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# Developing a novel patient reported outcomes measure for prostate cancer patients receiving radionuclide therapy

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Running Title: Developing a prostate cancer PRO measure



**ABSTRACT**

The field of radionuclide therapy (RNT) for prostate cancer (PC) is growing rapidly with recent Food and Drug Administration approval of the first Lutetium-177-PSMA-ligand. We aimed to develop the first patient-reported outcomes (PRO) measure for PC patients receiving RNT. Methods: We identified relevant symptoms/toxicities by reviewing published trials and interviews with PC patients receiving RNT (n=29), caregivers (n=14), and clinicians (n=11). Second, we selected items for measure inclusion. Third, we refined the item list with input from experts in RNTs and PROs. Fourth, we finalized the FACT-RNT with patient input. Results: This multi-step process yielded a brief 15-item measure deemed by key stakeholders to be relevant and useful in the context of RNT for PC. Conclusion: The Functional Assessment of Cancer Therapy – Radionuclide Therapy (FACT-RNT) is a new standardized tool to monitor relevant symptoms/toxicities among PC patients in RNT trials and real-world settings.

## INTRODUCTION

Radionuclide therapy (RNT) is a rapidly emerging class of oncology agents for metastatic castration-resistant PC, spurred by Food and Drug Administration (FDA)-approval of Radium-223 dichloride and $^{177}$Lu-PSMA-617. RNTs, such as $^{177}$Lu-PSMA-617, improve radiographic progression-free survival and overall survival vs. standard care (*1*) with higher biochemical response rate, fewer grade 3/4 adverse events vs. cabazitaxel (*2*), and improved or preserved health-related quality of life (HRQOL) (*3,4*).

The FDA encourages patient-reported outcomes (PROs) as trial primary endpoints (*5*) or complements to clinical/physiologic endpoints (*6*). Because clinicians may underestimate patient-reported toxicities (*7*), PROs are crucial to assessing treatment tolerability. HRQOL in RNT recipients was better than placebo (e.g., ALSYMPCA trial (*8*)) or similar to cabazitaxel (e.g., TheraP trial (*2*)).

PROs are associated with clinical outcomes, such as improved HRQOL among patients with better $^{177}$Lu-PSMA-617 biochemical response (*9*). Phase 1 trials (n=79) of $^{177}$Lu-PSMA-617 or $^{225}$Ac-J591 showed that RNT response was associated with PRO changes (*10*). PRO importance is underscored by recent evidence that PRO monitoring improved post-chemotherapy survival and other important outcomes over usual care (*11,12*).

Commonly-used PRO measures (e.g., EORTC QLQ-C30 (*13*), FACT-P (*14*)) are long and were designed to assess impacts of traditional therapies (e.g., chemotherapy, radiation). Shorter PRO measures designed for RNT are needed to optimize measurement, prognostic value, and cross-trial comparison. This study aimed to develop a brief, targeted PRO measure for PC patients receiving RNT. We hypothesized that a multi-step approach to identifying relevant symptoms/toxicities and iterative refinement would yield a brief measure relevant to RNT recipients and experts in the fields of RNT and PROs.

## MATERIALS AND METHODS

Figure 1 shows the study flow for FACT-RNT development from 2021-2022, following a similar approach to other studies developing PRO instruments for cancer patients (*15*). The protocol was deemed exempt from IRB review, and participants consented verbally. We recruited English- or Spanish-speaking adults, including PC patients who received RNT, informal caregivers (e.g., spouse, relative) to RNT recipients with PC, and RNT-experienced clinicians at University of California, Los Angeles or Moffitt Cancer Center. Following qualitative research guidelines (*16,17*), we aimed to interview ≥10 participants per group until reaching saturation.

This study was conducted in four steps. In Step 1, we identified an intentionally broad, comprehensive list of RNT symptoms/toxicities (e.g., hematotoxicity, nephrotoxicity) experienced by PC patients during/after RNT via review of published trials and semi-structured interviews with patients, caregivers, and clinicians to elicit common, distressing, and/or clinically meaningful symptoms/toxicities. Each participant was compensated $25. Interviews were audio recorded, transcribed verbatim, and analyzed with NVivo 12 using the immersion/crystallization method by

two qualitative research staff with strong inter-rater reliability (κ≥.80) until no new qualitative themes were identified within each group (*17,18*).

In Step 2, we searched for RNT symptoms/toxicities reported in Step 1 within the Functional Assessment of Chronic Illness Therapy (FACIT) item library (*19*), a rigorously developed catalogue of ≥700 items and 100 validated measures of chronic illness management.

In Step 3, we interviewed internationally renowned experts in the fields of RNT and PROs to seek consensus on RNT-relevant symptoms/toxicities and corresponding FACIT items, iteratively refine the item list based on recommended item additions/deletions, and draft the FACT-RNT.

In Step 4, patients from Step 1 reviewed the draft FACT-RNT and participated in semi-structured interviews assessing measure acceptability, comprehensibility, RNT relevance, and self-efficacy for completing the measure. The FACT-RNT was subsequently finalized.

## RESULTS

Literature review and interviews with 29 PC RNT recipients, 14 caregivers of RNT recipients, and 11 clinicians identified RNT-relevant symptoms/toxicities (e.g., fatigue, bone pain, xerostomia). See Table 1 for participant characteristics. Patients interviewed received $^{177}$Lu-PSMA-617 and/or $^{225}$Ac-J591; comprehensive literature review also identified symptoms/toxicities of other RNTs (e.g., Ra223). Notably, interviews identified social isolation as an unexpected and distressing concern due to recommendations to briefly avoid close social contact and public venues post-infusion.

We selected FACIT items corresponding to each symptom/toxicity and to assess functional impacts (e.g., “I am bothered by side-effects of treatment”). In some instances, multiple FACIT items could be used (e.g., “I have a lack of energy” vs. “I feel fatigued”).

Nine RNT and PRO experts from 5 institutions across 3 continents reviewed the draft FACT-RNT and advised on item selection, addition of RNT-relevant symptoms/toxicities (e.g., dry eyes), and removal of less relevant symptoms/toxicities (e.g., neuropathy).

Lastly, 10 RNT recipients from Step 1 reported in interviews that FACT-RNT instructions were clear, items were comprehensible and relevant to RNT, response options (e.g., “not at all” vs. “a little bit”) were conceptually distinct, and baseline administration is important to assess changes. Experts and patients recommended adding a bone pain severity item to distinguish among different pain types. Table 2 provides the final FACT-RNT.

## DISCUSSION

This study describes development of the FACT-RNT, the first PRO measure designed for PC patients receiving RNT and developed with multi-step feedback from patients, caregivers, clinicians, and experts in RNTs and PROs. FACT-RNT capitalizes on the FACIT item library’s

strong validity and reliability, multi-language translation and validation, and utility as self-administered PROs or via interview.

The FACT-RNT for PC addresses the current gap in measuring RNT-specific symptoms/toxicities and responds to FDA guidance on implementing PROs in therapeutic trials (*5*) and real-world settings to identify PC patients at risk for deterioration. The FACT-RNT was designed for use and future adaptation with a broad variety of RNT agents with different molecular targeting mechanisms and radioisotopes.

The sample was primarily non-Hispanic White; future studies should validate the FACT-RNT in large, diverse PC samples. Interviews with leading RNT experts helped ensure consideration of symptoms/toxicities relevant to newer-generation RNT agents and ensure long-term relevance of FACT-RNT items.

## CONCLUSION

We present the FACT-RNT for PC, a new measure developed through multi-step collaboration with patients, caregivers, clinicians, and international experts. Next steps include assessment of internal consistency, validity, and reliability and use in RNT clinical trials and real-world settings.

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## KEY POINTS

Question: Can a brief, targeted patient-reported outcomes (PROs) measure be developed for patients receiving radionuclide therapy (RNT) for prostate cancer (PC)?

Pertinent Findings: The FACT-RNT was developed through a multi-step, iterative process with input from patients, caregivers, clinicians, and experts in RNT and PROs.

Implications for Patient Care: The FACT-RNT can assess PROs in PC patients receiving RNT.

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Figure 1. Developing a patient-reported outcomes measure for radionuclide therapy (RNT) for prostate cancer (PC).

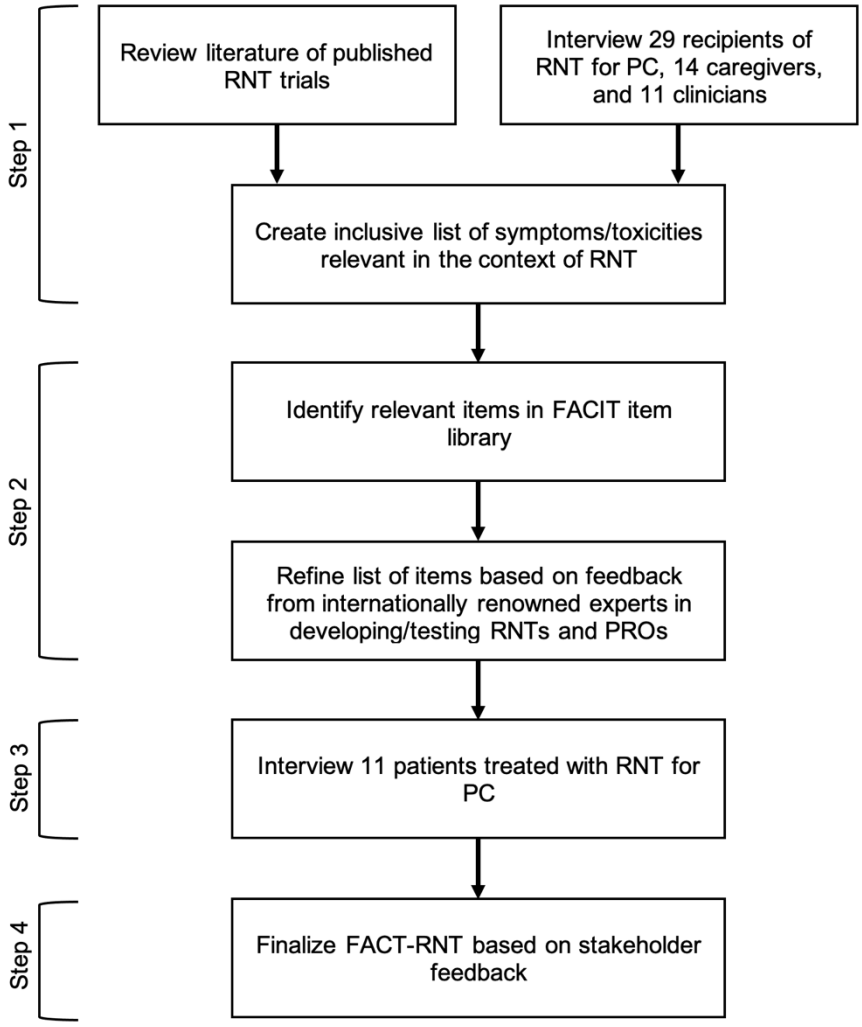

Table 1. Characteristics of interviewed radionuclide therapy (RNT) recipients, informal caregivers, and clinicians.

| | Step 1 | | | Step 4 |
|---|---|---|---|---|
| | **RNT recipients (n = 29)** | **Caregivers (n = 14)** | **Clinicians (n = 11)** | **RNT recipients (n = 11)** |
| Age in years, M (SD) | 72 (8) | 64 (11) | 56 (8) | 71 (9) |
| Male Sex, n (%) | 29 (100%) | 0 (0%) | 7 (64%) | 11 (100%) |
| Ethnicity, n (%) | | | | |
| Hispanic | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Non-Hispanic | 26 (90%) | 13 (93%) | 8 (73%) | 9 (82%) |
| Unknown/Not reported | 3 (10%) | 1 (7%) | 3 (27%) | 2 (18%) |
| Race, n (%) | | | | |
| White | 24 (83%) | 11 (79%) | 6 (55%) | 8 (73%) |
| Black / African American | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Asian | 1 (3%) | 2 (14%) | 2 (18%) | 0 (0%) |
| Native American/Alaska Native | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hawaiian/Pacific Islander | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unknown/Not reported | 4 (14%) | 1 (7%) | 3 (27%) | 3 (27%) |
| Years since diagnosis, M (SD) | 11.72 (7.02) | | | 11.84 (7.74) |
| RNT injections received, M (SD) | 4.00 (1.65) | | | 4.45 (1.44) |

Table 2. FACT-RNT items

| Item Code | Symptom/toxicity |
|---|---|
| HN2 | My mouth is dry |
| ST16 | My eyes are dry |
| P7 | I have difficulty urinating |
| GP2 | I have nausea |
| O2 | I have been vomiting |
| C5 | I have diarrhea (diarrhoea) |
| Pal5 | I am constipated |
| Ga1 | I have a loss of appetite |
| BP1 | I have bone pain |
| HI7 | I feel fatigued |
| AA1 | My fatigue keeps me from doing the things I want to do |
| GP4 | I have pain |
| P3 | My pain keeps me from doing things I want to do |
| GP5 | I am bothered by side effects of treatment |
| Leu7 | I feel isolated from others because of my illness or treatment |

Note: The FACT-RNT will be available at FACIT.org. Response options range from 1 (“not at all”) to 5 (“very much”).

Graphical abstract