Quality-of-Life Outcomes of Radioligand Therapy Used in Combination with Systemic Therapies for Neuroendocrine Tumors: A Systematic Review

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Background

- In neuroendocrine tumors (NETs), a group of heterogeneous tumors, one notable feature is hypersecretory syndrome caused by excess hormone production, e.g., carcinoid syndrome characterized by flushing, diarrhea, and abdominal pain. Hormonal syndromes along with other symptoms due to tumor burden significantly impact patients' health-related quality of life (QoL).
- Radioligand therapy (RLT), or peptide receptor radionuclide therapy (PRRT), is a new drug class used to treat NETs. Currently, ^{177}Lu-DOTATATE combined with long-acting octreotide is the only FDA-approved PRRT in NETs.
- Ongoing studies are investigating other combinations of RLT with systemic agents such as cytotoxic chemotherapy and immunotherapy. However, there is limited evidence about the effect of these combination treatments on QoL outcomes.

Objective

- This systematic review aimed to summarize QoL outcomes of studies evaluating combination PRRT treatment with another PRRT or other systemic treatment regimens.

Methods

- PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched.
- Using Covidence, studies were independently screened by two reviewers for inclusion.
- Relevant data was extracted by one reviewer, and another reviewer verified the accuracy of all extracted data. Discrepancies were discussed between two reviewers. When consensus could not be reached, a third reviewer was involved.

Table 1. Screening criteria

Category	Inclusion	Exclusion
Population	• Human patients with NET, including but not limited to: GEP-NET, pancreatic NET, lung NET, paraganglioma	• Non-human subjects • Patients with diseases not classified as NET
Exposure	• Use of intravenous RLT* in combination with another systemic anticancer medication therapy	• Use of RLT for diagnosis, imaging, or other non-treatment purposes • Use of RLT as the only systemic agent
Comparator	• No restriction	
Outcome	• QoL outcomes reported	
Timing and setting	• From database inception to Nov 2024 • No restriction on setting or country	
Study design	• Interventional studies • Observational studies • Study published in English language	• Case report and case series • Review articles or editorials • Conference abstracts

*Radioembolization and intra-arterial RLT were not included.

Results

Figure 1. PRISMA flow diagram

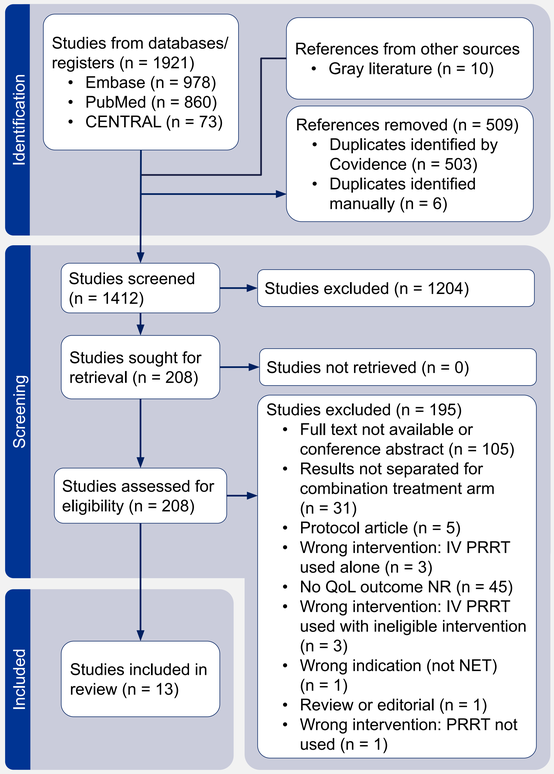
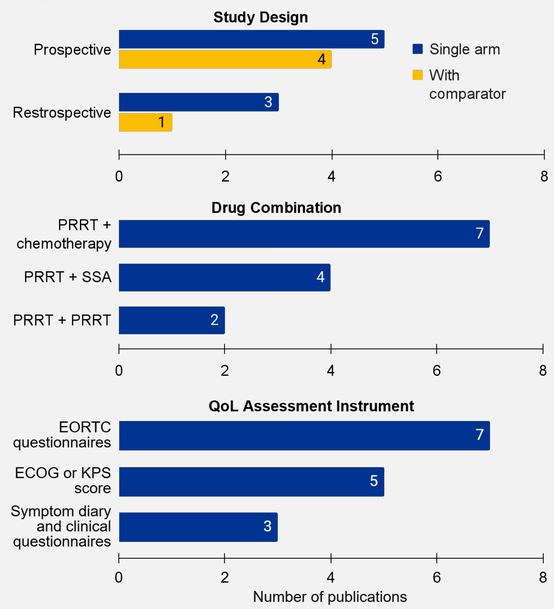


Figure 2. Characteristics of included studies



ECOG = Eastern Cooperative Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, KPS = Karnofsky performance status, SSA = somatostatin analog

Results

Table 2. Results of included studies

Study	Drug agents	Disease	N	Median follow up, months	Assessment tools[a]	Results
Claringbold 2011	^{177}Lu* + CAP	NET	33	16	EORTC QLQ-C30	*Median, baseline to follow-up* • **Overall health**: 5 to 5 • **Quality of life**: 5 to 5
Kashyap 2015	^{177}Lu* + 5FU	NET	52	36	EORTC QLQ-C30, EORTC QLQ-GINET21	• **Physical functioning**: improvement, P < 0.05 • **Social functioning**: improvement, P < 0.05 • **Endocrine**: improvement, P < 0.05
Singh 2024	^{177}Lu* + OCT vs OCT	GEP-NET	226	23.2	EORTC QLQ-C30	*Median TTD* • **GHS**: 13.2 vs 8.6 months, HR n.s. • **Pain**: 10.3 vs 8.6 months, HR n.s. • **Diarrhea**: 17.4 vs 17.3 months, HR n.s..
Strosberg 2018[b]	^{177}Lu* + OCT vs OCT	Midgut NET	231	NR	EORTC QLQ-C30, EORTC QLQ-GINET21	*HR based on TTD* • **GHS**: HR 0.41 (95% CI 0.24-0.69), P<0.001 • **Pain**: HR 0.57 (95% CI 0.34-0.94), P=0.025 • **Diarrhea**: HR 0.47 (95% CI 0.26-0.85), P=0.011
Strosberg 2020[b]	^{177}Lu* + OCT vs OCT	Midgut NET	231	NR	EORTC QLQ C30, EORTC QLQ-GINET21	*Median TTD* • **GHS**: Low liver tumor burden: 28.8 vs 6.1 months, HR 0.376, P = 0.002; Moderate/high tumor burden: not reached vs 6.0 months, HR 0.45, P=0.087
Yadav 2019	^{177}Lu* + CAP	PGL	25	30	EORTC QLQ-H&N35, KPS, AS	*Mean (baseline to follow-up)* • **EORTC QLQ H&N35**: **Pain**: 51.8 to 26.8 (P=0.001) • **KPS**: PR: 62.5 to 80.0 (P=0.068), SD: 66.9 to 78.5 (P<0.002), PD: 65.0 to 18.0 (P<0.008)
Yadav 2022	^{255}Ac* + CAP	PGL	9	22.5	EORTC QLQ-H&N35, KPS, ECOG, AS	*Mean (baseline to follow-up)* • **EORTC QLQ H&N35**: **Pain**: 80.9 to 28.5 (P=0.0002) • **KPS**: 60 to 85 (P=0.005) • **ECOG**: 3 to 1 (P=0.001)
Ballal 2017	^{177}Lu* + CAP vs ^{177}Lu*	NET	167	mean: 33.4	ECOG, KPS	• **ECOG, KPS**: significant improvement in both groups, no numeric data
Ballal 2022	^{255}Ac* + CAP	GEP-NET	91	24	ECOG, KPS	• **ECOG**: change in median: 0 • **KPS**: change in median: +10
Parghane 2021	^{177}Lu* + CAPTEM	NET	38	36	ECOG, KPS	• **ECOG**: change in mean: -1 • **KPS**: change in mean: +7
Strosberg 2021[b]	^{177}Lu* + OCT vs OCT	Midgut NET	231	NR	Symptoms diary	*Mean difference in days with symptom between intervention vs control groups:* • **Flushing**: -1.98 days per 4 weeks (P=0.041) • **Diarrhea**: -3.11 days per 4 weeks (P=0.0017)
Seregni 2010[c]	^{177}Lu* + ^{90}Y*	NET	26	6.6	Other clinical questionnaire	• **Pain**: pain relief in 83% • **Carcinoid syndrome**: benefit experienced in 19%
Seregni 2014[c]	^{177}Lu* + ^{90}Y*	NET	26	29.8	Other clinical questionnaire	• **Pain**: pain relief in 83% of symptomatic patients • **Carcinoid treatment**: reduced flushing, diarrhea, and/or pain in 90% of symptomatic patients

* = DOTATATE, 5FU = 5-fluorouracil, AS = analgesic score, CAP = capecitabine, CAPTEM = capecitabine and temozolomide, EORTC QLQ = EORTC Quality of Life Questionnaire (-C30 = Core Module, -H&N35 = Head and Neck Cancer Module, -GINET21 = Gastrointestinal NETs questionnaire), GEP-NET = gastroenteropancreatic NET, GHS = global health status, HR = hazard ratio, n.s. = not significant, OCT = octreotide, PD = progressive disease, PGL = paraganglioma, PR = partial response, SD = stable disease, TTD = time to 10-point deterioration

[a]Descriptions of different QoL assessment tools are available in the Supplemental Materials.

[b]Multiple publications from the same clinical trial reporting different QoL endpoints and one subgroup analysis.

[c]Preliminary and final results of the same clinical trial.

DISCUSSION

- Although some studies used the same standardized QoL questionnaires, reporting of results in specific domains was inconsistent.
- Heterogenous reporting of results limited feasibility of quantitative comparisons.

CONCLUSIONS

Limited studies reported QoL outcomes of RLT combination therapies in NETs, suggesting a need for additional QoL evidence to better understand patient experience in these novel treatment regimens.

Scan QR code for Supplemental Materials

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