Poster C-27

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Efficacy and Safety of Peptide Receptor Radionuclide Therapy Retreatment (r-PRRT) Practices in Progressive Neuroendocrine Tumors (prog-NETs): Systematic Review and Meta-Analysis

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INTRODUCTION

- In patients with prog-NETs, PRRT in the form of radiolabeled somatostatin analogs, bind to somatostatin receptors on cancer cells to deliver targeted radiation, and has emerged as a treatment option with low toxicity and prolonged survival outcomes[1]
- In the absence of established standard of care and limited alternative therapeutic options, r-PRRT is being increasingly utilized for prog-NETs, especially in patients with sustained responses to initial PRRT (i-PRRT)[2,3]
- There is a paucity of high-quality evidence as to the optimal treatments or sequence of these treatments, leading to the initiation of prospective r-PRRT studies (NET RETREAT [NCT05773274], ACTION-1 [NCT05477576])[4–7]
- While we eagerly await results from NET RETREAT, this systematic review of the literature aimed to gain a better understanding of the safety and efficacy of r-PRRT in patients with prog-NETs, by conducting a systematic review and meta-analysis of r-PRRT practices between 2020–2024

METHODS

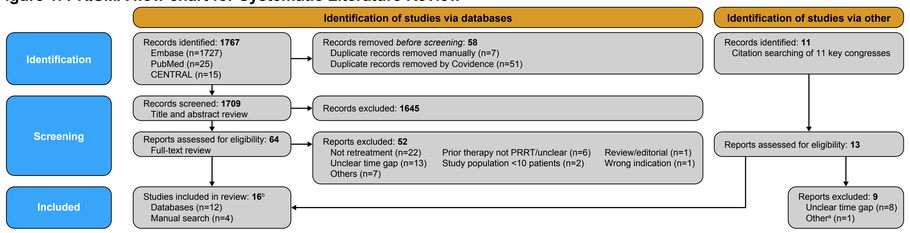
- A systematic search of PubMed, Embase, and CENTRAL databases and a manual search of key conference abstracts were performed to identify studies published between 2020–2024, in adult patients with prog-NETs previously treated with PRRT and retreated with ^{177}Lu-, ^{90}Y-, or α-emitting PRRT
- Results were screened by two independent reviewers and a third independent adjudicator selected studies for inclusion using Covidence systematic review software (www.covidence.org)
- Eligible studies were those with ≥10 patients, in which the time gap between i-PRRT and r-PRRT was specified or indicated
- Efficacy and safety outcomes were investigated, including progression-free survival (PFS), overall survival (OS), response rates, hematotoxicity, and nephrotoxicity
- Outcomes were summarized descriptively, with pooled median PFS weighted by sample size, and pooled disease control rate (DCR) estimated from a meta-analysis using a random effects model in R

RESULTS

Characteristics of Included Studies

- Of 1709 studies screened, 12 studies were included along with four studies identified through manual searches (n=16; 1149 patients) (**Figure 1**)

Figure 1. PRISMA flow chart for Systematic Literature Review



[a]Abstracts were excluded from results as full-text versions were already included from database searches; [b]**Aberle**, et al. *Neuroendocrinol.* 2020;110(Suppl 1):246; **Ballal**, et al. *J Nucl Med.* 2022:jnumed.122.264043; Miljavila **Casanovas** M, et al. *Eur J Nucl Med Mol Imaging.* 2024;51(Suppl 1):S126; **Delpassand** ES, et al. *J Nucl Med.* 2024;65(5):746-752. **Durma** AD, et al. *Nucl Med Rev Cent East Eur.* 2023;26(0):143-152; **Galler** M, et al. *Cancers (Basel).* 2022;14(7):1768; **Ghaleb** N, et al. *Neuroendocrinol.* 2020;110(Suppl 1):255; **Grewal** US, et al. *J Gastrointest Cancer.* 2024;55(3):1165-1170; **Hartrampf** P, et al. *J Nucl Med.* 2024;65(Suppl 2):241926; **Hoe** HJ, et al. *J Clin Oncol.* 2022;40(Suppl 16):e16212; Martinez **Lago** NP, et al. *Neuroendocrinol.* 2024;36(Suppl 1):208; **Mattke** M, et al. *Eur J Nucl Med Mol Imaging.* 2024;51(Suppl 1):S671; **Navalkissoor** S, et al. *Pancreas.* 2021;50(3):453; **Sitani** K, et al. *Br J Radiol.* 2022;95(1137):20210896; **Zacho** MD, et al. *Scand J Gastroenterol.* 2021;56(3):289-297; **Zemczak** A, et al. *Int J Endocrinol.* 2021;2021:6615511
CENTRAL, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRRT, peptide receptor radionuclide treatment.

- i-PRRT included ^{177}Lu- and/or ^{90}Y-, or unspecified PRRT, with ^{177}Lu-DOTATATE being the most common
- r-PRRT included ^{177}Lu- and/or ^{90}Y-, or unspecified PRRT and ^{225}Ac-DOTATATE
- Most studies (n=14) reported ≥12 months (mean or median) from i-PRRT completion to r-PRRT, with one study inexplicitly reporting ≥6 weeks and another ≥6 months
- Median follow-up after r-PRRT ranged from 6.5–25.8 months (n=9)
- Generally, patients received at least 2 cycles of r-PRRT (in 13/16 studies reporting number of cycles of r-PRRT)
- Demographics were generally similar across studies with a mean age ranging from 54–70 years and most studies reporting a larger male cohort (**Table 1**)

Table 1. Patient characteristics in selected studies

		Demographics		Primary tumor, %			Metastatic site, %			Grade, %			
Study	n	Age, years	Male, %	GEP	Lung	Unknown/Other	Bone	Liver	Peritoneum	1	2	3	NS
Aberle 2020	523	59[a]	61.8	75	7	18	–	–	–	x	x	0.0	0.0
Ballal 2023	33	54[a,b]	59.3[b]	100	0.0	0.0	27.5	96.7	–	x	x	x	x
Casanovas 2024	71	55[a]	59.2	69	–	–	27	85	14	37	49	14	0.0
Delpassand 2024	31	62[a]	61.3	90.3	6.5	3.2	83.9	100.0	–	–	–	–	100
Durma 2023	13	63	38.5	38.5	0.0	61.5	–	–	–	61.5	38.5	0.0	0.0
Galler 2022	32	67	59.4	71.9	3.1	25.0	50.0	96.9	21.9	18.6	78.1	3.1	0.0
Ghaleb 2020	11	55[a]	63.6	81.8	9.1	9.1	–	–	–	x	x	0.0	0.0
Grewal 2024	11	66	54.5	90.9	0.0	9.1	–	–	–	0.0	18.2	81.8	0.0
Hartrampf 2024	19	NR	NR	100	0.0	0.0	–	–	–	–	–	–	100
Hoe 2022	37	NR	NR	64.9	10.8	24.3	–	–	–	–	–	–	100
Lago 2024	31	NR	61.3	80.7	16.1	3.2	45.2	90.9	35.5	32.3	51.6	16.1	0.0
Mattke 2024	29	NR	48.3	86.2	3.4	10.3	–	–	–	13.8	72.4	13.8	0.0
Navalkissoor 2020	224	62	NR	65.2	–	–	37	92	–	–	42.0	–	58.0
Sitani 2022	22	55	54.5	81.8	4.5	13.6	27.3	59.1	–	18.2	68.2	0.0	13.6
Zacho 2021	36	70[a,b]	54.1[b]	80.6	11.1	8.3	30.1	86.5	–	22.2	61.1	8.3	8.3
Zemczak 2021	26	55[a]	23.1	92.3	3.8	3.8	–	–	–	34.6	65.4	0.0	0.0

Values represented by an "x" indicate an unknown number of cases reported, cells with a "–" indicate that no information was provided on the incidence.
[a]Results reported represent the mean age, all other reported values represent the median age; [b]Results reported are for the full population (Ballal, n=91; Zacho, n=133).
GEP, gastroenteropancreatic; NR, not reported; NS, not specified.

- Among known primary NETs, gastroenteropancreatic and lung NETs were the most common tumor type in the included studies
- Available data show that the selected studies included tumor grades ranging from Grade 1–3; however, most studies (10/12 with available data [83%]) seem to report results from Grade 1–2 NETs

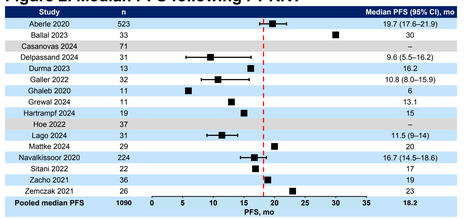
PFS and OS

- Median PFS were reported for 14 studies (n=1041) following r-PRRT
- The pooled median PFS reported across these studies weighted by the sample size was calculated as 18.2 months (**Figure 2**)
- OS were only reported in 25% of the included studies (four studies; n=108) and ranged from 7.0–27.7 months

DCR

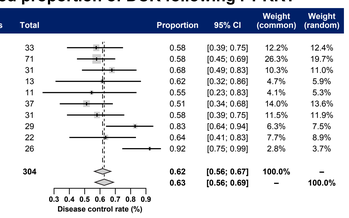
- The pooled DCR (95% CI), defined as stable disease, complete response, or partial response with RECIST v1.1, reported at any time following r-PRRT across 10 studies (n=304) was estimated as 62.8% (55.8–69.4), with no significant heterogeneity (p=0.07) (**Figure 3**)
- Two studies only reported the percentage of patients that showed progression, without additional response data and were removed
- No significant heterogeneity (I^2=42.5%) were reported for the remaining 10 studies, and deemed to be acceptable for a meta-analysis of proportions

Figure 2. Median PFS following r-PRRT



The dashed red line represents the weighted pooled median PFS across all studies.
CI, confidence interval; PFS, progression-free survival; r-PRRT, peptide receptor radionuclide therapy retreatment.

Figure 3. Pooled proportion of DCR following r-PRRT



CI, confidence interval; DCR, disease control rate; r-PRRT, peptide receptor radionuclide therapy retreatment.

Safety

- Of the 16 studies included, only one did not report any safety data, and 696 patients were included in the safety analysis (**Table 2**)
- Reported safety results were mainly concerned with hemato-, nephro-, and hepatotoxicity
- Hematotoxicity was generally transient and mild, with low rates of Grade ≥3 events; anemia was the most common
- Only one study reported myelodysplastic syndrome or acute myeloid leukemia (0.243 per 100 person-years)
- Nephrotoxicity was mostly low grade, with only one study reporting one patient (10.0%) with Grade ≥3 nephrotoxicity
- Hepatoxicity was only discussed in six studies, with four of these studies (66.7%) reporting no cases

Table 2. AEs of interest reported across selected studies

		Nephrotoxicity	Hepatotoxicity	Anemia		Leukopenia		Thrombocytopenia	
Study	n	Any grade	Any grade	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Aberle 2020	523	NR	NR	NR	NR	NR	NR	NR	NR
Ballal 2023	91[a]	0 (0)	0 (0)	51 (56.0)	0 (0)	5 (5.5)	0 (0)	17 (18.7)	1 (1.1)
Casanovas 2024	71	NR	NR	NR	NR	NR	NR	NR	NR
Delpassand 2024	31	6 (19.4)[b]	NR	23 (74.2)	1 (3.2)	15 (48.4)	1 (3.2)	19 (61.3)	2 (6.5)
Durma 2023	13	0 (0)	0 (0)	x	0 (0)	x	0 (0)	x	0 (0)
Galler 2022	32	NR	NR	0 (0)	1 (3.1)	0 (0)	0 (0)	6 (18.8)	0 (0)
Ghaleb 2020	11	0 (0)	2 (18.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9.1)	0 (0)
Grewal 2024	10	3 (30)	NR	7 (70)	0 (0)	NR	NR	3 (30)	1 (10)
Hartrampf 2024	19	NR	NR	NR	0 (0)	NR	0 (0)	NR	0 (0)
Hoe 2022	37	3 (8.1)	NR	NR	1 (2.7)	NR	NR	NR	1 (2.7)
Lago 2024	31	0 (0)	NR	NR	2 (6.5)	NR	1 (3.2)	NR	4 (12.9)
Mattke 2024	29	x	x	29 (100)	1 (3.4)	12 (41.4)	2 (6.9)	13 (44.8)	1 (3.4)
Navalkissoor 2020	237	NR	NR	NR	x	NR	x	NR	x
Sitani 2022	22	4 (18.2)	0 (0)	18 (81.8)	0 (0)	2 (9.1)	0 (0)	6 (27.3)	0 (0)
Zacho 2021	36	NR	NR	NR	0 (0)	NR	NR	NR	0 (0)
Zemczak 2021	26	9 (34.6)	0 (0)	15 (57.7)	0 (0)	8 (30.8)	0 (0)	3 (11.5)	0 (0)

Values represented by an "x" indicate an unknown number of cases reported.
[a]Safety data are only available for the full population, n=91; [b]Based on values reported for hypercreatininemia.
AE, adverse event; NR, not reported.

LIMITATIONS

- Heterogeneity was observed across studies, specifically with regards to DCR, and limited availability of data reporting OS after r-PRRT
- The effects of treatment exposure (dosing and number of cycles), which were variable across studies, were not considered in the efficacy or safety analysis
- Other confounding effects related to baseline characteristics (tumor types, tumor grades, tumor locations, etc.) further limits the generalizability of results
- Finally, inconsistent reporting of outcomes could have led to incorrect assumptions/estimations or data adjustments

CONCLUSIONS

- These data suggest that r-PRRT is well tolerated and effective in patients with prog-NETs
- Clinically meaningful PFS benefit and high DCR following r-PRRT supports r-PRRT as a viable treatment option in patients with prog-NETs who otherwise have limited treatment options
- Overall, r-PRRT was well tolerated and comparable to i-PRRT with no unexpected or new safety signals noted in our meta-analysis
- While results confirm previous observations with r-PRRT, widespread generalization of results is limited by inconsistent reporting of baseline characteristics and study outcomes
- Prospective randomized evaluation of r-PRRT strategy and investigating the role of predictive biomarkers for optimal patient selection is warranted

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