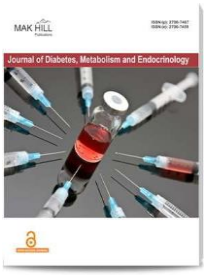

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Research Article

# Lutetium-177 Peptide Receptor Radionuclide Therapy in Metastatic Neuroendocrine Tumours: A Case Series from a Tertiary Care Centre.

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**Abstract: Background:** Lutetium-177 (Lu-177) peptide receptor radionuclide therapy (PRRT) has emerged as a transformative treatment for somatostatin-receptor-positive metastatic neuroendocrine tumors (NETs).1,2 This case series documents our institutional experience with Lu-177 PRRT in patients with advanced metastatic NETs. ***Methods:*** We retrospectively analyzed 10 consecutive patients with metastatic NETs treated with Lu-177 PRRT between January 2022 and June 2025. Patient demographics, disease characteristics, prior systemic therapies, PRRT cycles administered, and radiological response at 4 months were documented. ***Results:*** The cohort comprised 8 males (80%) and 2 females (20%) with median age 52 years. Five patients (50%) had Grade I NETs and 5 (50%) had Grade II NETs. All patients received prior long-acting release somatostatin analogues (median 12 cycles). Eight patients completed 4 cycles of Lu-177 PRRT, while 2 received fewer cycles. Grade I NETs (n=5) achieved 40% ORR (2/5) with 80% disease control, progressive disease in 20% compared to Grade II NETs (n=5) at 40% ORR (2/5) with 60% disease control, progressive disease in 40%. Patients completing 4 cycles demonstrated 37.5% ORR with stable disease in 37.5% and progressive disease in 25%. No grade 3+ hematologic, renal, or hepatic toxicity was documented. Grade I NETs showed superior Disease Control Rate (80% vs 66.6%) ***Conclusion:*** Lu-177 PRRT demonstrates effective disease control in 75% of metastatic NET patients, completing 4 cycles. Tumor grade and treatment completion appear to influence response outcomes. Larger prospective studies are needed to validate biomarkers and optimize patient selection.

**Keywords:** Lutetium-177, neuroendocrine tumors, PRRT, targeted radionuclide therapy, metastatic cancer.



## INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies with increasing incidence globally, rising from 1.09 per 100,000 in 1973 to 2.5–5 per 100,000 in recent decades.3,4 Approximately 50% of patients present with metastatic disease, which carries significantly poorer prognosis despite advances in targeted therapies.5 Traditional management relies on somatostatin analogues (SSAs), which prolong progression-free survival but are often associated with eventual disease progression.6

Somatostatin receptors (SSTR), particularly SSTR2 and SSTR5, are highly expressed on most well-differentiated NETs, enabling both diagnostic imaging via 68Gallium-DOTATATE PET/CT and therapeutic targeting.7 Lutetium-177 (177Lu), a beta-minus-emitting radionuclide with ideal physical characteristics (half-life 6.64 days, max energy 497 keV), enables selective targeting of SSTR-positive tumor cells while minimizing normal tissue exposure.8

The NETTER-1 trial established Lu-177 PRRT efficacy, demonstrating median progression-free survival not reached in the PRRT arm versus 8.4 months in controls (HR 0.21), with objective response rate of 43% versus 9%.9 Subsequent real-world data reported pooled response rates of 35.3% across 2,000+ patients, with higher rates in well-differentiated tumours.10 However, limited data exist from resource-limited healthcare settings. We present our institutional experience with Lu-177 PRRT in metastatic NETs.

## MATERIALS AND METHODS

This retrospective case series included 10 consecutive patients with histologically confirmed metastatic NETs who received ≥1 cycle of Lu-177 PRRT at our institution between January 2022 and June 2025. Inclusion criteria: (1) metastatic disease; (2) somatostatin-receptor-positive imaging; (3) ECOG performance status 0–1; (4) available baseline and follow-up data. Radiological response was assessed using RECIST v1.1 at 12 months post-initiation, categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) comprised CR+PR. Disease control rate (DCR) comprised CR+PR+SD. Data were analyzed using descriptive statistics. The study was approved by the Institutional Ethics Committee.

## RESULTS

**Patient Characteristics and Treatment Details**

The cohort comprised 8 males (80%) and 2 females (20%), median age 52 years (range 43–79). Five patients (50%) had Grade I NETs and 5 (50%) had Grade II NETs. Primary tumour sites included small bowel carcinoid (n=4), pancreatic NET (n=4), and Stomach (n=2). All patients presented with metastatic disease with liver involvement. All patients received prior LAR (median 12 cycles; range 4–18), and 2 patients received prior CAPTEM chemotherapy.

**Table 1. Patient Demographics, Disease Characteristics, and Treatment Outcomes**

| Pt | Age/ Sex | Primary Site | Grade | Metastatic Sites | Prior LAR Cycles | Prior Chemo | Lu-177 Cycles | Response at 4months | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 43/F | Small intestine | I | Liver | 15 | None | 4 | Good PR (>50%) | Responder |
| 2 | 77/M | Pancreas | I | Liver, lymph nodes | 4 | CAPTEM (16) | 4 | Stable disease | Non responder |
| 3 | 71/M | Pancreas | II | Liver, peritoneum | 18 | None | 3 | Good PR (≥40%) | Responder |
| 4 | 52/M | Pancreas | II | Liver (large burden) | 8 | None | 4 | Progressive disease | Non responder |
| 5 | 45/F | Stomach | I | Liver, peritoneal | 6 | CAPTEM (6) | 4 | Stable disease | Non responder |
| 6 | 55/M | Small intestine | I | Liver, lymph nodes | 12 | None | 4 | PR (>30%) | Responder |
| 7 | 79/M | Pancreas | II | Liver, vertebral | 12 | None | 2 | Progressive disease | Non responder |
| 8 | 45/M | Small intestine | II | Liver, regional nodes | 18 | None | 4 | Stable disease | Non responder |
| 9 | 46/M | Stomach | I | Liver (extensive) | 15 | None | 4 | Progressive disease | Non responder |
| 10 | 51/M | Small intestine | II | Liver, peritoneal, nodes | 4 | None | 4 | PR (≥30%) | Responder |

Pt, patient; F, female; M, male; Grade I, well-differentiated; Grade II, moderately differentiated; CAPTEM, capecitabine-temozolomide; PR, partial response; LAR, Long acting release: PRRT, peptide receptor radionuclide therapy.

**Treatment Administration and Response Outcomes**

Grade I NETs (n=5) achieved 40% ORR (2/5) with 80% disease control, progressive disease in 20% compared to Grade II NETs (n=5) at 40% ORR (2/5) with 60% disease control, progressive disease in 40%.

Eight patients completed 4 cycles of Lu-177 PRRT. Radiological response after 4 cycles of Lu-177 PRRT Therapy demonstrated:

- Objective Response Rate (CR+PR): 3/8 (37.5%)
- Stable Disease: 3/8 (37.5%)
- Progressive Disease: 2/8 (25%)
- Disease Control Rate (ORR+SD): 6/8 (75%)

Grade I NETs showed superior Disease Control Rate (80% vs 66.6%). No grade 3+ hematologic, renal, or hepatic toxicity was documented.

## DISCUSSION

This case series demonstrates that Lu-177 PRRT achieves clinically meaningful disease control in 70% of metastatic NET patients, with 40% achieving objective radiological response. These findings align closely with NETTER-1 (43% ORR) and real-world pooled data (35.3% ORR across 2,000+ patients),9,10 supporting the reproducibility of PRRT efficacy across diverse healthcare settings. Tumor grade significantly influenced Disease Control Rate. Grade I NETs showed 80% compared to 66.6 % in Grade II, consistent with published literature demonstrating that well-differentiated tumors express higher and more uniformly distributed somatostatin receptors.11,12 This biologic difference translates to superior target engagement and therapeutic benefit in low-grade disease.

Treatment completion emerged as a potential predictor of response, with 4-cycle completion yielding 37.5% ORR. This observation supports the NETTER-1 protocol design and published evidence that full treatment courses optimize outcomes.13 The two patients with incomplete treatment (patients 3 and 7) had circumstances limiting full completion—patient 3 with renal decline after 3 cycles still achieved response, while patient 7 with extensive metastatic disease and aggressive progression received only 2 cycles before clinical deterioration. Progressive disease in 25% of patients highlights treatment resistance mechanisms. These include: (1) heterogeneous receptor expression within tumors, leaving receptor-negative populations resistant to PRRT; (2) high tumor burden overwhelming radionuclide therapy capacity; (3) activation of alternative growth pathways (mTOR, FGF, VEGF); and (4) potential baseline receptor downregulation following prolonged LAR therapy.14,15 Patient 7 exemplifies this challenge—pancreatic primary with extensive hepatic and skeletal metastases experienced rapid progression despite PRRT initiation.

All patients had received substantial prior LAR exposure (median 12 cycles), reflecting progressive SSA-refractory disease. Two patients additionally received CAPTEM chemotherapy prior to PRRT. Although NETTER-1 excluded chemotherapy-treated patients, retrospective data suggest prior chemotherapy does not impair PRRT efficacy.16 Patient sequencing strategies remain incompletely defined, and prospective trials comparing direct PRRT after LAR versus post-chemotherapy PRRT are warranted. Tolerability was excellent, with no documented grade 3+ toxicity observed. This contrasts favorably with chemotherapy profiles and aligns with published safety data demonstrating Lu-177 PRRT as generally well tolerated with reversible, grade 1–2 adverse events predominating.9 Regular renal function monitoring throughout treatment ensured safety.

Limitations include small size (n=10), retrospective design, heterogeneous NET primaries, short follow-up, and incomplete toxicity documentation. Seventeen Larger prospective studies with extended follow-up and comprehensive biomarker assessments (receptor expression density, Ki-67, genomic profiles) are needed to identify response predictors and optimize patient selection. Future priorities include prospective trials clarifying optimal treatment sequencing, investigation of combination approaches with mTOR inhibitors or immunotherapy, and expansion of PRRT access to resource-limited settings. Development of predictive biomarkers would enable precision medicine approaches to maximize efficacy in individual patients.

## CONCLUSION

Lu-177 PRRT effectively controls metastatic NET disease in 75% of patients completing 4 cycles, with tumor grade and treatment completion influencing response outcomes. Well-differentiated NETs demonstrate superior Disease Control to poorly differentiated disease, reflecting molecular differences in somatostatin receptor expression. The excellent tolerability profile supports PRRT as a cornerstone therapy in the multimodal NET management paradigm, particularly for somatostatin-

receptor-positive metastatic disease. Prospective studies with longer follow-up and biomarker integration are essential to validate these observations and optimize patient selection strategies.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**ETHICAL APPROVAL**

This retrospective study was approved by the Institutional Ethics Committee of Kidwai Memorial Institute of Oncology, Bangalore, India. Given the retrospective nature of the analysis, informed consent was waived. All procedures were performed in accordance with the Declaration of Helsinki and applicable institutional guidelines.

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