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Diagnostic and Therapeutic Challenges of Neuroendocrine Tumors in Low-and Middle-Income Countries: A Clinical Perspective

Afolabi Adebayo Oladeji[1*], Kirti Koushik AS[2], Bismarck Oghenegueke Edijana[3]

[1]Department of Radiation Oncology, College of Medicine, University of Ibadan, Ibadan, Nigeria

[2]Department of Radiation Oncology, HCG Hospitals, Bangalore, India

[3]Department of Radiation Oncology, University College Hospital, Ibadan, Nigeria

[*]**Corresponding Author:** Afolabi Adebayo Oladeji, Department of Radiation Oncology, College of Medicine, University of Ibadan, Ibadan, Nigeria.

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Abstract

Background: Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms with indolent growth and diverse biological behavior, commonly arising in the gastrointestinal tract, lungs, and pancreas. Their non-specific symptoms contribute to diagnostic delays, especially in low- and middle-income countries (LMICs), where limited access to advanced diagnostic tools and therapies further exacerbates the challenges.

Clinical Case: A 53-year-old university lecturer from Nigeria presented with a 14-month history of recurrent abdominal pain, intermittent diarrhea, and significant weight loss. Initially misdiagnosed and treated for peptic ulcer disease, advanced diagnostics confirmed a well-differentiated ileal neuroendocrine tumor with hepatic metastases. Resource limitations necessitated seeking care abroad, where transarterial chemoembolization (TACE), somatostatin analogs, and Lutetium-177 therapy were initiated for disease control.

Conclusion: This case highlights the diagnostic and therapeutic barriers in managing NETs in LMICs, underscoring the need for strategic investments in healthcare infrastructure, international collaboration, and policy reforms to address disparities and improve patient outcomes.

Keywords: Neuroendocrine Tumors, Low- and Middle-Income Countries, Diagnostic Challenges, Therapeutic Barriers, Healthcare Disparities

Introduction

Neuroendocrine tumors (NETs) are a group of rare malignancies derived from neuroendocrine cells, predominantly affecting the gastrointestinal tract, lungs, and pancreas. While improvements in diagnostic technologies have contributed to the rising incidence globally, the disparity in access to these tools between high-income countries (HICs) and low- and middle-income countries (LMICs) has widened the gap in care delivery **[1,2]**.

The indolent course, variable presentation, and non-specific symptoms of NETs often result in delayed diagnoses, with patients in LMICs frequently presenting at advanced stages. Challenges include limited availability of advanced imaging, biomarkers, and therapeutic options such as somatostatin analogs, targeted therapies, and peptide receptor radionuclide therapy (PRRT) **[3,4]**. This paper provides a clinical perspective on these challenges, supported by a detailed case report, while advocating for scalable interventions to address these barriers in LMICs.

Literature review

Epidemiology and Trends

The global incidence of NETs has substantially increased, with gastrointestinal and lung NETs accounting for the majority of cases. While most data are derived from HICs, underreporting in LMICs due to inadequate cancer registries likely underestimates the true burden **[5]**. NETs account for approximately 0.5% of all malignancies globally, but LMIC-specific statistics remain sparse **[6]**.

Diagnostic Challenges in LMICs

1.Delayed Diagnosis: NETs often present with vague, non-specific symptoms that mimic more common conditions, leading to delayed diagnoses. Limited awareness among primary care providers in LMICs further exacerbates this issue **[7]**.

2.Limited Access to Diagnostic Tools: Advanced imaging modalities such as 68Gallium-DOTATATE PET-CT and octreotide scintigraphy, crucial for accurate staging, are often unavailable **[8]**. Biomarker assays, including chromogranin A and synaptophysin, remain inaccessible in many settings due to high costs and inadequate laboratory infrastructure **[9]**.

3.Pathological and Imaging Limitations: Histopathological confirmation of NETs is frequently delayed due to a shortage of trained pathologists and lack of advanced immunohistochemical facilities **[10]**.

Therapeutic Challenges in LMICs

1.Surgical Limitations: Surgical resection is a cornerstone of NET treatment. However, delays in diagnosis often result in advanced

disease stages where curative surgery is no longer feasible. The shortage of specialized surgeons and facilities further complicates management **[11]**.

2.Limited Access to Medications: Somatostatin analogs, such as octreotide and lanreotide, are standard for symptom control but are often unavailable or unaffordable [(12).] Similarly, targeted therapies like everolimus and sunitinib are rarely accessible in LMICs**[13]**.

3.Restricted Access to PRRT: Peptide receptor radionuclide therapy (PRRT), a highly effective option for metastatic NETs, requires specialized facilities and expertise that are largely unavailable in LMICs **[14]**.

Socioeconomic and Policy Factors

High out-of-pocket expenses, inadequate insurance coverage, and limited government funding for rare cancers contribute to significant disparities in care **[15]**. The prioritization of more common cancers often leaves NET patients with limited options for diagnosis and treatment **[16]**.

Case Report

A 53-year-old woman presented with a history of recurrent upper abdominal pain, intermittent diarrhea, and weight loss over 14 months.

Diagnostic Timeline:

• July 2022: Initial symptoms misdiagnosed as irritable bowel syndrome and peptic ulcer disease.

• February 2024: Ultrasound revealed multiple hyperechoic hepatic lesions (2–12 cm), suspicious for metastases.

• May 2024: Biopsy confirmed metastatic well-differentiated NET (Grade I, Ki-67: 1%) with immunohistochemistry suggestive of a gastrointestinal origin.

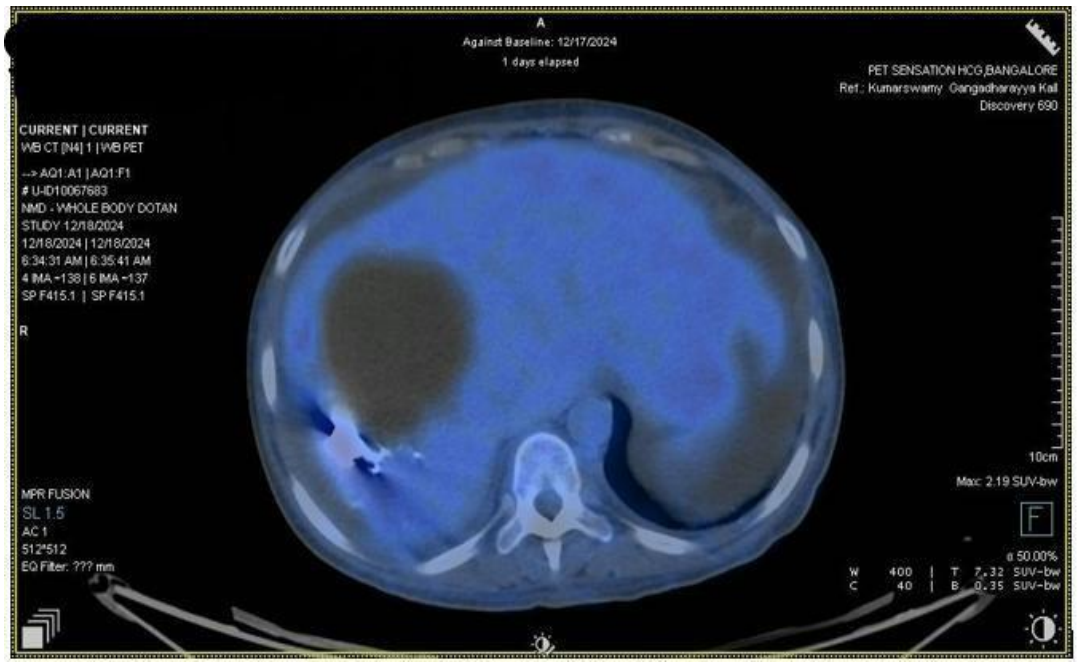
• June 2024: DOTANOC PET/CT identified an ideal primary lesion with mesenteric nodal and hepatic metastases.

Therapeutic Interventions:

• June 2024: Transarterial chemoembolization (TACE) was performed, and oral anticoagulants were initiated for right atrial thrombi.

• August 2024: Symptom management with octreotide initiated.

• December 2024: Progressive hepatic metastases and significant ascites noted; Lutetium-177 therapy was commenced, combined with Sandostatin LAR (30 mg every 28 days).



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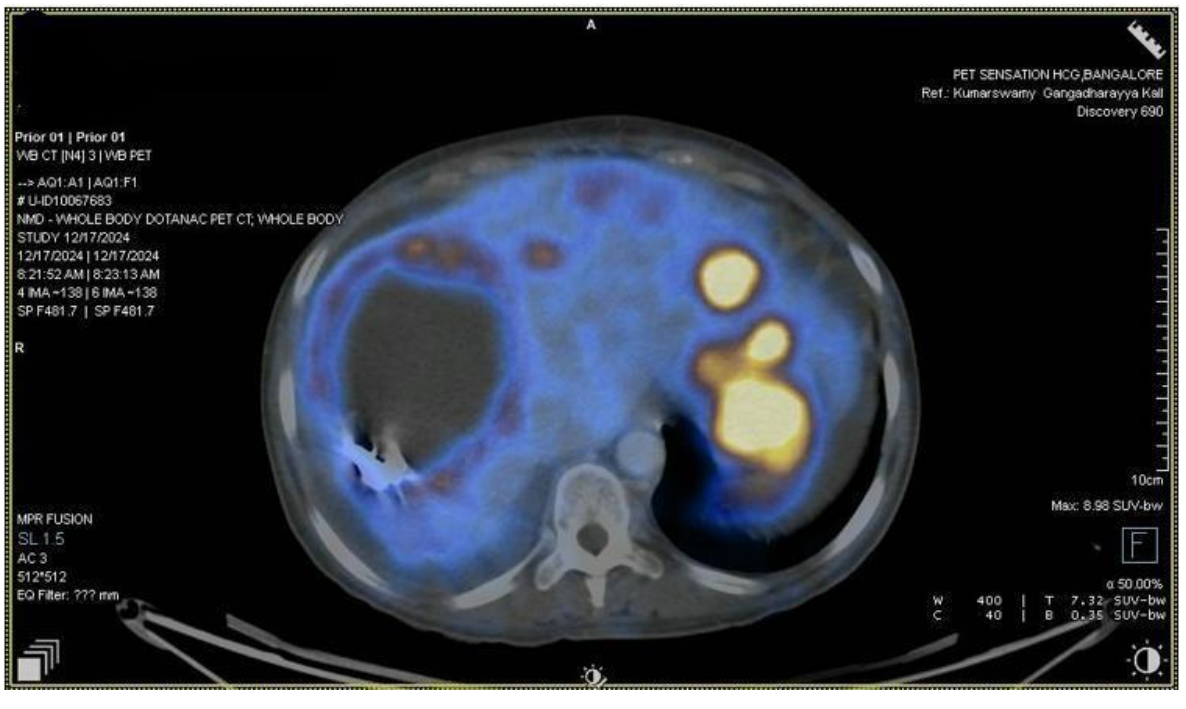

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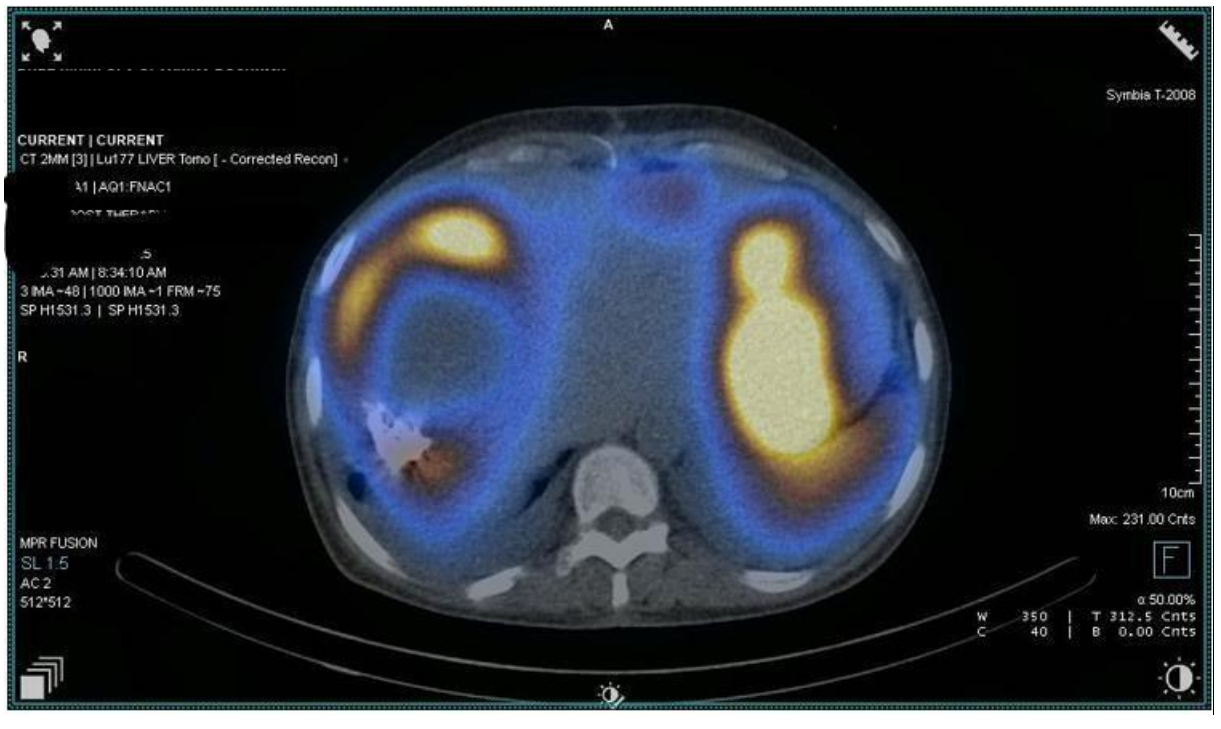

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Discussion

This case highlights the multifaceted challenges in managing NETs in LMICs:

1. Diagnostic Challenges

• Delayed Diagnosis: Non-specific symptoms mimic common gastrointestinal disorders, leading to diagnostic delays.

• Resource Limitations: Restricted access to imaging modalities such as DOTATATE PET-CT and biomarkers (e.g., chromogranin A) hinders early and accurate diagnosis **[17]**.

• Pathological Constraints: The shortage of pathologists and immunohistochemical facilities delays tumor grading and localization **[18]**.

2. Therapeutic Barriers

• Limited Access to Medications: Somatostatin analogs, critical for symptom control, remain inaccessible for many due tohigh costs **[19]**.

• Restricted PRRT Availability: Peptide receptor radionuclide therapy (PRRT), a mainstay for metastatic NETs, requires specialized facilities often unavailable in LMICs **[20]**.

3. Socioeconomic and Policy Limitations

- Financial Constraints: Out-of-pocket payments for diagnostics and treatment create significant barriers **[21]**.
- Policy Gaps: Rare cancers like NETs are deprioritized, leaving patients with suboptimal care options **[22]**.

International Comparisons

In HICs, patients benefit from multidisciplinary care teams and access to novel therapies, such as PRRT and targeted drugs **[23]**. Replicating these strategies in LMICs will require innovative, cost-effective solutions tailored to resource limitations.

Future Directions

To improve NET care in LMICs, several key areas need to be addressed:

1. Enhanced Diagnostics: Increased availability of PET-CT imaging and biomarker testing **[24]**.

2. Training Programs: Strengthening the knowledge base of healthcare providers for early NET detection and management **[25]**.

3. Accessible Therapies: Reducing costs of somatostatin analogs and PRRT through subsidies or collaborations **[26]**.

Conclusion

The management of neuroendocrine tumors in LMICs remains fraught with challenges, including delayed diagnoses, limited therapeutic options, and socioeconomic constraints. Addressing these disparities requires strategic investments in diagnostic tools, provider training, and accessible therapies. International collaboration and policy reforms are critical to improving outcomes for NET patients in resource-constrained settings.

Statement of Ethics

1. Informed Consent: informed consent was obtained from the patient prior to the use of their clinical data for research purposes. This includes informing them about the nature of the study, its purpose, potential risks, and their right to withdraw consent at any time without affecting their medical care.

2. Confidentiality and Anonymity; The confidentiality of patient information is maintained by anonymizing any identifying details in the manuscript. This includes removing names, addresses, and other personal identifiers that could link the data back to individual patients.

3. Ethical Approval: We acknowledge that ethical approval was not required for this study, as it is a review of cases previously treated.

4. Patient Welfare: we prioritized the well-being of patients by ensuring that any treatment or diagnostic protocols followed in the cases presented were performed according to the best medical standards. The research did not compromise patient safety or quality of care.

5. Accurate Reporting: We Ensured that all clinical findings, treatment outcomes, and patient histories are reported accurately and without embellishment.

6. Conflict of Interest: There are no conflicts of interest to disclose related to this study.

7. Beneficence and Non-maleficence: we Upheld the ethical principles of beneficence (acting in the best interest of patients) and non-maleficence (avoiding harm) throughout the study.

8. Funding Sources: This study was entirely self-funded. No external sponsorship or grants were received for this research.

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Author Contributions

Afolabi Adebayo Oladeji is the main author and corresponding author, having managed the patient and contributed to the overall study. Dr. Kirti Koushik A S was involved in the management of the patient. Bismarck Oghenegueke Edijana was responsible for collecting the data and writing the summary of both cases.

Data Availability Statement

All data used in this study are available in the records department of Alpha Specialist Hospital, Ibadan, Nigeria and HCG Hospitals, Bangalore, India.

Research Highlights:

1. Neuroendocrine Tumor (NET) Burden in LMICs: The manuscript underscores the increasing incidence of neuroendocrine tumors globally and the disproportionate challenges faced in low- and middle-income countries (LMICs) due to inadequate healthcare infrastructure.

2. Diagnostic Barriers: It highlights significant delays in diagnosing NETs in LMICs, driven by limited access to advanced imaging modalities (e.g., PET-CT, immunohistochemistry) and a lack of trained pathologists.

3. Therapeutic Challenges: The study identifies barriers to optimal treatment, including the high costs and limited availability of therapies such as somatostatin analogs, targeted drugs, and peptide receptor radionuclide therapy (PRRT).

4. Case Report Insight: A detailed case of a Nigerian patient illustrates the real-world implications of these challenges, showcasing diagnostic delays, inadequate local resources, and eventual reliance on international healthcare facilities for advanced care.

5. Call for Action: The manuscript advocates strategic investments in healthcare infrastructure, affordable diagnostic and therapeutic solutions, capacity building, and international collaboration to bridge disparities in NET care.

6. Future Directions: Recommendations include improved access to diagnostic tools, enhanced healthcare provider training, multidisciplinary care networks, policy reforms, and prioritization of NETs in LMIC healthcare systems.

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