conducted using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], US).

RESULTS

PRRT was performed on 23 Chinese patients between August 2018 and August 2022 at Queen Elizabeth Hospital. Two patients were excluded from this study because they had paragangliomas, leaving a total of 21 patients included in the study. Patient characteristics are summarised in Table 1. The median age at diagnosis was 55 years (range, 31-72), with 11 male and 10 female patients. All patients had an Eastern Cooperative Oncology Group performance status score of 0 to 1. The most common primary tumour site was the pancreas (71.4%), followed by the rectum (23.8%) and stomach (4.8%). According to World Health Organization tumour grading, 23.8% were Grade 1, 71.4% were Grade 2, and 4.8% were Grade 3. Liver metastases were present in 90.5% of patients, followed by bone metastases (19.0%) and peritoneal metastases (4.8%). About 43% of patients had a hepatic metastatic burden of 50% or more of liver volume on baseline imaging.

The median interval between diagnosis and initiation of PRRT was 12.5 months (range, 2.5-86.2). A total of 42.9% of patients had received prior locoregional treatment, including surgery or transarterial chemoembolisation, before undergoing PRRT. Overall, 85.7% of patients received PRRT after the failure of at least one systemic treatment, which included somatostatin analogues (n = 12), everolimus (n = 9), and chemotherapy agents such as temozolomide plus capecitabine or oxaliplatin plus capecitabine (n = 8). The median number of systemic treatments before PRRT was 1 (range, 0-3). PRRT was used as first-line treatment in 14.3% of patients,

Table 1. Patient demographics (n = 21).*

Age at diagnosis, y	55 (31-72)
Sex	
Male	11 (52.4%)
Female	10 (47.6%)
Primary NET location	
Pancreas	15 (71.4%)
Rectum	5 (23.8%)
Stomach	1 (4.8%)
NET grade	
Grade 1	5 (23.8%)
Grade 2	15 (71.4%)
Grade 3	1 (4.8%)
Metastasis location at the start of PRRT	
Liver	19 (90.5%)
Bone	4 (19.0%)
Peritoneum	1 (4.8%)
Liver metastatic burden	
<50%	12 (57.1%)
≥50%	9 (42.9%)
Previous treatment before PRRT	
Local treatment	9 (42.9%)
Somatostatin analogues	12 (57.1%)
Targeted therapy	9 (42.9%)
Chemotherapy	8 (38.1%)
Type of PRRT isotope	
^{177}Lu	19 (90.5%)
^{177}Lu plus ^{90}Y	2 (9.5%)
Dose of PRRT given per session, MBq	
^{177}Lu	7696 (4662-8140)
^{90}Y	3633 (3330-3848)
PRRT sessions per patient, mean (range)	4.2 (1-6)

Abbreviations: ^{177}Lu = lutetium-177; ^{90}Y = yttrium-90; NET = neuroendocrine tumour; PRRT = peptide receptor radionuclide therapy.
* Data are shown as No. (%) or median (range), unless otherwise specified.

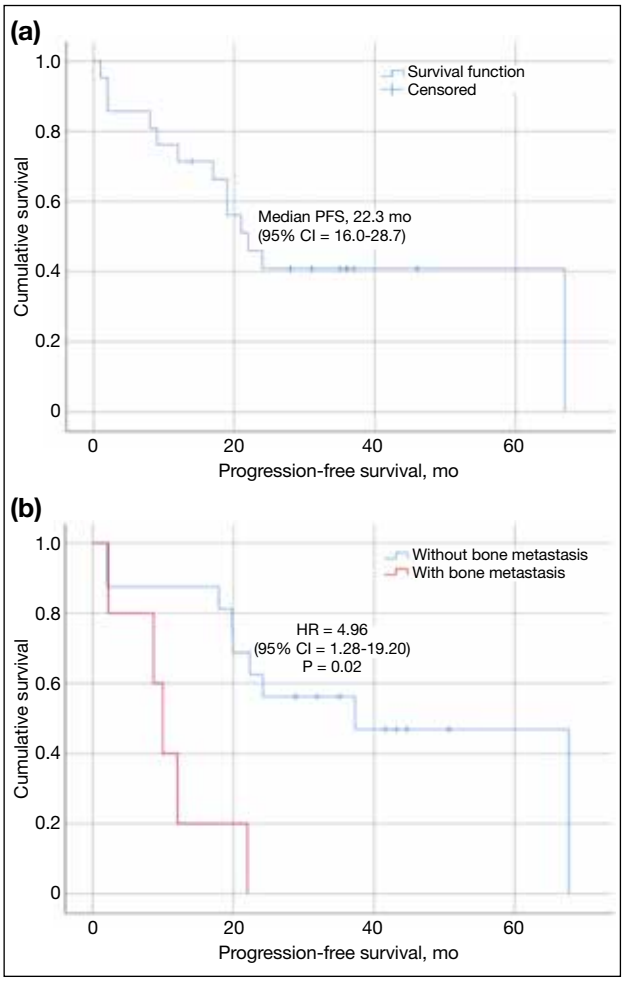

Figure 1. Kaplan–Meier plots of progression-free survival (PFS) following peptide receptor radionuclide therapy. (a) PFS for the entire cohort. (b) PFS comparison based on bone metastasis status.
Abbreviations: 95% CI = confidence interval; HR = hazard ratio.

as second-line in 61.9%, and as third-line or beyond in 23.8%. No patient received additional local or systemic treatment between PRRT cycles.

^{177}Lu was used as monotherapy in 90.5% of patients, while a combination of ^{177}Lu and ^{90}Y was used in 9.5%. In the ^{177}Lu alone group, patients received a median dose of 7622 MBq per injection (range, 4662-8140). In the combination group, the median dose was 7844 MBq of ^{177}Lu (range, 5920-8140) and 3633 MBq of ^{90}Y (range, 3330-3848). Patients underwent a mean of 4.2 PRRT cycles. Five patients were unable to complete at least four cycles: two received one cycle, two received two cycles, and one received three cycles, due to disease progression or death.

All patients were assessed for radiological response using the RECIST 1.1 criteria. Among the 21 patients, partial response was observed in 47.6%, stable disease in 23.8%, and disease progression in 28.6%. No patient achieved a complete response. The disease control rate (defined as the proportion of patients with either partial response or stable disease) was 71.4%.

Progression-Free Survival

The median follow-up duration after the last PRRT treatment was 19 months (range, 2-44). Median PFS was estimated at 22.3 months (95% confidence interval [95% CI] = 16.0-28.7) [Figure 1a]. Univariate analysis (Table 2) identified significantly shorter PFS in patients with bone metastasis (p = 0.006) and GI primary NETs (p = 0.039). Bone metastases remained an independent prognostic factor in multivariate analysis, with a hazard ratio (HR) of 4.96 (95% CI = 1.28-19.20; p = 0.02)

Table 2. Univariate and multivariate analyses of factors associated with progression-free survival and overall survival.

Variable	Progression-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio	p Value	Hazard ratio	p Value	Hazard ratio	p Value	Hazard ratio	p Value
Male sex	0.45	0.176			0.50	0.281		
Age ≥55 y	0.99	0.998			0.504	0.301		
Bone metastasis	6.15 (1.68-22.6)	0.006	4.96 (1.28-19.20)	0.02	6.63 (1.42-30.8)	0.016	5.27 (1.09-25.4)	0.038
Liver burden ≥50%	2.58 (0.85-7.81)	0.094	1.37 (0.41-4.59)	0.614	9.00 (1.793-44.7)	0.008	5.80 (1.07-31.4)	0.042
Functional tumour	0.037	0.331			0.038	0.434		
Gastrointestinal origin	3.39 (1.06-10.8)	0.039	2.43 (0.669-8.80)	0.177	4.15 (1.05-16.4)	0.042	1.97 (0.44-8.89)	0.378
Previous local treatment	0.943	0.916			0.837	0.786		
Previous treatment with somatostatin analogues	0.70	0.515			1.08	0.904		
Previous treatment with targeted therapy	1.47	0.489			1.54	0.496		
Previous treatment with chemotherapy	2.42	0.120			2.83	0.125		
Maintenance treatment given	0.46	0.179			0.723	0.633		
Two or more prior lines of systemic therapy	1.16	0.818			1.54	0.545		

[Figure 1b]. Age, sex, prior treatment with somatostatin analogues, targeted therapy, chemotherapy, and maintenance treatment were not significantly associated with PFS.

Overall Survival

The median OS was 45.2 months (95% CI = 33.4-57.0) [Figure 2a]. Univariate analysis of baseline factors potentially associated with OS is shown in Table 2. In the unadjusted analysis, significantly shorter OS was associated with bone metastasis (p = 0.016), liver metastatic burden of 50% or more (p = 0.008), and GI primary tumours (p = 0.042). Following multivariate analysis, both bone metastasis (HR = 5.27, 95% CI = 1.09-25.4; p = 0.038) and a high liver metastatic burden of 50% or more (HR = 5.80, 95% CI = 1.07-31.4; p = 0.042) remained independently associated with poorer OS (Figure 2b and c).

Toxicities

Patients were evaluated for haematologic, hepatic, or renal toxicity using CTCAE version 4.03 (Table 3). Among haematological toxicities, lymphopenia was the only Grade 3/4 event in 42.9% of patients. No cases of myelodysplastic syndrome were reported. Hepatotoxicity (defined as elevation of alanine transaminase or bilirubin level) was observed in 33.3% of patients at any grade, with 4.8% experiencing Grade 3/4 toxicity. No renal toxicity (defined as elevated plasma creatinine level) was observed. Additionally, nausea was reported in 19.0% and fatigue in 23.8% of patients.

Retreatment with Peptide Receptor Radionuclide Therapy

Two patients in our cohort underwent retreatment with PRRT after initial tumour progression. The first patient, who achieved a PFS of 19.9 months after the initial five cycles of ^{177}Lu PRRT, received a further five cycles of PRRT upon progression and achieved a partial response, with a subsequent PFS of 20 months. The second patient was undergoing a fourth cycle of PRRT retreatment, and the initial post-therapy scan showed partial response. No Grade 3/4 toxicities were observed except for Grade 3 lymphopenia in one patient.

DISCUSSION

To the best of our knowledge, this is the first local study to examine how effective PRRT is for treating NETs in Chinese patients from Hong Kong. An objective response rate (ORR) of 47.6% was observed, with a median PFS of 22.3 months, and a median OS of 45.2 months. The OS outcome closely mirrors that reported in the NETTER-1 trial, which included only patients with well-differentiated midgut NETs and reported a median OS of 48 months in the ^{177}Lu group, compared to 36.3 months in the control group.[16] In contrast, our study included a more heterogeneous group of primary tumours, particularly characterised by a significant proportion

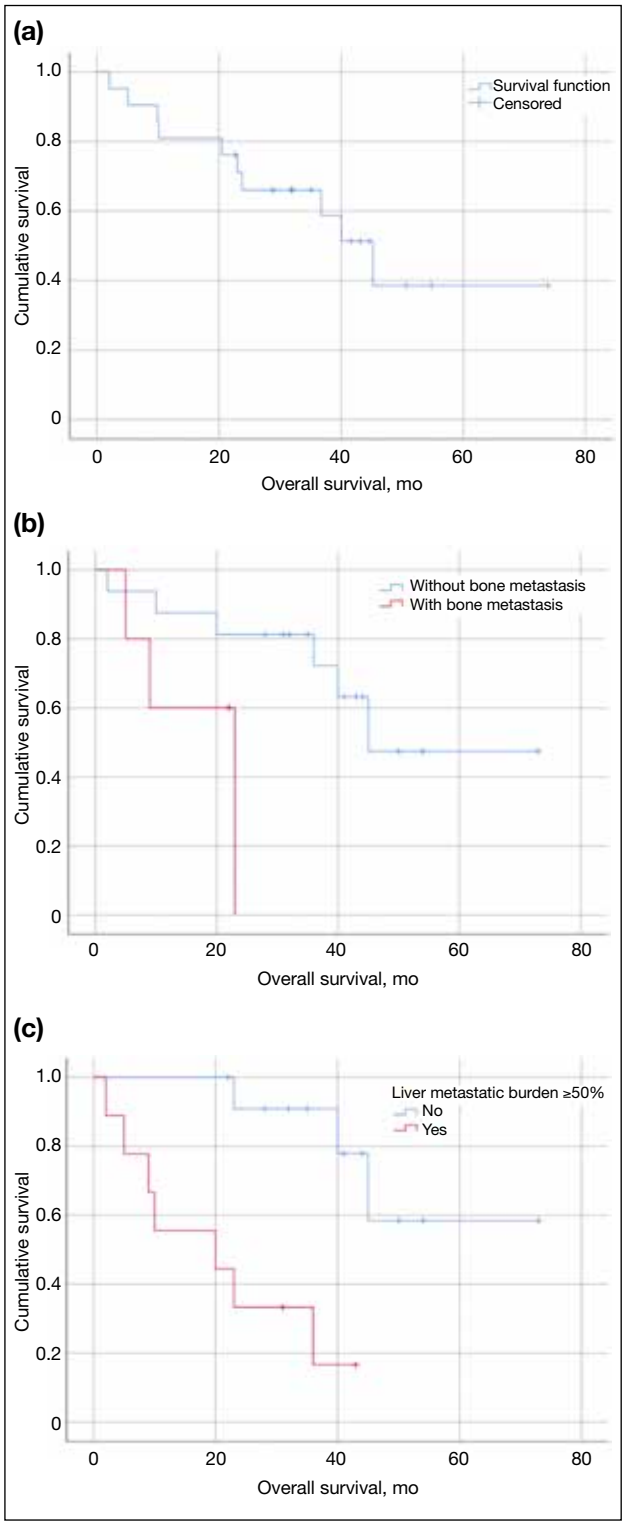

Figure 2. Kaplan–Meier plots of overall survival (OS) following peptide receptor radionuclide therapy. (a) OS for the entire cohort. (b) OS comparison based on bone metastasis status. (c) OS comparison based on liver metastatic burden.

Table 3. Adverse events.

	All grades	Grade 3/4
Anaemia	61.9%	0%
Neutropenia	33.3%	0%
Lymphopenia	81.0%	42.9%
Thrombocytopenia	33.3%	0%
Hepatotoxicity	33.3%	4.8%
Nephrotoxicity	0%	0%
Nausea	19.0%	Not available
Fatigue	23.8%	Not available

of pancreatic NETs. A recent large retrospective study by Mitjavila et al,[17] which evaluated 522 patients with a heterogeneous group of NETs including pancreatic, midgut, and bronchopulmonary subtypes, reported an ORR of 33.9%, a median PFS of 24.3 months and a median OS of 42.3 months. Our results align with these findings, further supporting the efficacy of PRRT in treating metastatic NETs across various primary sites in a Chinese patient population.

Our study demonstrated that bone metastases were significantly associated with poorer PFS and OS in multivariate analysis. This finding aligns with the results from Sitani et al,[18] who analysed a cohort of 468 patients and reported that bone metastasis significantly impacted OS. Similarly, Abou Jokh Casas et al[19] observed an inverse relationship between OS and the presence of bone metastases in their cohort of 36 patients treated with PRRT for gastroenteropancreatic NETs. The concordance of our findings with these studies supports the role of bone metastases as a potentially negative prognostic factor in metastatic NETs. The challenges posed by bone metastases may be attributed to the more aggressive nature of the disease, as bone metastases are considered a late event in NETs[20] and predisposes patients to serious skeletal events such as spinal cord compression.[21]

Our study also showed that a high liver metastatic burden of 50% or more, as assessed by radiological evaluation, was associated with poorer OS. A visual semi-quantitative assessment method for liver tumour burden was used, as recommended by the European Neuroendocrine Tumor Society,[22] and has been shown to be reliably reproducible.[20] The presence of neuroendocrine liver metastases is one of the most significant negative prognostic factors for long-term

survival in patients with NETs.[23] A retrospective study by Ezziddin et al[11] analysed 68 patients with pancreatic NETs treated with ^{177}Lu PRRT and showed that a liver metastatic burden greater than 25% or above was associated with reduced OS. Our findings also align with a recent retrospective study by Swiha et al,[24] which demonstrated that liver metastases involving more than 50% of liver volume was associated with poorer OS. Although there was a trend towards poorer PFS with high liver metastatic burden, this was not statistically significant in multivariate analysis, likely due to the limited sample size and confounding factors.

Previous studies have suggested that tumours of GI origin generally have a better prognosis compared to those of pancreatic origin.[25,26] However, our univariate analysis showed that pancreatic origin might have a better prognosis, though this was not significant in the multivariate analysis, indicating the influence of potential heterogeneity and confounding factors. Notably, prior research has shown that GI-origin NETs are typically associated with lower-grade tumours.[27] In contrast, within our cohort, 83.3% of GI-origin cases were classified as Grade 2 tumours or higher (including one Grade 3 tumour), whereas 73% of pancreatic-origin cases were all Grade 2 tumours and no Grade 3 tumours. Because only patients with progressive disease were referred for PRRT, our GI subgroup likely represents a selection of more aggressive cases. The inclusion of more aggressive histological subtypes within the GI-origin group in our cohort may explain the unexpected findings in our analysis.

Grade 3 NETs are associated with a worse prognosis compared to their lower-grade counterparts,[25] making treatment more challenging due to their aggressive nature. In our study, we had only one case of Grade 3 NET treated with PRRT, limiting further statistical analysis. The use of PRRT in Grade 3 NETs has mainly been supported by retrospective studies of heterogeneous groups.[12,17-19] However, the recent phase 3 NETTER-2 trial demonstrated significant improvements in PFS and ORR with ^{177}Lu-dotatate as a first-line treatment for higher-grade Grade 2 and Grade 3 NETs.[28] The primary analysis showed a median PFS of 22.8 months in the ^{177}Lu-dotatate group compared to 8.5 months in the control group, and an ORR of 43.0% versus 9.3%, respectively.[28] These findings underscore the potential efficacy of PRRT in treating high-grade NETs and suggest a promising therapeutic option for this challenging subgroup.

The toxicity profile observed in our study was generally favourable. The NETTER-1 study reported no Grade 3 anaemia, 1% neutropenia, and 2% thrombocytopenia.[16] Our study similarly found no Grade 3/4 anaemia or neutropenia. However, while NETTER-1 reported 9% Grade 3/4 lymphopenia,[16] our study observed a higher rate (42.9%), which may be attributed to the greater number of PRRT cycles administered. The toxicities were reversible, and none of the patients developed myelodysplastic syndrome. Only one patient developed Grade 3/4 liver derangement, and none developed any grade of renal toxicity, aligning with published retrospective studies that showed minimal Grade 3 toxicities of liver and renal function.[13,17]

Finally, two patients in our cohort underwent retreatment with PRRT after tumour progression, receiving additional distinct PRRT treatment courses. Both patients showed a partial response. One patient is still undergoing treatment at the time of writing, and the other demonstrated a similar PFS between the two series of PRRT. No significant toxicities other than Grade 3 lymphopenia were observed.

According to a meta-analysis by Strosberg et al,[29] the median PFS following PRRT retreatment was 12.5 months, and the median OS was 26.8 months. The study also reported a low rate of Grade 3/4 toxicities,[29] confirming that PRRT retreatment generally maintains a manageable safety profile. It was also observed that PFS decreased after the second treatment course compared to the first.[30] Despite a limited number of retreatment cases in our cohort, the results are encouraging.

Limitations

Our study has several limitations. First, as a retrospective study, it is subject to inherent selection bias and recall bias. Selection bias may have occurred because PRRT is an expensive treatment, making it more accessible to patients with better overall health and higher socio-economic status, potentially skewing the results towards more favourable outcomes. Recall bias may have influenced our findings since the data relied on medical records and follow-up reports, which might not have consistently captured all relevant information. Second, the sample size is relatively small and the study population was heterogeneous, which may limit the generalisability of the findings and introduce variability that could confound the results. Third, the estimation of PFS may have been affected by variability in the timing of CT scans across different patients, potentially

leading to inconsistencies and bias in assessing disease progression. Finally, the small number of patients undergoing PRRT retreatment limited our ability to draw robust conclusions about the efficacy and safety of repeat treatments.

CONCLUSION

This study provides important insights into the use of PRRT in Chinese patients with metastatic NETs. Our findings suggest that PRRT is an effective and generally well-tolerated treatment option for this population, supporting its use in local clinical practice. We identified bone metastasis as a significant factor for worse PFS and OS, while a high liver metastatic burden was significantly associated with worse OS. These results can help clinicians in Hong Kong optimise patient selection and management strategies for the treatment of NETs. However, larger prospective studies are needed to further validate these findings.

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